Ph.D. Thesis

KORAH P KURUVILLA

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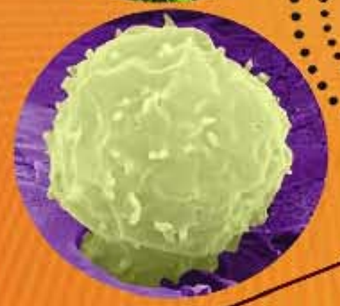
Serotonin receptor subtypes functional regulation and oxidative stress mediated apoptosis in 6-hydroxydopamine lesioned Parkinsonian rats: Functional recovery with Serotonin, GABA and Bone Marrow Cells



Ph.D. Thesis

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SEROTONIN RECEPTOR SUBTYPES FUNCTIONAL REGULATION AND OXIDATIVE STRESS MEDIATED APOPTOSIS IN 6-HYDROXYDOPAMINE LESIONED PARKINSONIAN RATS: FUNCTIONAL RECOVERY WITH SEROTONIN, GABA AND BONE MARROW CELLS

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BY

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CERTIFICATE

This is to certify that the thesis entitled "**Serotonin receptor subtypes functional regulation and oxidative stress mediated apoptosis in 6-hydroxydopamine lesioned Parkinsonian rats: Functional recovery with Serotonin, GABA and Bone Marrow Cells**" is a bonafide record of the research work carried out by Mr. Korah P Kuruvilla, under my guidance and supervision in the Department of Biotechnology, Cochin University of Science and Technology and that no part thereof has been presented for the award of any other degree.

Cochin – 682 022
May 23, 2012

(C. S. Paulose)

DECLARATION

I hereby declare that the thesis entitled "**Serotonin receptor subtypes functional regulation and oxidative stress mediated apoptosis in 6-hydroxydopamine lesioned Parkinsonian rats: Functional recovery with Serotonin, GABA and Bone Marrow Cells"** is based on the original research carried out by me at the Department of Biotechnology, Cochin University of Science and Technology, under the guidance of Prof. C. S. Paulose, Director, Centre for Neuroscience, Department of Biotechnology and no part thereof has been presented for the award of any other degree, diploma, associateship or other similar titles or recognition.

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My tribute…..to a number of animals who have paid a price with their lives and suffering in the name of human protection. I pay my tribute to their sacrifice and pray that it is not in vain.

The woods are lovely, dark and deep.
But I have promises to keep, and miles to go before I sleep
Robert Frost

In all, the journey to my Ph.D. has been a long and challenging road. And I am thrilled it is done. But most of all, I am excited for what the future holds….

Korah P Kuruvilla

Dedicated to my beloved family. . .

ABBREVIATIONS

5-HIAA	5-Hydroxyindoleacetic acid
5-HT	Serotonin
5-HTT	Serotonin Transporter
6-OHDA	6-hydroxydopamine
8-OHDG	8-hydroxy-2'-deoxyguanosine
AC	Adenylyl Cyclases
ACh	Acetylcholine
AD	Alzheimer's disease
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	Brain-derived neurotrophic factor
BMC	Bone marrow cells
BMSC	Bone marrow stromal cells
BrdU	Bromodeoxyuridine
CAT	Catalase
CN	Caudate nucleus
CNS	Central Nervous System
CSF	Cerebrospinal fluid
DA	Dopamine
DAT	Dopamine transporter
DEPC	Diethylpyrocarbonate
DHA	Docosahexanoic acid
DLB	Dementia with lewy bodies

DOI	(±)-2,5-dimethoxy-4-iodoamphetamine
DRN	Dorsal raphe nucleus
EBST	Elevated body swing test
ECD	Electrochemical detector
EDTA	Ethylene diamine tetra acetic acid
GABA	Gamma amino butyric acid
GAD	Glutamic acid decarboxylase
GAP	GTPase-activating protein
GDNF	Glial cell line-derived neurotrophic factor
GP	Globus pallidus
GPi	Globus pallidus internus
GPm	Medial globus pallidus
GPx	Glutathione peroxidase
GSH	Glutathione
H_2O_2	Hydrogen peroxide
HPLC	High performance liquid chromatography
IP_3	Inositol trisphosphate
L-DOPA	L-3,4-dihydroxyphenylalanine
LID	Levodopa-induced dyskinesia
LTD	Long-term depression
LTM	Long-term memory
LTP	Long term potentiation
MANF	Mesencephalic astrocyte-derived neurotrophic factor
MAO	Monoamine oxidase

MFB	Medial forebrain bundle
MHPG	3-methoxy-4-hydroxyphenylglycol
MPP^+	1-methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydroxypyridine
nAChRs	Nicotinic acetylcholine receptors
NE	Norepinephrine
NeuN	Neuronal-specific nuclear protein
NF-κB	Nuclear factor-kappa B
NGF	Nerve growth factor
NMDA	N-methyl-D-aspartate
NMSs	Non-motor symptoms
NTF	Neurotrophic factors
p75NTR	p75 neurotrophin receptor
PBS	Phosphate buffered saline
PCPA	Parachlorophenylalanine
PD	Parkinson's disease
PFA	Paraformaldehyde
PI3	Phosphatidyl inositol-3
PI3-K	Phosphatidylinositol 3-kinase
PLC	Phospholipase C
PPE	Preproenkephalin
PPN	Pedunculopontine nucleus
ROS	Reactive oxygen species
SDS	Sodium dodecyl sulfate

SGZ	Subgranular zone
SMC	Smooth muscle cells
SN	Substantia nigra
SN*pc*	Substantia nigra *pars compacta*
SN*pr*	Substantia nigra *pars reticulata*
SOD	Superoxide dismutase
STN	Sub thalamic nucleus
TBARs	Thiobarbituic acid reactive material
TH	Tyrosine hydroxylase
Trk	Tropomyosin-related kinase
VTA	Ventral tegmental area

CONTENTS

Introduction

Parkinson's disease (PD), originally described by British apothecary James Parkinson in "*An Essay on the Shaking Palsy*" (1817), is a neurodegenerative disease caused by the progressive degeneration of the nigrostriatal dopaminergic pathway. It is the second most common neurodegenerative disorder, with an incidence of 1.5–2% in the population over 60 years of age, which increases significantly with advancing age. As life expectancy is significantly increasing in the modern world, the incidence of PD is steadily escalating. Consequently, the financial and economical burden of the treatment and care of PD patients is substantial and increasing (Toulouse & Sullivan, 2008). Thus, research on the causes of this debilitating disease is critical, as is the development of new treatments.

PD is caused by the progressive degeneration of the nigrostriatal (A9) dopaminergic pathway, which projects from the substantia nigra (SN) in the midbrain to the caudate-putamen (striatum) in the forebrain (Hoehn & Yahr, 1967; Fearnley & Lees, 1991). The resulting loss of dopamine (DA) neurotransmission in the striatum causes the cardinal symptoms of the disease: tremor at rest, cogwheel rigidity, bradykinesia, stooped posture and shuffling gait (Thomas & Beal, 2007; Wu *et al.*, 2011). Although subject to intensive research, the etiology of PD is still enigmatic and the treatment is basically symptomatic. Approximately 5% of PD cases are caused by heritable genetic mutations (Stewart & William, 2008). The remaining cases are sporadic and of unknown origin, although many theories have been proposed to explain the cause of dopaminergic neuronal death which occurs in PD, such as environmental toxins, mitochondrial dysfunction with resulting oxidative stress, disturbances of intracellular calcium homeostasis and inflammatory mechanisms (Dauer & Przedborski, 2003; Lev *et al.*, 2003; Long-Smith *et al.*, 2009). There is no gender preference. Mortality among affected individuals is 2–5 times greater than for their age-matched unaffected peers (Bennet *et al.*, 1996; Morens *et al.*, 1996; Driver *et al.*, 2009).

The loss of dopaminergic cells in the substantia nigra *pars compacta* (SN*pc*) results in insufficient DA innervation of the basal ganglia and subsequent increased inhibition of excitatory thalamo-cortical connections. Lewy bodies, intracellular inclusions principally containing α-synuclein, are also found in the remaining nigral neurons of PD patients (Schlossmacher, 2007; Eller & Williams, 2011). The ultimate result of cell loss and cell dysfunction in the SN is the depletion of the neurotransmitter DA in the basal ganglia. This insufficient DA innervation is principally localized to the postcommissural putamen and results in the overdrive of globus pallidus and subthalamic nuclear outputs. The resulting inhibition of thalamocortical function results in the characteristic bradykinesia experienced by PD patients (Soderstrom *et al*., 2009).

Non-motor symptoms (NMSs) are often an integral part of the disease and some of them, such as depression, anxiety and hyposmia, can precede the onset of Parkinsonism. Other NMSs, such as psychosis, dementia, impulse-control disorders, somnolence and autonomic dysfunctions, are almost invariably present in advanced disease and in various combinations they may represent the principal complaints and therapeutic challenges (Ceravolo *et al*., 2010; Jellinger, 2012). The dysfunction of striatum results in deficient input to the pre-frontal cortex from the striatum and causes cognitive decline in PD patients (Dubois & Pillon, 1997). These NMSs including cognitive deficits determine the patients' quality of life and are equally important to the motor deficits occurring in PD (Weerkamp *et al*., 2012; Wood, 2012).

The therapies presently available for PD are not effective in the long-term and cannot stop the ongoing neurodegeneration. The most commonly used treatment is the DA precursor, levodopa (L-DOPA), which replaces lost DA in the denervated striatum and relieves motor symptoms. However long-term administration of levodopa is associated with the development of dyskinesias (Hollingworth *et al*., 2011) and does little to treat non-dopaminergic motor and NMSs, which are an important source of morbidity, including dementia, sleep disturbances, depression, orthostatic hypotension and postural instability leading to falls (Henchcliffe & Severt, 2011). It is critical, therefore, to develop a broader

and more fundamental therapeutic approach to PD and major research efforts have focused upon developing neuroprotective interventions.

Animal models are an invaluable tool for studying the pathogenesis and progression of human diseases, as well as for testing new therapeutic intervention strategies. Lesions with the neurotoxin, 6-hydroxydopamine (6-OHDA) have provided an important tool to study DA neurons in the brain. The most common version of such lesions is the unilateral one where the toxin is placed in the area of dopaminergic cell bodies in the SN (Schwarting & Huston, 1996; Duty & Jenner, 2011). The 6-OHDA model mimics many of the biochemical features of PD, including reduced levels of striatal DA and tyrosine hydroxylase (TH; rate-limiting step of DA biosynthesis). The DA analog, 6-OHDA, because of its similarity in molecular structure can be taken up into dopaminergic terminals through the DA transporter. Once inside dopaminergic neurons, 6-OHDA initiates degeneration through a combination of oxidative stress and mitochondrial respiratory dysfunction. 6-OHDA readily oxidizes to form reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) (Mazzio *et al.*, 2004), to reduce striatal levels of antioxidant enzymes - total glutathione (GSH) and superoxide dismutase (SOD) (Perumal *et al.*, 1992; Kunikowska & Jenner, 2001), to elevate levels of iron in the SN (Oestreicher *et al.*, 1994) and to interact directly with complexes I and IV of the mitochondrial respiratory chain, leading to subsequent respiratory inhibition and further oxidative stress (Glinka *et al.*, 1997; Soderstrom *et al*., 2009). 6-OHDA causes apoptotic cell death of dopaminergic neurons with loss of TH immunoreactivity in the SN (He *et al.*, 2000; Zuch *et al.*, 2000). Oxidative stress triggers apoptosis *via* a signalling pathway initiated by the generation of ROS leading to activation of caspase-9 and caspase-3 (Barzilai *et al.*, 2000; Junn & Mouradian, 2001). Depletion of neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in the nigrostriatal dopaminergic region trigger the process of apoptosis in PD (Mogi & Nagatsu, 1999; Mogi *et al.*, 1999). All these effects are thought to mirror events occurring in PD brain (Jenner, 1989), thereby supporting a high degree of construct validity for the 6-OHDA model. This lesion model has been used to investigate the

behavioural functions of the basal ganglia and to examine the brain's ability to compensate for specific neurochemical depletions. 6-OHDA lesion model have served as an experimental basis to develop new antiparkinsonian drugs and treatment strategies, or surgical approaches, including transplantation of neural tissue.

Brain serotonergic and monoamine dopaminergic systems are closely related (Alex & Pehek, 2007). The dopaminergic disturbance in the brain leads to serotonergic changes. *In vivo* microdialysis studies in the prefrontal cortex and corpus striatum have showed that local infusion of the DAD_2 receptor antagonist raclopride significantly inhibited the tail pinch induced increases in serotonin (5-HT) (Mendlin *et al.*, 1999). Similar results also indicated that local administration of the nonselective DA receptor agonist apomorphine into the hippocampus increased 5-HT release in a concentration-dependent manner and this increase was abolished by pre-treatment with the selective DAD_2 receptor antagonist, S(-)-sulpiride (Matsumoto *et al.*, 1996). Reciprocally, 5-HT afferents are able to facilitate the release of DA. It has been shown that DA release is induced in different brain regions following local cerebral application with 5-HT (West & Galloway, 1991; Parsons & Justice, 1993).

In addition to the correlation between 5-HT and DA transmission, there is tight functional interaction between these receptors. 5-HT receptors modulate dopaminergic function. 5-HT, by entering DA terminals, may elicit a carrier mediated release of DA or inhibit enhanced DA release (Navailles & De Deurwaerdère, 2011). 5-HT generally facilitates dopaminergic release via the $5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, $5\text{-}HT_{2A}$, $5\text{-}HT_3$ and $5\text{-}HT_4$ receptors whereas $5\text{-}HT_{2C}$ receptors tend to inhibit DA release (Alex & Pehek, 2007; Fox *et al.*, 2009). Intracortical infusion of the $5\text{-}HT_{2A}$ receptor antagonist M100907 profoundly attenuated DA release induced by systemic administration of the 5-HT agonist, suggesting that stimulation of cortical $5\text{-}HT_{2A}$ receptors increased DA release from the mesocortical system (Pehek *et al.*, 2006). Similar DA modulation was also observed by systemic or local administration of the $5\text{-}HT_{2C}$ receptor agonist mCPP or SB 206553 (Alex *et al.*, 2005). The 5-HT system directly and indirectly

participate in the mechanisms of action of L-3,4-dihydroxyphenylalanine (L-DOPA), the metabolic precursor of DA and the gold standard medication of PD. Numerous data have shown that 5-HT drugs ameliorate the motor and psychotic side effects induced by L-DOPA (Jenner *et al.*, 1983; Carta *et al.*, 2007; Navailles & De Deurwaerdère, 2011). Thus, the pharmacological treatments that modulate 5-HT receptors activity limit the extent of nigro-striatal damage, improve motor and NMS's of PD (Zoldan *et al.*, 1995; Pact & Giduz 1999) and prevent or reduce levodopa-induced dyskinesia (LIDs) (Melamed *et al.*, 1996; Carta *et al*., 2008) in animal models of PD.

Cell transplantation to replace lost neurons is a promising approach for the treatment of progressive neurodegenerative diseases. Replacement of dopaminergic neurons in patients with PD has spearheaded the development of this approach and was the first transplantation therapy to be tested in the clinic (Björklund *et al*., 2003). The success of the cell transplantation will depend on the ability of the cells to replace those neurons lost as a result of the disease process in the DA-deficient striatum and reverse, at least in part, the major symptoms of the disease. The fetal brain tissue used in clinical transplantation studies is ethically challenging to obtain (Lindvall, 2001). Also the Central Nervous System (CNS) immune response can mount a well-organized innate immune reaction in response to allogeneic antigens (Boulanger & Shatz, 2004; Arias-Carrión & Yuan, 2009). Number of reports claim that Bone marrow cells (BMC) can generate endoderm and ectoderm derivates including neural cells (Jiang *et al*., 2002; Kim *et al*., 2002). Hematopoietic system can be used as a source of progenitor cells for the CNS and it also has the property to differentiate into both microglia and macroglia when injected directly to the brain of adult mice (Martin & ´Eva, 1997). Intrastriatal grafts of mesenchymal stem cells derived from bone marrow protects against 6-OHDA (Blandini *et al.*, 2010), elevates TH expression and DA levels in adult rats and differentiates into neurons, astrocytes and oligodendrocytes (Jin *et al.*, 2009). BMC can differentiate into dopaminergic neurons (Chai *et al.*, 2007), exert neuroprotection on dopaminergic neurons (Park *et al.*, 2008; Kim *et al.*, 2009; Wang *et al.*, 2010) and holds potential as a readily available autologous

cellular therapy for ameliorating the degeneration of DA and 5-HT neurons in PD (Glavaski-Joksimovic *et al.*, 2009). Autologous BMC to treat neurological disorders offers several unique advantages over other cell replacement therapies. Immunological reactions are avoided and it also bypasses ethical issues in the use of embryonic cells.

Alterations in the brain monoamines DA, 5-HT and gamma amino butyric acid (GABA) have been implicated in the etiology and/or pharmacotherapy of PD. Most of the effects of 5-HT and GABA on DA neurons are indirect, mediated through actions on complex neuronal circuitry, rather than direct effects on DA terminals. Since the different 5-HT receptor subtypes are differently distributed in dopaminergic brain regions, it is possible to specifically “target” individual brain regions with serotonergic ligands and thereby affect dopaminergic function selectively in these areas (Alex & Pehek, 2007). As GABA helps "quiet" excessive neuronal firing and has been deficient in patients in the advanced stages of PD, directly targeting GABA production rather than DA replacement is an effective way of improving brain function in late-stage PD which also avoids the known therapeutic limitations and complications associated with the over-production of DA. 5-HT and GABA can be also used as agents for cell proliferation and differentiation. 5-HT plays an important trophic role during neurogenesis (Lauder *et al.*, 1981; Hernández Rodríguez, 1994). 5-HT can influence both biochemical and morphological differentiation of neurons and have an organizing function in the developing nervous system which involves effects on neurite outgrowth and other aspects of neuronal differentiation, including synaptogenesis (Lauder, 1990). GABA, the main inhibitory neurotransmitter in the mature CNS, was recently implicated in playing a complex role during neurogenesis. GABA acts as a chemoattractant and involves in the regulation of neural progenitor proliferation. GABA induces migration and motility of embryonic cortical neurons (Behar *et al.*, 1996, 2000; Haydar *et al.*, 2000). GABA acts as a trophic factor not solely during prenatal neurogenesis but also postnatally and promotes cell proliferation and NGF secretion (Ben-Yaakov & Golan, 2003). Our earlier studies showed that 5HT and GABA acting through specific receptor

subtypes $5HT_2$ (Sudha & Paulose, 1998) and $GABA_B$ (Biju *et al*., 2002) respectively, control cell proliferation and act as co-mitogens.

In the present study, a detailed investigation on the alterations of 5-HT and its receptors in the brain regions of unilateral 6-OHDA infused rats were carried out. 5-HT receptor subtypes - $5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$ and 5-HT transporter (5-HTT) gene expression were also studied in the 6-OHDA lesioned Parkinsonian rats. Oxidative stress induced neuronal damage was studied by assessing the activities of antioxidant enzymes - SOD and Catalase (CAT), gene expression of SOD and glutathione peroxidase (GPx) and the extent of lipid peroxidation. In addition to that the possible linkage between the 6-OHDA induced oxidative stress and subsequent apoptosis was studied by the gene expression of Akt, nuclear factor-kappa B (NF-κB) and Caspase-8. Expression of Neurotrophins – BDNF and Glial cell line-derived neurotrophic factor (GDNF) were also studied. Behavioural studies were conducted to evaluate motor deficits in Parkinson's rats and functional recovery by 5-HT and GABA in combination with BMC. We also demonstrated the autologous differentiation of BMC to neurons using comitogenic 5-HT and GABA by confocal studies with BrdU labelling and NeuN expression. Our present study on 5-HT, GABA and BMC dependent regulation of serotonergic receptors and oxidative stress in the brain will certainly enlighten novel therapeutic possibilities for PD management.

OBJECTIVES OF THE PRESENT STUDY

1. To induce Parkinson's disease in rats by unilateral infusion of 6-OHDA and to study the effects of 5-HT, GABA and BMC in combinations.

2. To study the behavioural changes in control and experimental rats using apomorphine induced rotational analysis, elevated body swing test (EBST), stepping test, footprint analysis test and beam-walk test.

3. To examine the dopaminergic neuronal regulation in SN*pc* by measuring DA content and studying TH gene expression and immunohistochemistry using specific antibody.

4. To measure 5-HT content in the brain regions – SN*pc,* corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of control and experimental rats using High Performance Liquid Chromatography (HPLC).

5. To study the total 5-HT, 5-HT_{2A} and 5-HT_{2C} receptor subtypes binding parameters in corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of control and experimental rats.

6. To study the 5-HT_{2A}, 5-HT_{2C} receptor subtypes and 5-HTT gene expression in the brain regions of control and experimental rats using Real-Time PCR.

7. To examine the oxidative stress by assessing the activities of antioxidant enzymes – SOD and CAT, gene expression status of SOD and GPx and the extent of lipid peroxidation in SN*pc* and corpus striatum of control and experimental rats

8. To study the oxidative stress mediated apoptosis by examining the gene expression status of Akt, NF-κB and Caspase-8 in the brain regions of control and experimental rats.

9. To study the gene expression of Neurotrophins – BDNF in SN*pc*, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem and GDNF in SN*pc* and corpus striatum of control and experimental rats.

10. To study the localisation and expression status of 5-HT_{2A}, 5-HT_{2C}, 5-HTT, BDNF, GDNF and TH by immunofluorescent specific antibodies in the brain slices of control and experimental rats using Confocal microscope.

11. To examine the BMC differentiation by BrdU and NeuN co-localisation studies.

Literature Review

In his classic 1817 monograph "Essay on the Shaking Palsy," James Parkinson described the core clinical features of Parkinson's disease - the second most common age-related neurodegenerative disease after Alzheimer's disease (AD). It is a degenerative neurological condition and the major neurological manifestations of this disease are: tremor, rigidity, bradykinesia (slowness of movement) and postural instability. PD primarily affects people over the age of 50 years and prevalence and incidence rates increase with age. Therefore, aging of the general population is likely to result in a dramatic increase in the number of people diagnosed with PD. One study projected that by the year 2030, the number of people over the age of 50 and consequently the number of persons with PD will double, resulting in an estimated 9 million persons with PD worldwide (Dorsey *et al.*, 2007; Pahwa & Lyons, 2010). Such an increase will place a significant burden on healthcare systems and caregivers given the progressive nature of PD, associated disability and significant caregiving required in the later stages of the disease. With the expected increase in PD prevalence, it can be anticipated that the disease will continue to exact a significant direct and indirect economic cost.

The primary pathology of PD is the degeneration of dopaminergic neurons in the SN*pc* with subsequent depletion of nigrostriatal DA and the development of Lewy bodies, proteinaceous intracytoplasmic inclusions (Forno, 1996; Choi *et al.*, 2011). Recent studies have shown that PD is also associated with extensive non-dopaminergic pathology involving noradrenergic neurons in the locus coeruleus, cholinergic neurons in the nucleus basalis of Meynert, serotonergic neurons in the midline raphe and neurons of the autonomic nervous system. Braak *et al.* (2003) has demonstrated that the pathological changes in PD occur in a relatively predictable, topographically distinct sequence of events beginning with the olfactory structures and medulla oblongata, spreading to the SN and eventually affecting neocortical structures. A great deal of the brain, especially the regions beneath the cortex, is heavily involved with movement regulation. Such areas

include the connected set of basal ganglia, portions of the thalamus and the cerebellum (Schiff, 2010). In PD, there is degeneration of neurons that use DA as a neurotransmitter, which have their cell bodies in the SN at the upper edge of the midbrain. The decrease in neural output from the SN causes a disturbance in the network balance of excitation and inhibition. The result is a net increase in inhibition from the globus pallidus internus (GPi) to thalamus (Obeso *et al.*, 2008).

Pathology, aetiology and pathogenesis

The hallmark of PD is the cell loss within the SN particularly affecting the ventral component of the pars compacta. By the time of death, this region of the brain has lost 50–70% of its neurons compared with the same region in unaffected individuals. The earliest documented pathological changes in PD (Braak *et al.*, 2006) have been observed in the medulla oblongata/pontine tegmentum and olfactory bulb. In these early stages, Braak stages 1 and 2 patients are pre-symptomatic. As the disease advances Braak stages 3 and 4 the SN, areas of the midbrain and basal forebrain become involved. Finally, the pathological changes appear in the neocortex. This pathological staging is based on the distribution of lewy bodies. Lewy bodies are the pathological hallmark of PD. They are α-synuclein immunoreactive inclusions made up of a number of neurofilament proteins together with proteins responsible for proteolysis. These include ubiquitin, a heat shock protein which plays an important role in targeting other proteins for breakdown. Mutations in the α-synuclein gene are responsible for some familial forms of PD in which lewy bodies are also seen. Mutations in the parkin protein produce a Parkinsonian syndrome without lewy bodies in juvenile cases suggesting that the parkin protein plays an important role in the development of the lewy body. It has been shown that parkin facilitates the binding of ubiquitin (ubiquination) to other proteins such as the α-synuclein interacting protein synphilin-1 leading to the formation of lewy bodies (Chung *et al.*, 2001). Lewy bodies are found in PD and Dementia with lewy bodies (DLB), but are not a pathological hallmark of any other neurodegenerative disease.

Identifying environmental factors that predispose to the development of PD has proved elusive. Living in a rural environment appears to confer an increased risk of PD, and perhaps causally linked to this some but not all epidemiological studies have shown a correlation between exposure to pesticide use and wood preservatives (Dick, 2006). Despite intensive research efforts during recent years, fundamental questions regarding the etiology and pathogenesis of the disease are still unresolved (Calne & Takahashi, 1991; Beal, 1995; Youdim & Riederer, 1997). With the progression of the disease, there are a number of non-motor complications in PD like sleep disorders (Frucht *et al.*, 1999; Vendette *et al.*, 2007), cognitive impairment (Emre *et al.*, 2004; Ravina *et al.*, 2005), dementia (McKeith 2005; McKeith 2007), Mood disturbance (Richard *et al.*, 2004), psychosis and confusion (Naimark *et al.*, 1996) that are often seen. In many cases, these are not directly related to involvement of dopaminergic pathways and therefore develop even in patients where motor symptoms are well controlled.

Current treatments for PD

The understanding of DA receptor function has expanded enormously since the recognition of their existence in brain and the realization of their importance in PD in the early 1970s. But for patients with PD, the pharmacological treatment options have not really changed since then. Recent years have witnessed a number of choices for the therapy of PD. At this time, no therapy has been firmly established to have a neuroprotective role. Preliminary data suggest that high doses (at least 1200 mg/day) of Coenzyme Q10 is associated with slower deterioration of motor disability (Shults *et al.*, 2002), but this finding awaits further confirmation. The propargylamine MAO-B inhibitor, rasagiline was recently reported to have a modest symptomatic effect in patients with early Parkinson's (Parkinson Study Group, 2002), but whether it has an effect on rate of progression has not been established. A trial of the sodium-dependent glutamate release inhibitor riluzole was terminated early based on futility analysis and trials of antiapoptotic agents, including non-MAO-inhibitor propargylamines and jun kinase inhibitors, are still under way. Although very preliminary results

have suggested symptomatic benefit from GDNF (Gill *et al.*, 2003), there is to date no evidence about GDNF or other trophic factors that interfere with disease progression. Thus, for the time being, the pharmacological management of PD is based entirely on symptom control and is in general instituted only when justified by disability.

Since the introduction of L-3,4-dihydroxyphenyalanine (L-DOPA) to treat PD over 40 years ago, numerous studies have examined the status of DA receptors in brain in an attempt to understand the mechanisms that underlie the decline in the efficacy of L-DOPA and the increase in the adverse effects of L-DOPA treatment (Péchevis *et al.*, 2005, Hollingworth *et al.*, 2011). In the early stages, PD treatment with L-DOPA or/and DA receptor agonists provides effective relief from the motor symptoms. After 4–6 years of treatment, 40% of patients experience motor side effects. The motor side effects increase with time so that following 10 years of L-DOPA and/or DA agonist treatment most individuals (95% in some studies) will exhibit some treatment-induced motor complications (Ahlskog & Muenter, 2001). In addition to the systemic side effects (nausea, vomiting and postural hypotension) produced by acute treatment with L-DOPA and DA agonists, chronic administration can result in the development of more serious adverse effects, namely, fluctuations in motor control (end of dose deterioration, on–off phenomenon) and dyskinesias (chorea, dystonia, athetosis). The debilitating motor side effects are compounded by treatment induced psychiatric disturbances such as, psychosis, mania or delirium (Schrag, 2004). Motor side effects were caused by alterations in DA receptor expression due to progression of the disease process and/or adaptive responses to the drug treatment (Crossman, 1990). The psychotic effects presumably stop from actions on DA receptors in limbic or cortical regions of the brain. The consequence of these motor complications is that the dose of L-DOPA has to be reduced to levels which do not provide the desired reversal of Parkinsonian symptoms.

The Unilateral 6-OHDA Lesion Model

All commonly accepted models of PD, like the actual disease itself, are thought to involve oxidative processes at the heart of dopaminergic injury. Examples of such models include neuronal death induced by exposure to the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydroxypyridine (MPTP) (Cadet & Brannock, 1998), methamphetamine (O'Dell *et al.*, 1991) and 6-OHDA. The DA analog 6-OHDA, because of its similarity in molecular structure, can be taken up into dopaminergic terminals through the DA transporter. Once inside the cell, it is metabolized, resulting in the production of H_2O_2 and free radicals. Ultimately these toxic molecules induce neuronal death through mitochondrial dysfunction.

Like DA itself, 6-OHDA is not able to cross the blood–brain barrier and therefore must be delivered directly to the brain of experimental animals through stereotaxic surgery. In 1968, Ungerstedt and colleagues demonstrated the utility of 6-OHDA lesions as animal models of PD. In their study, 6-OHDA was unilaterally injected into the medial forebrain bundle, extensively depleting the nigrostriatal pathway on one side. Ungerstedt noted that lesioned animals rotated toward the side of their lesions spontaneously as well as after administration of the dopaminergic drug D-amphetamine. Conversely, apomorphine, a drug that acts upon up regulated DA receptors on the side ipsilateral to the lesion, induces rotations contralateral to the lesion. The number of rotations performed by a lesioned animal can be quantified to serve as an index of the integrity of nigrostriatal function. Experimental therapeutic strategies, such as neural or stem cell transplantation and gene therapy, can use the number of rotations an animal performs as an index of the intervention's efficacy.

Using this model, neuronal loss is detected as soon as 12 h postinjection and peaks at 48 h. In addition, striatal fibers are found to degenerate between 1 and 7 days after 6-OHDA delivery, ultimately resulting in more than 90% striatal DA depletion. This provides an ideal environment to evaluate cellular replacement strategies. Alternatively, 6-OHDA delivery to the striatum can result in levels of DA depletion more representative of early-stage PD. Kirik *et al.*, (2001) demonstrated the location of striatal injections, either 'terminal' (within the

caudate–putamen) or 'preterminal' (at the caudate–putamen boundary), greatly affecting the resulting lesion, with preterminal injections creating greater levels of DA depletion. In addition, they found variable reductions in TH+ fiber densities and TH+ SN neurons after either single or multiple 6-OHDA intrastriatal injections.

Role of neurotransmitters in PD

Dopamine

DA is the predominant catecholamine neurotransmitter in the mammalian brain, where it controls a variety of functions including locomotor activity, cognition, emotion, positive reinforcement, food intake and endocrine regulation. This catecholamine also plays multiple roles in the periphery as a modulator of cardiovascular function, catecholamine release, hormone secretion, vascular tone, renal function and gastrointestinal motility (Missale *et al.*, 1998). DA containing neurons arise mainly from DA cell bodies in the SN and ventral tegmental area in mid-brain region (Carlsson, 1993; Lookingland *et al.*, 1995; Tepper *et. al.*, 1997; Tarazi *et al.*, 1997 a, b, 1998, 2001). Dopaminergic system is organized into four major subsystems (i) the *nigrostriatal* system involving neurons projecting from the SN*pc* to the caudate-putamen of the basal ganglia. This is the major DA system in the brain as it accounts for about 70% of the total DA in the brain and its degeneration makes a major contribution to the pathophysiology of PD (ii) *the mesolimbic system* that originates in the midbrain tegmentum and projects to the nucleus accumbens septi and lateral septal nuclei of the basal forebrain as well as the amygdala, hippocampus and the entorhinal cortex. They are all considered components of the limbic system and hence of particular interest for the pathophysiology of idiopathic psychiatric disorders (iii) the *mesocortical* system, which also arises from neuronal cell bodies in the tegmentum which project their axons to the cerebral cortex, particularly the medial prefrontal regions; (iv) the *tuberinfundibular* pathway, which is a neuroendocrinological pathway arising

from the arcuate and other nuclei of the hypothalamus and ending in the median eminence of the inferior hypothalamus.

There are 5 types of DA receptor, which can be subdivided into DA D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4), based on their sequence homologies, pharmacology and functional properties (Sokoloff & Schwartz, 1995). In the striatum, DA D_1 and D_2 receptors are mainly present on dendrites of GABAergic striatopallidal neurons which receive input from afferent DA neurons. DA D_1 receptors are also found on the terminals of glutamatergic projections from the cortex and thalamus. Expression of each receptor subtype is enriched on subpopulations of striatopallidal neurons. DA D_1 receptors are more highly expressed on GABAergic neurons which innervate the internal segment of the globus pallidus and SN*pr* (the direct pathway) and co-localize with substance P and dynorphin, while DA D_2 receptors have higher levels of expression on GABAergic neurons which innervate the external segment of the globus pallidus (the indirect pathway) and co-localize with enkephalin (Gerfen *et al.*, 1995; Le Moine & Bloch, 1995; Aubert *et al.*, 2000). However, there is a degree of overlap, with co-expression of each receptor subtype on most striatal GABAergic neurons, such that the division of striatal neurons should be based on the relative levels of DA D_1 or D_2 receptors, rather than the presence or absence of a particular receptor subtype (Surmeier *et al.*, 1993; Aizman *et al.*, 2000). DA D_2 receptors are also present on the terminals of DA neurons and therefore also function as autoreceptors. Cholinergic interneurons express DA D_2 receptor mRNA, indicating that a proportion of DA D_2 receptors found in the striatum is present on these neurons. DA D_3 receptors have a similar distribution to DA D_2 receptors, except that their density is very low in the caudate nucleus (CN) and putamen, with higher levels only found in the islands of Calleja and ventral areas of the striatum. DA D_3 receptors co-localize with either DA D_1 or D_2 receptors in up to a quarter of ventral striatal neurons (Le Moine & Bloch, 1996). DA D_5 receptors, like the DA D_3 receptor, are found at highest densities in the ventral striatum, but unlike the DA D_2 and D_3 receptors, they are not located on dopaminergic neuron terminals, but are found on cholinergic interneurons (Bergson *et al.*, 1995). DA D_4

receptors have a very low level of expression in the striatum. The significance of DA D_4 and D_5 receptors in the symptoms or treatment of PD is unknown.

The function of DA receptors in PD is altered not only by the disease but also as a consequence of drug treatment. Alterations in the abundance of receptor density contribute to the complications of treatment. But, for the DA D_2 receptor in particular, there is no temporal correlation between the alterations in expression levels and the occurrence of motor complications of treatment. It is increasingly recognised however that DA receptor signaling cascades are altered both as a consequence of the denervation occurring in PD and as a result of the dopaminergic drug treatment used to treat the disorder. The functional response of DA receptors can therefore change despite no alteration in their expression level by virtue of changes in their coupling to second messengers. Before the cloning and definitive demonstration of 5 DA receptor subtypes, DA D_1 receptors were defined as being positively linked to adenylate cyclase, while DA D_2 receptors had negative coupling to the enzyme (Kebabian & Calne, 1979). The number of signalling cascades that DA receptors are known to interact with has grown considerably since then and has been extensively reviewed by Neve *et al.* (2004). The majority of data was derived from studies using transfected cells or animal models since the experimental techniques cannot be used in post-mortem human tissue or living human subjects. However, it is reasonable to assume that DA receptors couple to a similar repertoire of second messengers in human brain. At the molecular level DA receptors can have opposing actions, even though the final cellular response is similar. For example, in cell lines, arachidonate release was increased by both the DA D_2 and D_4 receptor subtypes, but required activation of protein kinase A for the DA D_2 receptor and protein kinase C for the DA D_4 receptor (Di Marzo *et al.*, 1993; Chio *et al.*, 1994; Lee *et al.*, 2004). It has also recently been demonstrated that different DA receptor subtypes (i.e. D_1 and D_2) can form hetero-oligomers in cells and can phosphorylate each other (Lee *et al.*, 2004; So *et al.*, 2005). This means a DA D_1 receptor agonist can elicit a DA D_2 receptor-mediated cellular response and vice versa. Evidently, caution must be observed when extrapolating data derived from such studies to how the native

receptors function in brain. But such interactions at the molecular level explain the synergy found between, for example, DA D_1 and D_3 receptors and the dysfunction of such interactions observed in animal models of PD (Ridray *et al.*, 1998; Guigoni *et al.*, 2005).

Receptor supersensitvity, leading to imbalance between the direct and indirect striatal output pathways, is believed to underlie some of the motor complications that occur following chronic treatment with L-DOPA or DA agonists (Obeso *et al.*, 2000). DA D_2 receptor mediated effects in PD and animal models of the disorder can be explained, at least in part, by the increase in receptor DA D_2 receptor density which occurs following dopaminergic denervation of the striatum. In the absence of consistent alterations in the levels of receptor expression, altered functional responses of DA D_1 receptors results from changes in signalling mechanisms. DA receptors present on DA neuron perikarya and dopaminergic projections to areas other than the striatum are also affected by the neurodegeneration which occurs in PD. Also, chronic stimulation of extrastriatal DA receptors by L-DOPA-derived DA or dopaminergic drugs alters extrastriatal DA receptor expression (Hurley & Jenner, 2006).

Acetylcholine

Acetylcholine (ACh) is one of the principal neurotransmitters of the parasympathetic system. Extensive evidence supports the view that cholinergic mechanisms modulate learning and memory formation. Evidence for cholinergic regulation of multiple memory systems notes that manipulations of cholinergic functions in many neural systems enhance or impair memory for tasks generally associated with those neural systems. The magnitude of ACh release in different neural systems regulates the relative contributions of these systems to learning. ACh is the neurotransmitter that is released by stimulation of the vagus nerve, which alters heart muscle contractions. It is important for the movement of other muscles as well. ACh induces movement by the locomotion of an impulse across a nerve that causes it to release neurotransmitter molecules onto the surface of the neighbouring cell. ACh is critical for an adequately functioning memory. Studies

of ACh release, obtained with *in vivo* microdialysis samples during training, together with direct injections of cholinergic drugs into different neural systems, provide evidence that release of ACh is important in engaging these systems during learning and the extent to which the systems are engaged is associated with individual differences in learning and memory (Gold, 2003; Xu *et al.*, 2012). Acetylcholine influences striatal DA release predominantly through an action at nicotinic acetylcholine receptors (nAChRs) (Exley *et al.*, 2008) and also muscarinic receptors to a lesser extent (Grilli *et al.*, 2008). These interactions of acetylcholine at the cellular level most likely have important behavioural consequences. Extensive work shows that nicotine, which acts at nAChRs, protects against nigrostriatal damage (Picciotto *et al.*, 2008). In addition, recent studies demonstrate that nicotine administration reduces a major side effect of L-DOPA, the primary treatment for PD (Bordia *et al.*, 2008).

Epinephrine and Norepinephrine

Nondopaminergic mechanisms are also responsible for some of the sensory symptoms in patients with PD. In PD, the level of Norepinephrine (NE) is reduced in the locus coeruleus (Zweig *et al.*, 1993) and this is associated with a loss of pigmented neurons and the formation of Lewy body inclusions. Moreover, NE concentrations in the neocortex, nucleus accumbens, amygdala and hippocampus are 40% to 70% lower than normal. In limbic regions, the level of the major metabolite of NE, 3-methoxy-4-hydroxyphenylglycol (MHPG), is also reduced (Riederer *et al.*, 1977) and depressive features commonly observed in PD patients is related to a central NE deficiency (Mayeaux *et al.*, 1984). These changes taken together suggest that the dorsal NE system degenerates in PD. Noradrenergic projections from the locus coeruleus to the dorsal horn of the spinal cord, along with direct and indirect noradrenergic fibers from A5/A7 groups in the pontine tegmentum, reportedly inhibit ascending nociceptive pathways (Buzas & Max, 2004). There appears to be changes in both central and peripheral adrenergic receptors in PD. Studies have shown that α-2 receptors are decreased in number in the cerebral cortex (Cash *et al.*, 1984). A decrease in α-2 adrenoceptors (α2A) and

decreased yohimbine-binding sites in platelets of untreated PD patients have been observed (Villeneuve *et al.*, 1985). Bernal *et al.*, (1989) suggest that untreated PD is associated with a significant reduction in α2A sensitivity. It is possible that patients with PD are more vulnerable to panic attacks because they have an alteration of α2A receptors. α2A receptor is thought to result in a decrease in the stimulation of GABA-enkephalin output neurons by striatal cholinergic interneurons and an increase in the GABA-mediated recurrent inhibition of these neurons. Antagonist activity at adenosine α2A receptors in the striatum might effectively compensate for the lack of DA-mediated inhibition of these neurons in PD (Richardson *et al.*, 1997).

Serotonin

The 5-HT systems are widespread throughout the brain, with most of the cell bodies of serotonergic neurons located in the raphe nuclei of the midline brain stem (Palacios *et al.*, 1990). The largest collections of 5-HT neurons are in the dorsal and median raphe nuclei of the caudal midbrain (Jacobs & Azmitia, 1992). The neurons of these nuclei project widely over the thalamus, hypothalamus, basal ganglia, basal forebrain and the entire neocortex. Interestingly, these 5-HT neurons also provide a dense subependymal plexus throughout the lateral and third ventricles. Activation of this innervations result in 5-HT release into the cerebrospinal fluid (CSF) and measurement of 5-HT content in CSF in disease states will largely reflect this pool (Chan-Palay, 1976). Several functions have been attributed to 5-HT in the brain, such as cognition, emotion, motor behaviour and regulation of the circadian rhythm (Gerson & Baldessarini, 1980; Benarroch, 2009; Berger *et al.*, 2009).

Over the past four decades there have been numerous reports describing the involvement of serotonergic and dopaminergic systems in the mechanism of action of antiparkinsonian agents. Alterations of 5-HT binding constants in PD might reflect an imbalance in serotonergic activity. Recent advances in our understanding of 5-HT receptor subtypes and their putative role in the control of

movement suggest possible novel intervention strategies for modulating dopaminergic and non-dopaminergic systems in PD patients (Thomas, 2004). Post-mortem analysis reveals reductions in the number of 5-HT_1 and/or 5-HT_2 brain binding sites in patients having suffered from various neurodegenerative disorders including PD (Cross, 1988). Based on the distribution, localization and function in the basal ganglia, 5-$HT_{1B/D}$ and 5-HT_{2A} and 5-HT_{2C} receptors are clearly linked with modulation of the nigrostriatal pathway (Barnes *et al.*, 1999). Serotonergic terminals have been reported to make synaptic contacts with both DA-containing and non-DA containing GABA interneurones in the SN*pc*, SN*pr*, striatum and ventral tegmental area (VTA) (Herve *et al.* 1987; Moukhels *et al.* 1997; Di Matteo *et al.*, 2001). These brain areas contain the highest concentration of 5-HT, with the SN*pr* receiving the greatest input. Raphe´ projections also innervate terminal areas to which the SN*pc* and VTA project to, the striatum and nucleus accumbens (Azmita & Segal, 1978). Therefore, receptor subtype-specific serotonergic drugs can act at several sites within the extrapyramidal system to modify DA activity.

Advances in the production of DA neurons from stem or precursor cells for transplantation in PD patients have clearly established an intimacy between 5-HT-DA cells, to the extent that elimination of 5-HT cells induces a marked increase in the generation of DA neurons from mesencephalic precursors cells (Rodriguez-Pallares *et al.* 2003). Thus, scientific rationale strongly suggests that therapeutic strategies that target 5-HT-dopaminergic systems, such as drugs acting on 5-HT transporters, 5-HT_{1A}, 5-$HT_{1B/D}$, 5-HT_{2A} and 5-HT_{2C} receptor subtypes, can fulfill the medical need for the symptomatic treatment of PD and the motor fluctuations associated with long-term L-DOPA therapy (Barnes *et al.*, 1999; Jones & Blackburn, 2002). Realistically, only with the use of these selective serotonergic agents will be able to unravel the complex monoaminergic circuitry in the basal ganglia and relate this to the pathophysiology of PD and drug-induced dyskinesias.

5-HT$_{2A}$ receptors

5-HT$_{2A}$ receptor is a $G_{\alpha q}$ protein-coupled receptor and its activation leads to the production of inositol triphosphate/diacylglycerol, arachidonic acid and 2-arachidonylglycerol (Urban *et al.*, 2007). 5-HT$_{2A}$ receptor activation induces Fos expression (Mackowiak *et al.*, 1999; Gresch *et al.*, 2002). 5-HT$_{2A}$ receptor desensitisation can occur with (Ivins & Molinoff, 1991) or without (Roth *et al.*, 1995a) down-regulation. Two serine residues appear to play a critical role in 5-HT$_{2A}$ receptor desensitisation (Gray *et al.*, 2003). 5-HT$_{2A}$ receptors modulate the release of glutamate in the cortex and striatum (Aghajanian & Marek, 1999b; Ferguson *et al.*, 2010a), and DA in the striatum and SN (Parsons & Justice, 1993; Lucas & Spampinato, 2000; Olijslagers *et al.*, 2004). 5-HT$_{2A}$ receptors are involved in a variety of behaviours and diseases, such as anxiety (Weisstaub *et al.*, 2006), cognition (Elliott *et al.*, 2009), movement (Dave *et al.*, 2004), schizophrenia (Burnet *et al.*, 1996), attention deficit and hyperactivity disorder (Quist *et al.*, 2000), aggression and suicide (Rosel *et al.*, 2004; Oquendo *et al.*, 2006) and social isolation (Schiller *et al.*, 2003).

In the normal rat striatum, 5-HT$_{2A}$ mRNA is present in neurons whether they express preproenkephalin (PPE) or not, whereas it seems restricted to PPE-expressing neurons in the DA denervated striatum lesioned during the neonatal period (Laprade *et al.*, 1996). In the adult rat, 6-OHDA lesion of the nigrostriatal pathway leads to reduced 5-HT$_{2A}$ receptor levels in the striatum, as well as in the cingulate, insular, prefrontal and primary somatosensory cortices (Li *et al.*, 2010). At odds with these results, a study performed by Zhang *et al.* (2007) reported increase in 5-HT$_{2A}$ receptor mRNA levels in the striatum but not in the sub thalamic nucleus (STN). In contrast, in the MPTP-lesioned macaque, no changes in 5-HT$_{2A}$ receptor levels occur in the cortex and basal ganglia following MPTP lesion. However, chronic L-DOPA treatment leads to an increase in 5-HT$_{2A}$ receptor levels in the striatum, middle layers of the motor cortex and anterior cingulate cortex (Huot *et al.*, 2010; Riahi *et al.*, 2011). In the MPTP-lesioned macaque, treatment with L-DOPA and docosohexaenoic acid for one month leads to increased 5-HT$_{2A}$ receptor levels in the nucleus accumbens, putamen,

ventromedial caudate nucleus and anterior cingulate cortex when compared to MPTP-lesioned macaques treated with L-DOPA/vehicle (Gregoire *et al.*, 2010). In idiopathic PD, 5-HT_{2A} receptor levels are decreased in the temporal cortex of patients with (Maloteaux *et al.*, 1988; Cheng *et al.*, 1991) and without (Maloteaux *et al.*, 1988) dementia. 5-HT_{2A} receptors could also play a role in pathological gambling and impulsive-compulsive behaviours in PD. Thus, the single nucleotide polymorphism His452Tyr is associated with pathological gambling in PD (Bocquillon *et al.*, 2009), whereas the T102C variant of the allele T102 might predispose to impulsive-compulsive behaviour in PD patients taking low-dose dopaminergic drugs (Lee *et al.*, 2011).

5-HT_{2A} receptor agonists and antagonists have been studied in PD for their potential effects on both motor and non-motor complications of treatment. In the neonatal 6-OHDA-lesioned rat, the non-selective 5-$HT_{2A/2C}$ agonist (±)-2,5-dimethoxy-4-iodoamphetamine (DOI) increases motor activity, an effect which is abolished by the 5-HT_{2A} antagonists ketanserin and volinanserin, but not by the 5-HT_{2C} antagonist RS-102,221 (Bishop *et al.*, 2004), suggesting that selectively stimulating 5-HT_{2A} receptors might increase movement in the parkinsonian state. Treatment with DOI also enhances the locomotor behaviour induced by the D_1 agonist SKF-82,958 (Bishop & Walker, 2003). Motor activity induced by DOI, either alone or in combination with SKF-82,958, is reduced by the administration of ritanserin (Bishop *et al.*, 2003). The non-selective 5-$HT_{2A/2C}$ antagonist ritanserin increases nigrostriatal neuronal firing in dopaminergic cells (Ugedo *et al.*, 1989), suggesting it might exert an anti-parkinsonian activity. Accordingly, ritanserin effectively alleviates neuroleptic-induced Parkinsonism (Bersani *et al.*, 1990). However, in a few trials performed in idiopathic PD patients, ritanserin was effective against L-DOPA-induced dyskinesia, but impaired L-DOPA antiparkinsonian action (Maertens de Noordhout & Delwaide, 1986; Meco *et al.*, 1988).

5-HT_{2A} receptors are linked to both motor and nonmotor complications of dopaminergic replacement therapy. The lack of selectivity of the purportedly selective 5-HT_{2A} antagonists studied in PD precludes strong conclusions based

exclusively on pharmacological premises with respect to their efficacy against motor and non-motor symptoms. A hypothetical mechanism by which 5-HT_{2A} receptors are involved in the pathophysiology of LID relates to the regulation of DA release by the surviving nigrostriatal axons (Huot *et al.*, 2010, 2011). Indeed, 5-HT_{2A} receptor activation enhances nigrostriatal dopaminergic neurotransmission (Schmidt *et al.*, 1994; Lucas *et al.*, 2000; Lucas & Spampinato, 2000; Pehek *et al.*, 2006); therefore, antagonising 5-HT_{2A} receptors would reduce striatal DA levels. Although decreasing striatal DA levels would reduce L-DOPA-induced dyskinesia severity, it might also impair L-DOPA anti-parkinsonian efficacy.

5-HT_{2C} receptors

5-HT_{2C} receptors are Gq/11 protein-coupled receptors that stimulate phospholipase C-catalysed hydrolysis of phosphatidylinositol bisphosphate (Milatovich *et al.*, 1992). 5-HT_{2C} receptors play a role in learning and stress (Du *et al.*, 2007), drug addiction (Bubar & Cunningham, 2006; Muller & Carey, 2006), weight control (Nilsson, 2006; Reynolds *et al.*, 2006), epilepsy (Tecott *et al.*, 1995), hallucinogenic drug effects (Smith *et al.*, 1998), anxiety (Hackler *et al.*, 2006; Harada *et al.*, 2006), suicide (Niswender *et al.*, 1999), depression (Iwamoto *et al.*, 2005) and schizophrenia (Sodhi *et al.*, 2001). In the rat brain, 5-HT_{2C} receptors are highly expressed in the choroid plexus and limbic areas (Pompeiano *et al.*, 1994; Abramowski *et al.*, 1995; Clemett *et al.*, 2000). Within the basal ganglia, they are highest in the STN and SN*pc* (Mengod *et al.*, 1990a). Moderate levels are found in the striatum and Globus pallidus (GP) (Abramowski *et al.*, 1995; Clemett *et al.*, 2000). 5-HT_{2C} receptors modulate neuronal activity and neurotransmission within the basal ganglia. *In vitro* studies have demonstrated that 5-HT_{2C} receptor blockade reduces STN neuronal firing (Stanford *et al.*, 2005), whereas 5-HT_{2C} receptor activation depolarises SN*pr* neurons (Rick *et al.*, 1995; Stanford & Lacey, 1996). 5-HT_{2C} receptor blockade increases DA release along the mesolimbic/mesocortical and to a lesser extent, nigrostriatal pathways, whereas 5-HT_{2C} receptor activation reduces DA release along these dopaminergic tracts (Di Giovanni *et al.*, 2000; Alex *et al.*, 2005).

Very little is known about 5-HT_{2C} receptors in PD. In the 6-OHDA lesioned rat, SB-206,553 increases the number of contraversive rotations induced by SKF-82,958, but does not cause any rotations when administered as monotherapy (Fox & Brotchie, 2000b). Systemic administration of the selective 5-HT_{2C} receptor antagonists SB-200,646A and SB-206,553 to the 6-OHDA lesioned rat enhances quinpirole anti-parkinsonian action (Fox *et al.*, 1998). Injection of SB-206,553 in the SN*pr* ipsilateral to the 6-OHDA lesion exerts an anti-parkinsonian effect (Fox *et al.*, 1998). In the hemi-parkinsonian rat, the 5-HT_{2C} antagonist mesulergine induces contralateral rotations (Ringwald *et al.*, 1982), an effect that might be mediated *via* its agonist action at D_2 receptors. In idiopathic PD patients, adding mesulergine to L-DOPA improves tremor, rigidity and bradykinesia (Baas *et al.*, 1985; Schneider *et al.*, 1985; Dupont *et al.*, 1986; Lieberman *et al.*, 1986; Fox & Brotchie, 1999). Two studies found that the addition of either mesulergine or bromocriptine to L-DOPA produces an extra anti-parkinsonian benefit of similar magnitude (Baas *et al.*, 1985; Burton *et al.*, 1985). In combination with L-DOPA, mesulergine improves mood, but trigger hallucinations (Hoehn, 1984) and exacerbate dyskinesia (Jankovic *et al.*, 1985). When administered *de novo* as monotherapy, mesulergine exerts an antiparkinsonian action (Dupont *et al.*, 1986; Wright *et al.*, 1986) which, although significant, is not as potent as the antiparkinsonian effect of L-DOPA (Dupont *et al.*, 1986). Since the 5-HT_{2C} receptors are involved in the modulation of nigrostriatal DA release, they represent an attractive, yet largely unexplored, therapeutic target against both Parkinsonism and dyskinesia.

5-HT transporter (5-HTT)

5-HTT is a Na^+/Cl^- dependent ionic transporter that codes for a 630 amino acid protein, and is expressed on neuronal, platelet, placental and pulmonary membranes. It is composed of monomers which agglomerate to form oligomers (Kilic & Rudnick, 2000). In the normal mouse, rat and rhesus macaque brain, autoradiographic binding studies have established that highest 5-HTT levels are encountered in the raphe nuclei, SN, ventral tegmental area (VTA) and thalamus.

5-HTT levels are moderate in the GP and relatively low in the striatum and neocortex (Ase *et al.*, 2000; Chalon *et al.*, 2003; Zeng *et al.*, 2006).

The serotonergic system undergoes degeneration in PD, leading to alterations in 5-HTT levels. Very few studies assessing 5-HTT levels have been performed in animal models of PD in the L-DOPA-naïve state. In the L-DOPA-naïve MPTP-lesioned cynomolgus macaque, 5-HTT binding levels are diminished in the putamen and GP (Rylander *et al.*, 2010). In early, drug- naïve, PD patients, there is a decrease in thalamic 5-HTT levels when compared to controls and, within PD subjects, thalamic 5-HTT levels are lower in patients with tremor than in non-tremulous patients (Caretti *et al.*, 2007, 2008). 5-HTT levels in early PD subjects also appear decreased in the temporal cortex and striatum (Marek *et al.*, 2009). Autoradiographic binding studies demonstrated decreased 5-HTT levels in the frontal and temporal cortices of PD patients, when compared to controls (D'Amato *et al.*, 1987). Throughout the progression of the disease, the reduction in 5-HTT levels seems to follow a rostro-caudal pattern in the prosencephalon and brain stem structures. Decreased 5-HTT levels in the medial frontal cortex and dorsal midbrain are associated with depressive symptoms. Additionally, 5-HTT levels are diminished in the striatum, claustrum, GP pars externa, SN*pr*, as well as frontal, insular and visual cortices of PD patients (Raisman *et al.*, 1986; Chinaglia *et al.*, 1993).

Serotonin as co-mitogen

In rats, 5-HT neurons in the brain stem raphe are among the first neurons to differentiate in the brain and play a key role in regulating neurogenesis (Kligman & Marshak, 1985). Lauder and Krebs (1978) reported that parachlorophenylalanine (PCPA), a 5-HT synthesis inhibitor, retarded neuronal maturation, while mild stress, a releaser of hormones, accelerated neuronal differentiation. These workers defined differentiation as the cessation of cell division measured by incorporation of [^{3}H]-thymidine. Since then, many other workers have shown a role for 5-HT in neuronal differentiation (Marois & Croll, 1992; Hernandez, 1994). The effects of 5-HT on morphology have long been

known. For more than 50 years, 5-HT has been known to constrict blood vessels and induce shape changes in skeletal muscle (at both the light and electron microscope level) (O'Steen, 1967), platelets (Leven *et al.*, 1983), endothelial cells (Welles *et al.*, 1985) and fibroblast (Boswell *et al.*, 1992). In the periphery, 5-HT originates largely from mast cells, which can produce, release and re-uptake 5-HT. The released 5-HT, then act as a chemotactic, increase vascular permeability, vasodilatation and smooth muscle spasm (Metcalfe *et al.*, 1981). In addition to its role in morphological changes, 5-HT also has been shown to play a role in cell proliferation. In cultured rat pulmonary artery smooth muscle cells (SMC), 5-HT induces DNA synthesis and potentiates the mitogenic effect of platelet-derived growth factor-BB (Eddahibi *et al.*, 1999). 5-HT effects on cell proliferation are involved with phosphorylation of GTPase-activating protein (GAP), an intermediate signal in 5-HT -induced mitogenesis of SMC (Lee *et al.*, 1997). Earlier studies from our laboratory showed that 5-HT acting through specific receptor subtypes 5-HT_2 (Sudha & Paulose, 1998) control cell proliferation and act as co-mitogens. Thus, there is evidence that 5-HT is involved in a variety of cellular processes involved in regulating metabolism, proliferation and morphology.

GABA

The inputs to the basal ganglia portion of the motor circuit are focused principally on the putamen, whereas the CN and the nucleus accumbens are the principal input sites of the limbic circuit (Albin *et al.*, 1989). This postulates that in the normal brain there exists a balance between direct inhibitory input (GABA, co-localised with substance P) and indirect excitatory input (aspartate/glutamate) to the medial globus pallidus (GPm), which in turn controls thalamocortical activation. The deprivation of DA-ergic nigrostriatal input, as in PD, reduces the positive feedback through the direct system and increases the negative feedback through the indirect system (Gerlach *et al.*, 1996). The critical consequences are an overactivity of the STN, GPm and SN*pr*, with the resulting inhibition of thalamocortical drive.

Because specific neural pathways are involved, one might propose that degeneration of nigrostriatal neurons in patients who had manisfested a Parkinsonian syndrome causes a characteristic pathologic pattern of neurotransmission in the motor circuit. In fact, electrophysiological, neurochemical and pharmacological studies using experimental models of Parkinsonism have shown a secondary increase of glutamatergic neurotransmission in the STN, the GPm and the SN*pr*, due to a decreased GABAergic input from the lateral GPi (Ossowska, 1994). On the other hand, these assumptions have been confirmed by studies using post mortem tissue. For example, Griffiths *et al.* (1990) found decreased binding of flunitrazepam (a ligand to the GABA/benzodiazepine receptor) in the GPi of PD brains. Assuming that there is a simple relationship between increased pre-synaptic neural activity and post-synaptic receptor down regulation and vice verse as in peripheral tissues, these data suggest that the GABA-ergic striatal neurons projecting to the GPi would be overactive in PD (Gerlach *et al.*, 1996). As GABA helps "quiet" excessive neuronal firing and has been deficient in patients in the advanced stages of PD, directly targeting GABA production rather than DA replacement is more effective way of improving brain function in late-stage PD. This also avoids the known therapeutic limitations and complications associated with the over-production of DA. GABA supplementation can help to decrease the over stimulation of neurotransmitters such as ACh and can possibly be used in PD to inhibit ACh.

GABA as co-mitogen

GABA, the main inhibitory neurotransmitter in the mature CNS, is implicated in playing a complex role during neurogenesis (Ben-Ari *et al.*, 1989; Baher *et al.*, 1996; Behar *et al.*, 2000; Haydar *et al.*, 2000). Through embryonic development, GABA was demonstrated as acting as a chemo-attractant and being involved in the regulation of progenitor cell proliferation. For example, GABA induces migration and motility of acutely dissociated embryonic cortical neurons (Baher *et al.*, 1996; Behar *et al.*, 2000). In addition, the neurotransmitters GABA

and glutamate reportedly reduce the number of proliferating cells in dissociated or organotypic cultures of neocortex (LoTurco *et al.*, 1995). In contrast, GABA was shown to promote cell proliferation in cultures of cerebellar progenitors (Fiszman *et al.*, 1999). GABA also dramatically increases proliferation in the ventricular zone of the embryonic cerebrum in organotypic cultures by shortening the cell cycle. However, a reverse effect was observed in the subventricular zone (Haydar *et al.*, 2000). Thus, during embryonic neurogenesis, GABA emerges as an important signal for cell proliferation and migration, but its precise regulation is dependent on the region and cell type affected. Cellular response to GABA is mediated through its known receptors and the intracellular signals associated with them. The contribution of $GABA_A$ receptor to both chemo-attraction (Behar *et al.*, 2000) and cell proliferation (Haydar *et al.*, 2000) was indicated. However, in some aspects of cell motility there is an apparent involvement of GABA dependent G-protein indicating a role of $GABA_B$ receptor (Behar *et al.*, 2000). GABA acts as a trophic factor not solely during prenatal neurogenesis but also in the postnatal period in injured tissue. The effect of GABA involves stimulation of cell proliferation and NGF secretion (Ben-Yaakov & Golan, 2003). We have previously shown that GABA acting through specific receptor subtypes $GABA_B$ (Biju *et al.*, 2002) control cell proliferation and act as comitogens.

Glutamate

Glutamate is a prominent neurotransmitter in the body, being present in over 50% of nervous tissue. A large proportion of the glutamate present in the brain is produced by astrocytes through synthesis *de novo* (Hertz *et al.*, 1999), but levels of glutamate in glial cells are lower than in neurons. During excitatory neurotransmission, glutamate-filled vesicles are docked at a specialized region of the presynaptic plasma membrane known as the active zone. Packaging and storage of glutamate into glutamatergic neuronal vesicles requires Mg^{2+}/ATP-dependent vesicular glutamate uptake systems, which utilize an electrochemical proton gradient as a driving force. Substances that disturb the electrochemical gradient inhibit this glutamate uptake into vesicles. In brain, low concentrations of

glutamate and aspartate perform as neurotransmitters, but at high concentration these amino acids act as neurotoxins.

There are two broad categories of glutamate receptors, the ion channel-forming or "ionotropic" receptors and the "metabotropic" receptors, those coupled to GTP- binding proteins (G proteins) and linked to the activation of phospholipase C (PLC) or the inhibition or activation of adenylyl cyclases (AC). The ionotropic receptors are further subdivided into three populations, those activated by N-methyl-D-aspartate (NMDA), those that respond to kainic acid and those sensitive to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). Activation of these receptors is responsible for basal excitatory synaptic transmission and many forms of synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD), which are thought to underlie learning and memory. It appears however, that aspartate aminotransferase and glutaminase account for a majority of glutamate production in brain tissue (McGeer *et al.*, 1987).

Glutamate functions as a fast excitatory transmitter in the mammalian brain. Glutamate triggers neuronal death when released in excessive concentrations by over excitation of its receptors (Vizi, 2000). Glutamate receptor activation and excitotoxicity has long been recognized as an upstream event in this cascade (Wieloch, 1985). In brain, glutamate accumulation is reported to cause neuronal degeneration (Berman & Murray, 1996; Budd & Nicholas, 1996; Atlante *et al.*, 1997). The excitatory amino acid glutamate is the most prevalent transmitter in the brain; its effect on postsynaptic receptors is limited by uptake process (Erecinska, 1997) and by diffusion of glutamate from the cleft. The extracellular accumulation of glutamate results in neuronal death by activating ionotropic glutamate receptors sensitive to NMDA or AMPA–kainate (Choi, 1988). The most consistent age-related change in the glutamatergic system is the loss of glutamate receptors. Significant decreases in the mRNA level of glutamate receptors were found in the aged cerebral cortex (Carpenter *et al.*, 1992). Among different glutamate receptors, NMDA receptors are preferentially altered in the aged brain. Decrease in NMDA binding was shown in both rodents and mammalian brain

(Wenk *et al.*, 1991; Cohen & Muller, 1992). mRNA level of both NMDAR1 and NMDA2B subunits of the NMDA receptors have been shown to decrease preferentially in the aged cerebral cortex, whereas no age-related change was observed in the NMDA2A subunit (Magnusson, 2000).

Neurons are expected to be more vulnerable to oxidative stress because of their high rate of metabolism, the presence of high amounts of lipids that is oxidized to form peroxides and the relatively low levels of some anti-oxidants when compared with other tissues. It is suspected that because neurons that are most vulnerable in PD are those that also receive strong input from glutamate pathways, for example striatum, that glutamate must play some role in the events that lead to neuronal damage during aging or PD. If this is the case, then cell degeneration or death is the result of a cumulative process of neurotoxicity produced by glutamate (Coyle & Puttfarcken, 1993).

Oxidative stress in PD

In Parkinsonian SN*pc* higher levels of iron (Good *et al.*, 1992) leads to an increase in ROS generation (Blum *et al.*, 2001b). The ratio between reduced and oxidized glutathione (GSH/GSSG) is decreased during degeneration thus enhancing the formation of toxic hydroxyl radicals (Sofic *et al.*, 1992; Sian *et al.*, 1994). This represents one of the earliest biochemical defects in PD. The impairment of GSH-dependent detoxification is due to increased DA turnover that could itself increase basal production of H_2O_2 and then deplete GSH stocks (Riederer *et al.*, 1989; Khuwaja *et al.*, 2011). Additionally, relative GSH depletion is accompanied by a drop in CAT (Ambani *et al.*, 1975; Venkateshappa *et al.*, 2012) and GSH-peroxidase expression (Kish *et al.*, 1985). All these above phenomena gives rise to increased ROS levels leading to damage of cellular macromolecules and their subsequent peroxidation.

6-OHDA is suggested to induce nigrostriatal dopaminergic lesions *via* the generation of H_2O_2 and derived hydroxyl radicals (Heikkila & Cohen, 1971). Several studies have confirmed that 6-OHDA produces oxidative stress *in vivo* (Permual *et al.*, 1989, 1992; Kumar *et al.*, 1995) as well as *in vitro* (Tiffany-

Castiglioni *et al.*, 1982; Decker *et al.*, 1993; Abad *et al.*, 1995; Choi *et al.*, 1999a; Lotharius *et al.*, 1999). This explains the protective effects afforded by antioxidants against 6-OHDA toxicity (Tiffany-Castiglioni *et al.*, 1982; Davison *et al.*, 1986; Cadet *et al.*, 1989; Yamada *et al.*, 1997; Mayo *et al.*, 1998; Blum *et al.*, 2000; Khan *et al.*, 2010) and the observation of decreased cell death in transgenic mice overexpressing SOD and GPx (Asanuma *et al.*, 1998; Bensadoun *et al.*, 1998). The generation of ROS arises from two distinct mechanisms, namely deamination by monoamine oxidase (MAO) or auto-oxidation and is presumably initiated and/or amplified by iron *via* the Fenton reaction. 6-OHDA, like DA, is a substrate for MAO (Breese & Traylor, 1971; Karoum *et al.*, 1993). This enzymatic reaction gives rise to H_2O_2. An involvement of MAO was suggested following the observation that selegiline, an inhibitor of MAO (MAO-I), prevents 6-OHDA toxicity (Knoll, 1986; Salonen *et al.*, 1996), even if the protective effects of MAO-I are subject to caution (Wu *et al.*, 1996). However, several lines of evidence suggest that ROS mediated 6-OHDA toxicity seems, rather, due to the generation of H_2O_2 and hydroxyl radicals *via* a non-enzymatic self-auto-oxidation process. Indeed, under physiological conditions, 6-OHDA undergoes a rapid and nonenzymatic auto-oxidation (Heikkila & Cohen, 1972; Seitz *et al.*, 2000; Soto-Otero *et al.*, 2000) shown to generate several toxic species including quinones (Saner & Thoenen, 1971), superoxide radicals, H_2O_2 and the highly reactive hydroxyl radical (Cohen & Heikkila, 1974). In keeping with this mechanism, the cytotoxicity of catecholamines, especially 6-OHDA, directly correlates with their rates of auto-oxidation (Graham *et al.*, 1978; Soto-Otero *et al.*, 2000). The formation of ROS generated by MAO and autooxidation is amplified by iron that catalyzes a Fenton reaction. Indeed, iron levels are increased in SN*pc* and striatum after 6-OHDA injection (Hall *et al.*, 1992; Oestreicher *et al.*, 1994; He *et al.*, 1996). The contribution of iron in 6-OHDA toxicity is also suggested by studies showing that the 6-OHDA-induced deleterious effects are prevented by iron chelating agents (Ben Shachar *et al.*, 1991; Borisenko *et al.*, 2000) and that direct injection of iron into the SN*pc* produces similar neurotoxic effects (Sengstock *et al.*, 1994). In summary, the combined occurrence of MAO activity, auto-oxidation

and elevation in iron levels is responsible for the strong ROS production following 6-OHDA treatment. The subsequent oxidative stress reduces cellular antioxidative capabilities (Kumar *et al.*, 1995), impairs intracellular redox potential regulation (Shiraga *et al.*, 1993) and causes lipid peroxidation as demonstrated by the decrease in phospholipid levels and the increase in malonaldialdehyde content (Kumar *et al.*, 1995; Tunçel *et al.*, 2012). In addition, 6-OHDA-generated ROS cause: (1) DNA strand break, characterized by an elevation in 8-hydroxy-2'-deoxyguanosine levels (8-OHDG), particularly *via* an activation of the poly-ADP-ribose polymerase (PARP; Bruchelt *et al.*, 1991); (2) mutations (Gee *et al.*, 1992); (3) a disorganization of the cytoskeleton (Davison *et al.*, 1986) and (4) an impairment of glucose and α-aminoisobutyric acid uptake (Vroegop *et al.*, 1995).

Apoptosis in PD

Neurochemical and neuropathological analyses clearly indicate that oxidative stress, mitochondrial dysfunction, neuroinflammation and impairment of the ubiquitin-proteasome system are major mechanisms of dopaminergic degeneration. Evidence from experimental models and postmortem PD brain tissues demonstrates that apoptotic cell death is the common final pathway responsible for selective and irreversible loss of nigral dopaminergic neurons. Apoptosis or programmed cell death is a genetically regulated death process of cells involving caspase activation and a lack of cell swelling. Apoptosis is recognized as a key fundamental and indispensable process in the normal cell function. Aberrant regulation of apoptosis is a common feature in many diseases including neurodegenerative diseases and cancer and is now widely accepted as a crucial cause of dopaminergic neuronal death in PD. This is based on extensive post-mortem analysis of PD brains as well as experimental models (Anglade *et al.*, 1997; Yuan & Yankner, 2000; Kaul *et al.*, 2003). Induction of apoptosis by both environmental insults and PD genetic predisposition suggests that biochemical events involved in the cell death process are highly conserved despite the differences in the nature of neurotoxic insults. 6-OHDA initiates cellular oxidative stress. It enters neurons *via* dopamine transporters (DAT) and initiates the

activation of cell death pathways by generation of intracellular free radicals and mitochondrial inhibition (Blum *et al.*, 2001). Recent advancements in the understanding of PD pathology have revealed that apoptosis is an active cell death process in the degeneration of dopaminergic neurons (Hirsch *et al.*, 1988; Hartmann *et al.*, 2000).

Akt

Attention has been drawn recently to the potential mechanistic role of defective signalling by the serine threonine kinase Akt in the neurodegeneration of PD, hypothesising that normalising defective Akt activity could be a viable treatment strategy for PD (Burke, 2007; Levy *et al.*, 2009). The Akt (PKB) pathway is activated by phosphatidylinositol 3-kinase (PI3-K) in response to insulin, growth factors, cytokines and cell stress (Manning & Cantley, 2007), causing production of PtdIns (3,4,5)P3 and recruiting Akt to the plasma membrane, where phosphorylation on threonine-308 and serine-473 induces Akt activation. Akt regulates a number of downstream signalling cascades that impact on a variety of cellular activities including survival, differentiation, proliferation, migration, polarity and metabolism (Greene *et al.*, 2011). A number of *in vitro* studies have shown that activation of Akt is both necessary and sufficient to maintain survival of a range of different neuron types as well as of other cell types and that Akt mediates the neuronal survival-promoting activities of a variety of neurotrophic factors (Orike *et al.*, 2001; Downward, 2004; Duronio, 2008). Akt promotes neurite outgrowth (Markus *et al.*, 2002; Read & Gorman, 2009) and increases axonal branching and regeneration (Namikawa *et al.*, 2000; Grider *et al.*, 2009). Akt signalling is important in mechanistic actions of dopaminergic receptors (Beaulieu *et al.*, 2007) and homeostatic regulation of dopaminergic transporters (Garcia *et al.*, 2005). Drugs targeting the dopaminergic system, used to treat PD, have been shown to be neuroprotective *via* Akt activation (Chen *et al.*, 2008; Lim *et al.*, 2008; Yu *et al.*, 2008). These include rasagiline, which up regulates active phospho^{Ser473}-Akt in the rodent MPTP PD model (Weinreb *et al.*, 2006; Sagi *et al.*, 2007). Akt phosphorylation at both Ser473 and Thr308 is

substantially lowered by treatment of cultured neuronal cells with PD mimetic toxins (Rodriguez-Blanco *et al.*, 2008; Tasaki *et al.*, 2010). Conversely, treatments that restore or block loss of Akt phosphorylation are protective in such models (Malagelada *et al.*, 2010; Tasaki *et al.*, 2010). Expression of constitutively active Akt protects against dopaminergic cell death induced by intrastriatal 6-OHDA (Ries *et al.*, 2006). Furthermore, GDNF, which protects against dopaminergic neurodegeneration, acts at least in part through Akt signalling (Onyango *et al.*, 2005; Du *et al.*, 2008) and Akt activation increases GDNF expression (Cen *et al.*, 2006). Certain Akt-1 haplotypes confer a protective role against PD (Xiromerisiou *et al.*, 2008) and Akt signalling is promoted by parkin (Fallon *et al.*, 2006) and DJ-1 (Yang *et al.*, 2005), mutations in whose genes cause autosomally recessive Parkinsonism. An investigation of the role of the protein RTP801 in PD pathogenesis discovered this to act *via* reduced Akt activation and provided the first report showing depletion of active Akt in PD SN (Malagelada *et al.*, 2008). Timmons *et al.* (2009) demonstrated high levels of expression of Akt and active Akt in the TH dopaminergic neurons that succumb to degeneration in PD and revealed that Akt and phospho^{Ser473}-Akt containing dopaminergic neurons are severely depleted in the brain in PD suggesting that therapeutic agents activating PI3-K-Akt have pro-neuronal survival capabilities even in advanced PD.

NF- κB transcription factor

The transcription factor NF-κB is a dimeric complex of proteins of the Rel-family that regulate several cellular functions upon activation by a variety of extracellular stimuli (Piette *et al.*, 1997). In the nervous system, NF-*κ*B is found in both glia and neurons (O'Neil & Kaltschmidt, 1997) and its activation is considered as a regulator of cell-stress response particularly oxidative stress. However, the precise activation pathways used by oxidants in many cell types are still ill defined (Piette *et al.*, 1997), although low levels of ROS, especially H_2O_2, are thought to act as messengers (Schreck *et al.*, 1991; Shi *et al.*, 1999). NF-*κ*B is activated by exposure of catecholaminergic cells to 6-OHDA and 1-methyl-4-

phenylpyridinium (MPP^+) (Cassarino *et al.*, 2000; Blum *et al.*, 2001a; Lee *et al.*, 2001; Panet *et al.*, 2001) and also in nigral neurons of PD patients (Hunot *et al.*, 1997). NF-*κ*B is gaining increased attention for its possible role as a critical regulator of cell death (Barkett & Gilmore, 1999). The inhibition of NF-*κ*B activity participates in the neuroprotective effect of melatonin and normelatonin against H_2O_2 insult (Lezoualc'h *et al.*, 1998a). The anti-apoptotic function of NF-*κ*B is supported by several studies showing that the activation of NF-*κ*B protects primary neuronal cells against β-amyloid (Barger *et al.*, 1995; Mattson *et al.*, 1997), mediates NGF-promoted survival of PC12 cells (Taglialatela *et al.*, 1997; Foehr *et al.*, 2000) and increases the resistance of neuronal cells against H_2O_2 (Lezoualc'h *et al.*, 1998b). Therefore, NF-*κ*B activation corresponds to a protective mechanism against deleterious effects of these neurotoxins (i.e. oxidative stress) (Cassarino *et al.*, 2000; Blum *et al.*, 2001b; Park *et al.*, 2004; Hu *et al.*, 2010). A role of NF-*κ*B-dependent transcription in the regulation of cell death genes has been demonstrated (Barkett & Gilmore, 1999). Several reports suggest that some bcl-2 family genes, i.e. bcl-xL and bfl-1/A1, contain NF-*κ*B sites in their promoter (Dixon *et al.*, 1997; Lee *et al.*, 1999; Zong *et al.*, 1999) and are up regulated through NF-*κ*B activation (Grumont *et al.*, 1999; Tamatani *et al.*, 1999; Wang *et al.*, 1999). From this point of view, several anti-apoptotic factors besides bcl-2 family members are regulated by Rel/NF-*κ*B including inhibitory apoptosis proteins (Chu *et al.*, 1997; Wang *et al.*, 1998; Kawakami *et al.*, 1999). NF-*κ*B induces BDNF, which in turn, activates a receptor tyrosine kinase (trkB) coupled to PI_3 kinase–Akt and MAP kinase signalling pathways, that promote cell survival and play a critical role in learning and memory (Mattson *et al.*, 2004; Mattson & Meffert, 2006; Peng *et al.*, 2011). NF-*κ*B activation thus could modulate the occurrence of cell death and would be an interesting potential target site for neuroprotection.

Caspase – 8

Apoptosis is a fundamental biochemical process for the selective and controlled elimination of cells within multicellular organisms. A vital component

of normal cellular differentiation, development and tissue homeostasis (Wyllie *et al.,* 1908; Ellis *et al.,* 1991; Raff, 1992), apoptosis is also a key mechanism for removal of damaged, infected or mutated cells that would otherwise present a risk to the organism. Caspases, a family of cysteinyl-aspartate-specific proteases, are executioners of apoptotic cell death and their activation is considered a commitment to cell death (Nicholson *et al.,* 1995; Cohen *et al.,* 1997**)**. Once activated, the caspases are responsible for cleavage of selective protein substrates that are cleaved after an aspartate residue. It has been reported that in neurodegenerative diseases, the affected neurons enter a degenerative phenotype that displays features associated with apoptosis, *e.g.* the presence of activated caspases (Troy & Salvesen, 2002). Apoptosis is generally considered a fast process, where activation of caspases rapidly is followed by cell fragmentation and phagocytosis. However, neurons show a relative resistance toward caspase activity that may allow a low level caspase activity to persist in long term neurodegenerative processes (Zhang *et al.,* 2000).

Activation of caspase-8 can be mediated through an extrinsic pathway where extracellular ligands bind to plasma membrane receptors, *e.g.* the TNF-α receptors (Schulze-Osthoff *et al.,* 1995) or through an intrinsic pathway where activated caspase-3 can cleave and activate caspase-8 (Earnshaw *et al.,* 1999) that allows a low level caspase activity to persist in long term neurodegenerative processes (Zhang *et al.,* 2000). Inhibition of caspase activation protects against neuronal loss in several animal models of brain diseases involving activated microglia, including hypoxic ischaemia/stroke, acute bacterial meningitis, brain trauma and 6-OHDA and MPTP lesioned Parkinsonism models **(**Schulz *et al.*, 1998; Braun *et al.*, 1999; Cutillas *et al.,* 1999; Depino *et al.,* 2003). Caspase-8 is believed to be at the apex of the death receptor mediated apoptosis pathway and can activate caspase-3/7 (Fernandes-Alnemri *et al.,* 1996; Nunez *et al.,* 1998; Slee *et al.,* 1999). PD and AD are known to be associated with neuroinflammation and the presence of activated microglia (Aarli, 2003).

Growing evidence suggests that inappropriate activation of apoptotic processes is involved in the pathology of degenerative diseases, including sporadic

PD (Troy & Salvesen, 2002; Andersen, 2001) and caspase activation could represent a link to parkin dysfunction in sporadic PD. Mounting evidence associates activation of caspase-8, which relays death signals from the death domain receptors for TNF-α and Fas ligand and the proinflammatory caspase-1, with the pathogenesis of several neurodegenerative disorders including PD (Andersen, 2001; Troy & Salvesen., 2002; Nagatsu, 2002). Elevated levels of the proinflammatory cytokines and TNF-α are present in the nigro-striatal dopaminergic system as well as in the CSF of patients with PD (Mogi *et al.,* 1994; Boka *et al.,* 1994; Nagatsu, 2002). This demonstrates an increase in the activation of the pro-interleukin-1β converting enzyme (caspase-1) and an increased potential for stimulating the caspase-8 activating TNF-α receptors on the dopaminergic neurons. This is corroborated by the increased activity of caspase-1 in SN from patients with PD as compared with SN from control patients (Mogi *et al.,* 2000) and by the demonstration of increased levels of activated caspase-8 in dopaminergic neurons of the SN in patients with PD compared with control patients (Bilsland & Harper, 2002; Karatas *et al.,* 2009).

Neurotrophins in PD

Neurotrophic factors (NTF) are molecules typically characterized for their role in neuronal development and maintenance. These factors have been shown to protect specific populations of cells within the brain thereby making them candidate growth factors for different diseases. Factors such as BDNF, mesencephalic astrocyte-derived neurotrophic factor (MANF), GDNF and neurturin have been used extensively in animal models of several neurodegenerative disorders. As PD is primarily caused by the degeneration of a single neuronal population, several factors have been investigated for their neurotrophic and protective effects on dopaminergic neurons (Ramaswamy & Kordower, 2009).

Brain-derived neurotrophic factor (BDNF)

BDNF was the first neurotrophin to be isolated after the discovery of NGF and was found to not only support the survival of neurons but also promote the outgrowth of fibers. BDNF signalling occurs via two major classes of receptors (Reichardt *et al.*, 2006). The first class of receptors is the tropomyosin-related kinase (Trk) family of receptor tyrosine kinases, specifically TrkB. Through TrkB, BDNF activates Ras, phosphatidyl inositol-3 (PI3)-kinase, PLC and consequently, the MAP kinases. Additionally, BDNF activates the p75 neurotrophin receptor (p75NTR), resulting in the activation of the nuclear factor-κB (NF-κB) and Jun kinase. BDNF mRNA is expressed widely throughout the SN, hippocampus, cortex, cerebellum and basal forebrain (Yan *et al.*, 1997a) and its receptor TrkB is expressed within the striatum and the SN (Yan *et al.*, 1997b). BDNF levels are down regulated in the SN of PD patients suggesting a role for this factor in the protection of dopaminergic neurons (Parain *et al.*, 1999). Additionally BDNF mRNA up regulation has been implicated as the mechanism of action of several different PD drugs like levodopa (Zhang *et al.*, 2006), selegiline (Gyarfas *et al.*, 2009) and omega-3 fatty acids (Bousquet *et al.*, 2009). BDNF protects against apoptotic death by inhibiting caspase activation following neuronal injury (Kim & Zhao, 2005). In a partial 6-OHDA rat model of PD, fibroblasts genetically engineered to produce BDNF and implanted into the striatum completely protected neurons within the SN and partially protected fibers within the striatum (Levivier *et al.*, 1995). BDNF secreting fibroblasts also significantly protect nigral dopaminergic neurons from degeneration in a MPTP rat model when implanted above the SN (Frim *et al.*, 1994). BDNF is known to influence the survival and function of neurons in the brain, including 5-HT neurons (Celada *et al.*, 1996). BDNF can promote the sprouting of mature, uninjured serotonergic axons and dramatically enhance the survival or sprouting of 5-HT axons (Mamounas *et al.*, 1995). 5-$HT_{2A/2C}$ receptors mediate the stress-induced down regulation of BDNF mRNA expression in hippocampus (Vaidya *et al.*, 1997). When BDNF was administered to the SN using a recombinant adeno-associated viral (rAAV) vector it significantly improved motor deficits caused by a 6-OHDA lesion (Klein *et al.*,

1999). BDNF-immunoreactivity became detectable in neurons and astrocytes within differentiated fetal ventral mesencephalic dopaminergic neurons grafted into rat striatum and BDNF released either from neurons or astrocytes affect the dopaminergic neurons in these grafts (Sautter *et al.*, 1998). BDNF delayed and significantly reduced the severity of MPTP-induced Parkinsonism in monkeys (Tsukahara *et al.*, 1995). It also provided significant neuroprotection of TH-positive nigral neurons compared to lesioned controls. Studies examining the effects of BDNF in PD animal models are limited and insufficient to warrant clinical trials. It is apparent that BDNF confers neuroprotective effects on dopaminergic neurons as is evidenced by its endogenous up regulation in response to other therapies. The extensive delivery of BDNF that will be required to the human brain is hampered by the widespread expression of the TrkB receptor which limits the spread of this protein within the striatum suggesting that methods for administering BDNF are inadequate to transfer the trophic factor to cells of the SN.

Glial cell line-derived neurotrophic factor (GDNF)

GDNF is well known to be a potent neurotrophic factor supporting the survival of dopaminergic neurons of the SN *in vitro* and *in vivo*. Many studies with *in vitro* and *in vivo* models have shown that GDNF supports neuritic outgrowth or survival of mesencephalic dopaminergic neurons (Connor & Dragunow, 1998; Gash *et al.*, 1998), cranial nerve and spinal cord motor neurons, brain stem noradrenergic neurons (Arenas *et al.*, 1995), basal forebrain cholinergic neurons, Purkinje cells and certain groups of dorsal ganglion and sympathetic neurons (Lin *et al.*, 1993; Kreiglestein *et al.*, 1995; Siegel & Chauhan, 2000). The binding of GDNF to GFRα receptors activates a transmembrane tyrosine kinase, c-Ret and induces further downstream signalling *via* multiple pathways including the MAP kinase pathway and phospolipase Cγ pathway. GDNF also induces responses through c-Ret-independent mechanisms such as the activation of Src family tyrosine kinases and interaction of the receptor complex with neural cell adhesion molecule (Sariola & Saarma, 2003; Chiocco *et al.*, 2007).

In primate neurotoxin models of PD, GDNF protects dopaminergic neurons in the SN, maintains DA levels in striatum and improves Parkinsonian symptoms such as bradykinesia, rigidity, posture and balance (Gash *et al.*, 1996; Miyoshi *et al.*, 1997; Costa *et al.*, 2001; Grondin *et al.*, 2002). GDNF has been shown to exert neurotrophic effects both at the level of the cell bodies in the SN and at the level of the axon terminals in the striatum. Intrastriatal administration of GDNF appears to be a particularly effective site for induction of axonal sprouting and regeneration accompanied by recovery of spontaneous sensorimotor behaviours in the chronically lesioned nigrostriatal DA system (Björklund *et al.*, 1997). GDNF treatment of cultured human fetal ventral mesencephalon nearly doubles the DA neuron survival while halving the rate of apoptosis from 6% to 3% (Clarkson *et al.*, 1997) and increases the density of calbindin-positive neurons, which are proposed to be less vulnerable to degeneration in PD (Meyer *et al.*, 1999). Injection of GDNF to the striatum in a 6-OHDA striatal lesioned rat preserves neurons within the SN (Kearns & Gash, 1995). Administration of GDNF to the region just above the SN one week post-lesion results in a partial but significant protection of nigral neurons indicating that GDNF administration closer to the site of lesion is more effective at producing neuroprotection (Sauer *et al.*, 1995). Down regulation of GDNF, even by only 40% in adulthood, causes a marked reduction in dopaminergic neurons in the SN, the locus coeruleus and VTA. This neuronal loss is accompanied by a detectable hypokinetic movement disorder in mice (Pascual *et al.*, 2008).

Cellular transplantation to the rescue

Pioneering work by Elizabeth Dunn in 1904 showed that transplanted fetal tissue can survive in the brain of another animal. For many years, fetal tissue has been used for treatment of human disorders, including fetal pancreatic transplants to treat diabetes mellitus and fetal thymic transplants to treat lymphogenic immunological deficiency. The defining basic science research that opened investigations on fetal tissue and brain transplantation was undertaken by Olson and Seiger (1972). They showed that fetal tissue grafted in the immunoprivileged

anterior chamber of the eye has the capacity to integrate with the host target neurons and that these graft-host connections were functional. The proof of principle providing evidence that fetal tissue transplantation exerts efficacious benefits against neurodegeneration came from research in PD.

A large variety of cell replacement strategies are under investigation in animal models of PD, which began with the success of transplanted fetal neurons in reconstructing the lesioned nigrostriatal pathway and ameliorating behavioural impairments (Bjorklund & Stenevi, 1979; Perlow *et al.*, 1979). Various types of cells have been tested, such as cells from the embryonic ventral mesencephalon which contains the primordial SN, neuronal stem or progenitor cells, dopaminergic cell lines, non-neuronal cells (usually fibroblasts or astrocytes) engineered to secrete DA or NTF's, adrenal medullary cells which naturally synthesize DA, testis-derived Sertoli cells which are rich in trophic factors and more recently, carotid body epithelial glomus cells which synthesize DA and co-grafting cells with fetal kidney cells which are rich in NTF's (Koutouzis *et al.*, 1994; Dunnett, 1995; Martinez-Serrano & Bjorklund, 1997; Raymon *et al.*, 1997; Rosenthal, 1998). Implanted cells are encapsulated in permselective polymer matrices or seeded on microcarrier beads (Borlongan *et al.*, 1996). Combining various cell types in co-grafts has often resulted in improvements (Meyer *et al.*, 1995; Takeyama *et al.*, 1995; Costantini & Snyder-Keller, 1997; Sautter *et al.*, 1998). Pretreating cells to be transplanted with trophic factors, antioxidants, or anti-apoptotic factors also improve graft survival and supplement behavioural recovery of the animal. Recently, treatment of ventral mesencephalic cells prior to transplantation with an inhibitor of the pro-apoptotic enzymes, the caspases, dramatically improved not only the survival of grafted dopaminergic neurons, but also the volume of the graft in 6-OHDA lesioned rats (Schierle *et al.*, 1999). Indeed, treated grafts became so robust that they caused an over abundance of dopaminergic activity on the grafted side of the brain which led to an imbalance and turning behaviour in the opposite direction. Many of these approaches have proven successful in ameliorating dopaminergic deficits and/or behavioural

impairments in rodent or primate animal models of PD. Several of these techniques have progressed to clinical application.

Cells are commonly grafted ectopically to striatum (which is the target tissue for dopaminergic nigral neurons) because DA is required in the striatum and neuronal or non-neuronal cells implanted into the adult degenerating SN will physically re-establish the long nigrostriatal pathway to innervate the striatum and supply it with DA. Fetal ventral mesencephalic cells transplanted into the striatum 2 weeks after 6-OHDA lesioning in rats have been found to survive out to a full 2 years with many TH neurons remaining and forming functional synaptic connections with host striatum, improving DA content and successfully eliminating methamphetamine-induced rotations (Nishino *et al.*, 1990). Grafting fetal ventral mesencephalic tissue into the SN rather than the striatum has surprisingly also proven successful (Nikkhah *et al.*, 1994). Grafted 6-OHDA lesioned rats showed a reduction of apomorphine-induced rotations that correlated with the number of TH cells. In addition, grafted dopaminergic neurons integrated into the host SN. However, amphetamine-induced rotations were not affected by the intranigral grafts, which is due to the differing roles of the striatum and SN in rodent drug-induced turning asymmetry. Bridging grafts created by injecting mesencephalic cells at multiple sites to lay down a tract from SN to striatum (Zhou *et al.*, 1996) have shown success in physically re-establishing the nigrostriatal pathway including reciprocal functional synapses, increased DA release and near full reduction of amphetamine-induced turning asymmetry (Zhou *et al.*, 1996). In addition, a bridging tract can be laid with fetal ventral mesencephalic cells along with neurotrophic factor-secreting substrate cells (providing both a physical growing substrate and a trophic factor) resulting in an improved survival of TH fibers along the nigrostriatal bridge and a reduction in amphetamine-induced rotations (Brecknell *et al.*, 1996). A large variety of cell types and strategies have evolved for creating bridging grafts (Olson, 1997).

However, major obstacles remain. The fetal brain tissue used in clinical transplantation studies is difficult or ethically challenging to obtain (Lindvall, 2001). Also, while under normal conditions the CNS immune response is limited

(Boulanger & Shatz, 2004), the CNS is continuously patrolled by the immune system and mount a well-organized innate immune reaction in response to allogeneic antigens and cerebral injury (Tambur, 2004). Finally, striatal transplants are difficult to ‘‘tune” for appropriate dopaminergic output, causing side effects such as dyskinesia (Carlsson *et al.*, 2006), thereby emphasizing the necessity to restore the complexity of nigrostriatal neuronal circuitry.

Bone marrow cells

Stem cells have been detected in multiple organs in the adult, leading to the emerging concept of stem cell plasticity. These cells exhibit the classical traits of self-renewal and multipotentiality. In addition to well known stem cells of the adult marrow lymphohematopoietic and stromal mesenchymal lineages (Krause *et al.*, 2001), stem cells have been provisionally identified in liver, muscle, CNS and skin (Toma *et al.*, 2001). Bone marrow cells (BMC), offer an alternative source of cells for treatment of neurodegenerative diseases and CNS injury. These cells normally differentiate into bone, cartilage and adipose tissue (Pittenger *et al.*, 1999), but can be experimentally induced to differentiate into cells with surface markers characteristic of neurons (Sanchez-Ramos *et al.*, 2000). The cells assumed characteristic neuronal forms and expressed a variety of neuron-specific genes and proteins, including neuron specific enolase, tau, neurofilament M, NeuN (neuronal-specific nuclear protein), β-III-tubulin and synaptophysin. When injected into the brain or administered systemically, BMC migrate to sites of injury, proliferate and engraft (Chen *et al.*, 2001). These cells offer several advantages over other sources of stem-like precursor cells as therapy for PD: they are easily harvested, isolated and purified, can be produced in large quantities, and their use does not pose ethical concerns (Munoz-Elias *et al.*, 2004). Potential roles for BMC in treatment of PD include their use as vectors for delivery of gene products to sites of tissue injury (Ye *et al.*, 2007), facilitation of recovery from neuronal damage by replacing injured and/or lost cells (Levy *et al.*, 2008) and production of trophic factors promoting survival and regeneration of host tissue (Crigler *et al.*, 2006). In support of these therapeutic concepts, modest

improvements in neurological function have been reported following BMC administration in animal models of PD, stroke, and acute CNS injury (Li *et al.*, 2001; Mahmood *et al.*, 2004; Himes *et al.*, 2006).

Materials and Methods

CHEMICALS USED IN THE STUDY AND THEIR SOURCES

Biochemicals

6-hydroxydopamine, serotonin, γ-aminobutyric acid, ketanserin, mesulergine, apomorphine, amphetamine, bovine serum albumin fraction V, SOD, sodium octyl sulfonic acid, ethylene diamine tetra acetic acid (EDTA), Tris HCl, sucrose, magnesium chloride, calcium chloride, ascorbic acid, bromodeoxyuridine (BrdU) and paraformaldehyde (PFA) were purchased from Sigma Chemical Co., St. Louis, USA. All other reagents were of analytical grade purchased locally from SRL, India. HPLC solvents were of HPLC grade obtained from SRL and MERCK, India. Tissue freezing medium Jung was purchased from Leica Microsystems Nussloch GmbH, Germany.

Radiochemicals

5-Hydroxy [G-^{3}H] tryptamine creatinine sulphate ([^{3}H]5-HT, Sp. Activity 18.4Ci/mmol) and [Ethylene-^{3}H]-ketanserin hydrochloride (Sp. Activity 63.3Ci/mmol) were purchased from Amersham Bioscience, USA. [N^{6}-methyl-^{3}H] mesulergine (Sp. Activity 79.0 Ci/mmol) was purchased from NEN Life Science Products, Inc., Boston, MA, USA.

Molecular Biology Chemicals

Tri-reagent kit was purchased from Sigma Chemical Co., St. Louis, USA. ABI PRISM High Capacity cDNA Archive kit, Primers and Taqman probes for Real-Time PCR were purchased from Applied Biosystems, Foster City, CA, USA. $5HT_{2A}$ (Rn01468302_m1), $5\text{-}HT_{2C}$ (Rn00562748_m1), 5-HTT (Rn00564737_m1), SOD (Rn01477289), GPx (Rn00577994), Akt (Rn00583646), NF-κB (Rn01399583), Caspase-8 (Rn00574069), BDNF (Rn01484924),

GDNF (Rn00569510) and TH (Rn00562500_m1) primers were used for the gene expression studies using Real-Time PCR.

Confocal Dyes

Rat primary antibody for 5-HT_{2A} (No: ab16028, Abcam), 5-HT_{2C} (No: ab32172, Abcam), 5-HTT (No: AB9726, Chemicon), TH (No. T2928, Sigma), BDNF (No: AB1534SP, Chemicon), GDNF (No: ab18956) and secondary antibody of FITC (No: AB7130F, Chemicon), Rhodamine (No: AP307R, Chemicon), Cy5 (No: AP124S, Chemicon), Alexa Fluor 488 (No: A11059, Invitrogen) and Alexa Fluor 594 (No: A11012, Invitrogen) were used for the immunohistochemistry studies using confocal microscope.

ANIMALS

Adult male Wistar rats of 250-300g body weight were purchased from Kerala Agriculture University, Mannuthy, India and Amrita Institute of Medical Sciences, Kochi, India and used for all experiments. They were housed in separate cages under 12 hours light and 12 hours dark periods and were maintained on standard food pellets and water *ad libitum*. Adequate measures were also taken to minimize pain and discomfort of the animals. All animal care and procedures were taken in accordance with the Institutional, National Institute of Health and CPCSEA guidelines.

EXPERIMENTAL DESIGN

The experimental rats were divided into the following groups i) Control, ii) 6-OHDA infused (6-OHDA), iii) 6-OHDA infused supplemented with BMC (6-OHDA + BMC), iv) 6-OHDA infused supplemented with 5-HT and BMC (6-OHDA + 5-HT + BMC), v) 6-OHDA infused supplemented with GABA and BMC (6-OHDA + GABA + BMC), vi) 6-OHDA infused supplemented with 5-HT, GABA and BMC (6-OHDA + 5-HT + GABA + BMC). Each group consisted of 4-6 animals.

Rats were anesthetized with Chloral Hydrate (400 mg/kg body weight, i.p.). The animal was placed in the flat skull position on a cotton bed on a stereotaxic frame (Benchmark^{TM}, USA) with incisor bar fixed 3.3 mm below the interaural line and the coordinates (Paxinos & Watson, 2005) of SN*pc* were measured accurately as antero-posterior = -0.53 cm, lateral = 0.2 cm and dorsi-ventral = 0.79 cm relative to bregma and ventral from dura. 6-OHDA, 8µg in 1µl in 0.2% ascorbic acid, was infused into the right SN*pc* at a flow rate of 0.2µl/min. After stopping the infusion of 6-OHDA, the probe was kept in the same position for a further 5 min for complete diffusion of the drug and then slowly retracted. All the groups except Control group were infused with 6-OHDA and in control animals, 1 µl of the vehicle, 0.2% ascorbic acid, was infused into the right SN*pc*. Proper postoperative care was provided till the animals recovered completely.

ROTATIONAL BEHAVIOUR

Amphetamine-induced (5 mg/kg, i.p.) rotational behaviour was assessed as described earlier (Ungerstedt, 1971). Rats were tested with amphetamine on the 14th day after intranigral injection of 6-OHDA and with apomorphine (1 mg/kg, s.c.) on the 16th day. Animals that had completed a 360° circle towards the intact (contralateral) and the lesioned (ipsilateral) sides were counted for 60 mins continuously and recorded separately. Animals that showed no significant contralateral rotations were excluded from the study.

TREATMENT

On the 18th day, stereotaxic single dose of 1µl of 5-HT (10µg/µl), GABA (10µg/µl) and BMC (10^6 cells/µl) in combinations were infused into the right SN*pc* at a flow rate of 0.2µl/min into the respective groups. Bone marrow cells were collected from femurs with saline using a syringe with a No. 18 G needle. Cells were disaggregated by gentle pipetting several times. Cells were passed through 30µm nylon mesh to remove remaining clumps of tissue. Cells were washed by adding fresh saline, centrifuging for 10 min at 200g and removing

supernatant. The cell pellet was resuspended in 1 ml of saline. Cell counting was done using haemocytometer.

TISSUE PREPARATION

All the control and experimental rats were sacrificed on the 30th day by decapitation. The brain regions – corpus striatum, cerebral cortex, cerebellum and brain stem were dissected out quickly over ice according to the procedure of Glowinski and Iversen, (1966) and SN*pc* was micropunched according to Palkovits and Brownstein (1983). Hippocampus was dissected out quickly over ice according to the procedure of Heffner *et al*., (1980). The tissues were stored at ⁻80°C for various experiments.

BEHAVIOURAL STUDIES

Animals were observed everyday for any overt abnormal activity. Body weight was recorded on the 18th day before the treatment and on the 30th day before decapitation. Apomorphine-induced (1 mg/kg, s.c.) rotational behaviour was assessed once again on the 30th day.

Elevated body swing test

The elevated body swing test (EBST) was performed 12 days after treatment to evaluate rotational asymmetry (Borlongan & Sanberg, 1995). The animal was placed in a Plexiglas box (40 x 40 x 35.5 cm), allowed to attain a neutral position, defined as having all four paws on the ground. Each rat was held approximately 3cm from the base of its tail and 3cm above the ground. The animal was held in the vertical axis. A swing was recorded whenever the animal moved its head out of the vertical axis to either side. Before attempting another swing, the animal must return to the vertical position for the next swing to be counted. The number of left-biased swings and right-biased swings were counted for a period of 30s. Biased swinging behaviour was calculated as follows: contra/(contra + ipsi) (%) for contralateral-biased swings (contra = number of contralateral-biased swings, ipsi = number of ipsilateral-biased swings).

Stepping Test

The rats were tested for forelimb akinesia in a stepping test as described by Olsson *et al.* (1995). The rat was held by the experimenter fixing the hindlimbs with one hand and the forelimb not to be monitored with the other, while the unstrained forepaw was touching the table. When the rats were moved backward along the table, the free forelimb had to step with the movement of the experimenter to keep balance. The number of adjusting steps made by the rat, using the free forelimb, was counted as it was moved sideways along the table surface over a distance of 30 cm. Data are expressed as the number of steps made by the contralateral paw to the site of lesion of 6-OHDA.

Footprint analysis Test

To determine the gait abnormalities in rats we performed footprint analysis 12 days after treatment as described earlier (Pandey *et al.*, 2008). Rats were acclimatized to walk on a platform (100cm length, 12cm breadth and 10 cm high walls) leading to a darkened enclosure. The gangway was lined with white paper for recording the feet impressions. The fore- and hind-paws of the animals were dipped in two different non-toxic watercolours so as to get differential footprints. Rats were made to walk on the platform lined with white paper to obtain the footprint pattern. The footprints were analyzed for stride length. The distance covered by three consecutive strides was taken as the outcome measure.

Beam-walk test

After 12 days of treatment, the animals were tested for the balance and motor coordination on a narrow beam maze (Allbutt & Henderson, 2007). This has a smooth wooden narrow beam of 105cm long, 4cm in width and thickness of 3cm. The beam was elevated from the ground by 1m with additional supports. It has a start platform of 20cm in dimension from the start of the beam and an end platform of 20cm dimension at the end of 105cm long beam. There was food on the end platform for the reward of the animals. The journey time between start and end goal was measured. The time was recorded when the animal placed a weight

bearing step entirely over the start line. The stopwatch was then stopped when all four feet were placed entirely upon the finishing platform at the opposite end of the beam. The maximum time allowed for the task was 2 min.

QUANTIFICATION OF 5-HT AND DA IN THE EXPERIMENTAL GROUPS OF RATS

The monoamines were assayed according to the modified procedure of Dakshinamurti *et al.,* (1988). The brain tissues of experimental groups of rats was homogenised in 0.4N perchloric acid. The homogenate was then centrifuged at 5000xg for 10 minutes at 4°C in a Sigma 3K30 refrigerated centrifuge and the clear supernatant was filtered through 0.22 μm HPLC grade filters and used for HPLC analysis.

5-HT and DA contents were determined in high performance liquid chromatography (HPLC) with electrochemical detector (ECD) (Waters, USA) fitted with CLC-ODS reverse phase column of 5 μm particle size. The mobile phase consisted of 50mM sodium phosphate dibasic, 0.03M citric acid, 0.1mM EDTA**,** 0.6mM sodium octyl sulfonate and 15% methanol. The pH was adjusted to 3.25 with orthophosphoric acid, filtered through 0.22 μm filter (Millipore) and degassed. A Waters model 515, Milford, USA, pump was used to deliver the solvent at a rate of 1 ml/minute. The neurotransmitters and their metabolites were identified by amperometric detection using ECD (Waters, model 2465) with a reduction potential of +0.80 V. Twenty microlitre aliquots of the acidified supernatant were injected into the system for quantification. The peaks were identified by relative retention times compared with external standards and quantitatively estimated using an integrator (Empower software) interfaced with the detector. Data from different brain regions of the experimental and control rats were statistically analysed and tabulated.

SEROTONIN RECEPTOR BINDING STUDIES USING [^{3}H] RADIOLIGANDS

5-HT receptor binding studies

5-HT receptor assay was done using [^{3}H]-5-hydroxytryptamine binding in crude synaptic membrane preparations of corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem by the modified method of Uzbekov *et al.,* (1979). Crude membrane preparation was suspended in 50 mM Tris-HCl buffer, pH 8.5, containing 1.0 µM paragyline. The incubation mixture contained 0.3-0.4 mg protein. In the saturation binding experiments, assays were done using different concentrations i.e., 1.0nM - 20nM of [^{3}H] 5-HT incubated with and without excess of unlabelled 10µM 5-HT. Tubes were incubated at 37°C for 15 minutes and filtered rapidly through GF/B filters (Whatman). The filters were washed quickly by three successive washing with 5.0 ml of ice cold 50mM Tris buffer, pH 8.5. Bound radioactivity was counted with cocktail-T in a Wallac 1409 liquid scintillation counter.

5-HT$_{2A}$ receptor binding studies

5-HT$_{2A}$ receptor assay was done using [^{3}H] ketanserin binding in crude synaptic membrane preparations of corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem by the modified method of Leysen *et al.,* (1982). Crude membrane preparation was suspended in 50 mM Tris-HCl buffer, pH 7.6. The incubation mixture contained 0.3-0.4 mg protein. In the saturation binding experiments, assays were done using different concentrations i.e., 0.5nM-10nM of [^{3}H] ketanserin which was incubated with and without excess of unlabelled 10µM ketanserin. Tubes were incubated at 37°C for 15 minutes and filtered rapidly through GF/B filters (Whatman). The filters were washed quickly by three successive washings with 5.0 ml of ice cold 50mM Tris buffer, pH 7.6. Bound radioactivity was counted with cocktail-T in a Wallac 1409 liquid scintillation counter.

5-HT_{2C} receptor binding studies

5-HT_{2C} receptor assay was done using [^{3}H] mesulergine in the synaptic membrane preparations of brain regions as previously described by Herrick-Davis *et al*., (1999). Crude synaptic membrane preparation was suspended in 50 mM Tris-HCl buffer, pH 7.4 and used for assay. In the saturation binding experiments, assays were done using different concentrations i.e., 0.1nM-5nM of [^{3}H] mesulergine was incubated with and without excess of unlabelled 100µM mesulergine. Tubes were incubated at 25°C for 60 min. and filtered rapidly through GF/C filters (Whatman). The filters were washed quickly by three successive washing with 5.0 ml of ice cold 50mM Tris-HCl buffer, pH 7.4. Bound radioactivity was counted with cocktail-T in a Wallac 1409 liquid scintillation counter.

Protein determination

Protein was measured by the method of Lowry *et al*., (1951) using bovine serum albumin as standard. The intensity of the purple blue colour formed was proportional to the amount of protein which was read in a spectrophotometer (Shimadzu UV-1700) at 660nm.

ANALYSIS OF THE RECEPTOR BINDING DATA

Linear regression analysis for Scatchard plots

The data was analysed according to Scatchard, (1949). The specific binding was determined by subtracting non-specific binding from the total. The binding parameters, maximal binding (B_{max}) and equilibrium dissociation constant (K_d), were derived by linear regression analysis by plotting the specific binding of the radioligand on X-axis and bound/free on Y-axis. The maximal binding is a measure of the total number of receptors present in the tissue and the equilibrium dissociation constant is the measure of the affinity of the receptors for the radioligand. The K_d is inversely related to receptor affinity.

GENE EXPRESSION STUDIES IN DIFFERENT BRAIN REGIONS OF CONTROL AND EXPERIMENTAL RATS

Preparation of RNA

RNA was isolated from the different brain regions - SN*pc*, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of control and experimental rats using Tri reagent from Sigma Chemical Co., St. Louis, USA.

Isolation of RNA

Tissue (25-50 mg) homogenates were made in 0.5ml Tri Reagent and was centrifuged at 12,000 x *g* for 10 minutes at 4°C. The clear supernatant was transferred to a fresh tube and it was allowed to stand at room temperature for 5 minutes. 100µl of chloroform was added to it, mixed vigorously for 15 seconds and allowed to stand at room temperature for 15 minutes. The tubes were then centrifuged at 12,000 x *g* for 15 minutes at 4°C. Three distinct phases appear after centrifugation. The bottom red organic phase contained protein, interphase contained DNA and a colourless upper aqueous phase contained RNA. The upper aqueous phase was transferred to a fresh tube and 250 µl of isopropanol was added and the tubes were allowed to stand at room temperature for 10 minutes. The tubes were centrifuged at 12,000 x *g* for 10 min at 4ºC. RNA precipitated as a pellet on the sides and bottom of the tube. The supernatants were removed and the RNA pellet was washed with 500µl of 75% ethanol, vortexed and centrifuged at 12,000 x *g* for 5 min at 4°C. The pellets were semi dried and dissolved in minimum volume of DEPC-treated water. 2µl of RNA was made up to 1ml and absorbance was measured at 260 nm and 280 nm in spectrophotometer (Shimadzu UV-1700). For pure RNA preparation the ratio of absorbance at 260/280 was ≥ 1.7. The concentration of RNA was calculated as one absorbance $_{260}$ = 42µg.

cDNA Synthesis

Total cDNA synthesis was performed using ABI PRISM cDNA Archive kit in 0.2ml microfuge tubes. The reaction mixture of 20µl contained 0.2µg total RNA, 10X RT buffer, 25X dNTP mixture, 10X Random primers, MultiScribe RT (50U/µl) and RNase free water. The cDNA synthesis reactions were carried out at 25°C for 10 minutes and 37°C for 2 hours using an Eppendorf Personal Cycler. The primers and probes were purchased from Applied Biosystems, Foster City, CA, USA designed using Primer Express Software Version (3.0).

Real-Time PCR Assay

Real Time PCR assays were performed in 96-well plates in ABI 7300 Real Time PCR instrument (Applied Biosystems). To detect gene expression, a TaqMan quantitative 2-step reverse transcriptase polymerase chain reaction (RT-PCR) was used to quantify mRNA levels. First-strand cDNA was synthesized with use of a TaqMan RT reagent kit, as recommended by the manufacturer. PCR analyses were conducted with gene-specific primers and fluorescently labeled TaqMan probe (designed by Applied Biosystems). Endogenous control, β-actin, was labelled with a reporter dye (VIC). All reagents were purchased from Applied Biosystems. The probes for specific gene of interest were labeled with FAM at the 5' end and a quencher (Minor Groove Binding Protein - MGB) at the 3' end. The real-time data were analyzed with Sequence Detection Systems software version 1.7. All reactions were performed in duplicate.

The TaqMan reaction mixture of 20µl contained 25ng of total RNA-derived cDNAs, 200nM each of the forward primer, reverse primer and TaqMan probes, endogenous control (β-actin) and 12.5µl of TaqMan 2X Universal PCR Master Mix (Applied Biosystems). The volume was made up with RNase free water. Each run contained both negative (no template) and positive controls.

The thermocycling profile conditions were as follows:

50ºC -- 2 minutes	--- Activation	
95ºC -- 10 minutes	--- Initial Denaturation	
95ºC -- 15 seconds	--- Denaturation	40 cycles
50ºC -- 30 seconds	--- Annealing	
60ºC -- 1 minute	--- Final Extension	

Fluorescence signals measured during amplification were considered positive if the fluorescence intensity was 20-fold greater than the standard deviation of the baseline fluorescence. The ΔΔCT method of relative quantification was used to determine the fold change in expression. This was done by first normalizing the resulting threshold cycle (CT) values of the target mRNAs to the CT values of the internal control β-actin in the same samples ($\Delta CT = CT_{Target} - CT_{\beta\text{-actin}}$). It was further normalized with the control ($\Delta\Delta CT = \Delta CT - CT_{Control}$). The fold change in expression was then obtained ($2^{-\Delta\Delta CT}$).

DETERMINATION OF SOD ACTIVITY

The SN*pc* and corpus striatum were homogenized in 0.1M potassium phosphate buffer, pH 7.8 and centrifuged at 100,000 x g for 60 min at 4°C. The supernatant corresponds to the cytosolic fraction containing CuZn-SOD. The pellets were resuspended in the buffer, freeze-thawed three times and centrifuged at 100,000 x g for 60 min at 4°C. The supernatant, the particulate fraction containing Mn-SOD, was mixed with the cytosolic fraction to obtain the total enzyme fraction. SOD was analyzed after inhibition by SOD of the pyrogallol autoxidation (Marklund & Marklund, 1974) at pH 8.2 in the presence of EDTA. A 3ml assay mixture contained 0.2 mM pyrogallol, 1 mM EDTA and 50 mM Tris-HCl buffer. Pyrogallol autooxidation was monitored at 420 nm for 3 min in a spectrophotometer (Shimadzu UV-1700) with or without the enzyme. The inhibition of pyrogallol oxidation was linear with the activity of the enzyme

present. Fifty percent inhibition/mg protein/min was taken as one unit of the enzyme activity.

DETERMINATION OF CATALASE ACTIVITY

CAT activity was assayed in SN*pc* and corpus striatum based on H_2O_2 decomposition monitored at 240nm for 30s (Aebi, 1984). An assay mixture of 500µl contained suitably diluted enzyme protein (100µg) in 50mM phosphate buffer, pH 7.0. The reaction was started by the addition of H_2O_2 (30mM). The decrease in absorbance was monitored and the enzyme activity was expressed as change in absorbance/min/mg protein.

BONE MARROW CELLS DIFFERENTIATION STUDIES USING BrdU AND NeuN

To study the differentiation of BMC, transplanted BMC's were labelled by BrdU and double stained with neuronal marker NeuN for identification of neurons. Forty-eight hours after the treatment with BMC individually and in combinations, the rats were injected intraperitoneally with BrdU, at a dose of 100 mg/kg body weight. This dose was administered twice weekly until the rats were sacrificed. Tissue fixation was done by transcardial perfusion with Phosphate buffered saline (PBS), pH 7.4, followed by 4% PFA in PBS (Chen *et al*., 2007). After perfusion the brains were dissected and immersion fixed in 4% PFA for 1 hr and then equilibrated with 30% sucrose solution in 0.1M PBS, pH- 7.0. 10µm sections were cut using Cryostat (Leica, CM1510 S). The sections were treated with PBST (PBS in 0.01% Triton X-100) for 20 min. To block unspecific binding the sections were incubated for 1 hour at room temperature with 5% bovine serum albumin in normal goat serum. Brain slices were incubated overnight at 4°C with rat primary antibody for BrdU diluted in PBST at 1:500 dilution. After overnight incubation, the brain slices were rinsed with PBST and then incubated with Alexa Fluor 594 secondary antibody (1:1000) for 2hours. At the end of incubation period, the brain slices were rinsed thrice with PBST and incubated overnight with rat primary antibody for NeuN (1:1000). The slides were washed with PBST after

the incubation time and secondary antibody Alexa Fluor 488 was added and incubated for 2 hours at room temperature. The brain slices were thoroughly washed, mounted, observed and photographed using confocal imaging system (Leica SP 5). The cells were counted under one 63x magnification field from the SN*pc* in each section of brain. Corresponding areas of SN*pc* were estimated in each section of brain when choosing the 63x field. Counting was completed by counting the total number of cells labelled for NeuN only, BrdU only and for BrdU co-labelled with NeuN in one field under 63x magnification in the SN*pc*.

$5HT_{2A}$, 5-HT_{2C}, 5-HTT, BDNF, GDNF AND TH EXPRESSION STUDIES IN THE BRAIN REGIONS OF CONTROL AND EXPERIMENTAL RATS USING CONFOCAL MICROSCOPE

Control and experimental rats were deeply anesthetized with Chloral Hydrate (400 mg/kg, i.p.). The rats were transcardially perfused with PBS, pH 7.4, followed by 4% PFA in PBS (Chen *et al*., 2007). After perfusion the brains were dissected and immersion fixed in 4% PFA for 1 hr and then equilibrated with 30% sucrose solution in 0.1M PBS, pH- 7.0. 10µm sections were cut using Cryostat (Leica, CM1510 S). The sections were treated with PBST (PBS in 0.01% Triton X-100) for 20 min. To block unspecific binding the sections were incubated for 1 hour at room temperature with 5% bovine serum albumin in normal goat serum. Brain slices were incubated overnight at 4°C with rat primary antibody for 5-HT_{2A}, 5-HT_{2C} receptors, 5-HTT, BDNF, GDNF and TH diluted in PBST at 1: 500 dilution. After overnight incubation, the brain slices were rinsed with PBST and then incubated with appropriate secondary antibody of either FITC (diluted in PBST at 1: 1000 dilution), Rhodamine (diluted in PBST at 1: 1000 dilution) or Cy5 (diluted in PBST at 1: 1000 dilution). The sections were observed and photographed using confocal imaging system (Leica SP 5). Expressions were analysed using pixel intensity method. The given mean pixel value is the net value which is deducted from the negative control pixel value.

STATISTICS

Statistical evaluations were done by ANOVA using InStat (Ver.2.04a) computer programme. Linear regression Scatchard plots were made using Sigma Plot software (version 2.0, Jandel GmbH, Erkrath, Germany). Competitive binding data were analysed using non-linear regression curve-fitting procedure (GraphPad PRISM™, San Diego, USA). Empower software was used for HPLC analysis. Relative Quantification Software was used for analyzing Real-Time PCR results.

Results

Body weight of control and experimental rats

6-OHDA infusion into rats showed a significant ($p<0.001$) decrease in body weight after 18 days compared to control. 12 days after the treatment 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT, GABA and BMC in combination significantly ($p<0.001$) regained the body weight near to control compared to the 6-OHDA infused group. Meanwhile BMC supplemented alone showed no significant reversal in the body weight towards the control (Table - 1).

Behavioural studies

Apomorphine induced rotational behaviour in control and experimental rats

Apomorphine induced rotational behaviour showed a significant ($p<0.001$) increase in rotation/10min in 6-OHDA infused rats compared to control. 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT, GABA and BMC in combination significantly ($p<0.001$) reversed the rotational behaviour near to control. However, BMC treated alone showed no significant reversal in the rotation towards the control (Figure - 1).

Elevated body swing test in control and experimental rats

6-OHDA lesioned rats exhibited significant ($p<0.001$) contralateral biased swings compared to control in the elevated body swing test. A significant reversal in the percentage of contralateral biased swings was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal of contralateral biased swings towards the control (Figure - 2).

Stepping test in control and experimental rats

Stepping test showed a significant ($p<0.001$) decrease in the number of stepping movement using contralateral forepaw in the 6-OHDA infused rats compared to control. Treatment groups significantly improved performance with

the contralateral paw: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT, GABA and BMC ($p<0.001$) near to control. BMC treated alone showed no significant improvement in the performance with contralateral paw (Figure - 3).

Footprint analysis test in control and experimental rats

6-OHDA infusion into rats showed significant ($p<0.001$) decrease in relative stride length compared to control. A significant reversal in relative stride length was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in the relative stride length compared to 6-OHDA infused rats (Figure - 4).

Beam-walk test in control and experimental rats

6-OHDA infused rats showed significant ($p<0.001$) increase in the duration to cross the beam compared to control. The treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) showed a significant reversal of 6-OHDA induced functional impairment. BMC treated alone did not show any significant reversal compared to 6-OHDA infused rats (Figure - 5).

Substantia nigra pars compacta

Dopamine content in the SN*pc* of control and experimental rats

6-OHDA infusion into the SN*pc* resulted in a significant ($p<0.001$) decrease in DA content in the PD rats compared to control. A significant reversal in the DA content was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treatment alone did not reverse DA content (Table - 2).

Real-Time PCR analysis of tyrosine hydroxylase

Gene expression study of TH in the SN*pc* showed a significant ($p<0.001$) down regulation in 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 6; Table - 3).

Tyrosine hydroxylase antibody staining in control and experimental groups of rats

Tyrosine hydroxylase antibody staining in the SN*pc* showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. A significant reversal in the mean pixel value was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone did not reverse the alteration compared to other groups (Figure - 7; Table - 4).

Serotonin content in the SN*pc* of control and experimental rats

6-OHDA infusion into the SN*pc* resulted in a significant ($p<0.001$) decrease in 5-HT content in the PD rats compared to control. A significant reversal in the 5-HT content was observed in the treatment groups: 5-HT + BMC

($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treatment alone did not reverse the 5-HT content (Table - 5).

Real-Time PCR analysis of 5-HT_{2A} receptors

The gene expression studies of 5-HT_{2A} receptors using Real-Time PCR in the SN*pc* showed a significant ($p<0.001$) down regulation in the expression in 6-OHDA infused rats compared to control rats. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 8; Table - 6).

Real-Time PCR analysis of 5-HT_{2C} receptors

The Real-Time PCR analysis of 5-HT_{2C} receptors in the SN*pc* showed a significant ($p<0.001$) up regulation in the gene expression in 6-OHDA infused rats compared to control. Treatment groups significantly reversed gene expression near to control: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 9; Table - 7).

Real-Time PCR analysis of 5-HT transporter

Gene expression study of 5-HTT in the SN*pc* showed a significant ($p<0.001$) down regulation in 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 10; Table - 8).

Superoxide dismutase activity in control and experimental rats

6-OHDA infused rats showed significant ($p<0.001$) decrease in activity of SOD in the SN*pc* compared to control. Treatment groups significantly reversed the activity of SOD enzyme near to control: 5-HT + BMC ($p<0.01$), GABA +

BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone did not show any significant reversal in SOD activity compared to 6-OHDA infused rats (Figure - 11; Table - 9).

Catalase activity in control and experimental rats

In SN*pc* of 6-OHDA infused rats, CAT showed a significant ($p<0.001$) decrease in activity compared to control. Treatment groups significantly reversed the CAT activity near to control: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone did not show any significant reversal in activity of CAT enzyme compared to 6-OHDA infused rats (Figure - 12; Table - 10).

Assessment of lipid peroxidation in control and experimental rats

A significant increase ($p<0.001$) in TBARS level was observed in 6-OHDA group when compared to control group. Rats of 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) groups exhibited significant attenuation in TBARS level in comparison to 6-OHDA group rats. BMC alone treated 6-OHDA rats exhibited no significant reversal of lipid peroxidation to near control (Figure - 13; Table - 11).

Real-Time PCR analysis of superoxide dismutase in control and experimental rats

Gene expression of antioxidant enzyme SOD showed significant ($p<0.001$) down regulation in the SN*pc* of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.001$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 14; Table - 12).

Real-Time PCR analysis of glutathione peroxidase in control and experimental rats

The gene expression of antioxidant enzyme GPx showed a significant down regulation ($p<0.001$) in the SN*pc* of 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 15; Table - 13).

Real-Time PCR analysis of Akt in control and experimental rats

Gene expression of Akt mRNA showed significant down regulation ($p<0.001$) in the SN*pc* of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.05$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 16; Table - 14).

Real-Time PCR analysis of NF-κB in control and experimental rats

Gene expression of NF-κB mRNA showed significant up regulation ($p<0.001$) in the SN*pc* of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 17; Table - 15).

Real-Time PCR analysis of Caspase-8 in control and experimental rats

Gene expression of Caspase-8 mRNA showed significant up regulation ($p<0.001$) in the SN*pc* of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC

($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 18; Table - 16).

Real-Time PCR analysis of BDNF in control and experimental rats

BDNF expression showed a significant down regulation ($p<0.001$) in the 6-OHDA infused rats compared to control. A significant reversal of the BDNF expression was observed in 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) groups. In BMC alone treated group, there was no significant reversal in BDNF mRNA expression to near control (Figure - 19; Table - 17).

Real-Time PCR analysis of GDNF in control and experimental rats

Gene expression study of GDNF in the SN*pc* showed a significant ($p<0.001$) up regulation in 6-OHDA infused rats and the rats treated with BMC, 5-HT + BMC, GABA + BMC and 5-HT + GABA + BMC compared to control rats. Prominent significant ($p<0.001$) expression was observed in the rats treated with 5-HT, GABA and BMC in combination (Figure - 20; Table - 18).

BrdU-NeuN co-labelling studies in control and experimental rats

BrdU positive BMC was visualized in red while the NeuN labelled neurons were visualized in green colour. BrdU-NeuN co-labelled cells appeared yellow in colour. Our results proved that BMC differentiate to neuronal cells once the proper conditions are given. When autologous BMC treatment was given to SN*pc*, they differentiated to neurons. Proliferating BMC were tagged by BrdU which expressed neuronal marker NeuN when administered along with 5-HT and GABA. 5-HT, GABA and BMC in combination expressed maximum number of co-labelled cells. (Figure – 21a, 21b, 21c, 22).

Corpus Striatum

Serotonin content in the Corpus Striatum of control and experimental rats

6-OHDA infusion resulted in a significant ($p<0.001$) decrease in 5-HT content in the Corpus Striatum of PD rats compared to control. A significant reversal in the 5-HT content was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treatment alone did not reverse the 5-HT content (Table - 20).

Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors

Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Corpus Striatum of 6-OHDA infused rats showed a significant ($p<0.001$) decrease in B_{max} compared to control rats. The treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the decreased receptor number to near control. BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure - 23, 24; Table - 21, 22).

Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT_{2A} receptors

Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT_{2A} receptors in the Corpus Striatum of 6-OHDA infused rats showed a significant ($p<0.001$) decrease in B_{max} compared to control rats. Significant reversal in the B_{max} was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure - 25, 26; Table - 23, 24).

Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors

Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors in the Corpus Striatum of 6-OHDA infused rats showed a significant ($p<0.001$) increase in B_{max} compared to control rats. Significant reversal in the B_{max} was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure - 27, 28; Table - 25, 26).

Real-Time PCR analysis of 5-HT$_{2A}$ receptors

The gene expression studies using Real-Time PCR was done in Corpus Striatum to confirm the receptor analysis which showed a significant ($p<0.001$) down regulation in 5-HT$_{2A}$ receptor expression in 6-OHDA infused rats compared to control rats. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 29; Table - 27).

Real-Time PCR analysis of 5-HT$_{2C}$ receptors

The Real-Time PCR analysis of 5-HT$_{2C}$ receptors in the Corpus Striatum showed a significant ($p<0.001$) up regulation in 6-OHDA infused rats compared to control rats. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 30; Table - 28).

Real-Time PCR analysis of 5-HT transporter

The Real-Time PCR analysis of 5-HTT in the Corpus Striatum showed a significant ($p<0.001$) down regulation in 6-OHDA infused rats compared to control rats. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 31; Table - 29).

Superoxide dismutase activity in control and experimental rats

6-OHDA infused rats showed significant ($p<0.001$) decrease in activity of SOD in the Corpus Striatum compared to control. Treatment groups significantly reversed the activity of SOD enzyme near to control: 5-HT + BMC ($p<0.001$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone did not show any significant reversal in SOD activity compared to 6-OHDA infused rats (Figure - 32; Table - 30).

Catalase activity in control and experimental rats

In Corpus Striatum of 6-OHDA infused rats, CAT showed a significant ($p<0.001$) decrease in activity compared to control. Treatment groups significantly reversed the CAT activity near to control: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone did not show any significant reversal in activity of CAT enzyme compared to 6-OHDA infused rats (Figure - 33; Table - 31).

Assessment of lipid peroxidation in control and experimental rats

A significant increase ($p<0.001$) in TBARS level was observed in 6-OHDA group when compared to control group. Rats of 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) groups exhibited significant attenuation in TBARS level in comparison to 6-OHDA group rats.

BMC alone treated 6-OHDA rats exhibited no significant reversal of lipid peroxidation to near control (Figure - 34; Table - 32).

Real-Time PCR analysis of superoxide dismutase in control and experimental rats

Gene expression of antioxidant enzyme SOD showed significant ($p<0.001$) down regulation in the Corpus Striatum of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.001$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 35; Table - 33).

Real-Time PCR analysis of glutathione peroxidase in control and experimental rats

The gene expression of antioxidant enzyme GPx showed a significant down regulation ($p<0.001$) in the Corpus Striatum of 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 36; Table - 34).

Real-Time PCR analysis of Akt in control and experimental rats

Gene expression of Akt mRNA showed significant down regulation ($p<0.001$) in the Corpus Striatum of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.05$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 37; Table - 35).

Real-Time PCR analysis of NF-κB in control and experimental rats

Gene expression of NF-κB mRNA showed significant up regulation ($p<0.001$) in the Corpus Striatum of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 38; Table - 36).

Real-Time PCR analysis of Caspase-8 in control and experimental rats

Gene expression of Caspase-8 mRNA showed significant up regulation ($p<0.001$) in the Corpus Striatum of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 39; Table - 37).

Real-Time PCR analysis of BDNF in control and experimental rats

BDNF expression showed a significant down regulation ($p<0.001$) in the Corpus Striatum of 6-OHDA infused rats compared to control. A significant reversal of the BDNF expression was observed in 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) groups. In BMC alone treated group, there was no significant reversal in BDNF mRNA expression to near control (Figure - 40; Table - 38).

Real-Time PCR analysis of GDNF in control and experimental rats

Gene expression study of GDNF in the Corpus Striatum showed a significant ($p<0.001$) up regulation in 6-OHDA infused rats and the rats treated with BMC, 5-HT + BMC, GABA + BMC and 5-HT + GABA + BMC compared to control rats. Prominent significant ($p<0.001$) expression was observed in the rats treated with 5-HT, GABA and BMC in combination (Figure - 41; Table - 39).

5-HT_{2A} receptor antibody staining in control and experimental groups of rats

5-HT_{2A} receptor antibody staining was carried out to confirm the receptor and gene expression studies. The 5-HT_{2A} receptor antibody staining in the Corpus Striatum showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.05$), GABA + BMC ($p<0.05$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 42; Table - 40).

5-HT_{2C} receptor antibody staining in control and experimental groups of rats

The 5-HT_{2C} receptor antibody staining in the Corpus Striatum showed significant ($p<0.001$) increase in the mean pixel value in 6-OHDA infused rats compared to control. Treatment with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 43; Table - 41).

5-HT transporter antibody staining in control and experimental groups of rats

5-HT transporter antibody staining was carried out to confirm the gene expression studies. The 5-HT transporter antibody staining in the Corpus Striatum showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.05$), GABA + BMC ($p<0.05$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 44; Table - 42).

BDNF expression by immunohistochemistry in control and experimental groups of rats

BDNF antibody staining was carried out to confirm the gene expression studies. The BDNF antibody staining in the Corpus Striatum showed significant

($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.05$), GABA + BMC ($p<0.05$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 45; Table - 43).

GDNF expression by immunohistochemistry in control and experimental groups of rats

GDNF antibody staining was carried out to confirm the gene expression studies. The GDNF antibody staining in the Corpus Striatum showed a significant ($p<0.001$) up regulation in 6-OHDA infused rats and the rats treated with BMC, 5-HT + BMC, GABA + BMC and 5-HT + GABA + BMC compared to control rats. Prominent significant ($p<0.001$) expression was observed in the rats treated with 5-HT, GABA and BMC in combination (Figure - 46; Table - 44).

Cerebral cortex

Serotonin content in the cerebral cortex of control and experimental rats

5-HT content in the cerebral cortex showed a significant ($p<0.001$) decrease in 6-OHDA infused rats compared to control. Significant reversal in the 5-HT content was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone did not show any significant reversal in 5-HT content compared to 6-OHDA infused rats (Table - 45).

Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors

Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors in the cerebral cortex of 6-OHDA infused rats showed a significant ($p<0.001$) decrease in B_{max} compared to control rats. Except BMC alone treated group, all the other treatment groups significantly reversed the receptor number to near control: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). There was no significant change in K_d in all experimental groups of rats (Figure - 47, 48; Table - 46, 47).

Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT$_{2A}$ receptors

The total 5-HT$_{2A}$ receptor status was assayed using the specific ligand, [^{3}H]ketanserin. Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the cerebral cortex of 6-OHDA infused rats showed a significant ($p<0.001$) decrease in B_{max} compared to control rats. The treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the receptor number to near control. BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure - 49, 50; Table - 48, 49).

Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors

Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors in the cerebral cortex of 6-OHDA infused rats showed a significant ($p<0.001$) increase in B_{max} compared to control rats. Significant reversal in the B_{max} was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure – 51, 52; Table – 50, 51).

Real-Time PCR analysis of 5-HT$_{2A}$ receptors

The gene expression studies of 5-HT$_{2A}$ receptors was done using Real-Time PCR in cerebral cortex to confirm the receptor analysis which showed a significant ($p<0.001$) down regulation in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 53; Table - 52).

Real-Time PCR analysis of 5-HT$_{2C}$ receptors

The Real-Time PCR analysis of 5-HT$_{2C}$ receptors in the cerebral cortex showed a significant ($p<0.001$) up regulation in 6-OHDA infused rats compared to control rats. Treatment groups significantly reversed gene expression near to control: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 54; Table - 53).

Real-Time PCR analysis of 5-HT transporter

The Real-Time PCR analysis of 5-HTT in the cerebral cortex showed a significant ($p<0.001$) down regulation in gene expression in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 55; Table - 54).

Real-Time PCR analysis of superoxide dismutase in control and experimental rats

The Real-Time PCR analysis of SOD mRNA in the cerebral cortex showed a significant ($p<0.001$) down regulation in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 56; Table - 55).

Real-Time PCR analysis of glutathione peroxidase in control and experimental rats

Gene expression of GPx mRNA showed significant down regulation ($p<0.001$) in the cerebral cortex of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 57; Table - 56).

Real-Time PCR analysis of Akt in control and experimental rats

Gene expression of Akt mRNA showed significant down regulation ($p<0.001$) in the cerebral cortex of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups:

5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 58; Table - 57).

Real-Time PCR analysis of NF-κB in control and experimental rats

Gene expression of NF-κB mRNA showed significant up regulation ($p<0.001$) in the cerebral cortex of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 59; Table - 58).

Real-Time PCR analysis of Caspase-8 in control and experimental rats

Gene expression of Caspase-8 mRNA showed significant up regulation ($p<0.001$) in the cerebral cortex of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 60; Table - 59).

Real-Time PCR analysis of BDNF in control and experimental rats

BDNF expression showed a significant down regulation ($p<0.001$) in the cerebral cortex of 6-OHDA infused rats compared to control. A significant reversal of the BDNF expression was observed in 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) groups. In BMC alone treated group, there was no significant reversal in BDNF mRNA expression to near control (Figure - 61; Table - 60).

5-HT_{2A} receptor antibody staining in control and experimental groups of rats

5-HT_{2A} receptor antibody staining was carried out to confirm the receptor and gene expression studies. The 5-HT_{2A} receptor antibody staining in the cerebral

cortex showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.05$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 62; Table - 61).

5-HT_{2C} receptor antibody staining in control and experimental groups of rats

The 5-HT_{2C} receptor antibody staining in the cerebral cortex showed significant ($p<0.001$) increase in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 63; Table - 62).

5-HT transporter antibody staining in control and experimental groups of rats

5-HT transporter antibody staining was carried out to confirm the gene expression studies. The 5-HT transporter antibody staining in the cerebral cortex showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 64; Table - 63).

BDNF expression by immunohistochemistry in control and experimental groups of rats

BDNF antibody staining was carried out to confirm the gene expression studies. The BDNF antibody staining in the cerebral cortex showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and

5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 65; Table - 64).

Hippocampus

Serotonin content in the Hippocampus of control and experimental rats

5-HT content in the hippocampus showed a significant ($p<0.001$) decrease in 6-OHDA infused rats compared to control rats. A significant reversal in the 5-HT content was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone did not show any significant reversal in 5-HT content compared to 6-OHDA infused rats (Table - 65).

Scatchard analysis of [^{3}H]5-HT binding against 5-HT

The total 5-HT receptors status was assayed using [^{3}H]5-HT binding against 5-HT. Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the hippocampus of 6-OHDA infused rats showed a significant ($p<0.001$) decrease in B_{max} compared to control rats. The treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the receptor number to near control. BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure - 66, 67; Table - 66, 67).

Scatchard analysis of [^{3}H]ketanserin binding against ketanserin

The total 5-HT_{2A} receptor status was assayed using the specific ligand, [^{3}H]ketanserin. Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the hippocampus of 6-OHDA infused rats showed a significant ($p<0.001$) decrease in B_{max} compared to control rats. The treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC

($p<0.001$) significantly reversed the receptor number to near control. BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure – 68, 69; Table – 68, 69).

Scatchard analysis of [^{3}H]mesulergine binding against mesulergine

Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT_{2C} receptors in the hippocampus of 6-OHDA infused rats showed a significant ($p<0.001$) increase in B_{max} compared to control rats. Significant reversal in the B_{max} was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure – 70, 71; Table – 70, 71).

Real-Time PCR analysis of 5-HT_{2A} receptors

The Real-Time PCR analysis of 5-HT_{2A} receptors in the hippocampus showed a significant ($p<0.001$) down regulation in 6-OHDA infused rats compared to control rats. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.05$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 72; Table - 72).

Real-Time PCR analysis of 5-HT_{2C} receptors

The Real-Time PCR analysis of 5-HT_{2C} receptors in the hippocampus showed a significant ($p<0.001$) up regulation in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 73; Table - 73).

Real-Time PCR analysis of 5-HT transporter

The Real-Time PCR analysis of 5-HTT in the hippocampus showed a significant ($p<0.001$) down regulation in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 74; Table - 74).

Real-Time PCR analysis of superoxide dismutase in control and experimental rats

Gene expression of SOD mRNA showed significant down regulation ($p<0.001$) in the hippocampus of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 75; Table - 75).

Real-Time PCR analysis of glutathione peroxidase in control and experimental rats

Gene expression of GPx mRNA showed significant down regulation ($p<0.001$) in the hippocampus of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 76; Table - 76).

Real-Time PCR analysis of Akt in control and experimental rats

Gene expression of Akt mRNA showed significant down regulation ($p<0.001$) in the hippocampus of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC

($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 77; Table - 77).

Real-Time PCR analysis of NF-κB in control and experimental rats

Gene expression of NF-κB mRNA showed significant up regulation ($p<0.001$) in the hippocampus of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 78; Table - 78).

Real-Time PCR analysis of Caspase-8 in control and experimental rats

Gene expression of Caspase-8 mRNA showed significant up regulation ($p<0.001$) in the hippocampus of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 79; Table - 79).

Real-Time PCR analysis of BDNF in control and experimental rats

BDNF expression showed a significant down regulation ($p<0.001$) in the hippocampus of 6-OHDA infused rats compared to control. A significant reversal of the BDNF expression was observed in 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) groups. In BMC alone treated group, there was no significant reversal in BDNF mRNA expression to near control (Figure - 80; Table - 80).

5-HT_{2A} receptor antibody staining in control and experimental groups of rats

5-HT_{2A} receptor antibody staining was carried out to confirm the receptor and gene expression studies. The 5-HT_{2A} receptor antibody staining in the hippocampus showed significant ($p<0.001$) decrease in the mean pixel value in

6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 81; Table - 81).

5-HT_{2C} receptor antibody staining in control and experimental groups of rats

The 5-HT_{2C} receptor antibody staining in the hippocampus showed significant ($p<0.001$) increase in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.05$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 82; Table - 82).

5-HT transporter antibody staining in control and experimental groups of rats

5-HT transporter antibody staining was carried out to confirm the gene expression studies. The 5-HT transporter antibody staining in the hippocampus showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 83; Table - 83).

BDNF expression by immunohistochemistry in control and experimental groups of rats

BDNF antibody staining was carried out to confirm the gene expression studies. The BDNF antibody staining in the hippocampus showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value.

BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 84; Table - 84).

Cerebellum

Serotonin content in the cerebellum of control and experimental rats

5-HT content in the cerebellum showed a significant ($p<0.001$) decrease in 6-OHDA infused rats compared to control rats. A significant reversal in the 5-HT content was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone did not show any significant reversal in 5-HT content compared to 6-OHDA infused rats (Table - 85).

Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors

The total 5-HT receptors status was assayed using [^{3}H]5-HT binding against 5-HT. Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the cerebellum of 6-OHDA infused rats showed a significant ($p<0.001$) decrease in B_{max} compared to control rats. Except BMC alone treated group, all the other treatment groups significantly reversed the receptor number to near control: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). There was no significant change in K_d in all experimental groups of rats (Figure - 85, 86; Table - 86, 87).

Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT$_{2A}$ receptors

The total 5-HT$_{2A}$ receptor status was assayed using the specific ligand, [^{3}H]ketanserin. Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the cerebellum of 6-OHDA infused rats showed a significant ($p<0.001$) decrease in B_{max} compared to control rats. The treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the receptor number to near control. BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure - 87, 88; Table - 88, 89).

Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors

Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors in the cerebellum of 6-OHDA infused rats showed a significant ($p<0.001$) increase in B_{max} compared to control rats. Significant reversal in the B_{max} was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure – 89, 90; Table – 90, 91).

Real-Time PCR analysis of 5-HT$_{2A}$ receptors

The gene expression studies using Real-Time PCR was done in cerebellum to confirm the receptor analysis which showed a significant ($p<0.001$) down regulation in 5-HT$_{2A}$ receptor expression in 6-OHDA infused rats compared to control rats. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression of 5-HT$_{2A}$ receptors compared to 6-OHDA infused rats (Figure - 91; Table - 92).

Real-Time PCR analysis of 5-HT$_{2C}$ receptors

The Real-Time PCR analysis of 5-HT$_{2C}$ receptors in the cerebellum showed a significant ($p<0.001$) up regulation in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 92; Table - 93).

Real-Time PCR analysis of 5-HT transporter

The Real-Time PCR analysis of 5-HTT in the cerebellum showed a significant ($p<0.001$) down regulation in gene expression in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 93; Table - 94).

Real-Time PCR analysis of superoxide dismutase in control and experimental rats

Gene expression of SOD mRNA showed significant down regulation ($p<0.001$) in the cerebellum of 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 94; Table - 95).

Real-Time PCR analysis of glutathione peroxidase in control and experimental rats

Gene expression of GPx mRNA showed significant down regulation ($p<0.001$) in the cerebellum of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 95; Table - 96).

Real-Time PCR analysis of Akt in control and experimental rats

Gene expression of Akt mRNA showed significant down regulation ($p<0.001$) in the cerebellum of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC

($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 96; Table - 97).

Real-Time PCR analysis of NF-κB in control and experimental rats

Gene expression of NF-κB mRNA showed significant up regulation ($p<0.001$) in the cerebellum of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 97; Table - 98).

Real-Time PCR analysis of Caspase-8 in control and experimental rats

Gene expression of Caspase-8 mRNA showed significant up regulation ($p<0.001$) in the cerebellum of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 98; Table - 99).

Real-Time PCR analysis of BDNF in control and experimental rats

BDNF expression showed a significant down regulation ($p<0.001$) in the cerebellum of 6-OHDA infused rats compared to control. A significant reversal of the BDNF expression was observed in 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) groups. In BMC alone treated group, there was no significant reversal in BDNF mRNA expression to near control (Figure - 99; Table - 100).

5-HT_{2A} receptor antibody staining in control and experimental groups of rats

5-HT_{2A} receptor antibody staining was carried out to confirm the receptor and gene expression studies. The 5-HT_{2A} receptor antibody staining in the cerebellum showed significant ($p<0.001$) decrease in the mean pixel value in

6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 100; Table - 101).

5-HT_{2C} receptor antibody staining in control and experimental groups of rats

The 5-HT_{2C} receptor antibody staining in the cerebellum showed significant ($p<0.001$) increase in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 101; Table - 102).

5-HT transporter antibody staining in control and experimental groups of rats

5-HT transporter antibody staining was carried out to confirm the receptor and gene expression studies. The 5-HT transporter antibody staining in the cerebellum showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 102; Table – 103).

BDNF expression by immunohistochemistry in control and experimental groups of rats

BDNF antibody staining was carried out to confirm the gene expression studies. The BDNF antibody staining in the cerebellum showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value.

BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 103; Table - 104).

Brain stem

Serotonin content in the brain stem of control and experimental rats

5-HT content in the brain stem showed a significant ($p<0.001$) decrease in 6-OHDA infused rats compared to control rats. A significant reversal in the 5-HT content was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone did not show any significant reversal in 5-HT content compared to 6-OHDA infused rats (Table - 105).

Scatchard analysis of [^{3}H]5-HT binding against 5-HT

The total 5-HT receptors status was assayed using [^{3}H]5-HT binding against 5-HT. Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the brain stem of 6-OHDA infused rats showed a significant ($p<0.001$) decrease in B_{max} compared to control rats. The treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the receptor number to near control. BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure - 104, 105; Table - 106, 107).

Scatchard analysis of [^{3}H]ketanserin binding against ketanserin

The total 5-HT_{2A} receptor status was assayed using the specific ligand, [^{3}H]ketanserin. Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the brain stem of 6-OHDA infused rats showed a significant ($p<0.001$) decrease in B_{max} compared to control rats. The treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the receptor number to near control. BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no

significant change in K_d in all experimental groups of rats (Figure – 106, 107; Table – 108, 109).

Scatchard analysis of [^{3}H]mesulergine binding against mesulergine

Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT_{2C} receptors in the brain stem of 6-OHDA infused rats showed a significant ($p<0.001$) increase in B_{max} compared to control rats. Significant reversal in the B_{max} was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in B_{max} compared to 6-OHDA infused rats. There was no significant change in K_d in all experimental groups of rats (Figure – 108, 109; Table – 110, 111).

Real-Time PCR analysis of 5-HT_{2A} receptors

The Real-Time PCR analysis of 5-HT_{2A} receptors in the brain stem showed a significant ($p<0.001$) down regulation in 6-OHDA infused rats compared to control rats. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 110; Table - 112).

Real-Time PCR analysis of 5-HT_{2C} receptors

The Real-Time PCR analysis of 5-HT_{2C} receptors in the brain stem showed a significant ($p<0.001$) up regulation in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 111; Table - 113).

Real-Time PCR analysis of 5-HT transporter

The Real-Time PCR analysis of 5-HTT in the brain stem showed a significant ($p<0.001$) down regulation in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) reversed the alteration. BMC treated alone did not show any significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 112; Table - 114).

Real-Time PCR analysis of superoxide dismutase in control and experimental rats

Gene expression of SOD mRNA showed significant down regulation ($p<0.001$) in the brain stem of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 113; Table - 115).

Real-Time PCR analysis of glutathione peroxidase in control and experimental rats

Gene expression of GPx mRNA showed significant down regulation ($p<0.001$) in the brain stem of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 114; Table - 116).

Real-Time PCR analysis of Akt in control and experimental rats

Gene expression of Akt mRNA showed significant down regulation ($p<0.001$) in the brain stem of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC

($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 115; Table - 117).

Real-Time PCR analysis of NF-κB in control and experimental rats

Gene expression of NF-κB mRNA showed significant up regulation ($p<0.001$) in the brain stem of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 116; Table - 118).

Real-Time PCR analysis of Caspase-8 in control and experimental rats

Gene expression of Caspase-8 mRNA showed significant up regulation ($p<0.001$) in the brain stem of 6-OHDA infused rats compared to control. A significant reversal in the gene expression was observed in the treatment groups: 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$). BMC treated alone showed no significant reversal in gene expression compared to 6-OHDA infused rats (Figure - 117; Table - 119).

Real-Time PCR analysis of BDNF in control and experimental rats

BDNF expression showed a significant down regulation ($p<0.001$) in the brain stem of 6-OHDA infused rats compared to control. A significant reversal of the BDNF expression was observed in 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) groups. In BMC alone treated group, there was no significant reversal in BDNF mRNA expression to near control (Figure - 118; Table - 120).

5-HT_{2A} receptor antibody staining in control and experimental groups of rats

5-HT_{2A} receptor antibody staining was carried out to confirm the receptor and gene expression studies. The 5-HT_{2A} receptor antibody staining in the brain stem showed significant ($p<0.001$) decrease in the mean pixel value in

6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 119; Table - 121).

5-HT_{2C} receptor antibody staining in control and experimental groups of rats

The 5-HT_{2C} receptor antibody staining in the brain stem showed significant ($p<0.001$) increase in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 120; Table - 122).

5-HT transporter antibody staining in control and experimental groups of rats

5-HT transporter antibody staining was carried out to confirm the gene expression studies. The 5-HT transporter antibody staining in the brain stem showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value. BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 121; Table - 123).

BDNF expression by immunohistochemistry in control and experimental groups of rats

BDNF antibody staining was carried out to confirm the gene expression studies. The BDNF antibody staining in the brain stem showed significant ($p<0.001$) decrease in the mean pixel value in 6-OHDA infused rats compared to control. Treatments with 5-HT + BMC ($p<0.01$), GABA + BMC ($p<0.01$) and 5-HT + GABA + BMC ($p<0.001$) significantly reversed the mean pixel value.

BMC treated alone did not reverse the alteration compared to 6-OHDA group (Figure - 122; Table - 124).

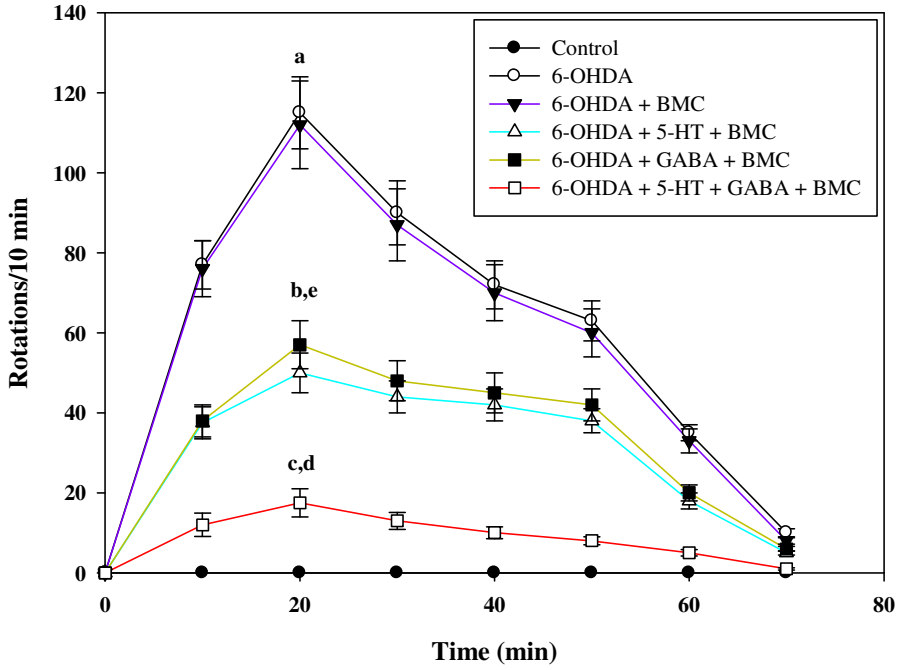
Table - 1
Body weight of control and experimental rats

Experimental groups	Body weight in grams	
	Day 18	Day 30
Control	253.8 ± 6.7	281.1 ± 6.3
6-OHDA	203.2 ± 4.5[a]	185.9 ± 4.2[a]
6-OHDA + BMC	203.6 ± 3.8[a]	187.3 ± 4.8[a]
6-OHDA + 5-HT + BMC	201.4 ± 4.2[a]	223.7 ± 5.2[b,e]
6-OHDA + GABA + BMC	201.9 ± 3.8[a]	223.1 ± 5.6[b,e]
6-OHDA + 5-HT + GABA + BMC	202.8 ± 3.2[a]	235.8 ± 3.5[c,d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

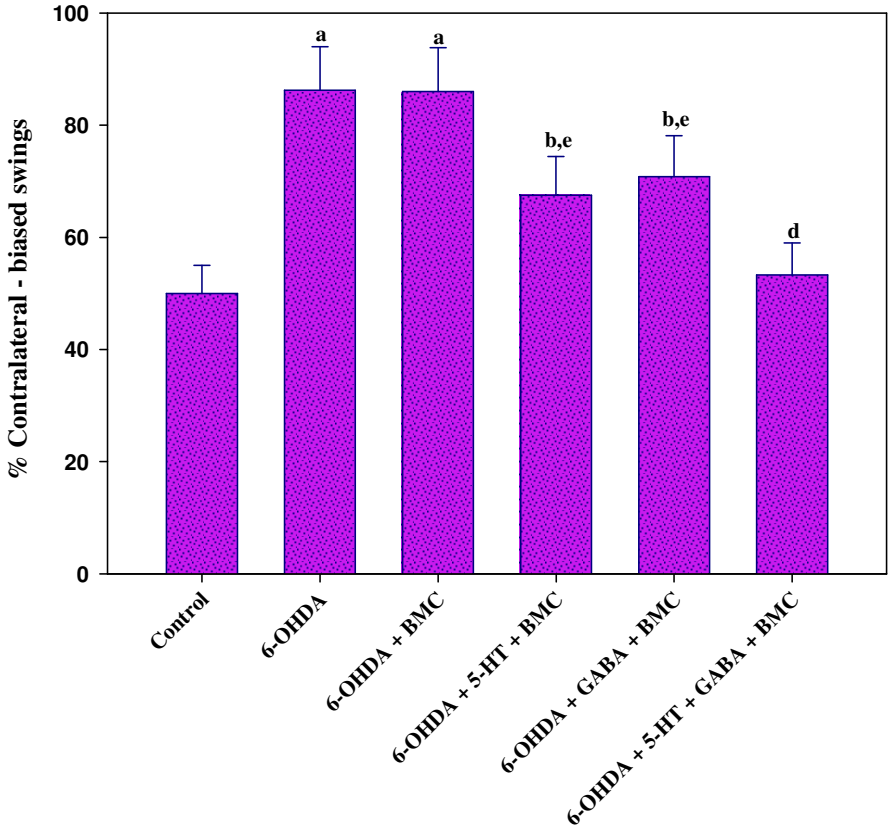
Figure - 1
Apomorphine induced rotational behaviour in control and experimental rats



Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

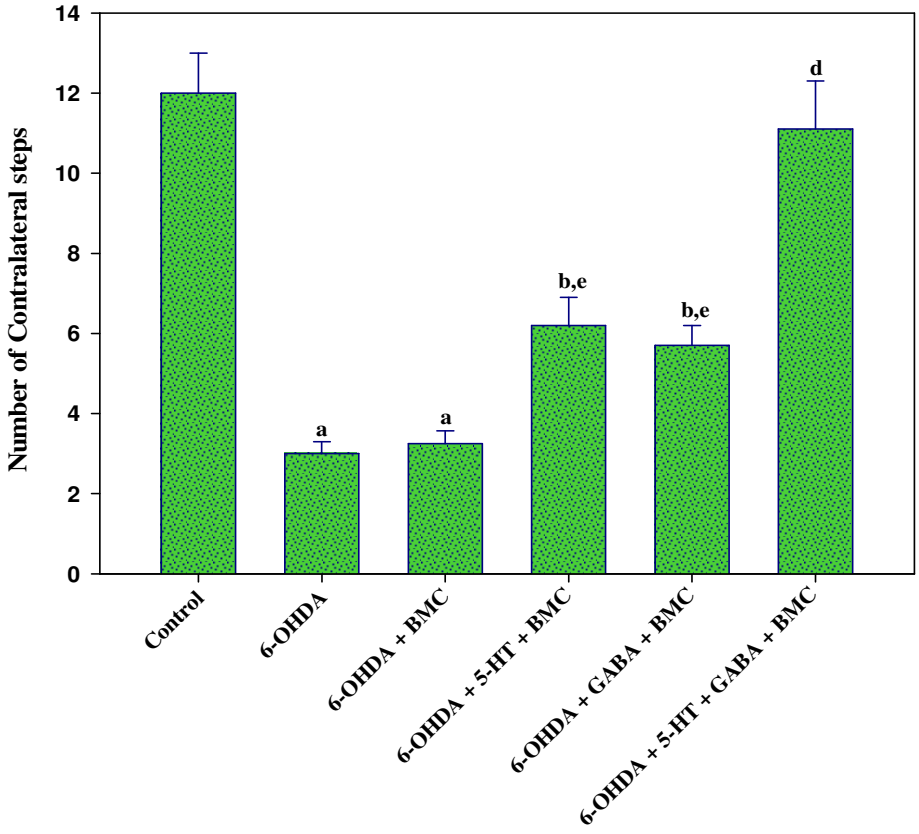
Figure - 2
Elevated body swing test in control and experimental rats



Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

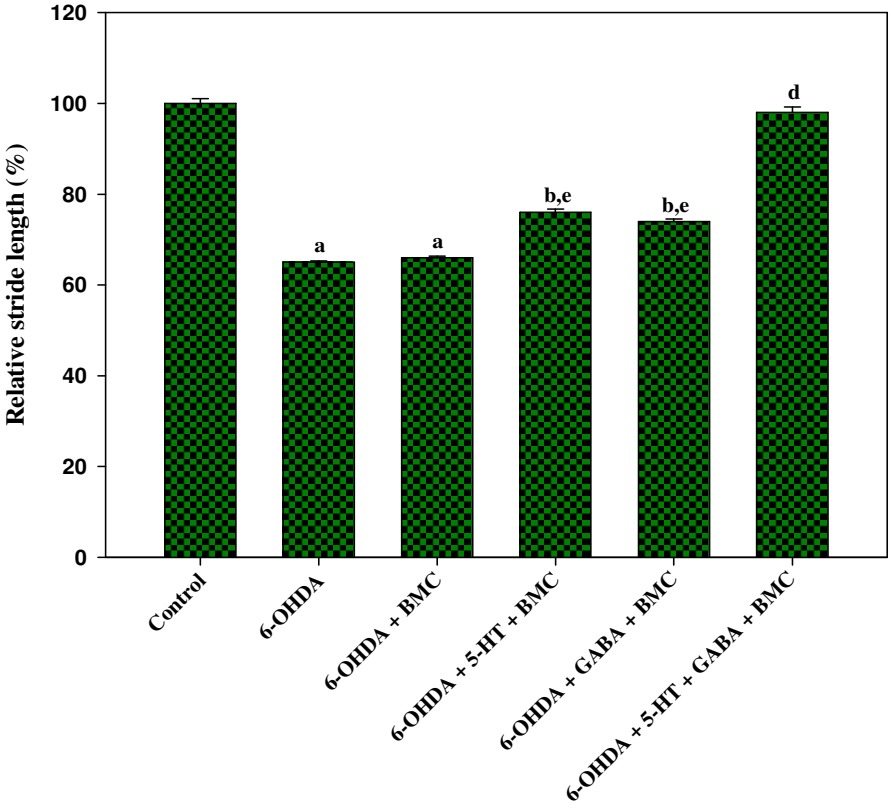
Figure - 3
Stepping test in control and experimental rats



Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

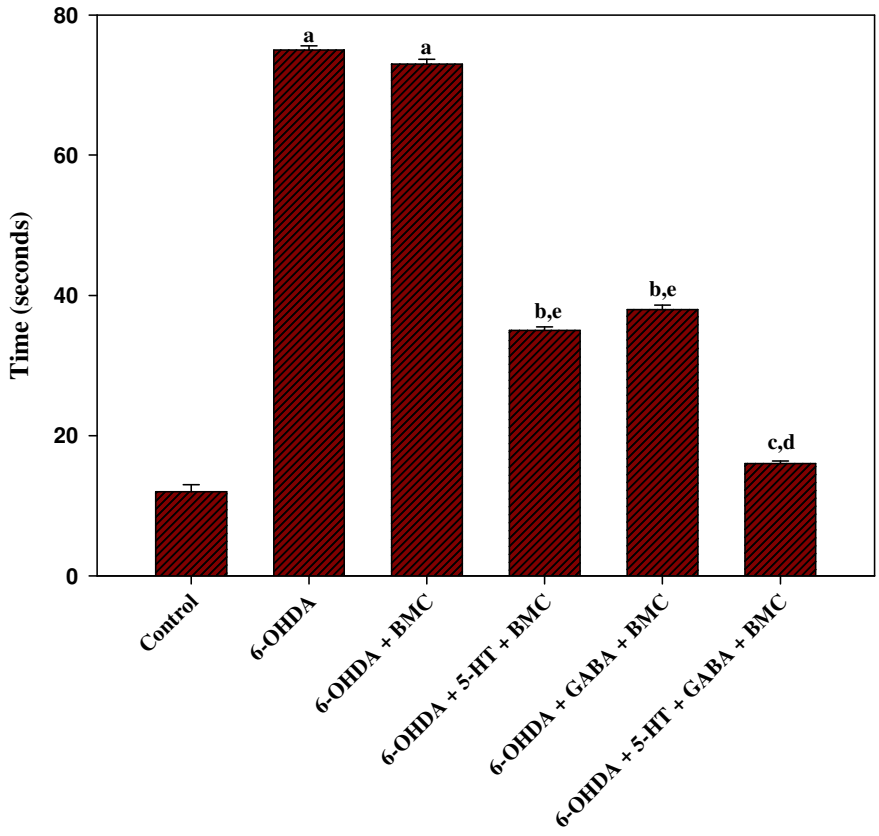
Figure - 4
Footprint analysis test in control and experimental rats



Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 5
Beam-walk test in control and experimental rats



Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Table - 2
Dopamine content in the substantia nigra *pars compacta* of control and experimental rats

Experimental Groups	DA Content (nmoles/g wet wt.)
Control	**26.24 ± 2.34**
6-OHDA	**5.09 ± 0.58[a]**
6-OHDA + BMC	**6.77 ± 0.62[a]**
6-OHDA + 5-HT + BMC	**18.86 ± 1.81[b,e]**
6-OHDA + GABA + BMC	**16.30 ± 1.59[b,e]**
6-OHDA + 5-HT + GABA + BMC	**24.01 ± 1.93[d]**

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 6
Real Time PCR amplification of TH mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

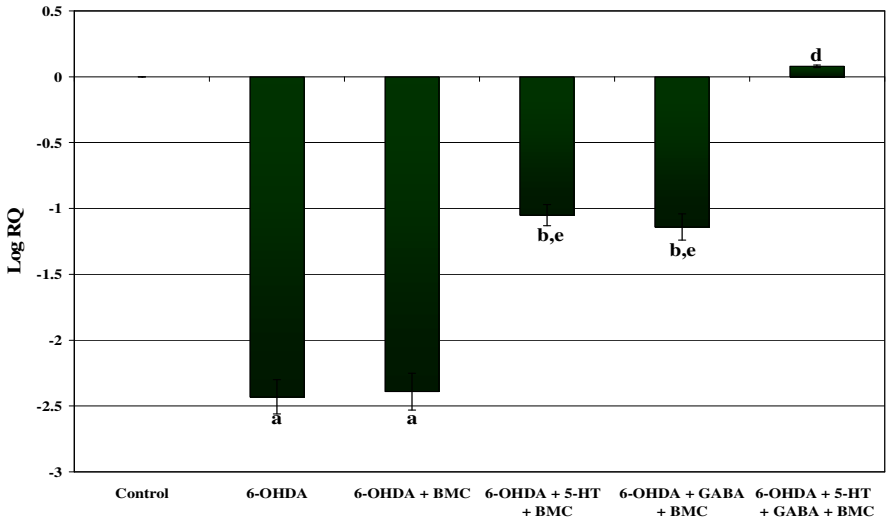


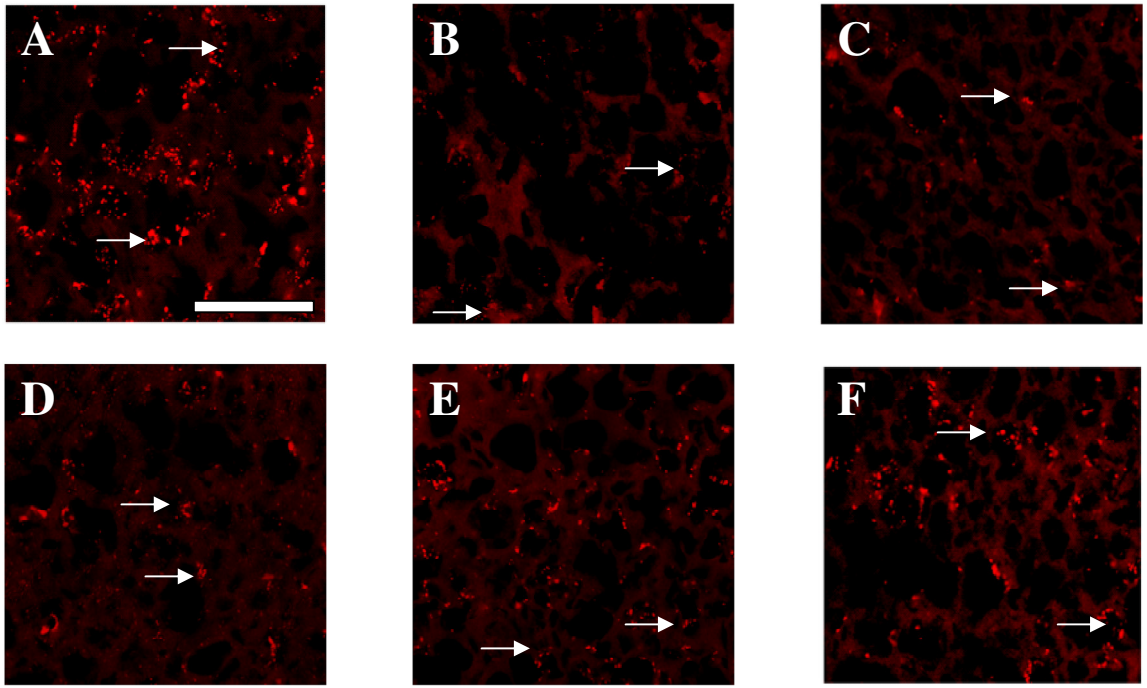
Table - 3
Real Time PCR amplification of TH mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.43 ± 0.13[a]
6-OHDA + BMC	-2.39 ± 0.14[a]
6-OHDA + 5-HT + BMC	-1.05 ± 0.08[b,e]
6-OHDA + GABA + BMC	-1.14 ± 0.10[b,e]
6-OHDA + 5-HT + GABA + BMC	0.08 ± 0.01[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 7
Tyrosine hydroxylase expression in the substantia nigra *pars compacta* of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 4
Tyrosine hydroxylase expression in the substantia nigra *pars compacta* of control and experimental rats

Experimental Groups	Mean Pixel Intensity
Control	60.47 ± 5.58
6-OHDA	15.10 ± 1.19[a]
6-OHDA + BMC	17.82 ± 1.04[a]
6-OHDA + 5-HT + BMC	36.27 ± 2.58[b,e]
6-OHDA + GABA + BMC	32.61 ± 2.94[b,e]
6-OHDA + 5-HT + GABA + BMC	53.33 ± 4.98[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Table - 5
Serotonin content in the substantia nigra *pars compacta* of control and experimental rats

Experimental Groups	5-HT Content (nmoles/g wet wt.)
Control	**2.37 ± 0.18**
6-OHDA	**0.52 ± 0.05[a]**
6-OHDA + BMC	**0.61 ± 0.06[a]**
6-OHDA + 5-HT + BMC	**1.78 ± 0.19[b,e]**
6-OHDA + GABA + BMC	**1.42 ± 0.17[b,e]**
6-OHDA + 5-HT + GABA + BMC	**2.14 ± 0.21[d]**

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 8
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

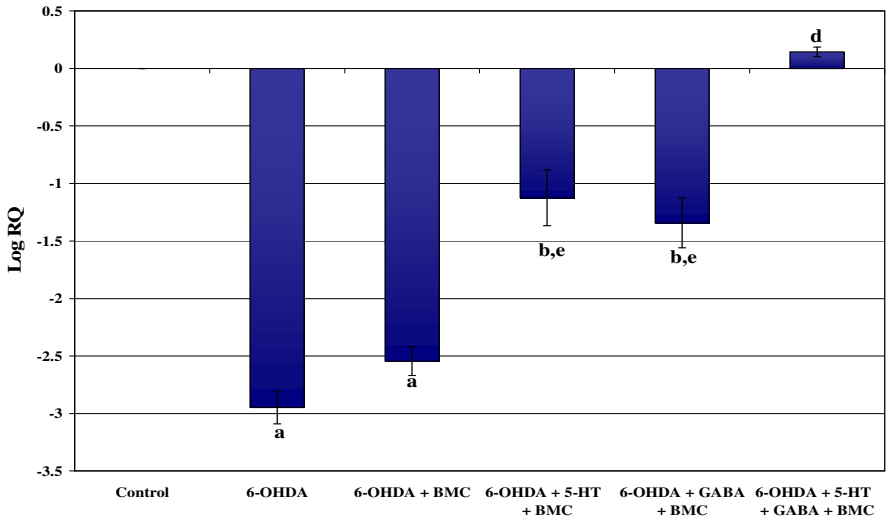


Table - 6
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.95 ± 0.14^{a}
6-OHDA + BMC	-2.55 ± 0.12^{a}
6-OHDA + 5-HT + BMC	$-1.12 \pm 0.24^{b,e}$
6-OHDA + GABA + BMC	$-1.34 \pm 0.22^{b,e}$
6-OHDA + 5-HT + GABA + BMC	0.14 ± 0.04^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 9
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

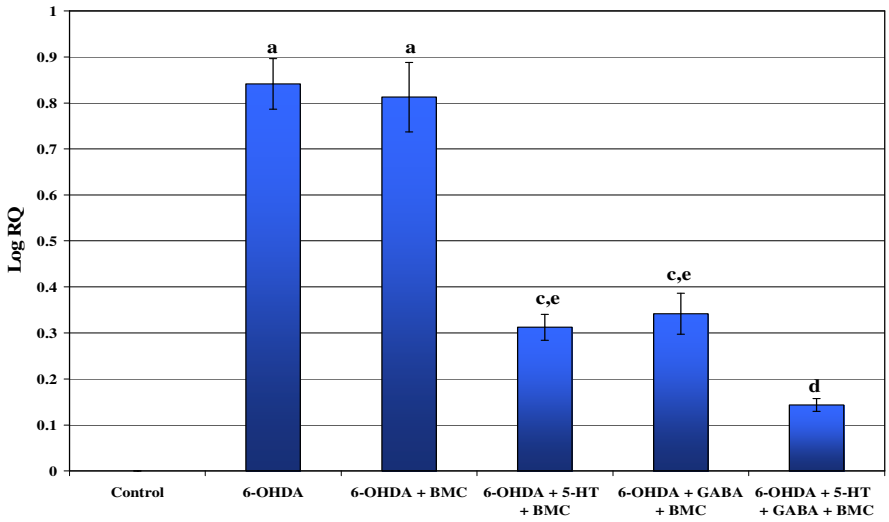


Table - 7
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	0.84 ± 0.05^{a}
6-OHDA + BMC	0.81 ± 0.08^{a}
6-OHDA + 5-HT + BMC	$0.31 \pm 0.03^{c,e}$
6-OHDA + GABA + BMC	$0.34 \pm 0.04^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.14 ± 0.01^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 10
Real Time PCR amplification of 5-HT transporter mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

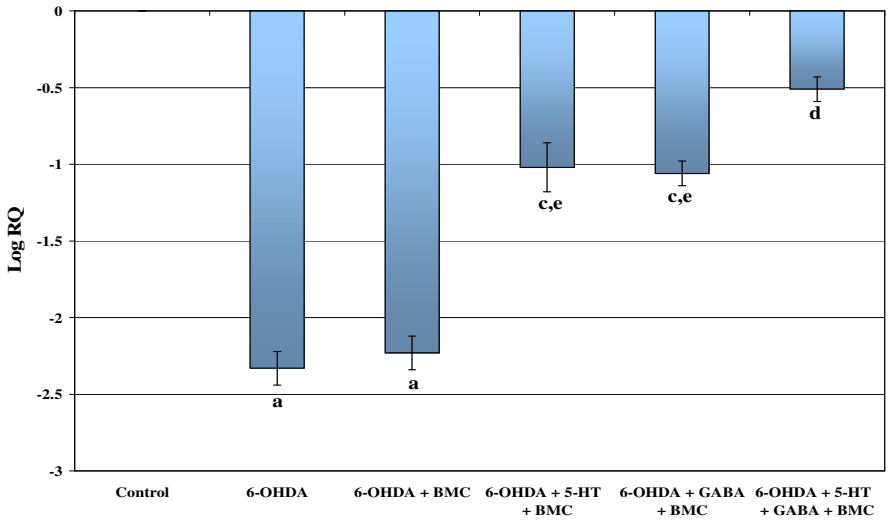


Table - 8
Real Time PCR amplification of 5-HT transporter mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.33 ± 0.11[a]
6-OHDA + BMC	-2.23 ± 0.11[a]
6-OHDA + 5-HT + BMC	-1.02 ± 0.16[c,e]
6-OHDA + GABA + BMC	-1.06 ± 0.08[c,e]
6-OHDA + 5-HT + GABA + BMC	-0.51 ± 0.08[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 11
SOD activity in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

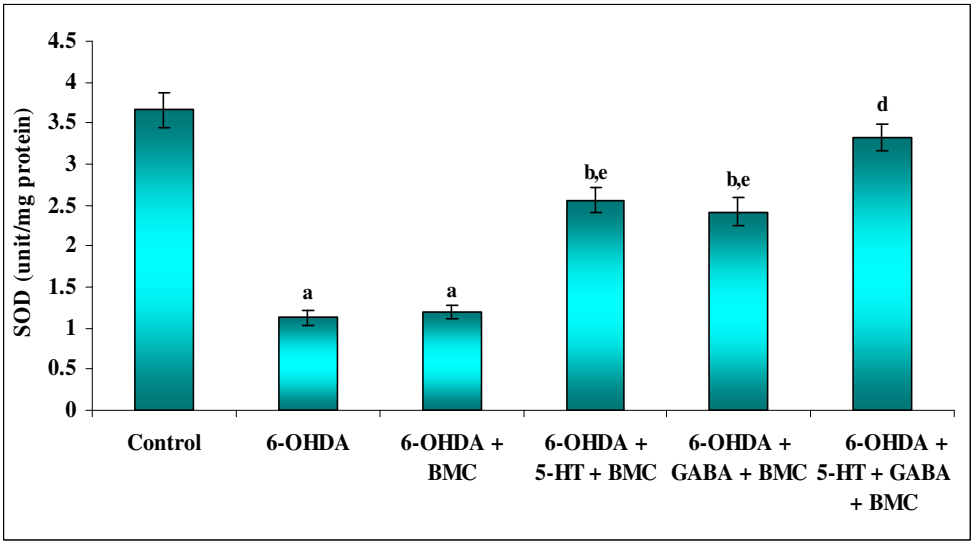


Table - 9
SOD activity in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	SOD activity (unit/mg protein)
Control	3.66 ± 0.22
6-OHDA	1.13 ± 0.09[a]
6-OHDA + BMC	1.19 ± 0.08[a]
6-OHDA + 5-HT + BMC	2.56 ± 0.15[b,e]
6-OHDA + GABA + BMC	2.42 ± 0.17[b,e]
6-OHDA + 5-HT + GABA + BMC	3.32 ± 0.16[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 12
CAT activity in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

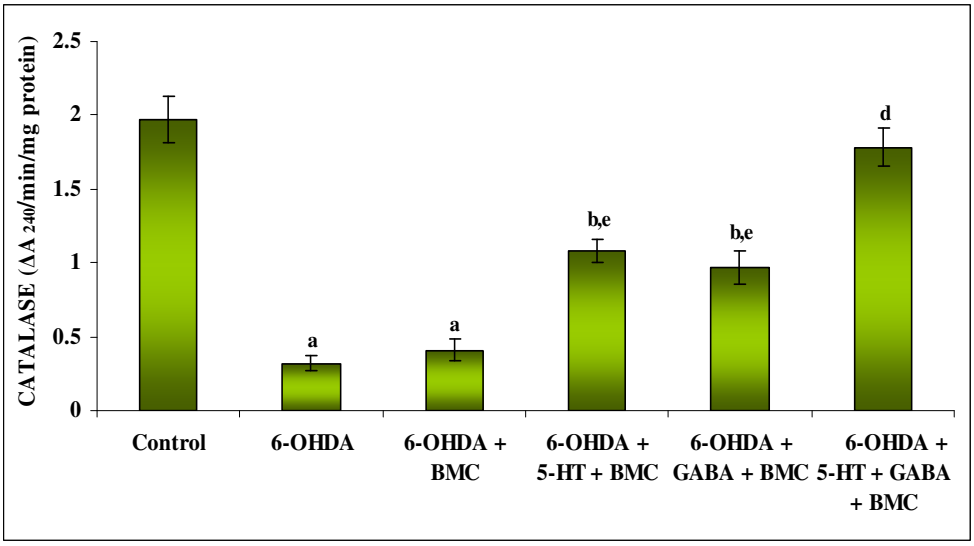


Table - 10
CAT activity in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	CAT activity (ΔA_{240}/min/mg protein)
Control	1.97 ± 0.16
6-OHDA	0.32 ± 0.05[a]
6-OHDA + BMC	0.41 ± 0.07[a]
6-OHDA + 5-HT + BMC	1.08 ± 0.08[b,e]
6-OHDA + GABA + BMC	0.97 ± 0.11[b,e]
6-OHDA + 5-HT + GABA + BMC	1.78 ± 0.13[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 13
Lipid peroxidation assay in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

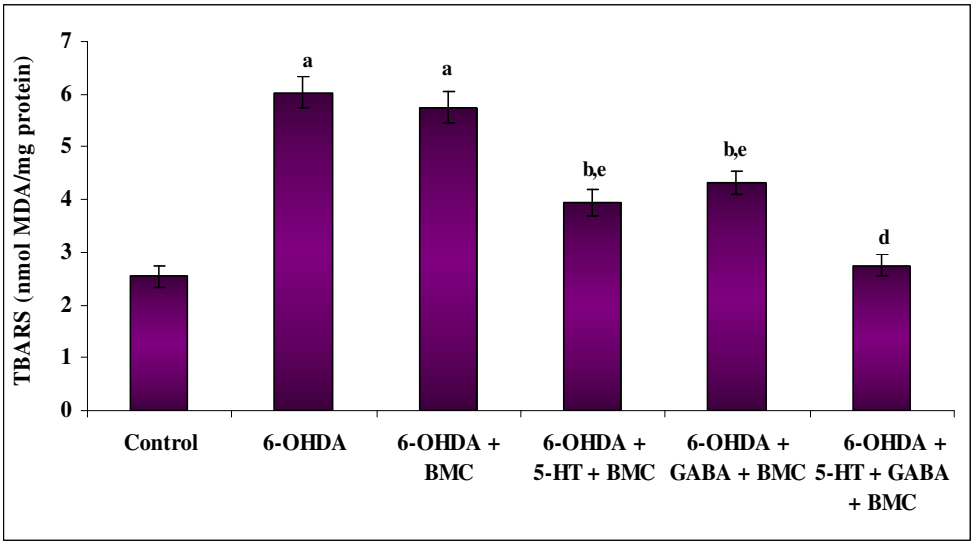


Table - 11
Lipid peroxidation assay in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	TBARS (nmol MDA/mg protein)
Control	2.54 ± 0.20
6-OHDA	6.03 ± 0.30[a]
6-OHDA + BMC	5.75 ± 0.30[a]
6-OHDA + 5-HT + BMC	3.95 ± 0.25[b,e]
6-OHDA + GABA + BMC	4.33 ± 0.22[b,e]
6-OHDA + 5-HT + GABA + BMC	2.75 ± 0.20[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 14
Real Time PCR amplification of SOD mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

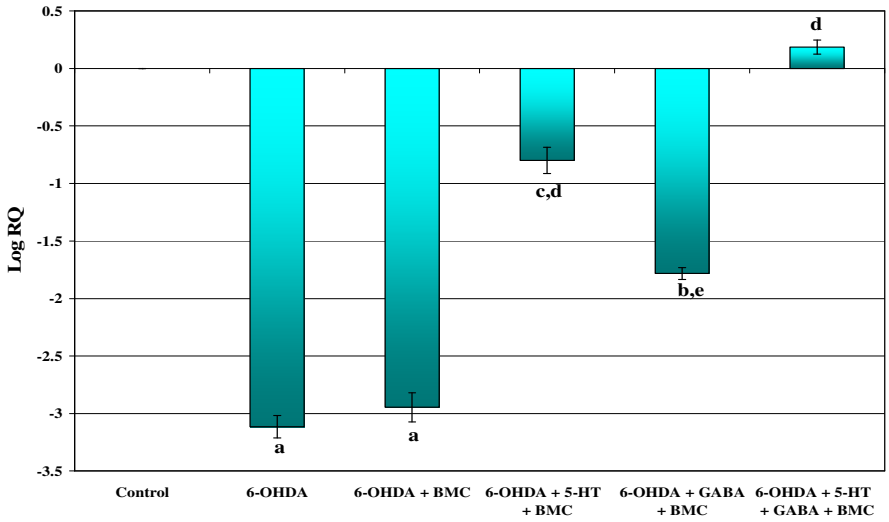


Table - 12
Real Time PCR amplification of SOD mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-3.12 ± 0.09[a]
6-OHDA + BMC	-2.95 ± 0.13[a]
6-OHDA + 5-HT + BMC	-0.79 ± 0.11[c,d]
6-OHDA + GABA + BMC	-1.78 ± 0.05[b,e]
6-OHDA + 5-HT + GABA + BMC	0.18 ± 0.06[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 15
Real Time PCR amplification of GPx mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

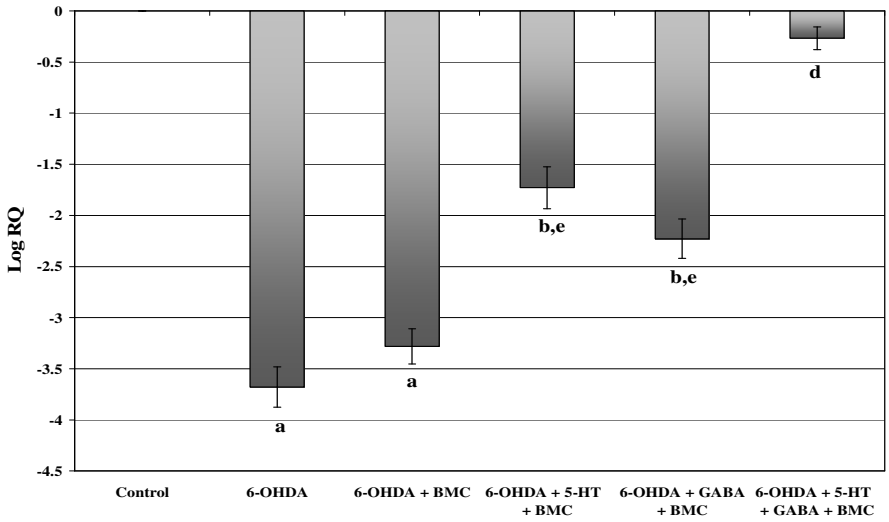


Table - 13
Real Time PCR amplification of GPx mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-3.68 ± 0.20^{a}
6-OHDA + BMC	-3.28 ± 0.17^{a}
6-OHDA + 5-HT + BMC	$-1.73 \pm 0.20^{b,e}$
6-OHDA + GABA + BMC	$-2.23 \pm 0.19^{b,e}$
6-OHDA + 5-HT + GABA + BMC	-0.27 ± 0.11^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 16
Real Time PCR amplification of Akt mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

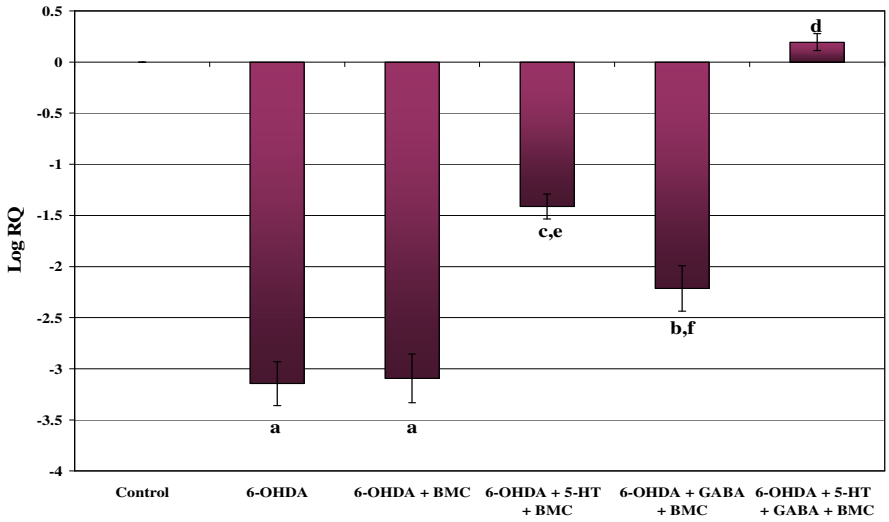


Table - 14
Real Time PCR amplification of Akt mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-3.15 ± 0.21[a]
6-OHDA + BMC	-3.09 ± 0.24[a]
6-OHDA + 5-HT + BMC	-1.41 ± 0.12[c,e]
6-OHDA + GABA + BMC	-2.21 ± 0.22[b,f]
6-OHDA + 5-HT + GABA + BMC	0.19 ± 0.08[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$, [f] $p<0.05$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 17
Real Time PCR amplification of NF-κB mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

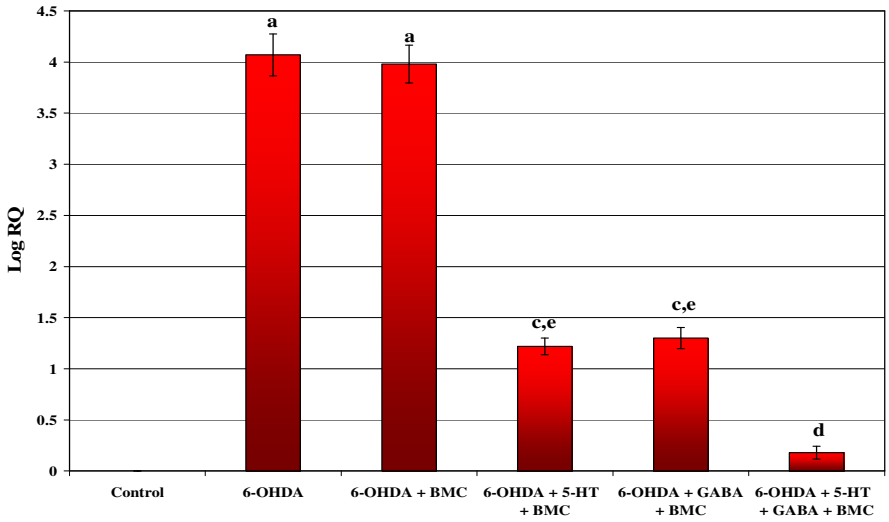


Table - 15
Real Time PCR amplification of NF-κB mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	4.07 ± 0.20^{a}
6-OHDA + BMC	3.98 ± 0.18^{a}
6-OHDA + 5-HT + BMC	$1.22 \pm 0.08^{c,e}$
6-OHDA + GABA + BMC	$1.30 \pm 0.10^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.18 ± 0.06^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 18
Real Time PCR amplification of Caspase-8 mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

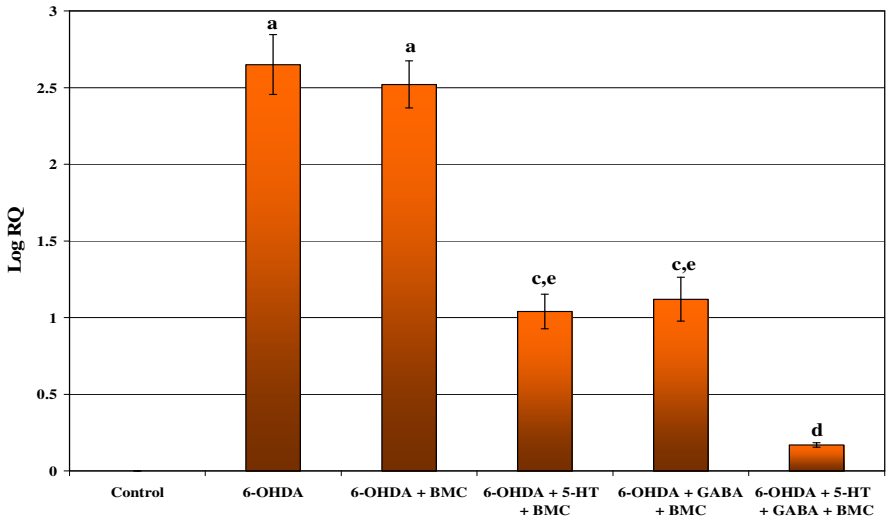


Table - 16
Real Time PCR amplification of Caspase-8 mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	2.65 ± 0.19^{a}
6-OHDA + BMC	2.52 ± 0.15^{a}
6-OHDA + 5-HT + BMC	$1.04 \pm 0.11^{c,e}$
6-OHDA + GABA + BMC	$1.12 \pm 0.14^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.17 ± 0.01^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 19
Real Time PCR amplification of BDNF mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

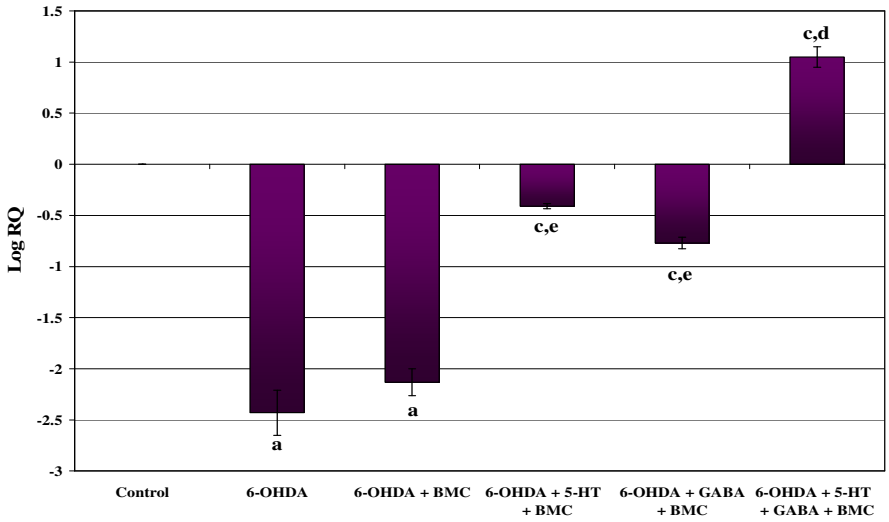


Table - 17
Real Time PCR amplification of BDNF mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.43 ± 0.21^{a}
6-OHDA + BMC	-2.13 ± 0.13^{a}
6-OHDA + 5-HT + BMC	$-0.41 \pm 0.02^{c,e}$
6-OHDA + GABA + BMC	$-0.77 \pm 0.05^{c,e}$
6-OHDA + 5-HT + GABA + BMC	$1.05 \pm 0.10^{c,d}$

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 20
Real Time PCR amplification of GDNF mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

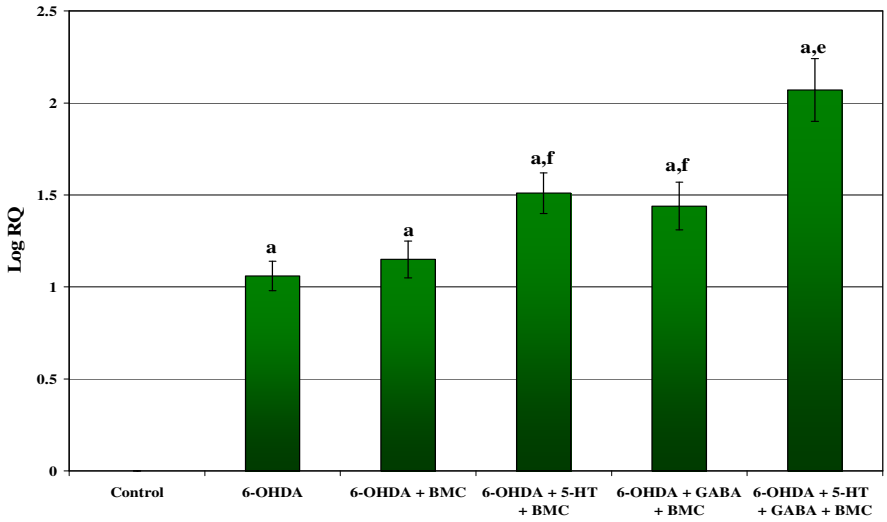


Table - 18
Real Time PCR amplification of GDNF mRNA in the Substantia nigra *pars compacta* of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

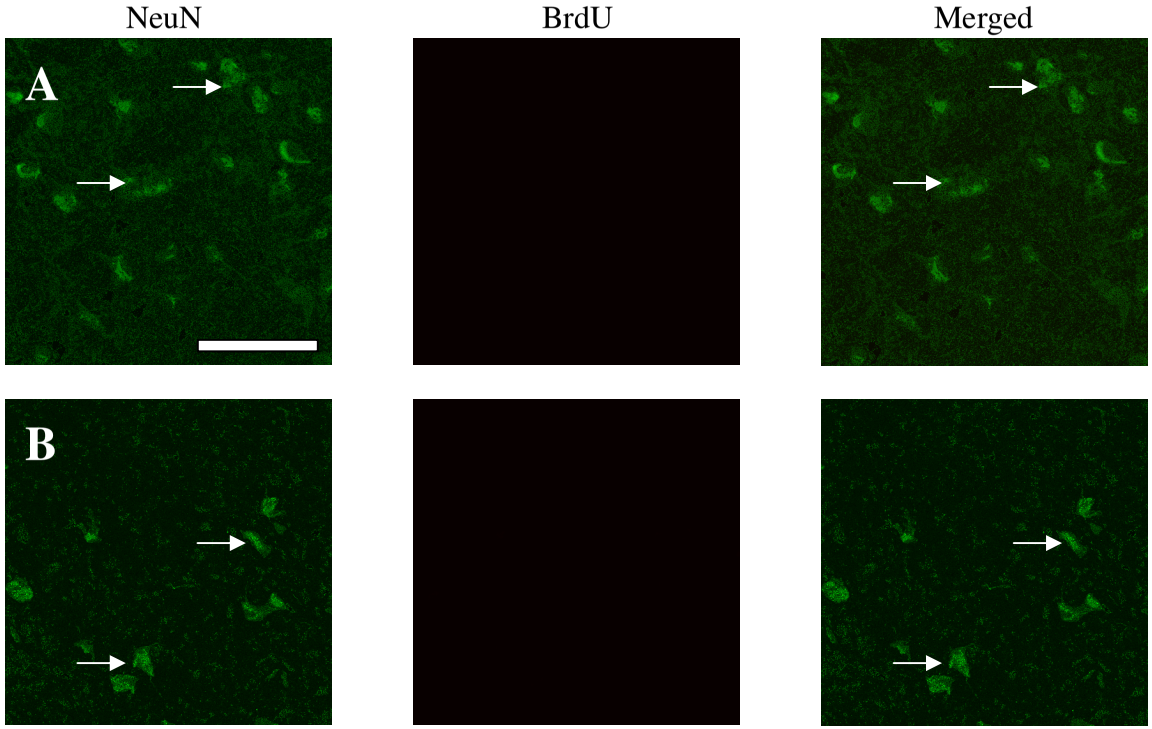
Animal Status	Log RQ
Control	0
6-OHDA	1.06 ± 0.08^{a}
6-OHDA + BMC	1.15 ± 0.10^{a}
6-OHDA + 5-HT + BMC	$1.51 \pm 0.11^{a,f}$
6-OHDA + GABA + BMC	$1.44 \pm 0.13^{a,f}$
6-OHDA + 5-HT + GABA + BMC	$2.07 \pm 0.17^{a,e}$

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$ when compared to Control.
[e] $p<0.01$, [f] $p<0.05$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure – 21a

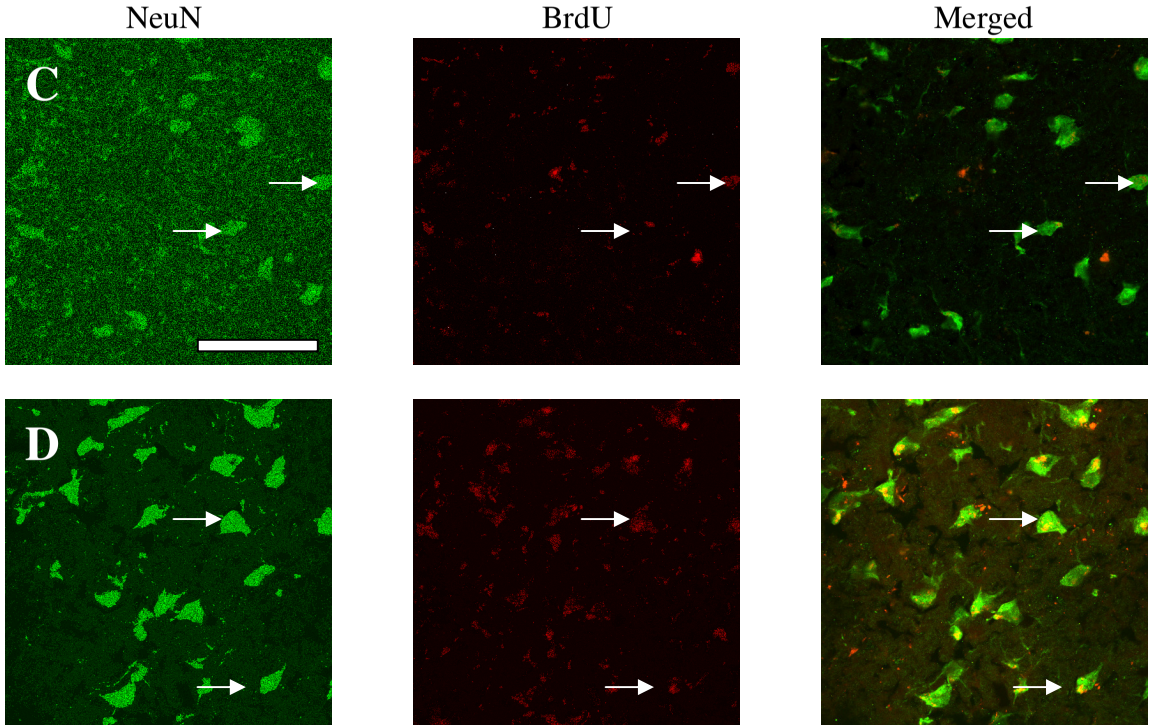
BrdU-NeuN co-labelling studies in the Substantia nigra *pars compacta* of control and experimental rats



A – Control, B – 6-OHDA infused. The scale bars represent 50 µm.

Figure – 21b

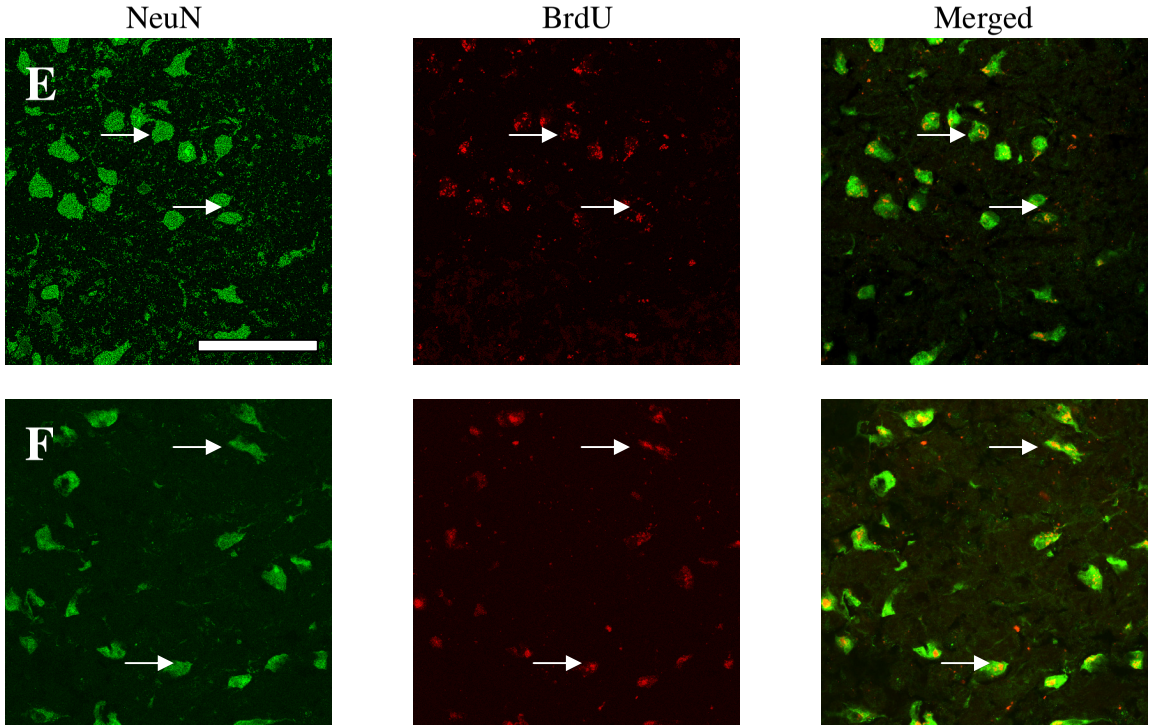
BrdU-NeuN co-labelling studies in the Substantia nigra *pars compacta* of control and experimental rats



C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC. The scale bars represent 50 µm.

Figure – 21c

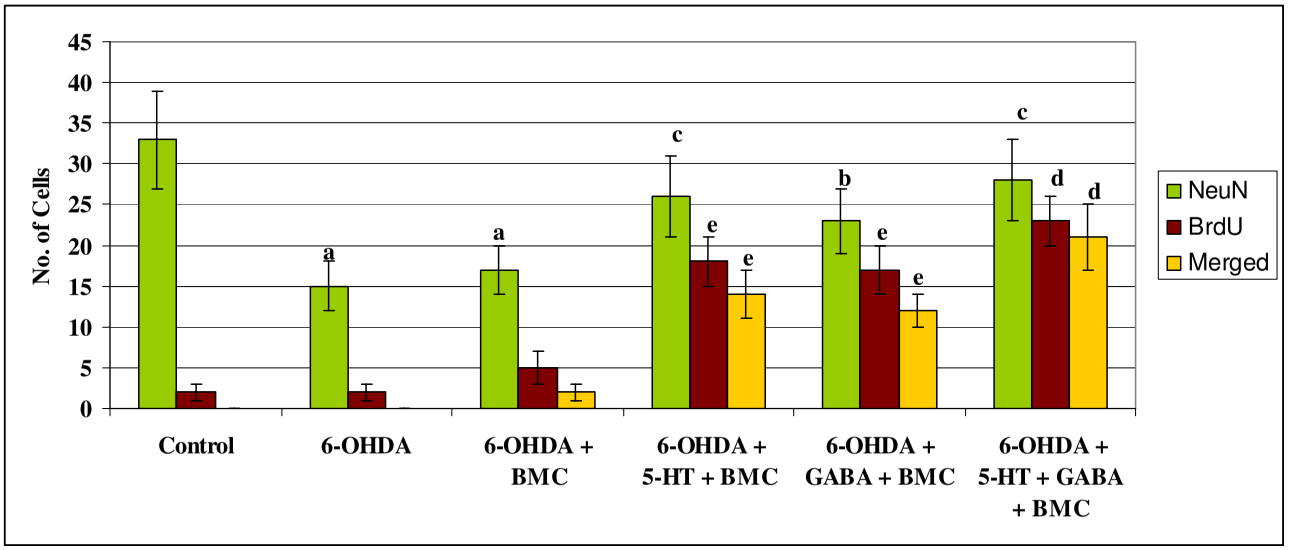
BrdU-NeuN co-labelling studies in the Substantia nigra *pars compacta* of control and experimental rats



E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 50 µm.

Figure – 22

BrdU-NeuN co-labelling studies in the Substantia nigra *pars compacta* of control and experimental rats



Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA + BMC group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Table - 20
Serotonin content in the Corpus Striatum of control and experimental rats

Experimental Groups	5-HT Content (nmoles/g wet wt.)
Control	**2.89 ± 0.24**
6-OHDA	**0.72 ± 0.06[a]**
6-OHDA + BMC	**0.79 ± 0.08[a]**
6-OHDA + 5-HT + BMC	**1.81 ± 0.17[b,e]**
6-OHDA + GABA + BMC	**1.57 ± 0.11[b,e]**
6-OHDA + 5-HT + GABA + BMC	**2.47 ± 0.24[d]**

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 23
Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

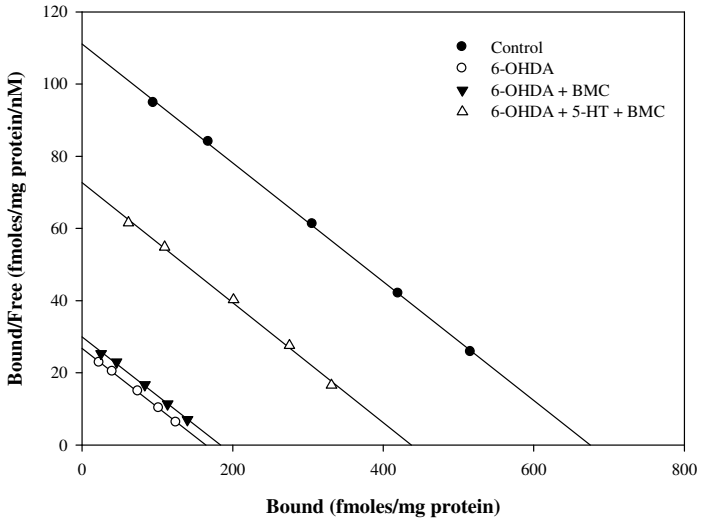


Table - 21
Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	673.68 ± 65.73	6.08 ± 0.58
6-OHDA	162.40 ± 15.21[a]	6.10 ± 0.64
6-OHDA + BMC	183.38 ± 12.95[a]	6.17 ± 0.61
6-OHDA + 5-HT + BMC	435.36 ± 32.31[b,e]	6.04 ± 0.55

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 24
Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

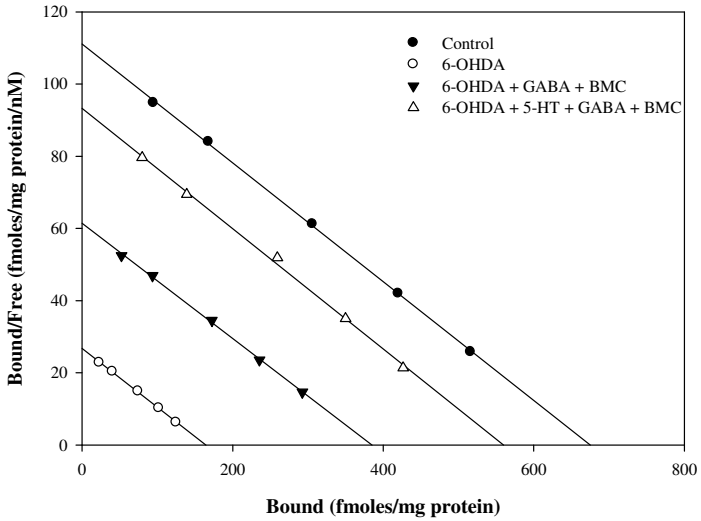


Table - 22
Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	673.68 ± 65.73	6.08 ± 0.54
6-OHDA	162.40 ± 15.21[a]	6.10 ± 0.52
6-OHDA + GABA + BMC	383.99 ± 41.69[b,e]	6.29 ± 0.68
6-OHDA + 5-HT + GABA + BMC	558.75 ± 60.32[d]	6.00 ± 0.57

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 25
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT$_{2A}$ receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

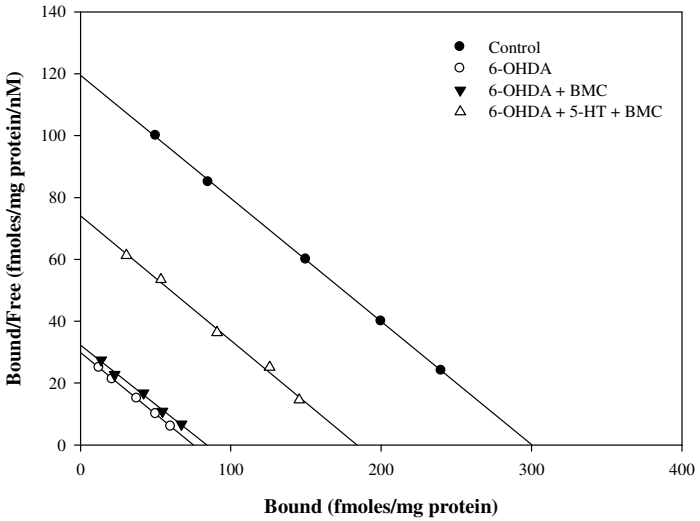


Table - 23
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT$_{2A}$ receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	300.35 ± 32.12	2.52 ± 0.24
6-OHDA	74.78 ± 7.02[a]	2.51 ± 0.27
6-OHDA + BMC	83.56 ± 6.30[a]	2.58 ± 0.23
6-OHDA + 5-HT + BMC	183.13 ± 19.37[b,e]	2.47 ± 0.24

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 26
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT$_{2A}$ receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

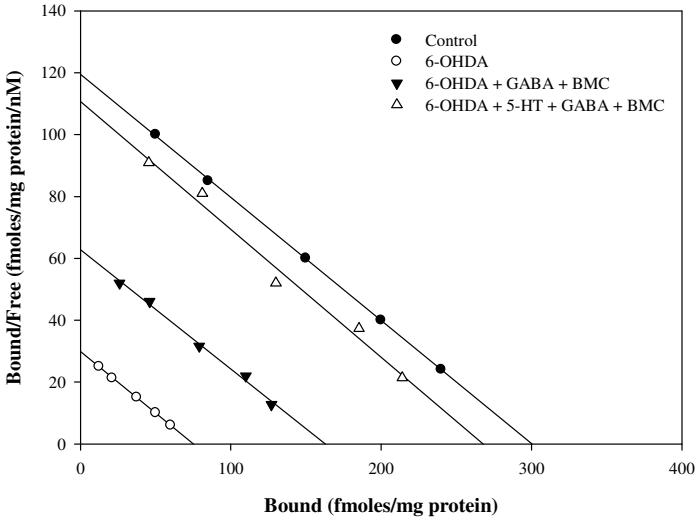


Table - 24
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT$_{2A}$ receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	300.35 ± 32.12	2.52 ± 0.24
6-OHDA	74.78 ± 7.02[a]	2.51 ± 0.27
6-OHDA + GABA + BMC	161.51 ± 12.55[b,e]	2.60 ± 0.25
6-OHDA + 5-HT + GABA + BMC	267.83 ± 22.64[d]	2.47 ± 0.24

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 27
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

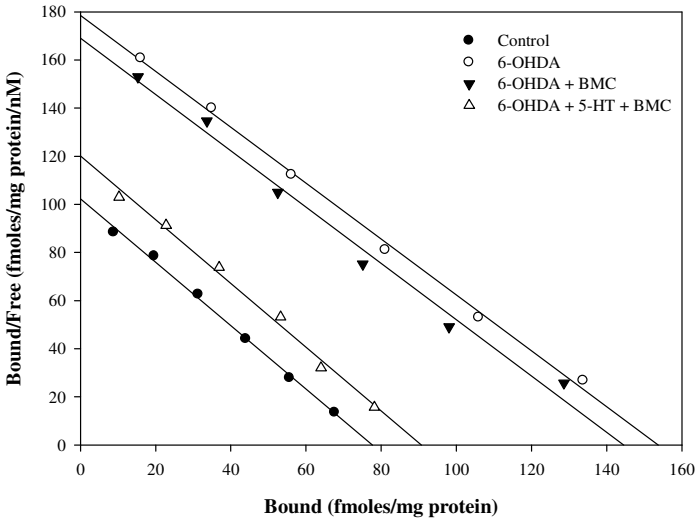


Table - 25
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	78.13 ± 2.23	0.76 ± 0.05
6-OHDA	153.73 ± 17.01[a]	0.84 ± 0.07
6-OHDA + BMC	144.26 ± 14.86[a]	0.83 ± 0.08
6-OHDA + 5-HT + BMC	90.62 ± 4.12[c,e]	0.76 ± 0.07

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 28
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

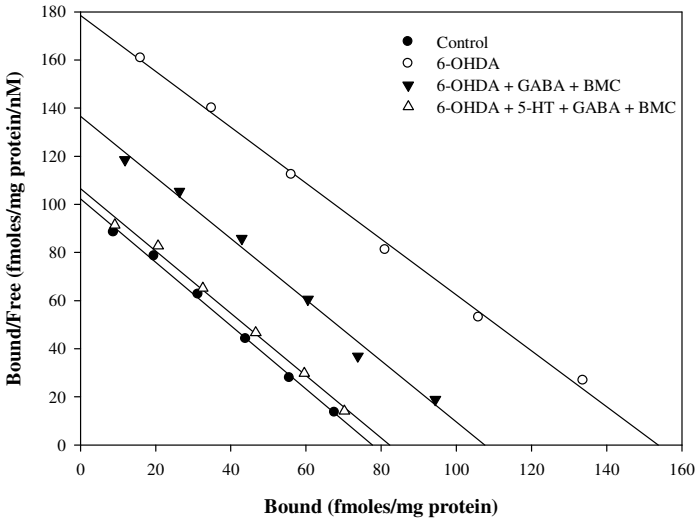


Table - 26
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	78.13 ± 2.23	0.76 ± 0.05
6-OHDA	153.73 ± 17.01[a]	0.84 ± 0.07
6-OHDA + GABA + BMC	107.69 ± 12.35[c,e]	0.79 ± 0.06
6-OHDA + 5-HT + GABA + BMC	81.93 ± 3.45[d]	0.77 ± 0.06

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 29
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

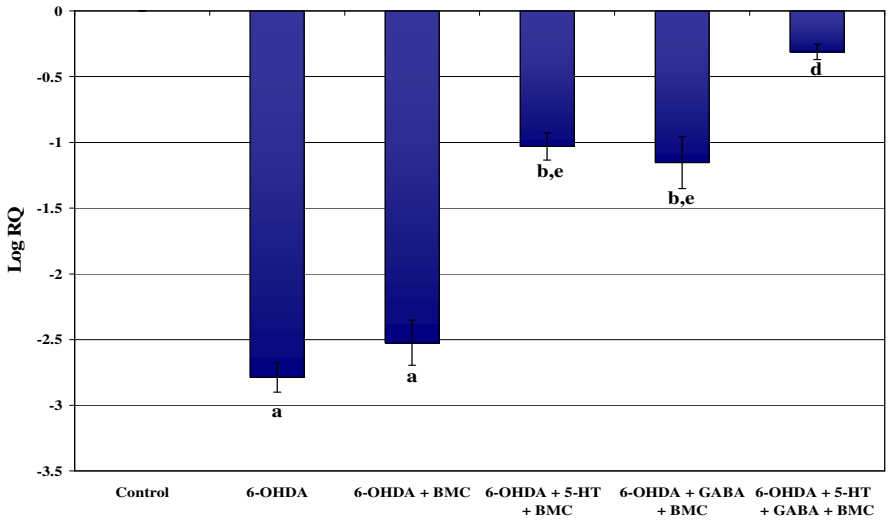


Table - 27
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.78 ± 0.11^{a}
6-OHDA + BMC	-2.52 ± 0.17^{a}
6-OHDA + 5-HT + BMC	$-1.03 \pm 0.10^{b,e}$
6-OHDA + GABA + BMC	$-1.15 \pm 0.20^{b,e}$
6-OHDA + 5-HT + GABA + BMC	-0.31 ± 0.06^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 30
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

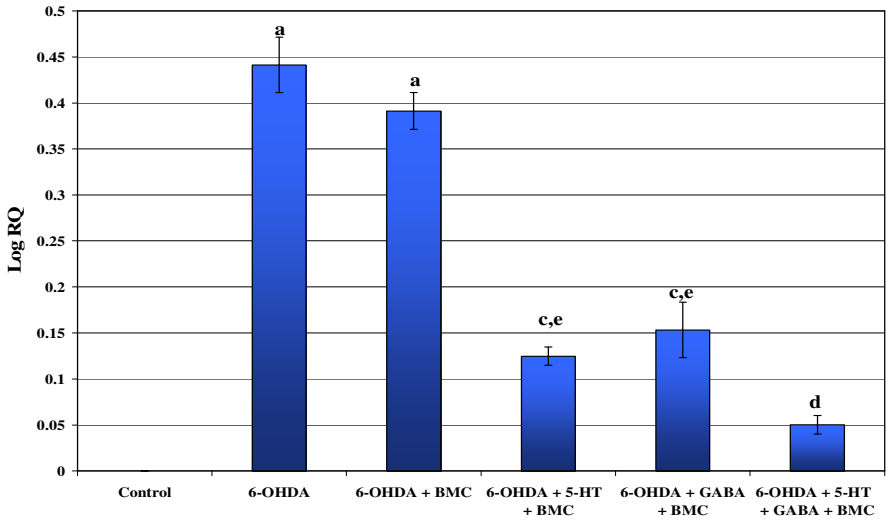


Table - 28
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	0.44 ± 0.03^{a}
6-OHDA + BMC	0.39 ± 0.02^{a}
6-OHDA + 5-HT + BMC	$0.12 \pm 0.01^{c,e}$
6-OHDA + GABA + BMC	$0.15 \pm 0.03^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.05 ± 0.01^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 31
Real Time PCR amplification of 5-HT transporter mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

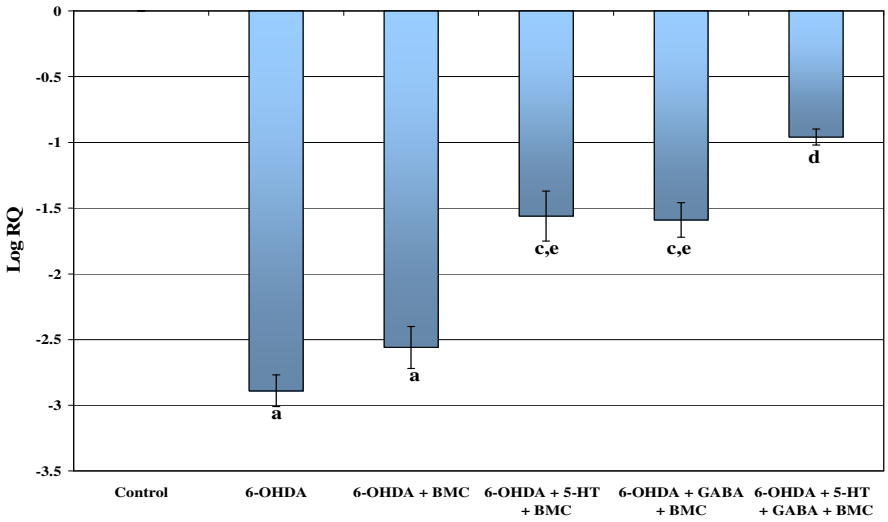


Table - 29
Real Time PCR amplification of 5-HT transporter mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.89 ± 0.12[a]
6-OHDA + BMC	-2.56 ± 0.16[a]
6-OHDA + 5-HT + BMC	-1.56 ± 0.19[c,e]
6-OHDA + GABA + BMC	-1.59 ± 0.13[c,e]
6-OHDA + 5-HT + GABA + BMC	-0.96 ± 0.06[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 32
SOD activity in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

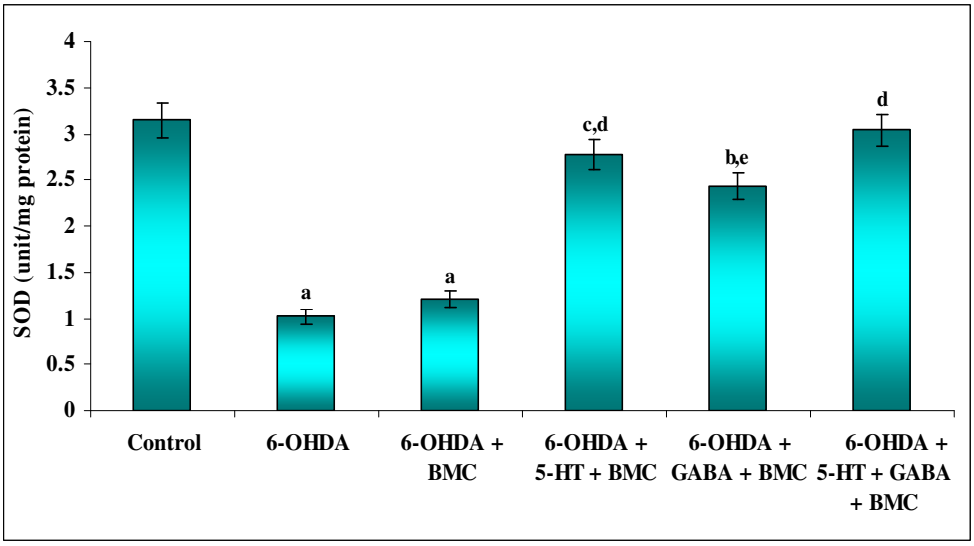


Table - 30
SOD activity in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	SOD activity (unit/mg protein)
Control	3.15 ± 0.19
6-OHDA	1.02 ± 0.08[a]
6-OHDA + BMC	1.21 ± 0.09[a]
6-OHDA + 5-HT + BMC	2.78 ± 0.16[c,d]
6-OHDA + GABA + BMC	2.43 ± 0.14[b,e]
6-OHDA + 5-HT + GABA + BMC	3.04 ± 0.17[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 33
CAT activity in the Corpus Striatum of
Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC,
6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

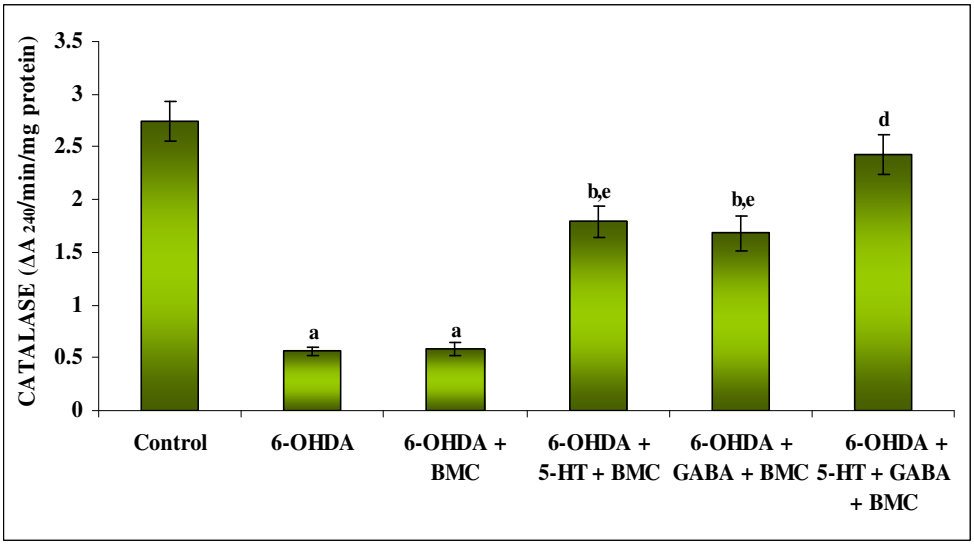


Table - 31
CAT activity in the Corpus Striatum of
Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC,
6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	CAT activity (ΔA_{240}/min/mg protein)
Control	2.74 ± 0.19
6-OHDA	0.56 ± 0.04[a]
6-OHDA + BMC	0.58 ± 0.06[a]
6-OHDA + 5-HT + BMC	1.79 ± 0.15[b,e]
6-OHDA + GABA + BMC	1.68 ± 0.17[b,e]
6-OHDA + 5-HT + GABA + BMC	2.43 ± 0.19[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 34
Lipid peroxidation assay in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

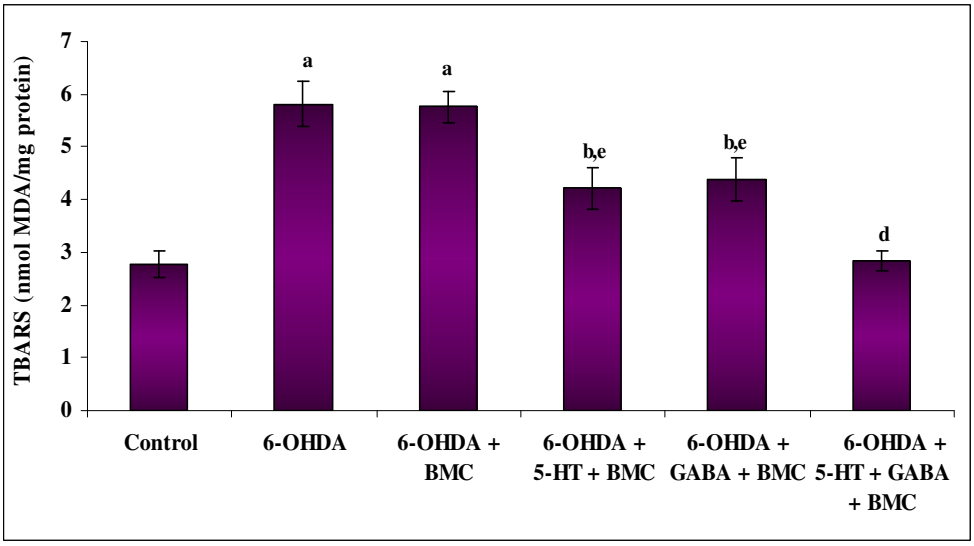


Table - 32
Lipid peroxidation assay in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	TBARS (nmol MDA/mg protein)
Control	2.78 ± 0.25
6-OHDA	5.81 ± 0.43[a]
6-OHDA + BMC	5.76 ± 0.29[a]
6-OHDA + 5-HT + BMC	4.21 ± 0.39[b,e]
6-OHDA + GABA + BMC	4.37 ± 0.41[b,e]
6-OHDA + 5-HT + GABA + BMC	2.85 ± 0.19[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 35
Real Time PCR amplification of SOD mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

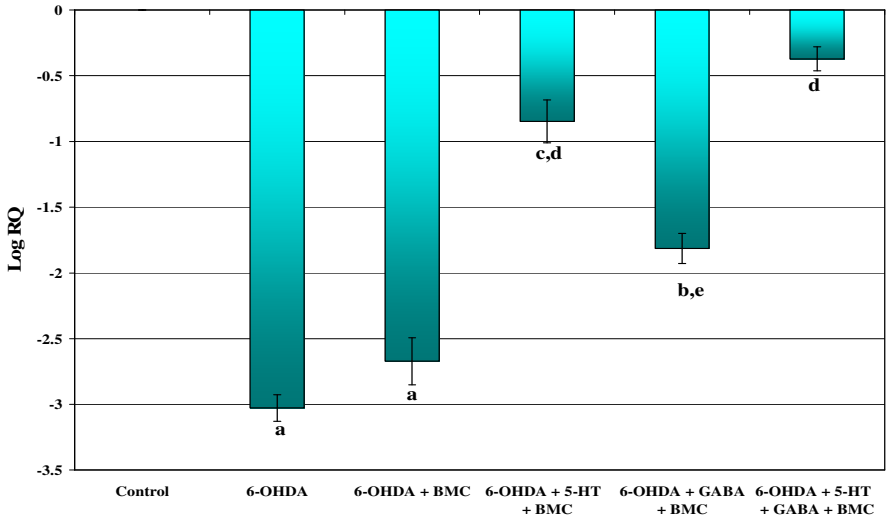


Table - 33
Real Time PCR amplification of SOD mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-3.03 ± 0.10[a]
6-OHDA + BMC	-2.67 ± 0.17[a]
6-OHDA + 5-HT + BMC	-0.84 ± 0.16[c,d]
6-OHDA + GABA + BMC	-1.81 ± 0.11[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.37 ± 0.09[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 36
Real Time PCR amplification of GPx mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

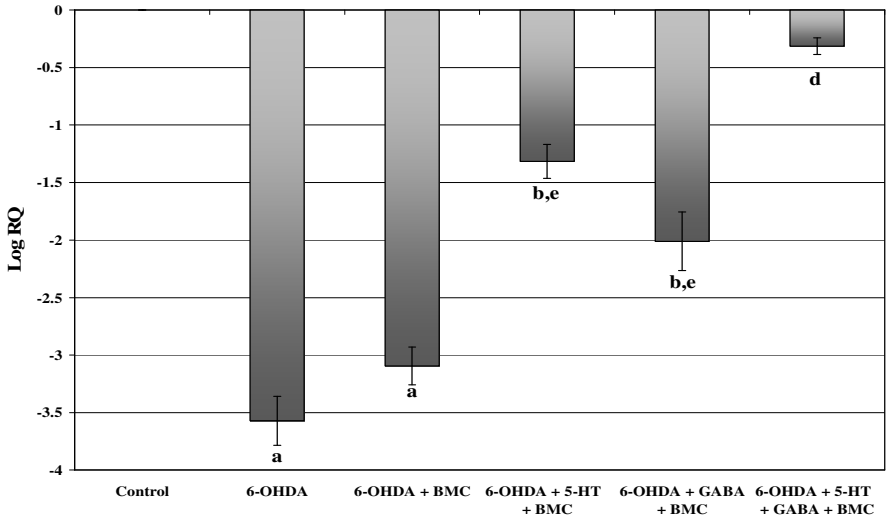


Table - 34
Real Time PCR amplification of GPx mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-3.57 ± 0.21^{a}
6-OHDA + BMC	-3.09 ± 0.16^{a}
6-OHDA + 5-HT + BMC	$-1.32 \pm 0.15^{b,e}$
6-OHDA + GABA + BMC	$-2.01 \pm 0.25^{b,e}$
6-OHDA + 5-HT + GABA + BMC	-0.31 ± 0.07^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 37
Real Time PCR amplification of Akt mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

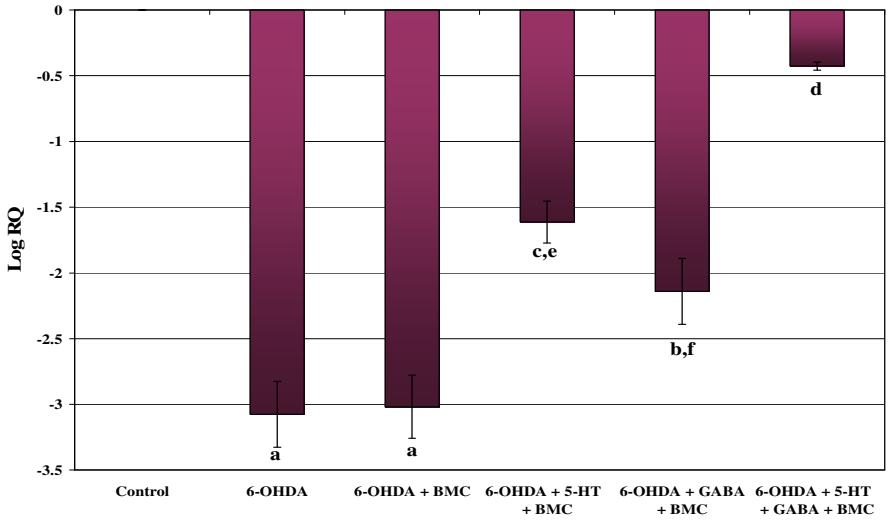


Table - 35
Real Time PCR amplification of Akt mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-3.07 ± 0.25^{a}
6-OHDA + BMC	-3.02 ± 0.24^{a}
6-OHDA + 5-HT + BMC	$-1.61 \pm 0.16^{c,e}$
6-OHDA + GABA + BMC	$-2.14 \pm 0.25^{b,f}$
6-OHDA + 5-HT + GABA + BMC	-0.43 ± 0.03^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$, [f] $p<0.05$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 38
Real Time PCR amplification of NF-κB mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

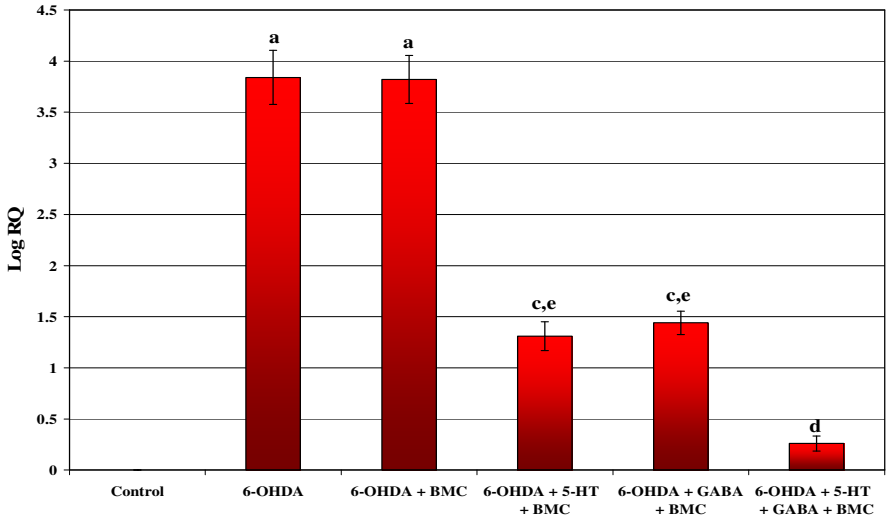


Table - 36
Real Time PCR amplification of NF-κB mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	3.84 ± 0.26^{a}
6-OHDA + BMC	3.82 ± 0.23^{a}
6-OHDA + 5-HT + BMC	$1.31 \pm 0.14^{c,e}$
6-OHDA + GABA + BMC	$1.44 \pm 0.11^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.26 ± 0.07^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 39
Real Time PCR amplification of Caspase-8 mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

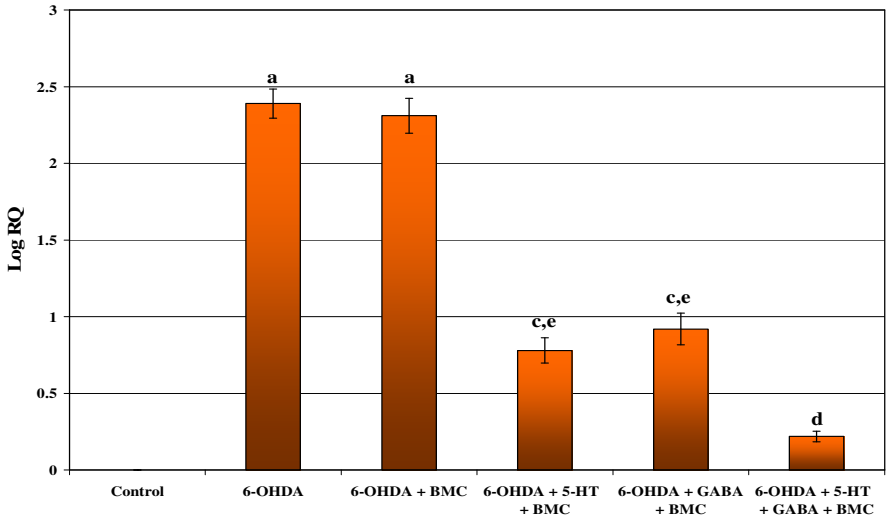


Table - 37
Real Time PCR amplification of Caspase-8 mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	2.39 ± 0.09^{a}
6-OHDA + BMC	2.31 ± 0.11^{a}
6-OHDA + 5-HT + BMC	$0.78 \pm 0.08^{c,e}$
6-OHDA + GABA + BMC	$0.92 \pm 0.10^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.22 ± 0.03^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 40
Real Time PCR amplification of BDNF mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

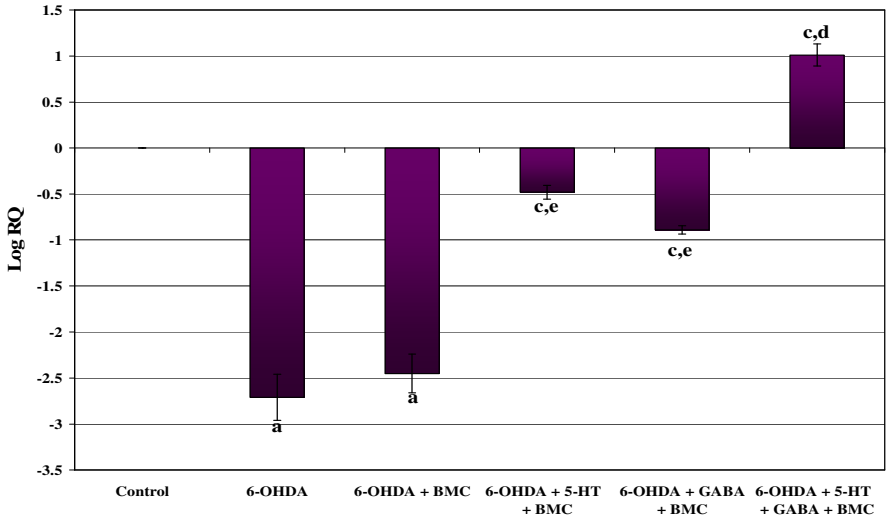


Table - 38
Real Time PCR amplification of BDNF mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.71 ± 0.25[a]
6-OHDA + BMC	-2.45 ± 0.21[a]
6-OHDA + 5-HT + BMC	-0.48 ± 0.07[c,e]
6-OHDA + GABA + BMC	-0.89 ± 0.04[c,e]
6-OHDA + 5-HT + GABA + BMC	1.01 ± 0.11[c,d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 41
Real Time PCR amplification of GDNF mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

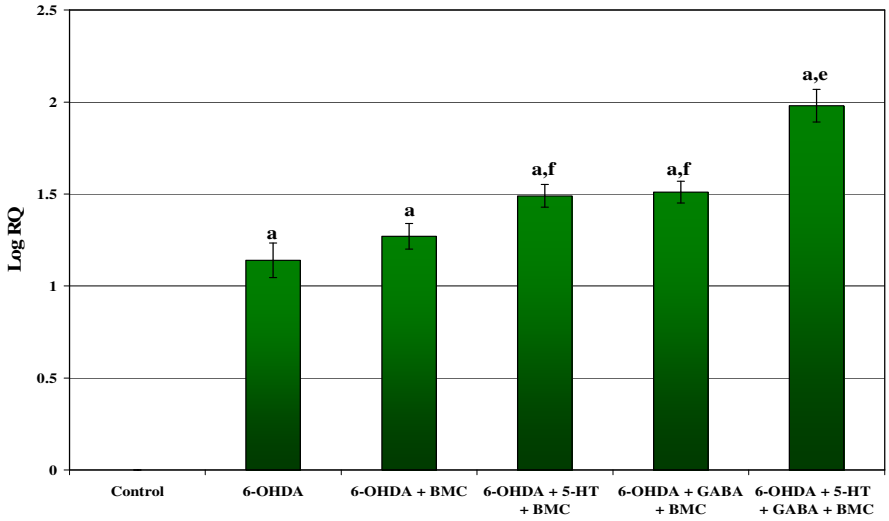


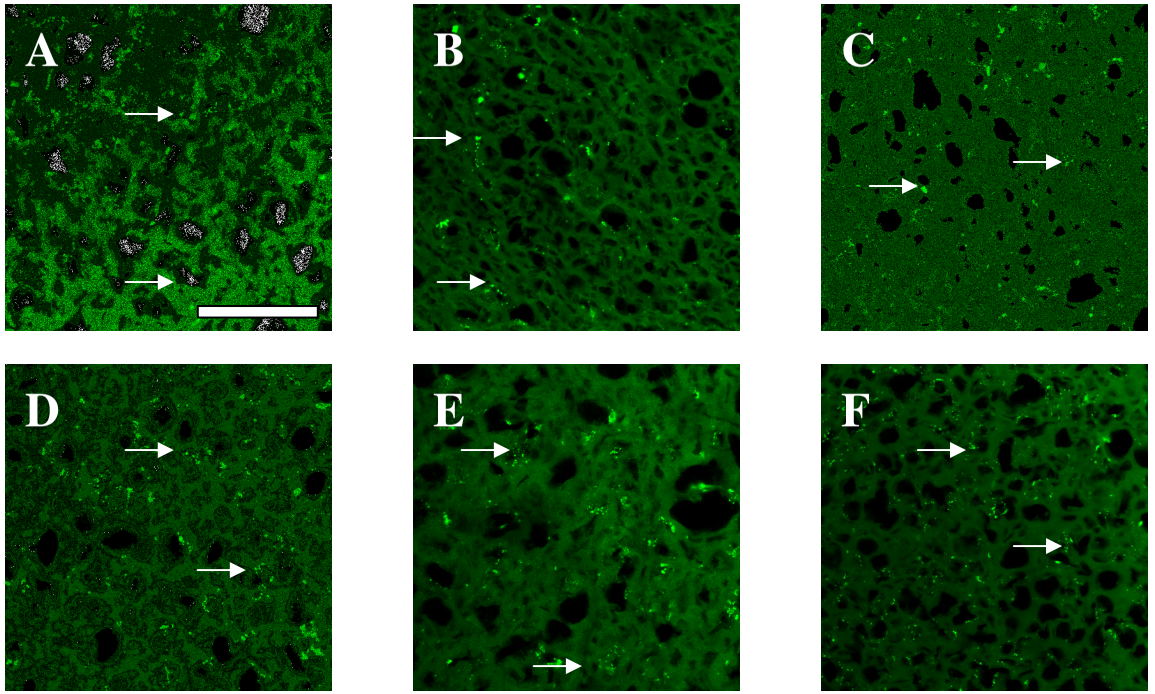
Table - 39
Real Time PCR amplification of GDNF mRNA in the Corpus Striatum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	1.14 ± 0.09^{a}
6-OHDA + BMC	1.27 ± 0.07^{a}
6-OHDA + 5-HT + BMC	$1.49 \pm 0.06^{a,f}$
6-OHDA + GABA + BMC	$1.51 \pm 0.05^{a,f}$
6-OHDA + 5-HT + GABA + BMC	$1.98 \pm 0.09^{a,e}$

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$ when compared to Control.
[e] $p<0.01$, [f] $p<0.05$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 42
5-HT_{2A} receptor expression in the Corpus Striatum of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 40
5-HT_{2A} receptor expression in the Corpus Striatum of control and experimental rats

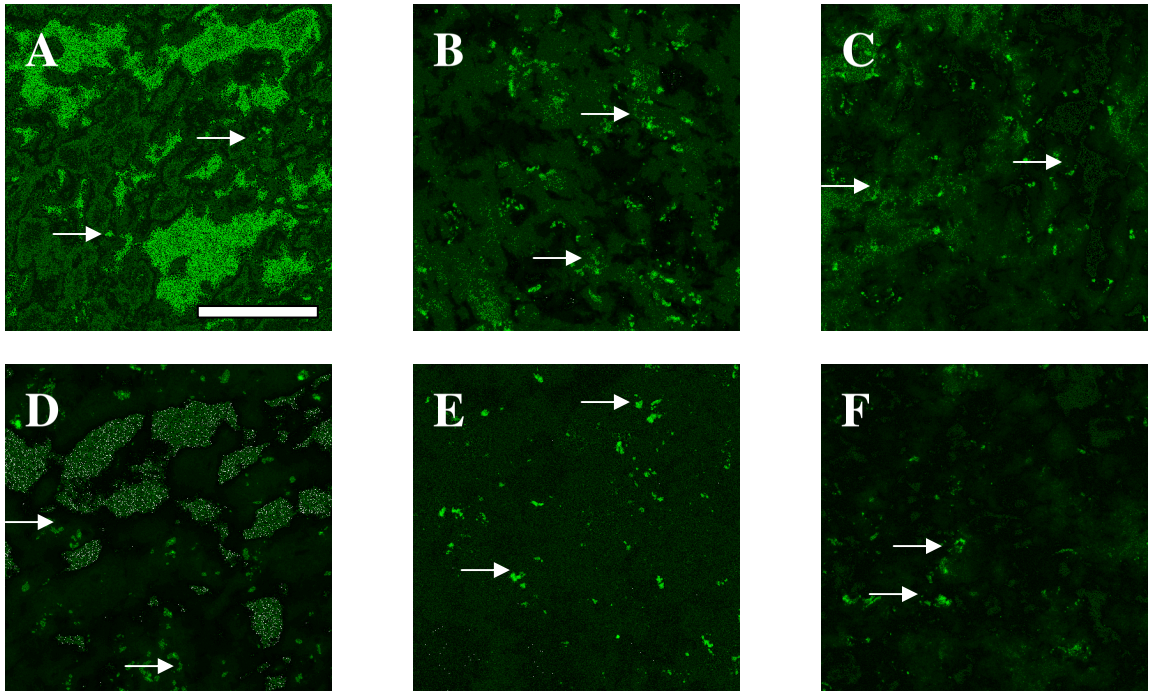
Experimental Groups	Mean Pixel Intensity
Control	63.34 ± 5.83
6-OHDA	23.19 ± 2.23[a]
6-OHDA + BMC	28.76 ± 2.91[a]
6-OHDA + 5-HT + BMC	35.23 ± 3.75[b,f]
6-OHDA + GABA + BMC	32.24 ± 3.98[b,f]
6-OHDA + 5-HT + GABA + BMC	58.45 ± 5.10[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [f] $p<0.05$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 43
5-HT_{2C} receptor expression in the Corpus Striatum of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 41
5-HT_{2C} receptor expression in the Corpus Striatum of control and experimental rats

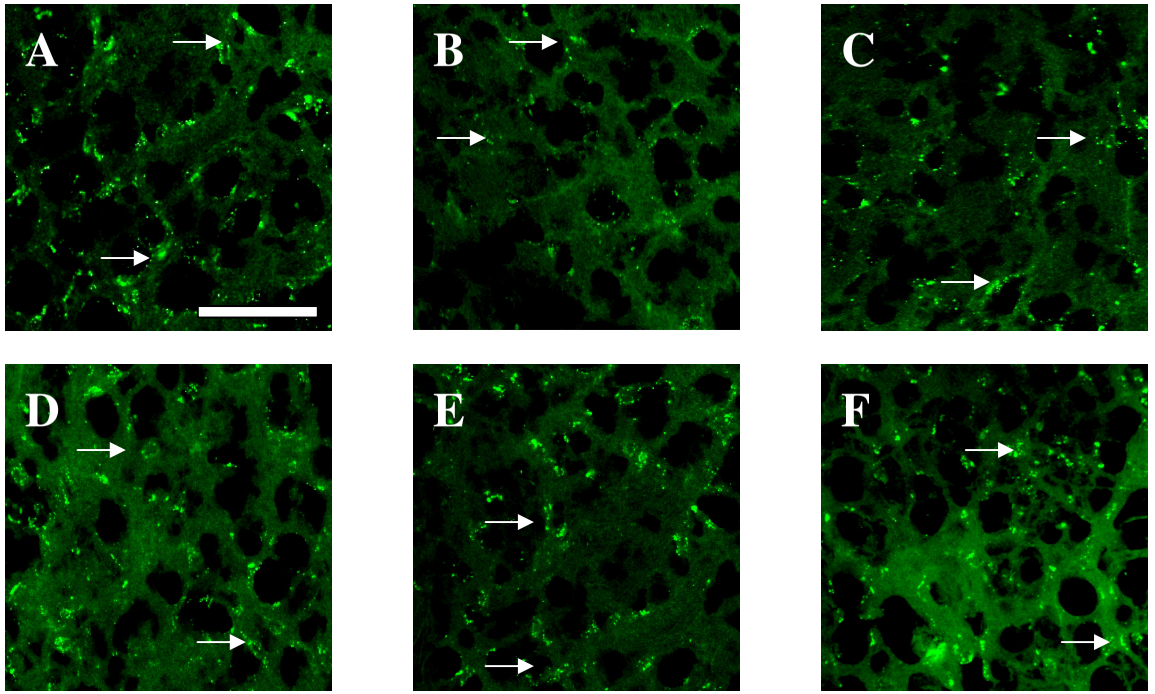
Experimental Groups	Mean Pixel Intensity
Control	13.12 ± 2.36
6-OHDA	42.91 ± 2.67[a]
6-OHDA + BMC	39.23 ± 2.33[a]
6-OHDA + 5-HT + BMC	23.22 ± 2.79[c,e]
6-OHDA + GABA + BMC	28.63 ± 2.18[b,e]
6-OHDA + 5-HT + GABA + BMC	16.10 ± 2.23[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 44
5-HT transporter expression in the Corpus Striatum of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 42
5-HT transporter expression in the Corpus Striatum of control and experimental rats

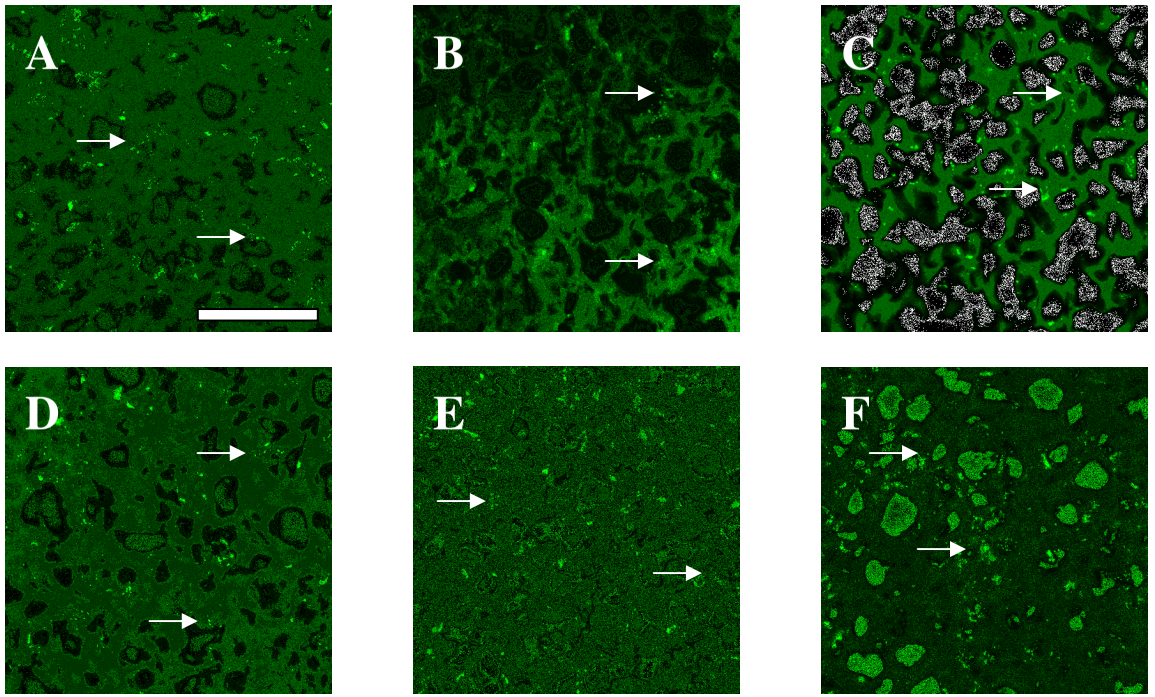
Experimental Groups	Mean Pixel Intensity
Control	50.25 ± 2.22
6-OHDA	32.33 ± 1.45[a]
6-OHDA + BMC	35.15 ± 1.52[a]
6-OHDA + 5-HT + BMC	45.11 ± 1.72[b,f]
6-OHDA + GABA + BMC	44.23 ± 1.89[b,f]
6-OHDA + 5-HT + GABA + BMC	48.32 ± 1.90[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [f] $p<0.05$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 45
BDNF expression in the Corpus Striatum of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 43
BDNF expression in the Corpus Striatum of control and experimental rats

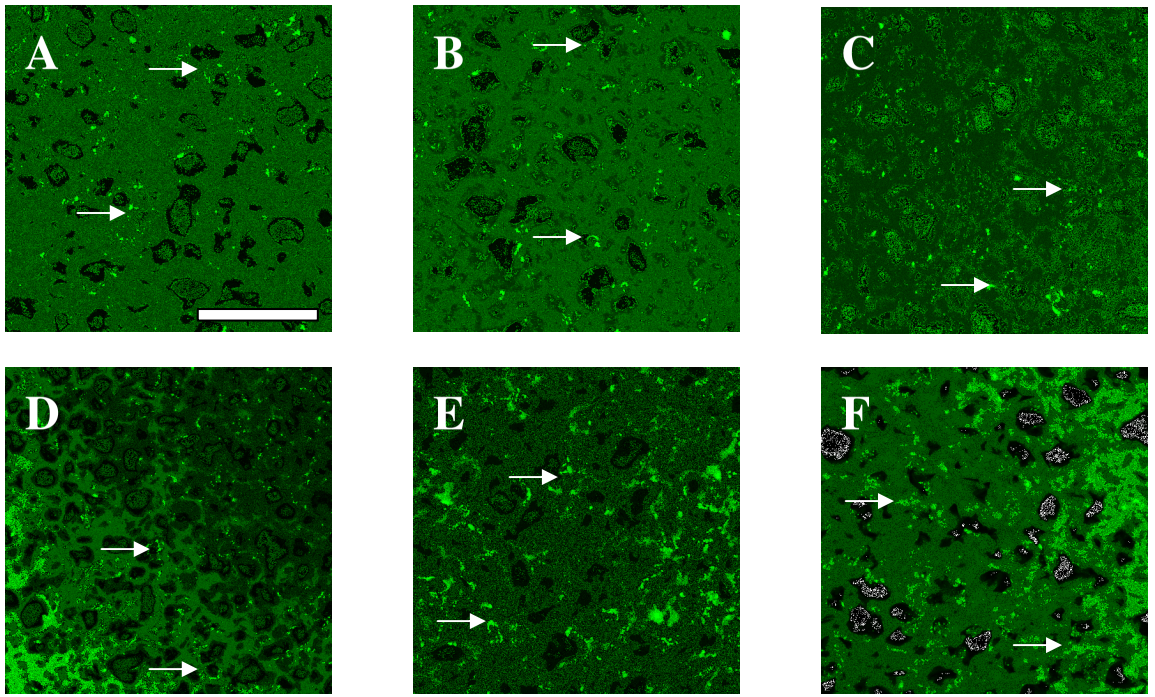
Experimental Groups	Mean Pixel Intensity
Control	53.80 ± 3.01
6-OHDA	19.25 ± 2.67[a]
6-OHDA + BMC	24.31 ± 2.52[a]
6-OHDA + 5-HT + BMC	44.97 ± 1.85[b,f]
6-OHDA + GABA + BMC	42.63 ± 1.74[b,f]
6-OHDA + 5-HT + GABA + BMC	48.41 ± 2.48[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [f] $p<0.05$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 46
GDNF expression in the Corpus Striatum of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 44
GDNF expression in the Corpus Striatum of control and experimental rats

Experimental Groups	Mean Pixel Intensity
Control	24.24 ± 1.48
6-OHDA	30.81 ± 1.39[a]
6-OHDA + BMC	33.28 ± 1.64[a]
6-OHDA + 5-HT + BMC	35.02 ± 1.22[a,f]
6-OHDA + GABA + BMC	34.84 ± 1.04[a,f]
6-OHDA + 5-HT + GABA + BMC	38.19 ± 1.21[a,e]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$ when compared to Control.
[e] $p<0.01$, [f] $p<0.05$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Table - 45
Serotonin content in the Cerebral Cortex of control and experimental rats

Experimental Groups	5-HT Content (nmoles/g wet wt.)
Control	**1.95 ± 0.10**
6-OHDA	**0.92 ± 0.07[a]**
6-OHDA + BMC	**1.01 ± 0.09[a]**
6-OHDA + 5-HT + BMC	**1.50 ± 0.13[b,e]**
6-OHDA + GABA + BMC	**1.36 ± 0.09[b,e]**
6-OHDA + 5-HT + GABA + BMC	**1.81 ± 0.13[d]**

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 47
Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

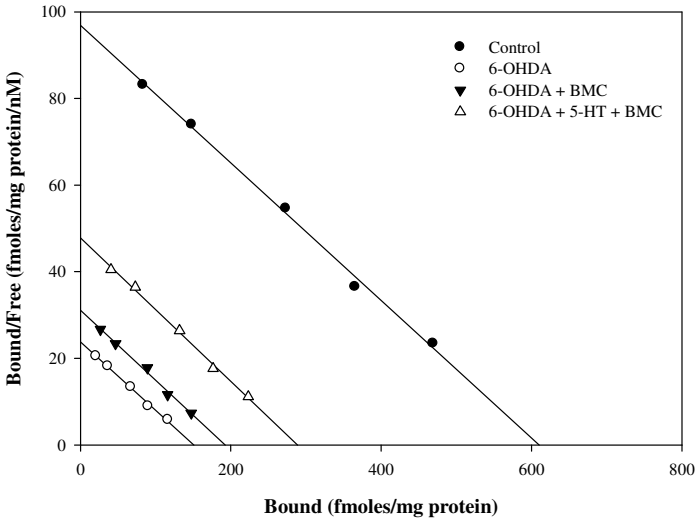


Table - 46
Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	608.82 ± 54.81	6.31 ± 0.45
6-OHDA	149.56 ± 16.32[a]	6.28 ± 0.53
6-OHDA + BMC	191.50 ± 18.37[a]	6.16 ± 0.67
6-OHDA + 5-HT + BMC	289.05 ± 27.18[b,e]	6.07 ± 0.59

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 48
Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

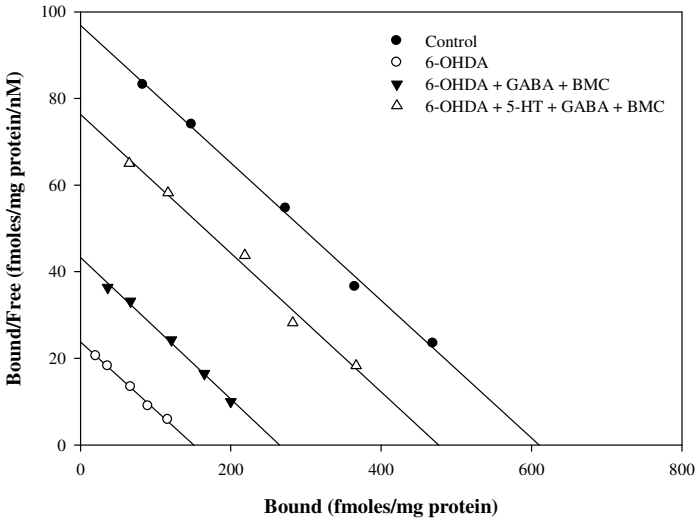


Table - 47
Scatchard analysis of [^{3}H]5-HT binding against 5-HT to total 5-HT receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	608.82 ± 54.81	6.31 ± 0.45
6-OHDA	149.56 ± 16.32[a]	6.28 ± 0.53
6-OHDA + GABA + BMC	263.36 ± 28.32[b,e]	6.08 ± 0.61
6-OHDA + 5-HT + GABA + BMC	477.46 ± 44.12[c,d]	6.30 ± 0.55

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 49
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT$_{2A}$ receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

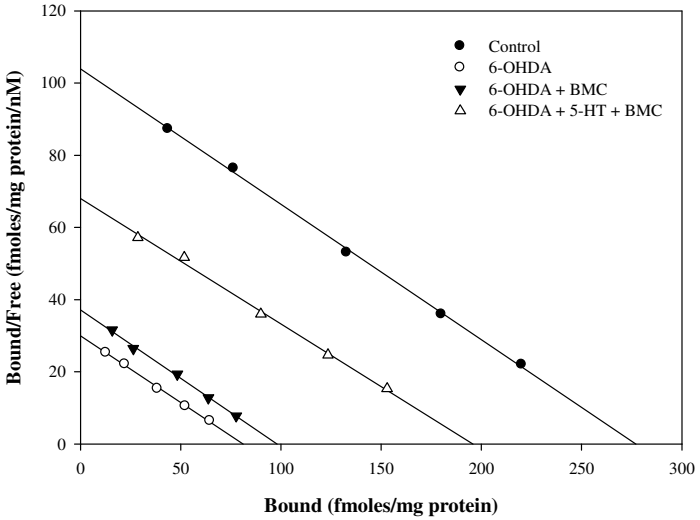


Table - 48
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT$_{2A}$ receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	277.34 ± 26.20	2.68 ± 0.26
6-OHDA	80.23 ± 8.96[a]	2.70 ± 0.25
6-OHDA + BMC	98.52 ± 10.03[a]	2.69 ± 0.25
6-OHDA + 5-HT + BMC	196.06 ± 18.30[b,e]	2.88 ± 0.26

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 50
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT$_{2A}$ receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

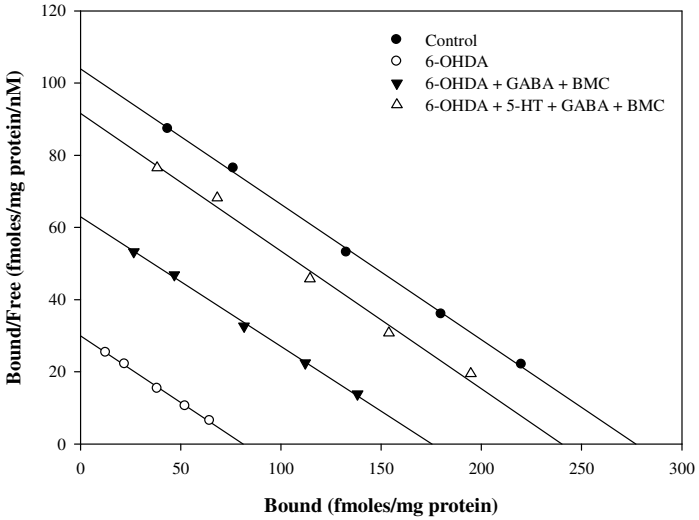


Table - 49
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin to 5-HT$_{2A}$ receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	277.34 ± 26.20	2.68 ± 0.26
6-OHDA	80.23 ± 8.96[a]	2.70 ± 0.25
6-OHDA + GABA + BMC	175.73 ± 15.37[b,e]	2.75 ± 0.27
6-OHDA + 5-HT + GABA + BMC	240.03 ± 23.65[d]	2.64 ± 0.27

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 51
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

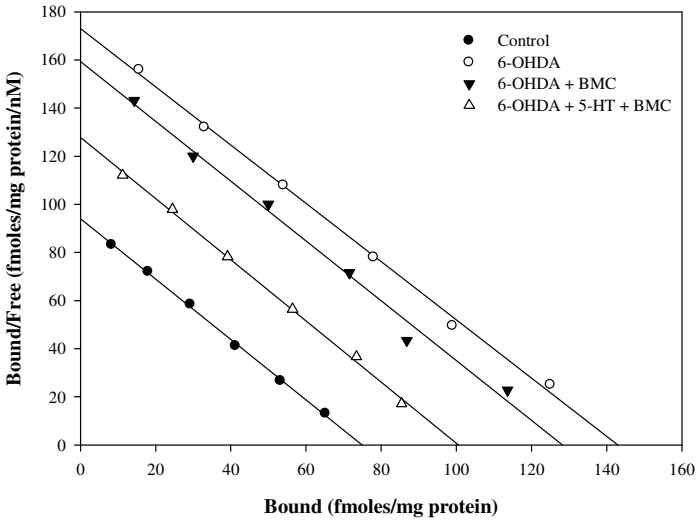


Table - 50
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	74.88 ± 8.12	0.80 ± 0.07
6-OHDA	142.90 ± 17.63[a]	0.83 ± 0.08
6-OHDA + BMC	128.26 ± 14.17[a]	0.81 ± 0.08
6-OHDA + 5-HT + BMC	100.37 ± 11.01[b,e]	0.78 ± 0.07

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 52
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

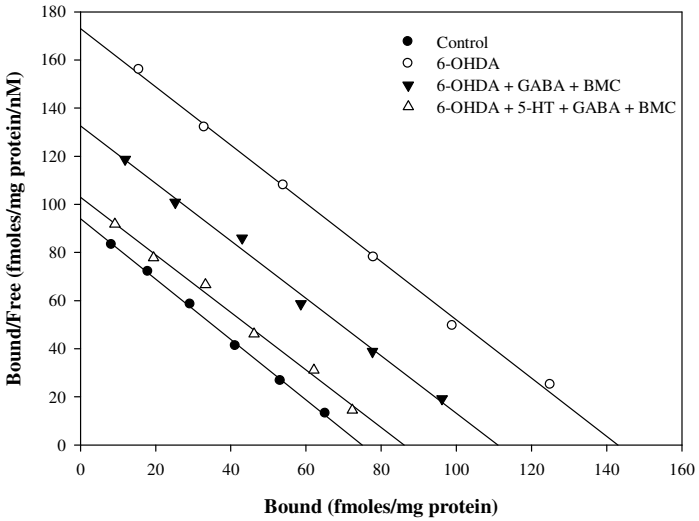


Table - 51
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine to 5-HT$_{2C}$ receptors in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	74.88 ± 8.12	0.80 ± 0.07
6-OHDA	142.90 ± 17.63[a]	0.83 ± 0.08
6-OHDA + GABA + BMC	110.94 ± 12.32[b,e]	0.83 ± 0.06
6-OHDA + 5-HT + GABA + BMC	86.01 ± 7.85[d]	0.84 ± 0.07

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 53
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

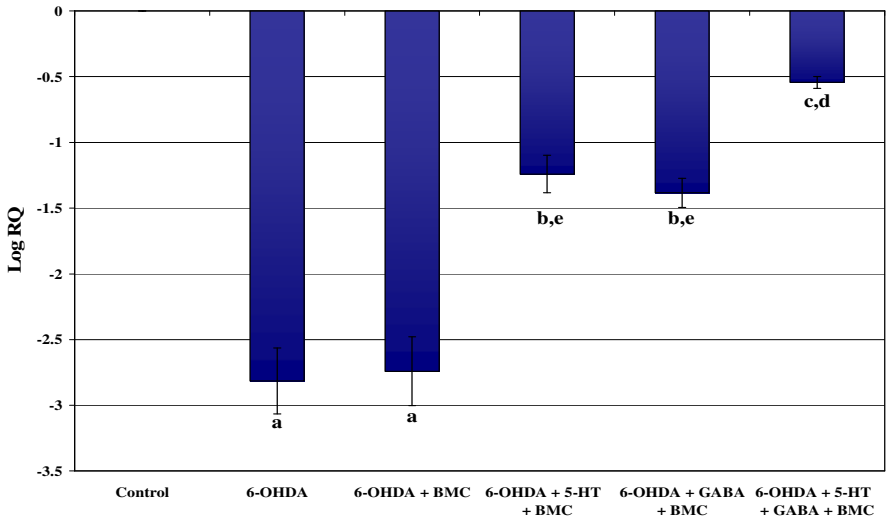


Table - 52
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.81 ± 0.25[a]
6-OHDA + BMC	-2.74 ± 0.26[a]
6-OHDA + 5-HT + BMC	-1.24 ± 0.14[b,e]
6-OHDA + GABA + BMC	-1.38 ± 0.11[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.54 ± 0.04[c,d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 54
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

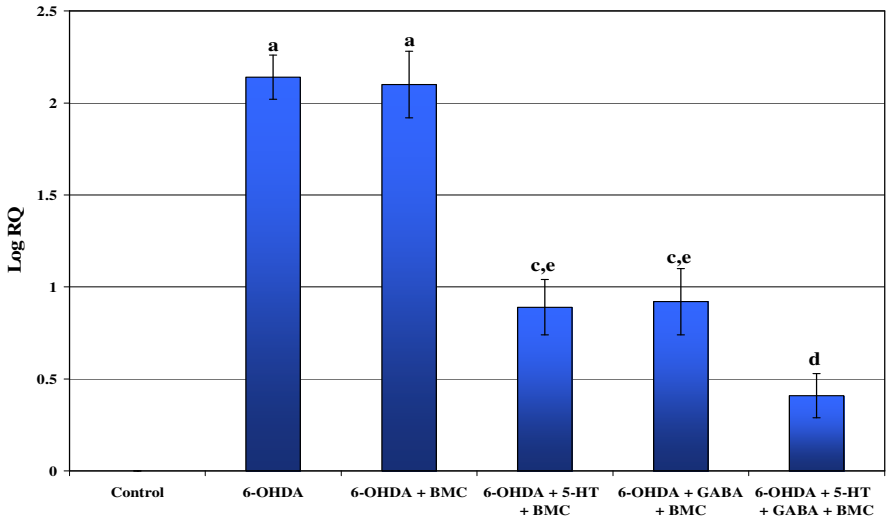


Table - 53
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	2.14 ± 0.12^{a}
6-OHDA + BMC	2.10 ± 0.18^{a}
6-OHDA + 5-HT + BMC	$0.89 \pm 0.15^{c,e}$
6-OHDA + GABA + BMC	$0.92 \pm 0.18^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.41 ± 0.12^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 55
Real Time PCR amplification of 5-HT transporter mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

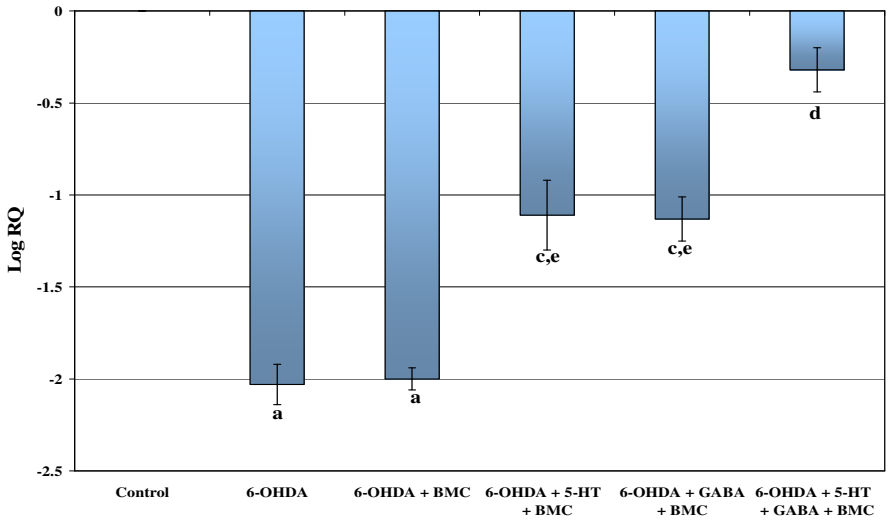


Table - 54
Real Time PCR amplification of 5-HT transporter mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.03 ± 0.11^{a}
6-OHDA + BMC	-2.00 ± 0.06^{a}
6-OHDA + 5-HT + BMC	$-1.11 \pm 0.19^{c,e}$
6-OHDA + GABA + BMC	$-1.13 \pm 0.12^{c,e}$
6-OHDA + 5-HT + GABA + BMC	-0.32 ± 0.12^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 56
Real Time PCR amplification of SOD mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

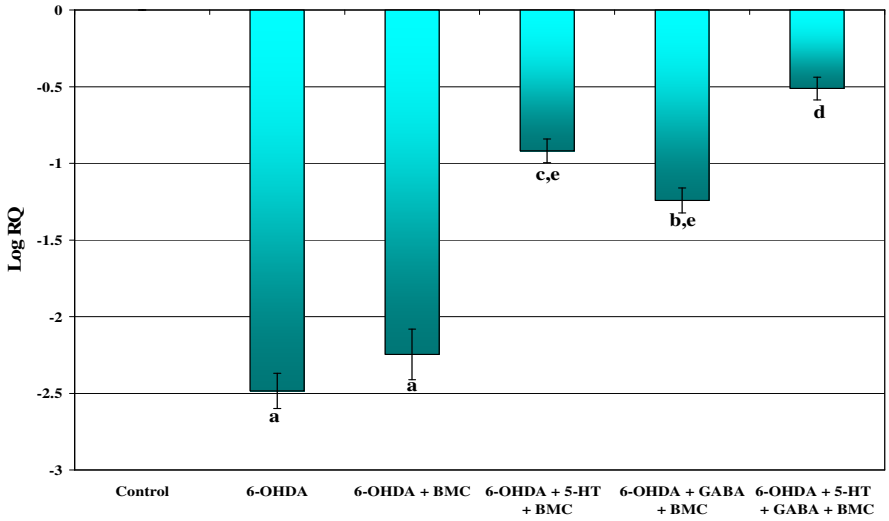


Table - 55
Real Time PCR amplification of SOD mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.48 ± 0.11[a]
6-OHDA + BMC	-2.25 ± 0.16[a]
6-OHDA + 5-HT + BMC	-0.92 ± 0.08[c,e]
6-OHDA + GABA + BMC	-1.24 ± 0.08[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.51 ± 0.07[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 57
Real Time PCR amplification of GPx mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

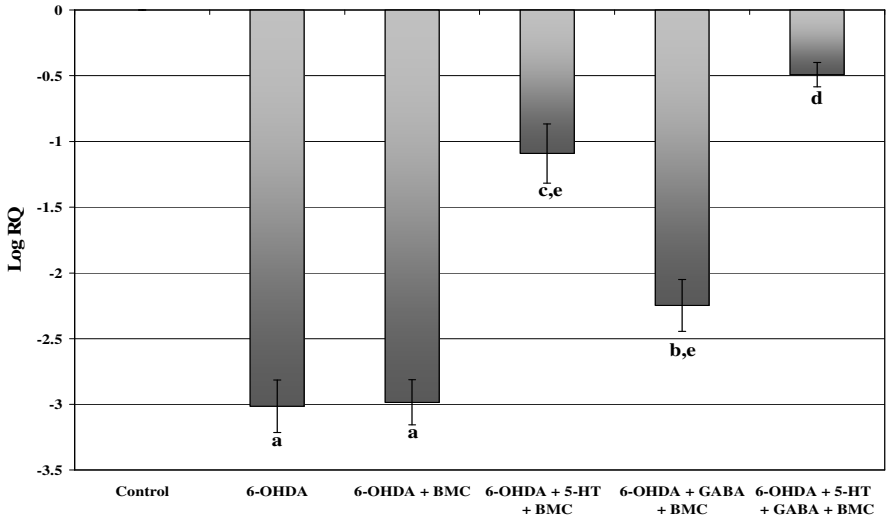


Table - 56
Real Time PCR amplification of GPx mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-3.01 ± 0.20[a]
6-OHDA + BMC	-2.98 ± 0.17[a]
6-OHDA + 5-HT + BMC	-1.09 ± 0.22[c,e]
6-OHDA + GABA + BMC	-2.25 ± 0.20[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.49 ± 0.09[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 58
Real Time PCR amplification of Akt mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

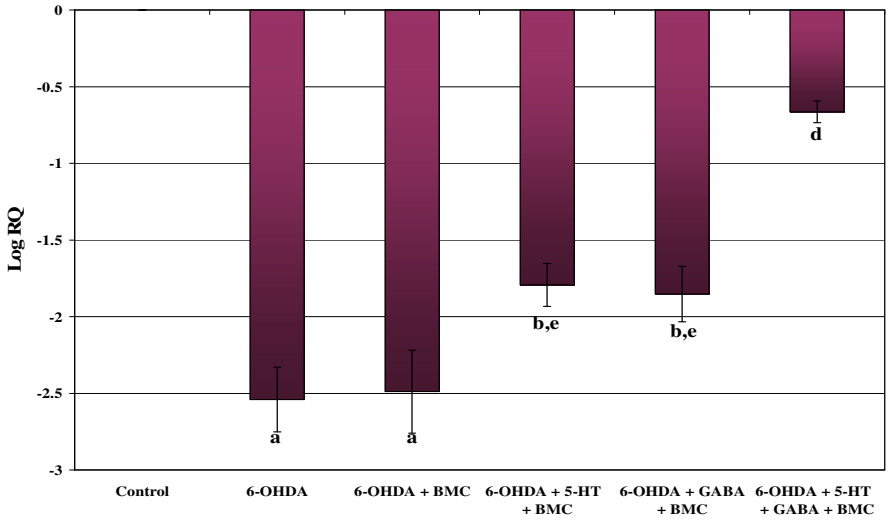


Table - 57
Real Time PCR amplification of Akt mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.54 ± 0.21^{a}
6-OHDA + BMC	-2.49 ± 0.27^{a}
6-OHDA + 5-HT + BMC	$-1.79 \pm 0.14^{b,e}$
6-OHDA + GABA + BMC	$-1.85 \pm 0.18^{b,e}$
6-OHDA + 5-HT + GABA + BMC	-0.66 ± 0.07^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 59
Real Time PCR amplification of NF-κB mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

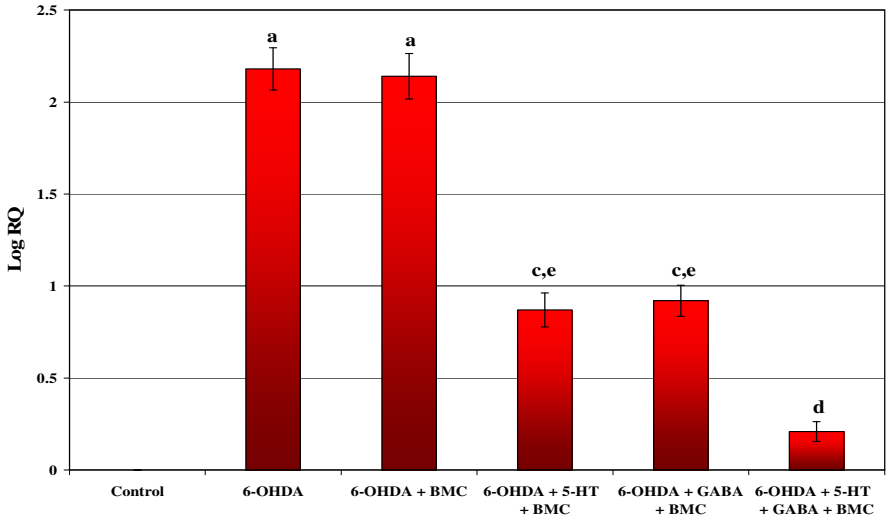


Table - 58
Real Time PCR amplification of NF-κB mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	2.18 ± 0.11^{a}
6-OHDA + BMC	2.14 ± 0.12^{a}
6-OHDA + 5-HT + BMC	$0.87 \pm 0.09^{c,e}$
6-OHDA + GABA + BMC	$0.92 \pm 0.08^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.21 ± 0.05^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 60
Real Time PCR amplification of Caspase-8 mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

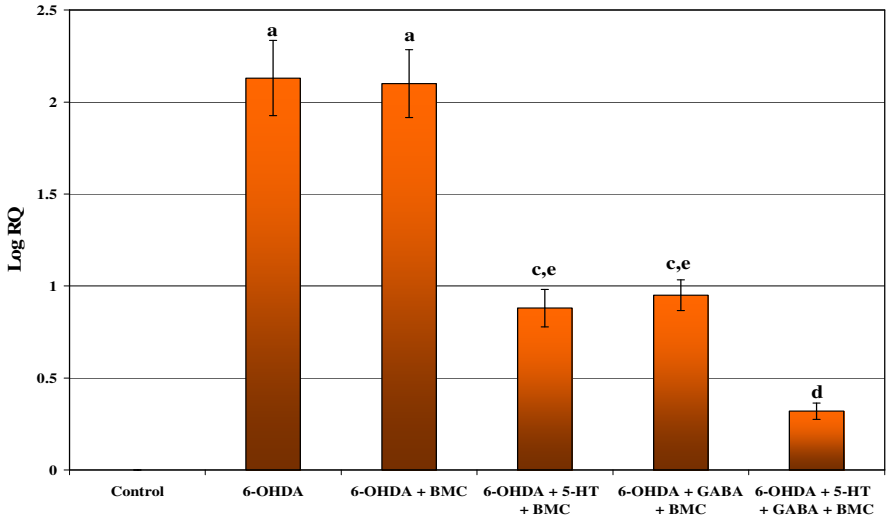


Table - 59
Real Time PCR amplification of Caspase-8 mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	2.13 ± 0.20^{a}
6-OHDA + BMC	2.10 ± 0.18^{a}
6-OHDA + 5-HT + BMC	$0.88 \pm 0.10^{c,e}$
6-OHDA + GABA + BMC	$0.95 \pm 0.08^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.32 ± 0.04^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 61
Real Time PCR amplification of BDNF mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

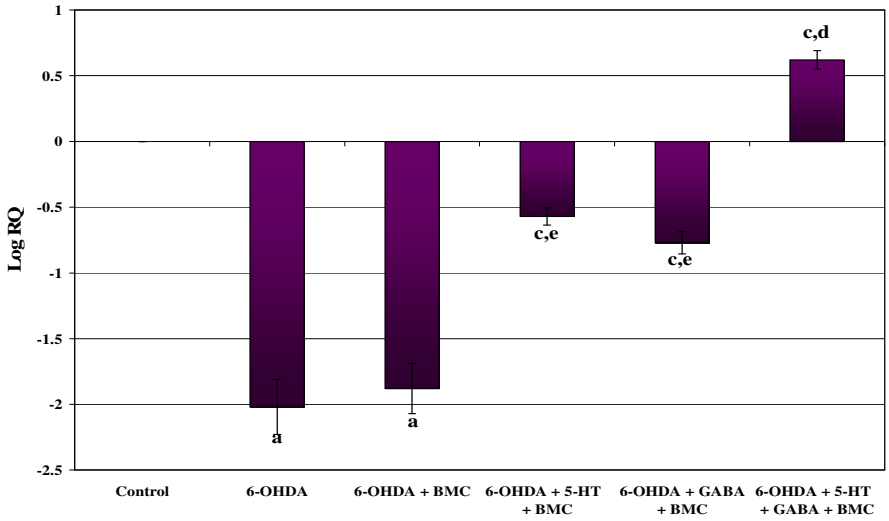


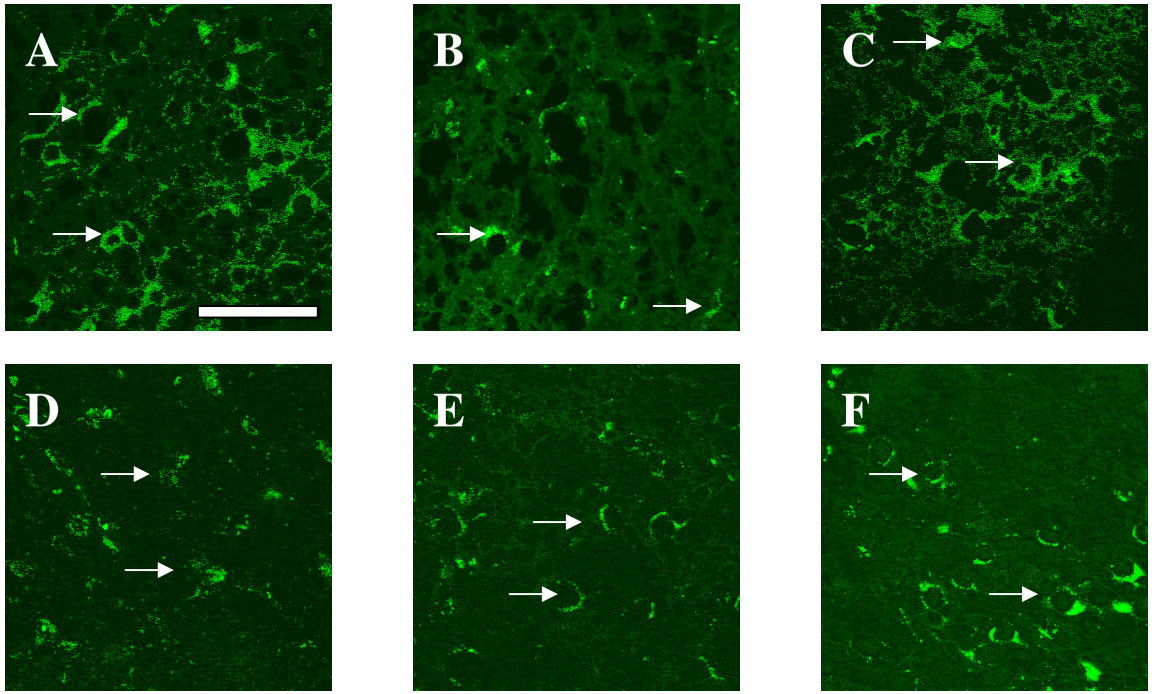
Table - 60
Real Time PCR amplification of BDNF mRNA in the Cerebral Cortex of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.02 ± 0.20[a]
6-OHDA + BMC	-1.88 ± 0.19[a]
6-OHDA + 5-HT + BMC	-0.57 ± 0.06[c,e]
6-OHDA + GABA + BMC	-0.77 ± 0.08[c,e]
6-OHDA + 5-HT + GABA + BMC	0.62 ± 0.07[c,d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 62
5-HT_{2A} receptor expression in the Cerebral Cortex of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 61
5-HT_{2A} receptor expression in the Cerebral Cortex of control and experimental rats

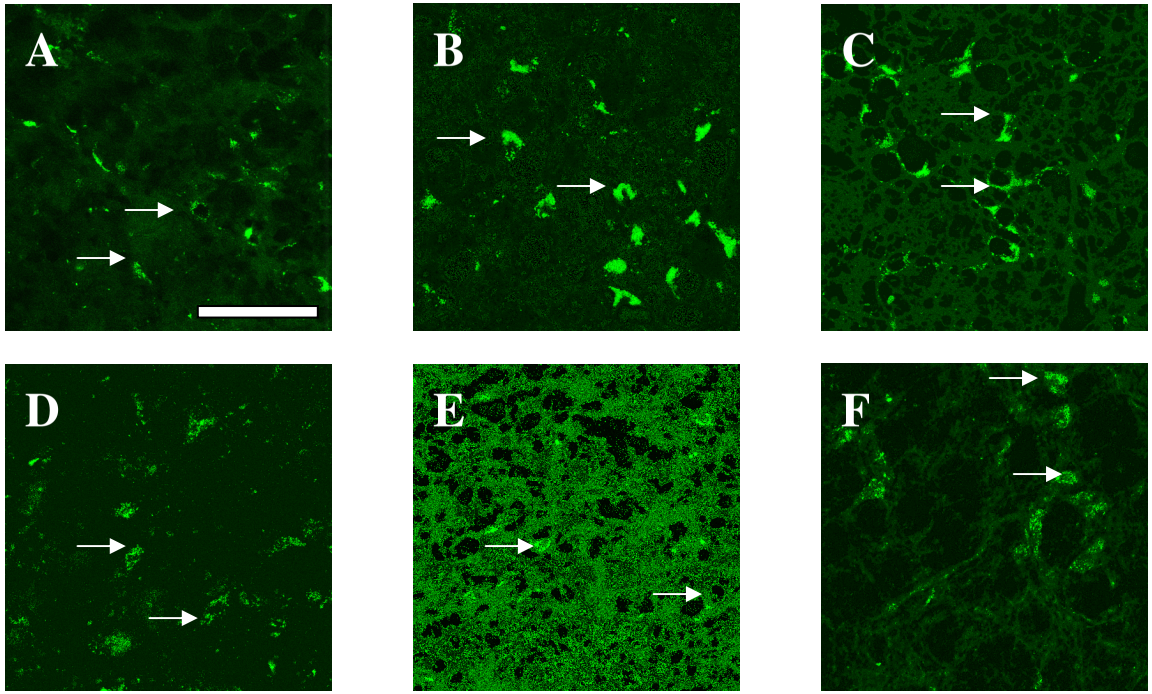
Experimental Groups	Mean Pixel Intensity
Control	46.12 ± 1.73
6-OHDA	23.25 ± 1.50[a]
6-OHDA + BMC	28.69 ± 1.42[a,f]
6-OHDA + 5-HT + BMC	37.12 ± 2.50[b,e]
6-OHDA + GABA + BMC	33.23 ± 2.05[b,e]
6-OHDA + 5-HT + GABA + BMC	45.33 ± 1.55[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$, [f] $p<0.05$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 63
5-HT_{2C} receptor expression in the Cerebral Cortex of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 62
5-HT_{2C} receptor expression in the Cerebral Cortex of control and experimental rats

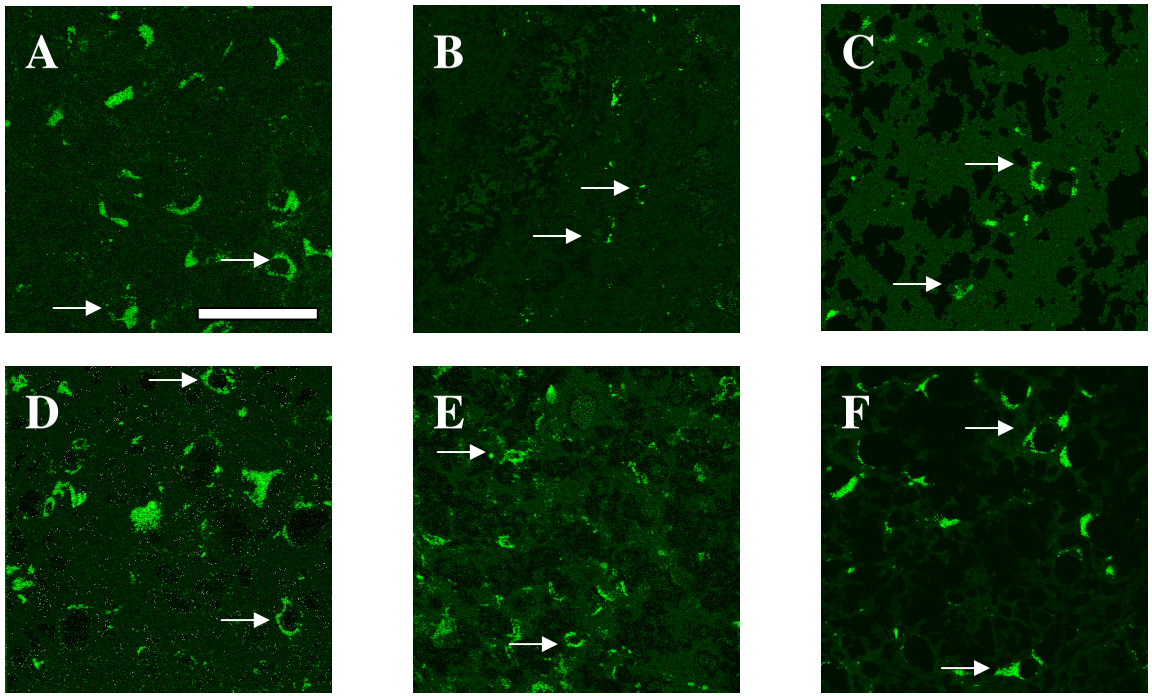
Experimental Groups	Mean Pixel Intensity
Control	28.55 ± 2.93
6-OHDA	62.11 ± 6.42[a]
6-OHDA + BMC	55.43 ± 8.96[a]
6-OHDA + 5-HT + BMC	39.71 ± 4.99[c,e]
6-OHDA + GABA + BMC	39.93 ± 5.62[c,e]
6-OHDA + 5-HT + GABA + BMC	30.19 ± 3.61[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 64
5-HT transporter expression in the Cerebral Cortex of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 63
5-HT transporter expression in the Cerebral Cortex of control and experimental rats

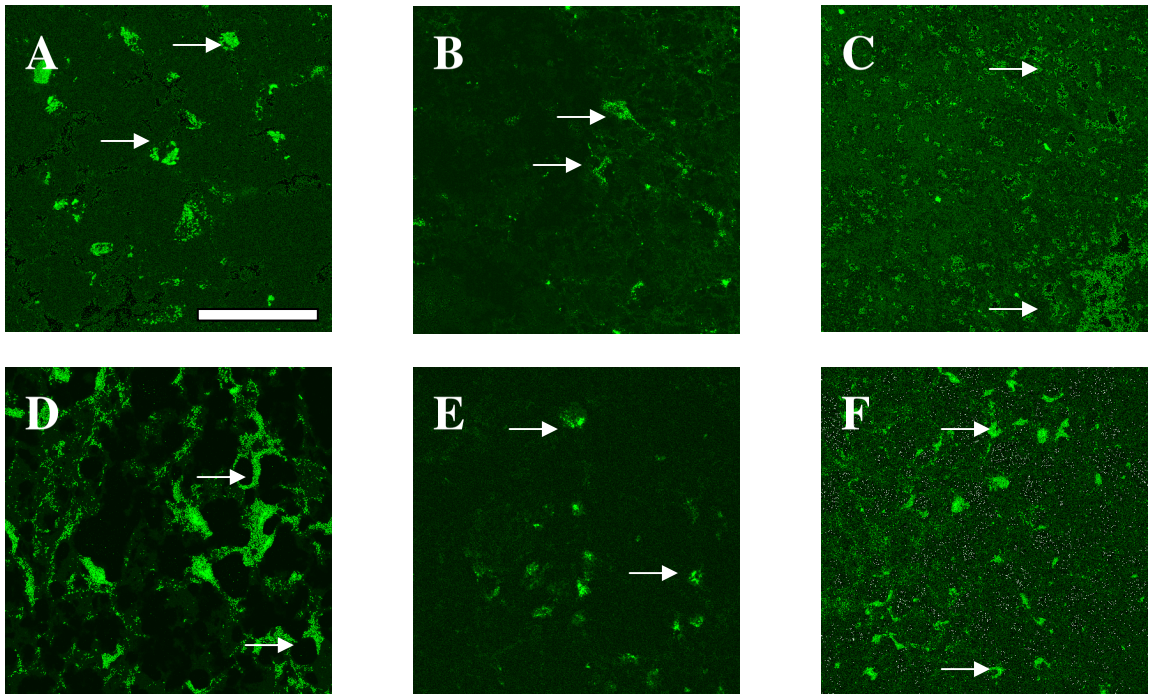
Experimental Groups	Mean Pixel Intensity
Control	49.74 ± 2.13
6-OHDA	21.12 ± 1.88[a]
6-OHDA + BMC	24.76 ± 2.14[a]
6-OHDA + 5-HT + BMC	44.12 ± 2.09[c,e]
6-OHDA + GABA + BMC	40.87 ± 1.12[b,e]
6-OHDA + 5-HT + GABA + BMC	48.75 ± 2.17[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 65
BDNF expression in the Cerebral Cortex of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 64
BDNF expression in the Cerebral Cortex of control and experimental rats

Experimental Groups	Mean Pixel Intensity
Control	49.12 ± 2.03
6-OHDA	17.37 ± 1.49[a]
6-OHDA + BMC	19.88 ± 1.18[a]
6-OHDA + 5-HT + BMC	42.41 ± 1.98[c,e]
6-OHDA + GABA + BMC	40.38 ± 2.09[c,e]
6-OHDA + 5-HT + GABA + BMC	44.86 ± 1.42[c,d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Table - 65
Serotonin content in the Hippocampus of control and experimental rats

Experimental Groups	5-HT Content (nmoles/g wet wt.)
Control	**1.61 ± 0.14**
6-OHDA	**0.88 ± 0.10[a]**
6-OHDA + BMC	**0.96 ± 0.08[a]**
6-OHDA + 5-HT + BMC	**1.23 ± 0.10[b,e]**
6-OHDA + GABA + BMC	**1.15 ± 0.09[b,e]**
6-OHDA + 5-HT + GABA + BMC	**1.53 ± 0.12[d]**

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 66
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

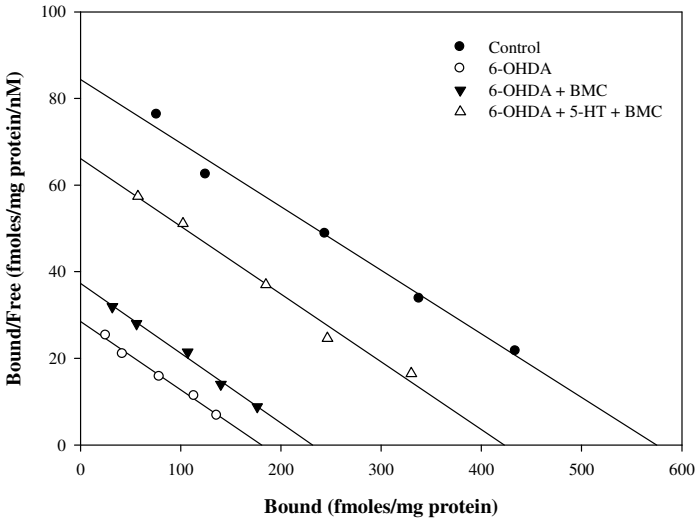


Table - 66
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	575.00 ± 35.52	6.86 ± 0.62
6-OHDA	180.77 ± 20.38[a]	6.39 ± 0.65
6-OHDA + BMC	232.15 ± 31.85[a]	6.32 ± 0.54
6-OHDA + 5-HT + BMC	421.87 ± 37.42[b,e]	6.42 ± 0.59

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 67
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

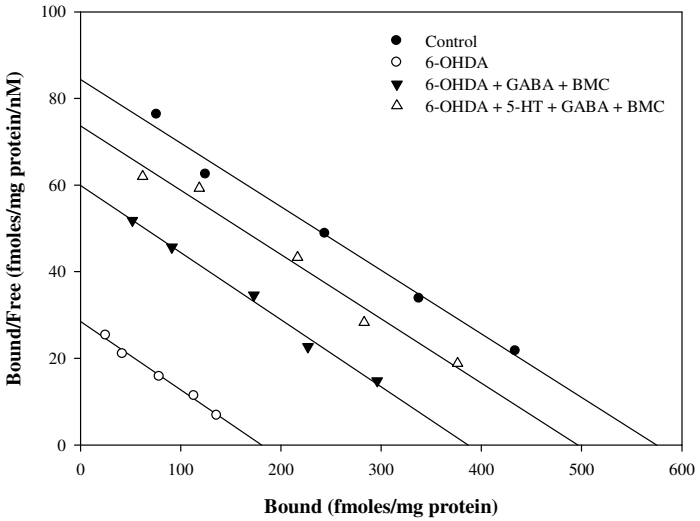


Table - 67
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	575.00 ± 35.52	6.86 ± 0.62
6-OHDA	180.77 ± 20.38[a]	6.39 ± 0.65
6-OHDA + GABA + BMC	385.53 ± 29.14[b,e]	6.47 ± 0.57
6-OHDA + 5-HT + GABA + BMC	495.27 ± 48.55[d]	6.72 ± 0.64

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 68
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

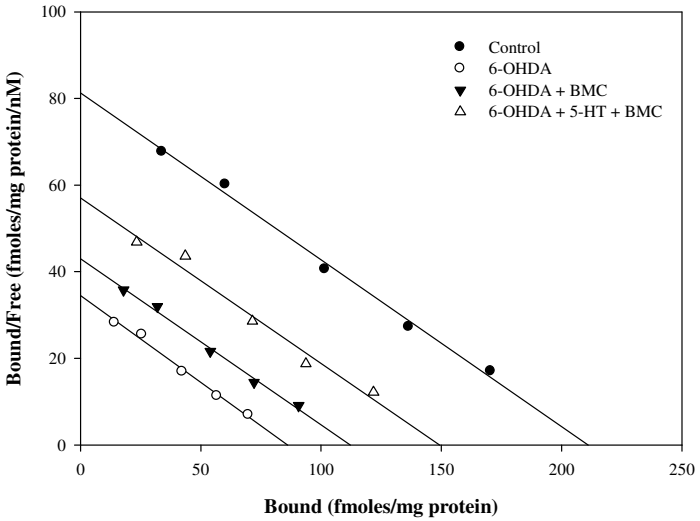


Table - 68
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	210.57 ± 19.57	2.60 ± 0.26
6-OHDA	86.11 ± 10.21[a]	2.52 ± 0.24
6-OHDA + BMC	112.38 ± 15.48[a]	2.61 ± 0.25
6-OHDA + 5-HT + BMC	149.20 ± 11.24[b,e]	2.63 ± 0.26

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 69
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

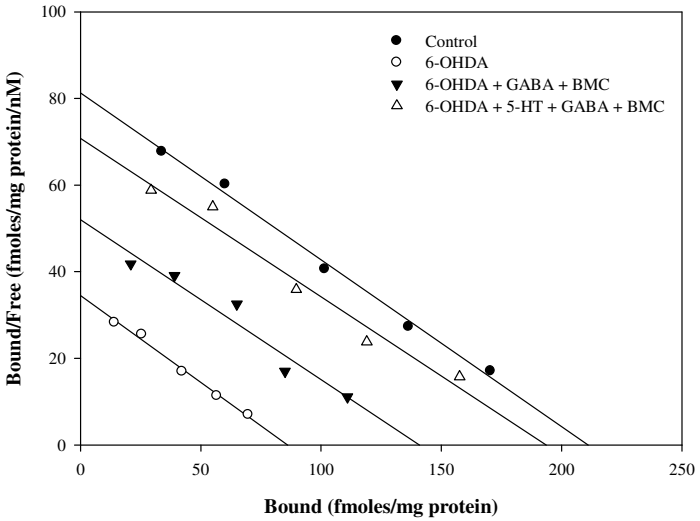


Table - 69
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	210.57 ± 19.57	2.60 ± 0.26
6-OHDA	86.11 ± 10.21[a]	2.52 ± 0.24
6-OHDA + GABA + BMC	139.86 ± 13.41[b,e]	2.70 ± 0.25
6-OHDA + 5-HT + GABA + BMC	193.20 ± 16.56[d]	2.71 ± 0.24

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 70
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

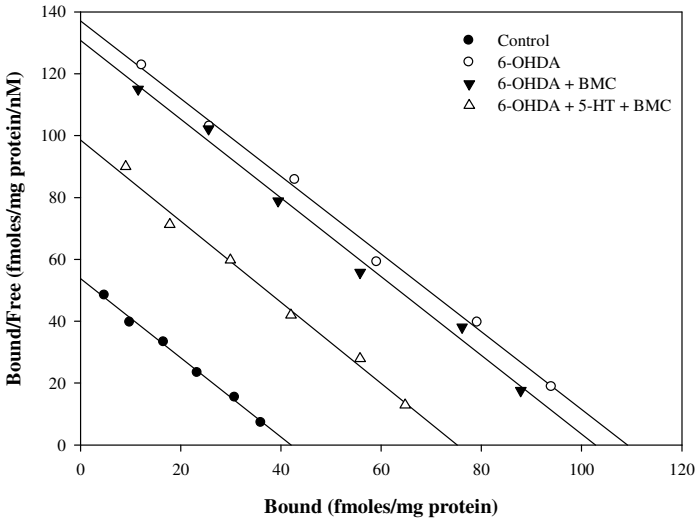


Table - 70
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	42.14 ± 4.67	0.78 ± 0.05
6-OHDA	109.20 ± 9.35[a]	0.80 ± 0.07
6-OHDA + BMC	102.50 ± 8.31[a]	0.78 ± 0.09
6-OHDA + 5-HT + BMC	75.28 ± 6.01[b,e]	0.76 ± 0.08

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 71
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

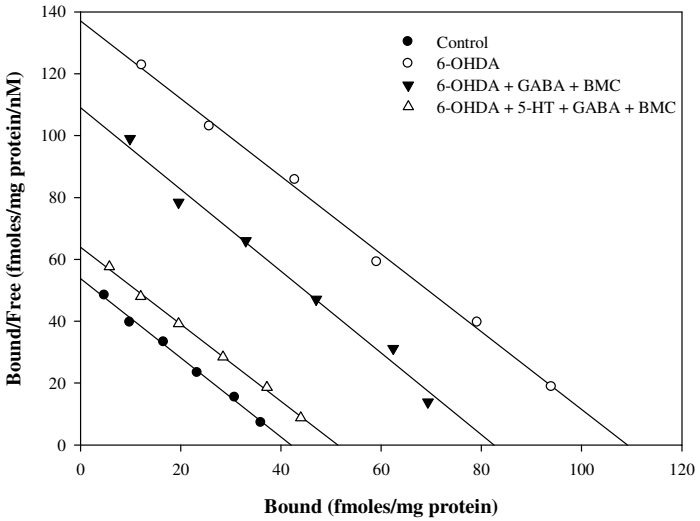


Table - 71
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	42.14 ± 4.67	0.78 ± 0.05
6-OHDA	109.20 ± 9.35[a]	0.80 ± 0.07
6-OHDA + GABA + BMC	82.37 ± 8.14[b,e]	0.76 ± 0.07
6-OHDA + 5-HT + GABA + BMC	51.28 ± 4.51[d]	0.81 ± 0.08

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 72
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

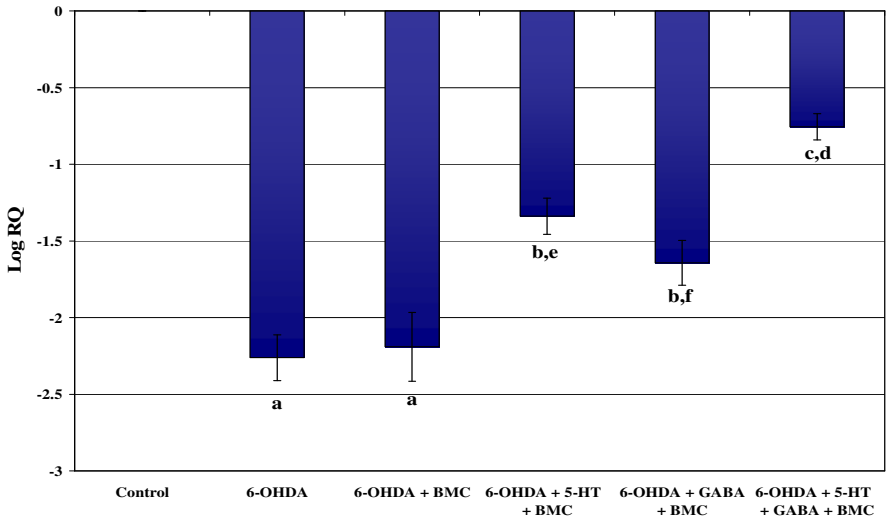


Table - 72
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.26 ± 0.15^{a}
6-OHDA + BMC	-2.19 ± 0.22^{a}
6-OHDA + 5-HT + BMC	$-1.34 \pm 0.12^{b,e}$
6-OHDA + GABA + BMC	$-1.64 \pm 0.15^{b,f}$
6-OHDA + 5-HT + GABA + BMC	$-0.76 \pm 0.09^{c,d}$

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$, [f] $p<0.05$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 73
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

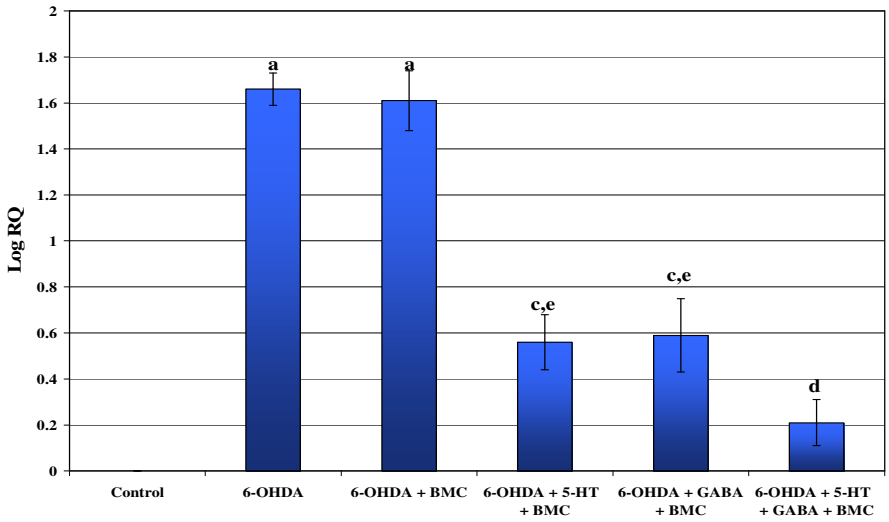


Table - 73
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	1.66 ± 0.07^{a}
6-OHDA + BMC	1.61 ± 0.13^{a}
6-OHDA + 5-HT + BMC	$0.56 \pm 0.12^{c,e}$
6-OHDA + GABA + BMC	$0.59 \pm 0.16^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.21 ± 0.10^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 74
Real Time PCR amplification of 5-HT transporter mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

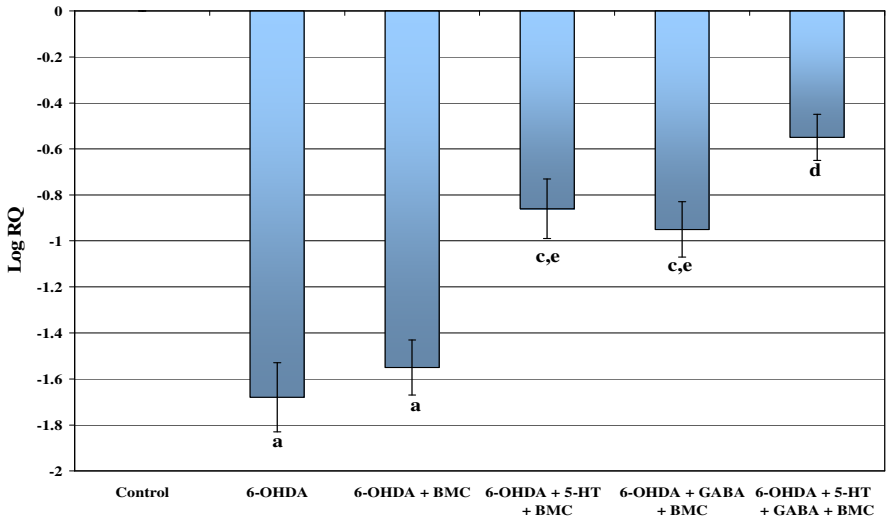


Table - 74
Real Time PCR amplification of 5-HT transporter mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-1.68 ± 0.15[a]
6-OHDA + BMC	-1.55 ± 0.12[a]
6-OHDA + 5-HT + BMC	-0.86 ± 0.13[c,e]
6-OHDA + GABA + BMC	-0.95 ± 0.12[c,e]
6-OHDA + 5-HT + GABA + BMC	-0.55 ± 0.10[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 75
Real Time PCR amplification of SOD mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

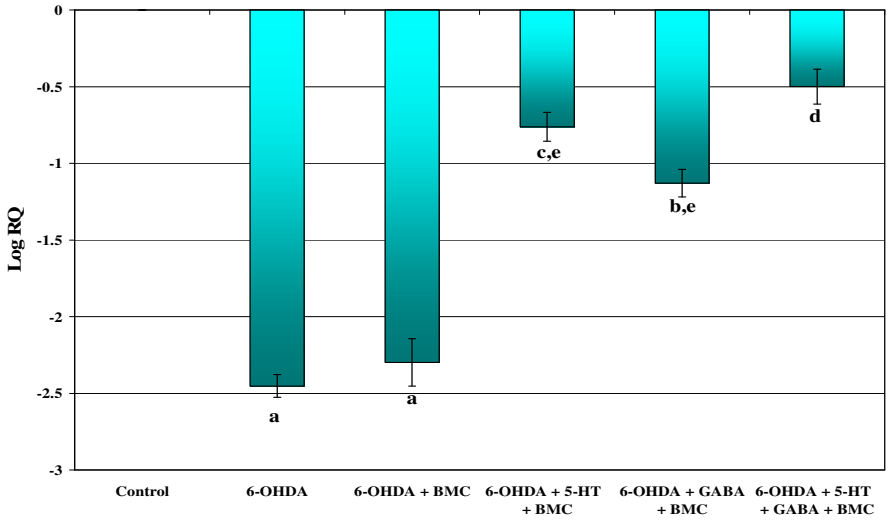


Table - 75
Real Time PCR amplification of SOD mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.45 ± 0.07[a]
6-OHDA + BMC	-2.30 ± 0.15[a]
6-OHDA + 5-HT + BMC	-0.76 ± 0.09[c,e]
6-OHDA + GABA + BMC	-1.13 ± 0.09[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.50 ± 0.11[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 76
Real Time PCR amplification of GPx mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

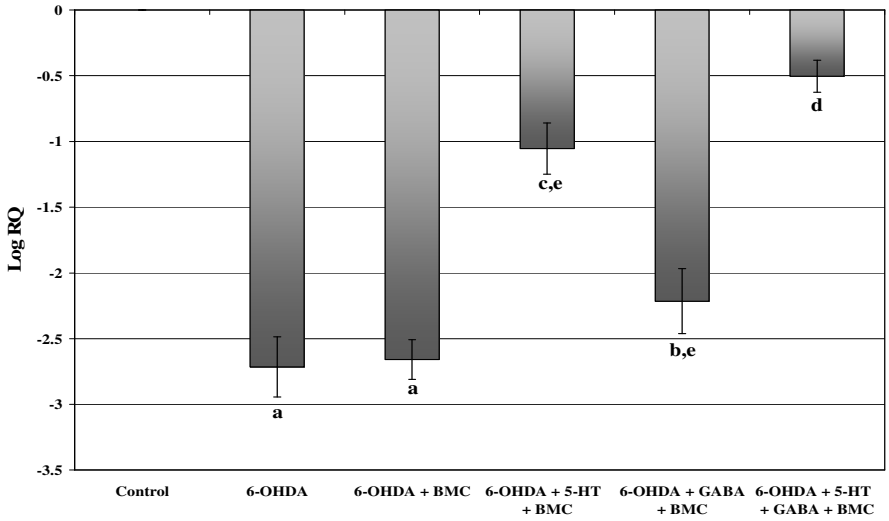


Table - 76
Real Time PCR amplification of GPx mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.71 ± 0.23[a]
6-OHDA + BMC	-2.66 ± 0.15[a]
6-OHDA + 5-HT + BMC	-1.05 ± 0.19[c,e]
6-OHDA + GABA + BMC	-2.21 ± 0.25[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.50 ± 0.12[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 77
Real Time PCR amplification of Akt mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

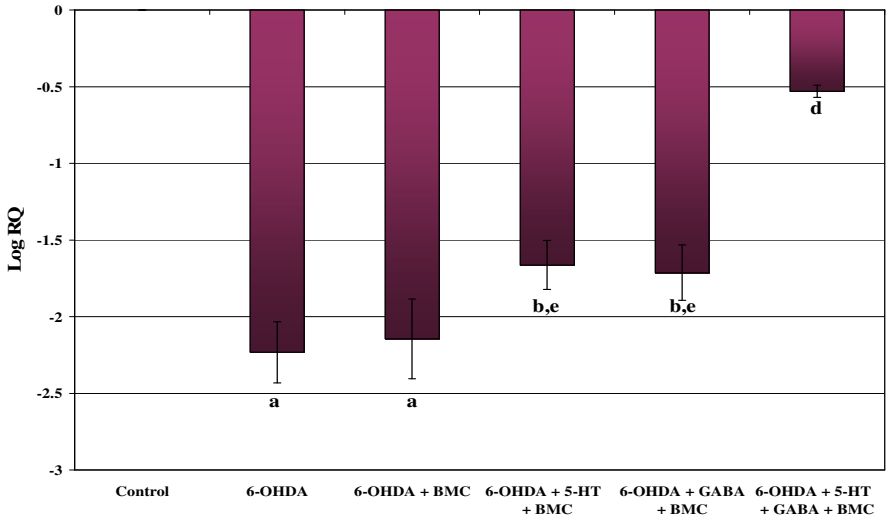


Table - 77
Real Time PCR amplification of Akt mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.23 ± 0.20[a]
6-OHDA + BMC	-2.14 ± 0.26[a]
6-OHDA + 5-HT + BMC	-1.66 ± 0.16[b,e]
6-OHDA + GABA + BMC	-1.71 ± 0.18[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.53 ± 0.04[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 78
Real Time PCR amplification of NF-κB mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

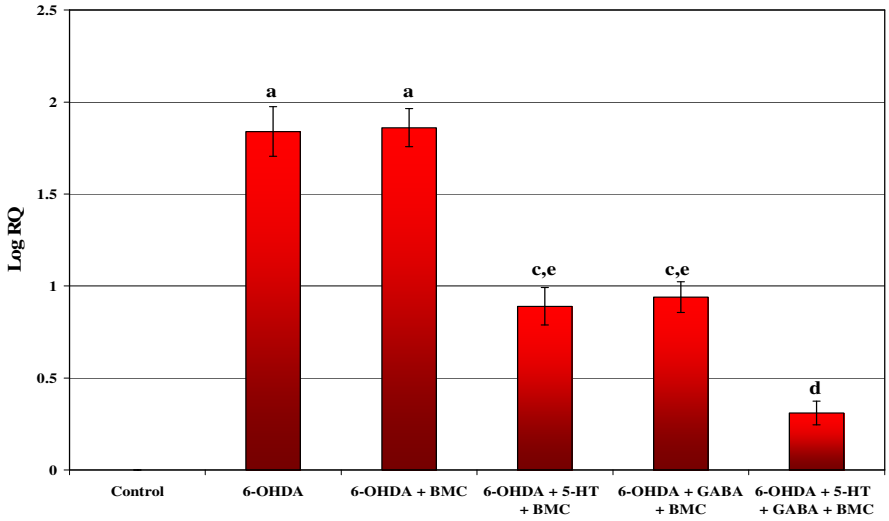


Table - 78
Real Time PCR amplification of NF-κB mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	1.84 ± 0.13^{a}
6-OHDA + BMC	1.86 ± 0.10^{a}
6-OHDA + 5-HT + BMC	$0.89 \pm 0.10^{c,e}$
6-OHDA + GABA + BMC	$0.94 \pm 0.08^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.31 ± 0.06^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 79
Real Time PCR amplification of Caspase-8 mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

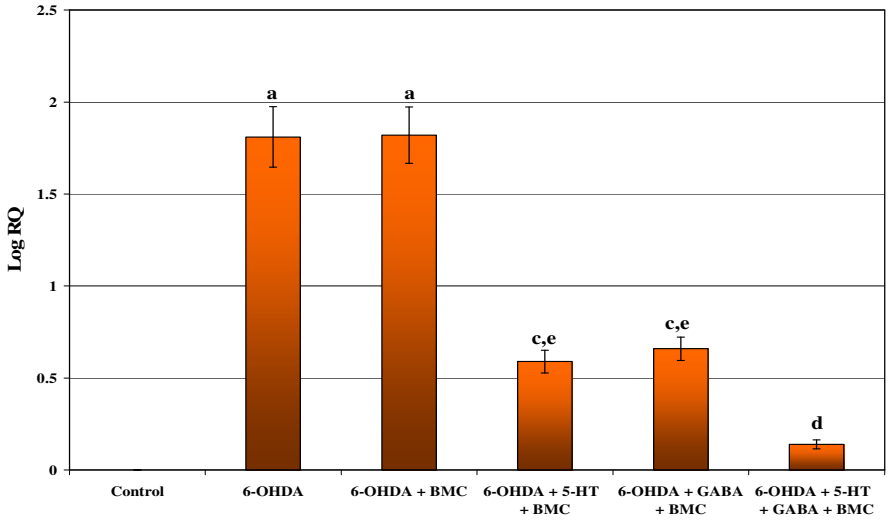


Table - 79
Real Time PCR amplification of Caspase-8 mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	1.81 ± 0.16^{a}
6-OHDA + BMC	1.82 ± 0.15^{a}
6-OHDA + 5-HT + BMC	$0.59 \pm 0.06^{c,e}$
6-OHDA + GABA + BMC	$0.66 \pm 0.06^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.14 ± 0.02^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 80
Real Time PCR amplification of BDNF mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

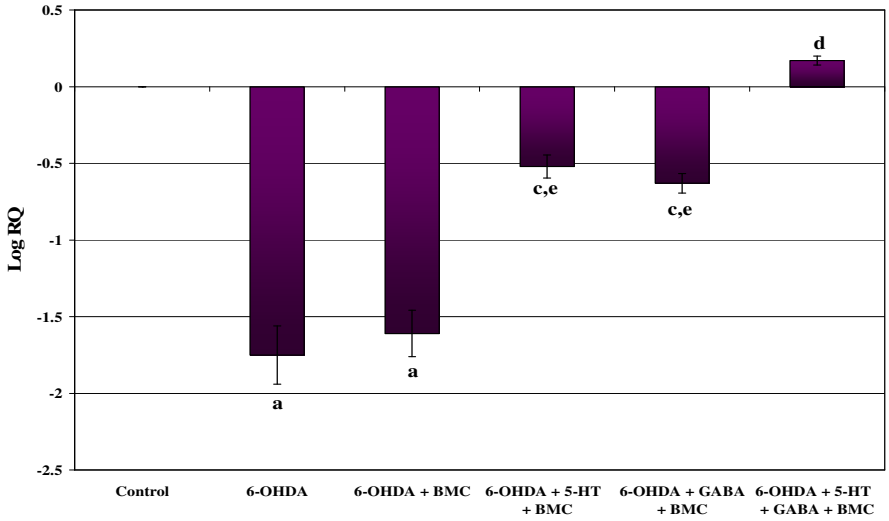


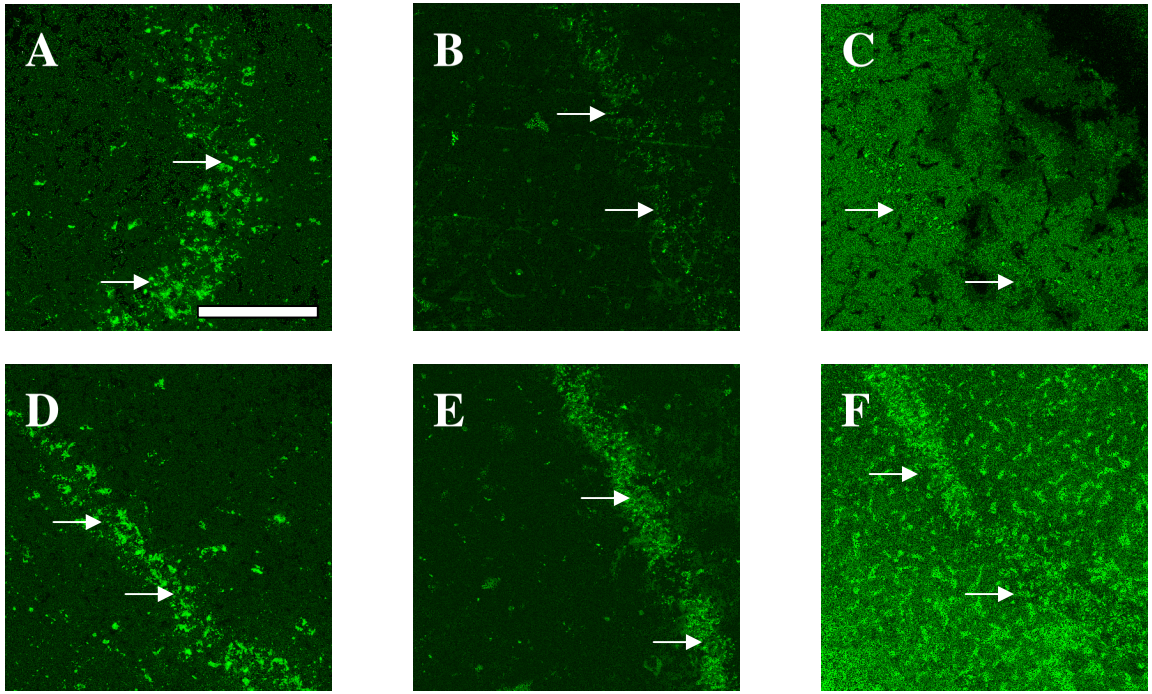
Table - 80
Real Time PCR amplification of BDNF mRNA in the Hippocampus of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-1.75 ± 0.18[a]
6-OHDA + BMC	-1.61 ± 0.15[a]
6-OHDA + 5-HT + BMC	-0.52 ± 0.07[c,e]
6-OHDA + GABA + BMC	-0.63 ± 0.06[c,e]
6-OHDA + 5-HT + GABA + BMC	0.17 ± 0.02[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 81
5-HT_{2A} receptor expression in the Hippocampus of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 150 μm.

Table - 81
5-HT_{2A} receptor expression in the Hippocampus of control and experimental rats

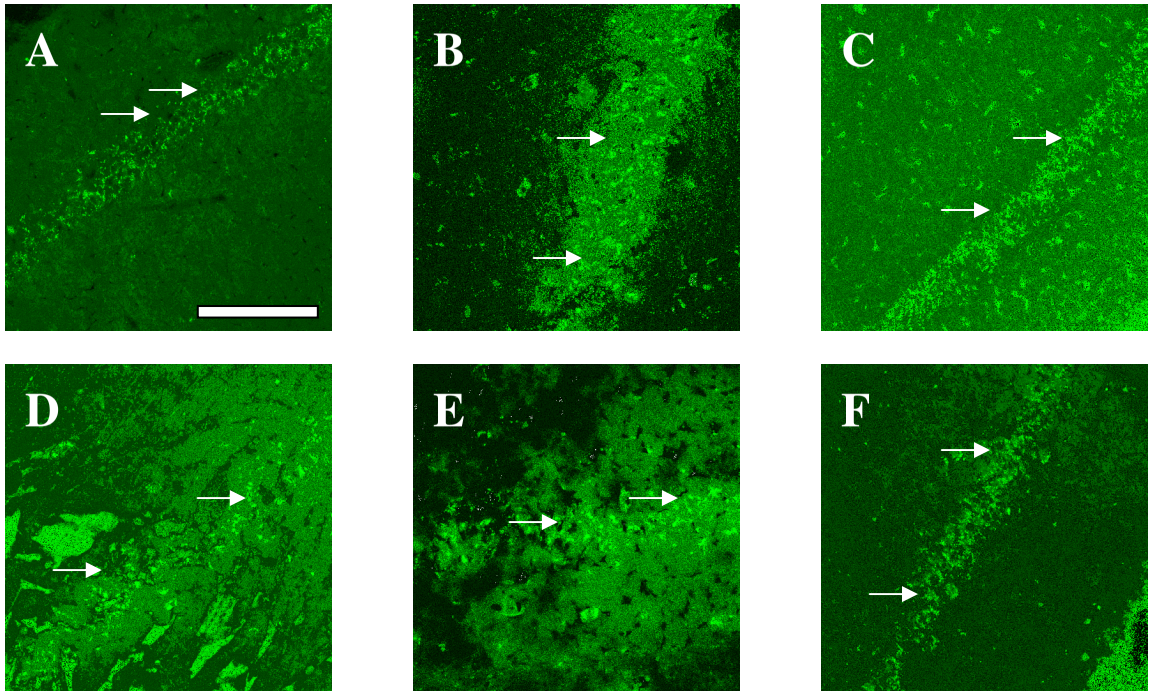
Experimental Groups	Mean Pixel Intensity
Control	56.52 ± 4.81
6-OHDA	19.38 ± 3.46[a]
6-OHDA + BMC	28.21 ± 3.97[a,f]
6-OHDA + 5-HT + BMC	45.14 ± 3.74[c,e]
6-OHDA + GABA + BMC	38.78 ± 2.09[b,e]
6-OHDA + 5-HT + GABA + BMC	51.27 ± 3.52[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$, [f] $p<0.05$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 82
5-HT_{2C} receptor expression in the Hippocampus of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 150 μm.

Table - 82
5-HT_{2C} receptor expression in the Hippocampus of control and experimental rats

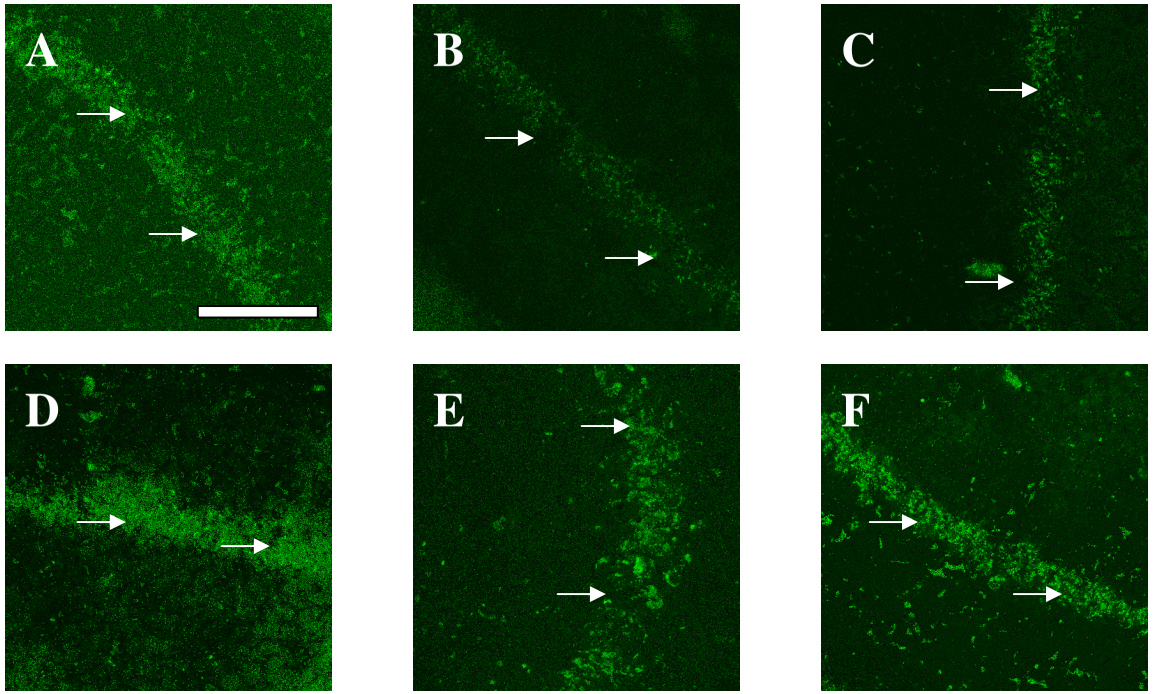
Experimental Groups	Mean Pixel Intensity
Control	14.32 ± 2.03
6-OHDA	40.85 ± 3.91[a]
6-OHDA + BMC	37.56 ± 2.67[a]
6-OHDA + 5-HT + BMC	27.14 ± 2.76[b,e]
6-OHDA + GABA + BMC	31.21 ± 2.25[b,e]
6-OHDA + 5-HT + GABA + BMC	21.01 ± 2.14[c,d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 83
5-HT transporter expression in the Hippocampus of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 150 μm.

Table - 83
5-HT transporter expression in the Hippocampus of control and experimental rats

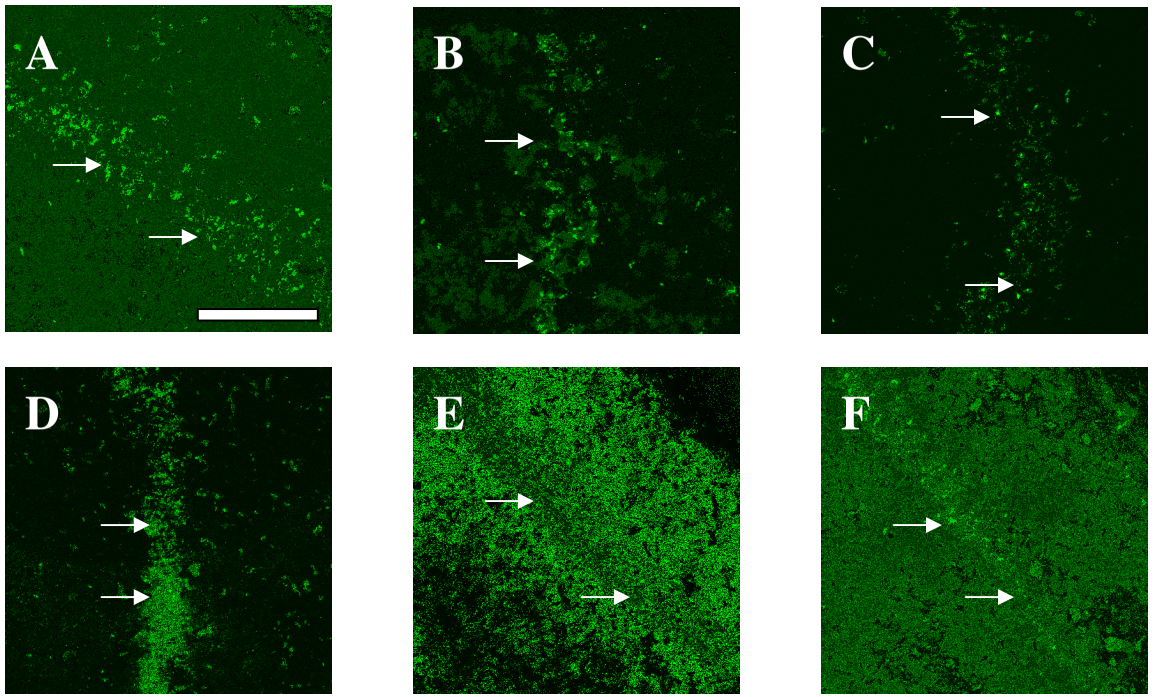
Experimental Groups	Mean Pixel Intensity
Control	52.42 ± 2.88
6-OHDA	21.85 ± 1.86[a]
6-OHDA + BMC	23.20 ± 1.52[a]
6-OHDA + 5-HT + BMC	43.59 ± 2.46[c,e]
6-OHDA + GABA + BMC	36.41 ± 2.05[b,e]
6-OHDA + 5-HT + GABA + BMC	47.63 ± 3.14[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 84
BDNF expression in the Hippocampus of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 150 μm.

Table - 84
BDNF expression in the Hippocampus of control and experimental rats

Experimental Groups	Mean Pixel Intensity
Control	45.21 ± 1.38
6-OHDA	23.20 ± 1.43[a]
6-OHDA + BMC	24.12 ± 1.78[a]
6-OHDA + 5-HT + BMC	36.25 ± 1.36[b,e]
6-OHDA + GABA + BMC	34.45 ± 1.74[b,e]
6-OHDA + 5-HT + GABA + BMC	42.71 ± 1.58[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Table - 85
Serotonin content in the Cerebellum
of control and experimental rats

Experimental Groups	5-HT Content (nmoles/g wet wt.)
Control	**1.79 ± 0.09**
6-OHDA	**1.02 ± 0.04[a]**
6-OHDA + BMC	**1.09 ± 0.03[a]**
6-OHDA + 5-HT + BMC	**1.44 ± 0.06[b,e]**
6-OHDA + GABA + BMC	**1.37 ± 0.06[b,e]**
6-OHDA + 5-HT + GABA + BMC	**1.74 ± 0.08[d]**

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 85
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

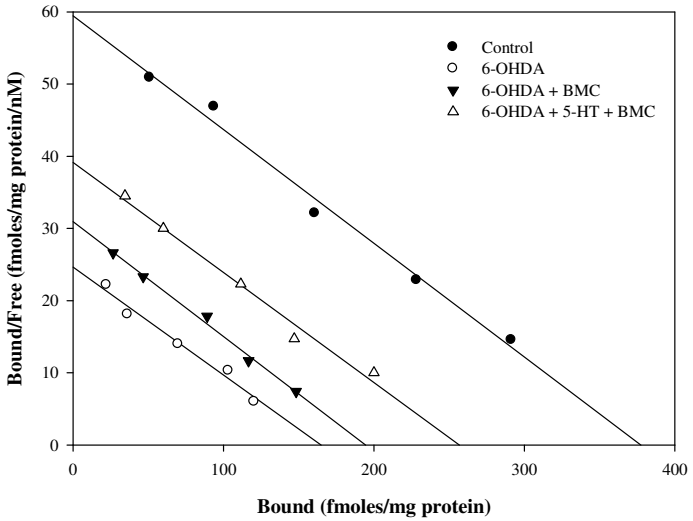


Table - 86
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	376.38 ± 32.24	6.34 ± 0.58
6-OHDA	164.01 ± 18.94[a]	6.68 ± 0.40
6-OHDA + BMC	193.49 ± 17.39[a]	6.22 ± 0.42
6-OHDA + 5-HT + BMC	256.41 ± 23.65[b,e]	6.60 ± 0.73

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 86
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

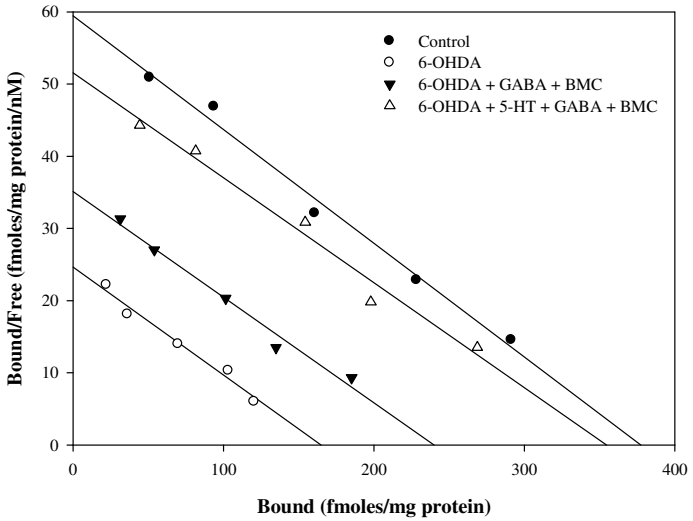


Table - 87
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	376.38 ± 32.24	6.34 ± 0.58
6-OHDA	164.01 ± 18.94[a]	6.68 ± 0.40
6-OHDA + GABA + BMC	239.22 ± 24.31[b,e]	6.81 ± 0.53
6-OHDA + 5-HT + GABA + BMC	352.98 ± 28.47[d]	6.90 ± 0.71

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 87
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

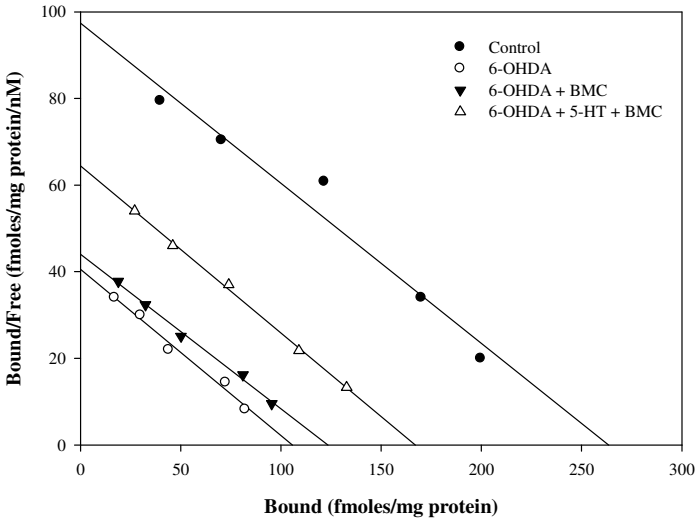


Table - 88
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	262.41 ± 20.85	2.68 ± 0.26
6-OHDA	105.43 ± 9.56[a]	2.59 ± 0.27
6-OHDA + BMC	123.01 ± 8.23[a]	2.80 ± 0.29
6-OHDA + 5-HT + BMC	166.60 ± 15.99[b,e]	2.60 ± 0.22

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 88
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

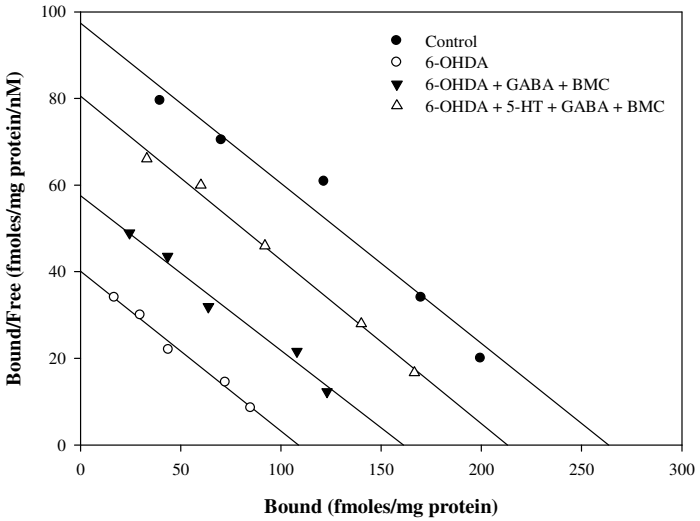


Table - 89
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	262.41 ± 20.85	2.68 ± 0.26
6-OHDA	105.43 ± 9.56[a]	2.59 ± 0.27
6-OHDA + GABA + BMC	160.76 ± 9.89[b,e]	2.82 ± 0.27
6-OHDA + 5-HT + GABA + BMC	212.58 ± 17.61[c,d]	2.65 ± 0.28

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 89
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

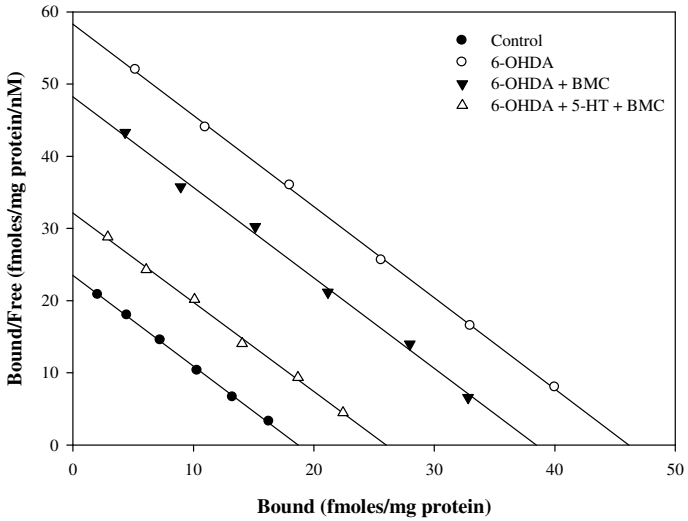


Table - 90
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	18.66 ± 2.01	0.81 ± 0.06
6-OHDA	46.01 ± 4.08[a]	0.79 ± 0.06
6-OHDA + BMC	38.39 ± 3.98[a]	0.80 ± 0.07
6-OHDA + 5-HT + BMC	25.86 ± 2.48[c,e]	0.81 ± 0.08

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 90
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

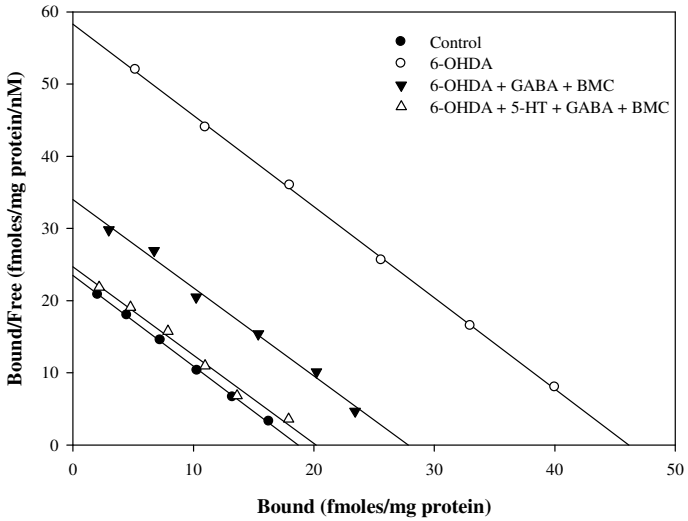


Table - 91
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	18.66 ± 2.01	0.81 ± 0.06
6-OHDA	46.01 ± 4.08[a]	0.79 ± 0.06
6-OHDA + GABA + BMC	27.64 ± 2.97[c,e]	0.82 ± 0.08
6-OHDA + 5-HT + GABA + BMC	20.10 ± 1.34[d]	0.81 ± 0.05

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 91
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

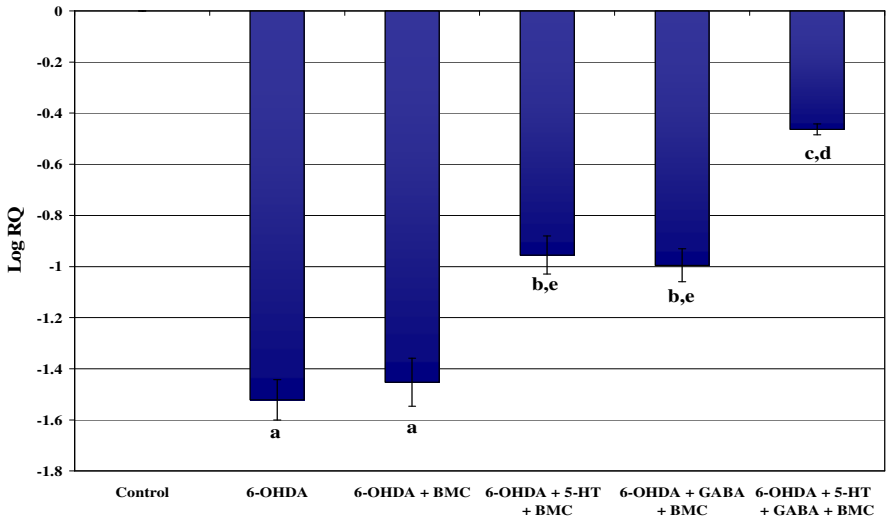


Table - 92
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-1.52 ± 0.08[a]
6-OHDA + BMC	-1.45 ± 0.09[a]
6-OHDA + 5-HT + BMC	-0.95 ± 0.07[b,e]
6-OHDA + GABA + BMC	-0.99 ± 0.06[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.46 ± 0.02[c,d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 92
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

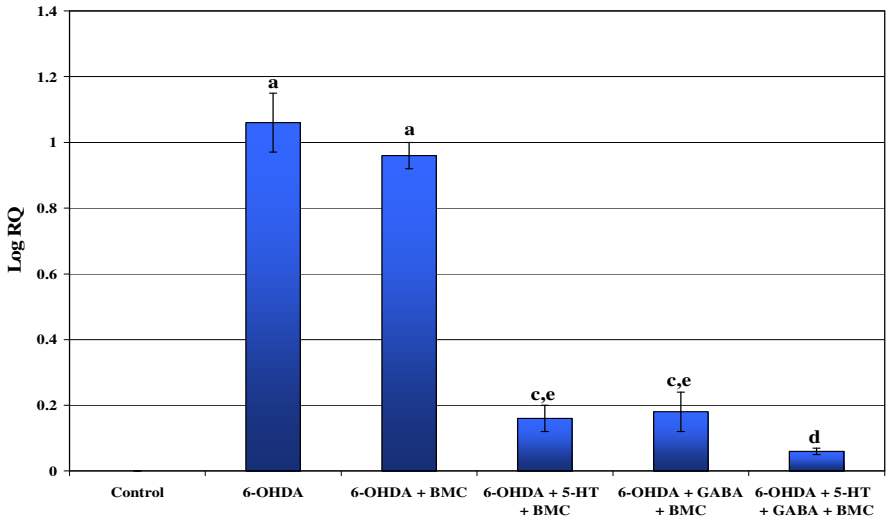


Table - 93
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	1.06 ± 0.09^{a}
6-OHDA + BMC	0.96 ± 0.04^{a}
6-OHDA + 5-HT + BMC	$0.16 \pm 0.04^{c,e}$
6-OHDA + GABA + BMC	$0.18 \pm 0.06^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.06 ± 0.01^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 93
Real Time PCR amplification of 5-HT transporter mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

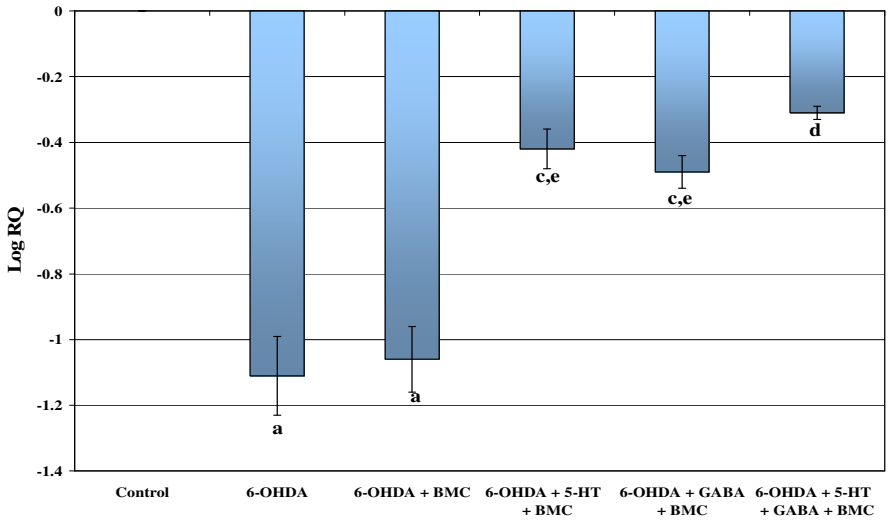


Table - 94
Real Time PCR amplification of 5-HT transporter mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-1.11 ± 0.12[a]
6-OHDA + BMC	-1.06 ± 0.10[a]
6-OHDA + 5-HT + BMC	-0.42 ± 0.06[c,e]
6-OHDA + GABA + BMC	-0.49 ± 0.05[c,e]
6-OHDA + 5-HT + GABA + BMC	-0.31 ± 0.02[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 94
Real Time PCR amplification of SOD mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

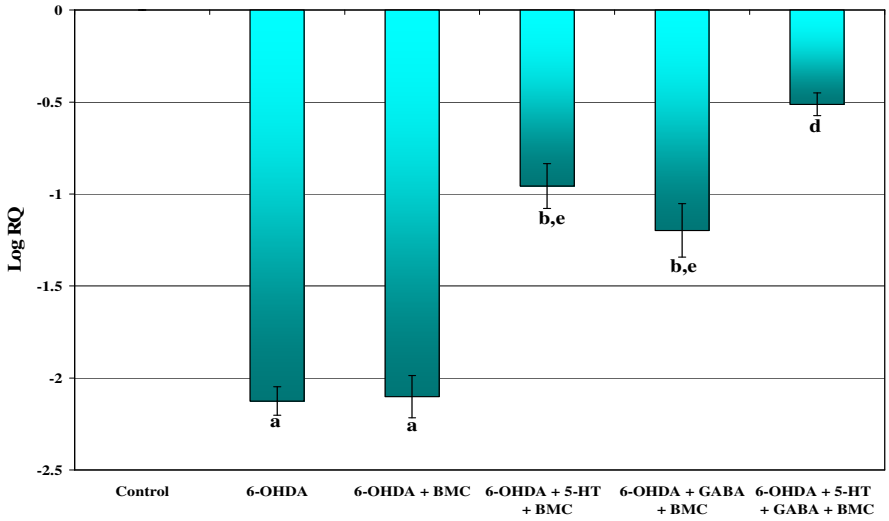


Table - 95
Real Time PCR amplification of SOD mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.12 ± 0.08[a]
6-OHDA + BMC	-2.10 ± 0.11[a]
6-OHDA + 5-HT + BMC	-0.96 ± 0.12[b,e]
6-OHDA + GABA + BMC	-1.20 ± 0.15[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.51 ± 0.06[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 95
Real Time PCR amplification of GPx mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

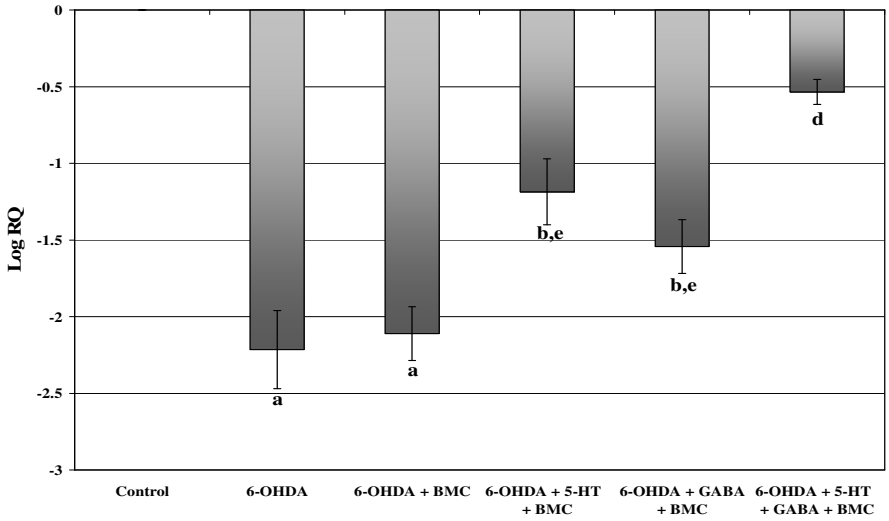


Table - 96
Real Time PCR amplification of GPx mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.21 ± 0.25[a]
6-OHDA + BMC	-2.11 ± 0.17[a]
6-OHDA + 5-HT + BMC	-1.19 ± 0.21[b,e]
6-OHDA + GABA + BMC	-1.54 ± 0.18[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.53 ± 0.08[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 96
Real Time PCR amplification of Akt mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

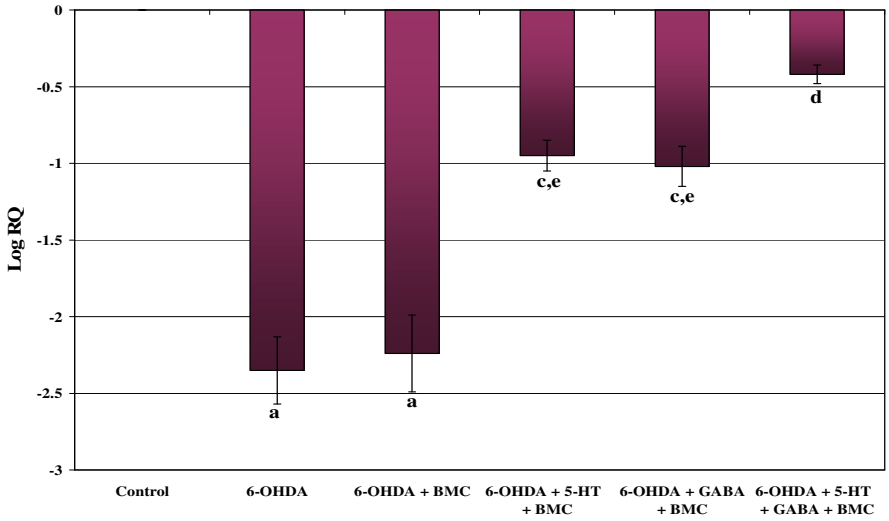


Table - 97
Real Time PCR amplification of Akt mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.35 ± 0.22[a]
6-OHDA + BMC	-2.24 ± 0.25[a]
6-OHDA + 5-HT + BMC	-0.95 ± 0.10[c,e]
6-OHDA + GABA + BMC	-1.02 ± 0.13[c,e]
6-OHDA + 5-HT + GABA + BMC	-0.42 ± 0.06[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 97
Real Time PCR amplification of NF-κB mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

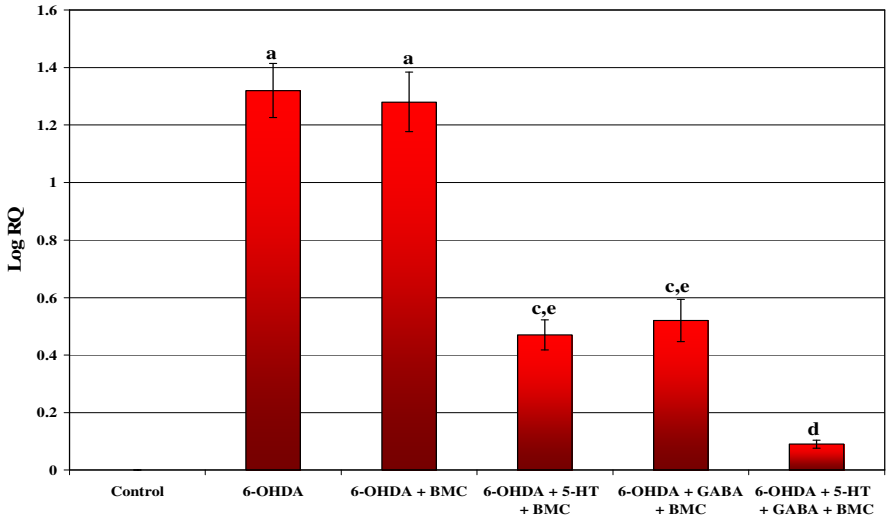


Table - 98
Real Time PCR amplification of NF-κB mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	1.32 ± 0.09^{a}
6-OHDA + BMC	1.28 ± 0.10^{a}
6-OHDA + 5-HT + BMC	$0.47 \pm 0.05^{c,e}$
6-OHDA + GABA + BMC	$0.52 \pm 0.07^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.09 ± 0.01^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 98
Real Time PCR amplification of Caspase-8 mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

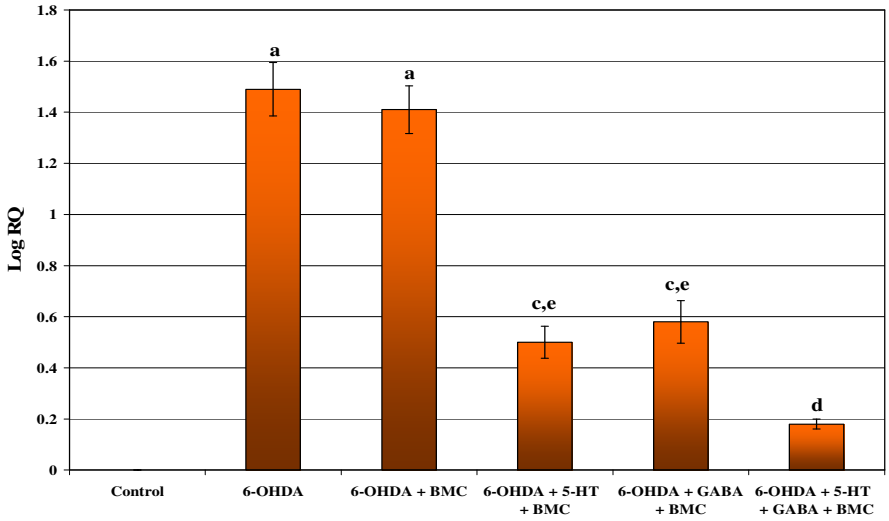


Table - 99
Real Time PCR amplification of Caspase-8 mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	1.49 ± 0.10^{a}
6-OHDA + BMC	1.41 ± 0.09^{a}
6-OHDA + 5-HT + BMC	$0.50 \pm 0.06^{c,e}$
6-OHDA + GABA + BMC	$0.58 \pm 0.08^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.18 ± 0.01^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 99
Real Time PCR amplification of BDNF mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

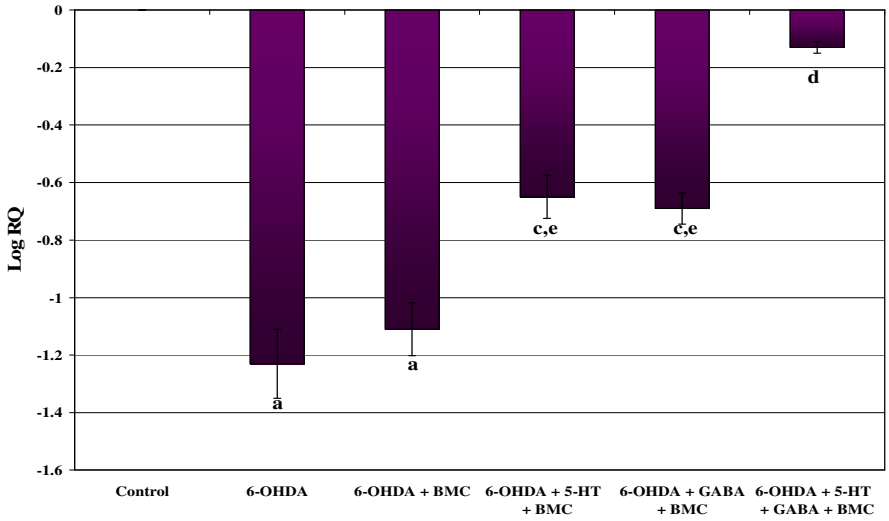


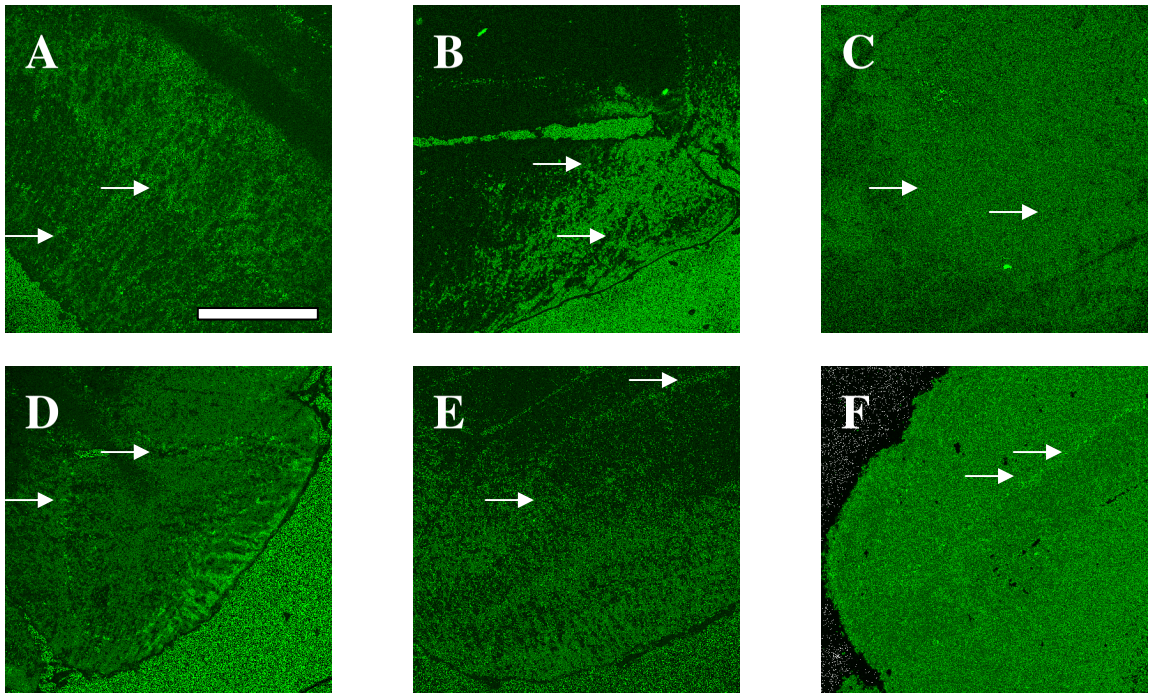
Table - 100
Real Time PCR amplification of BDNF mRNA in the Cerebellum of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-1.23 ± 0.12[a]
6-OHDA + BMC	-1.11 ± 0.09[a]
6-OHDA + 5-HT + BMC	-0.65 ± 0.08[c,e]
6-OHDA + GABA + BMC	-0.69 ± 0.05[c,e]
6-OHDA + 5-HT + GABA + BMC	-0.13 ± 0.02[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 100
5-HT_{2A} receptor expression in the Cerebellum of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 250 μm.

Table - 101
5-HT_{2A} receptor expression in the Cerebellum of control and experimental rats

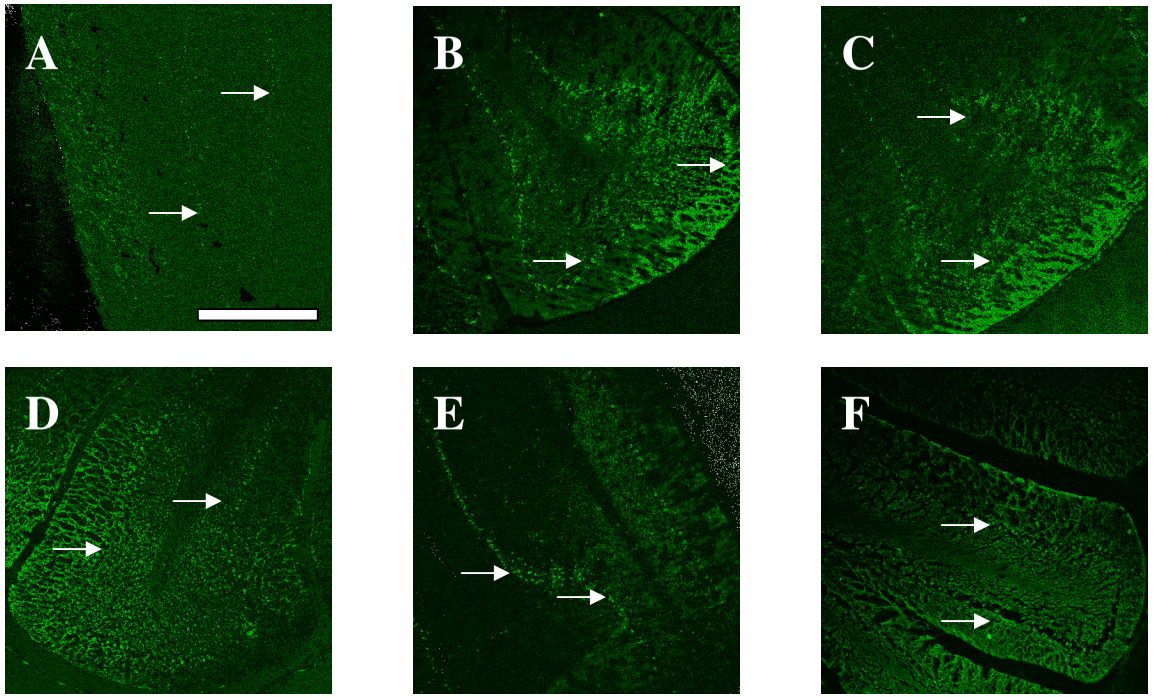
Experimental Groups	Mean Pixel Intensity
Control	41.32 ± 2.52
6-OHDA	24.82 ± 1.84[a]
6-OHDA + BMC	26.14 ± 1.02[a]
6-OHDA + 5-HT + BMC	34.91 ± 1.71[b,e]
6-OHDA + GABA + BMC	32.85 ± 1.86[b,e]
6-OHDA + 5-HT + GABA + BMC	38.33 ± 2.37[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 101
5-HT_{2C} receptor expression in the Cerebellum of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 250 μm.

Table - 102
5-HT_{2C} receptor expression in the Cerebellum of control and experimental rats

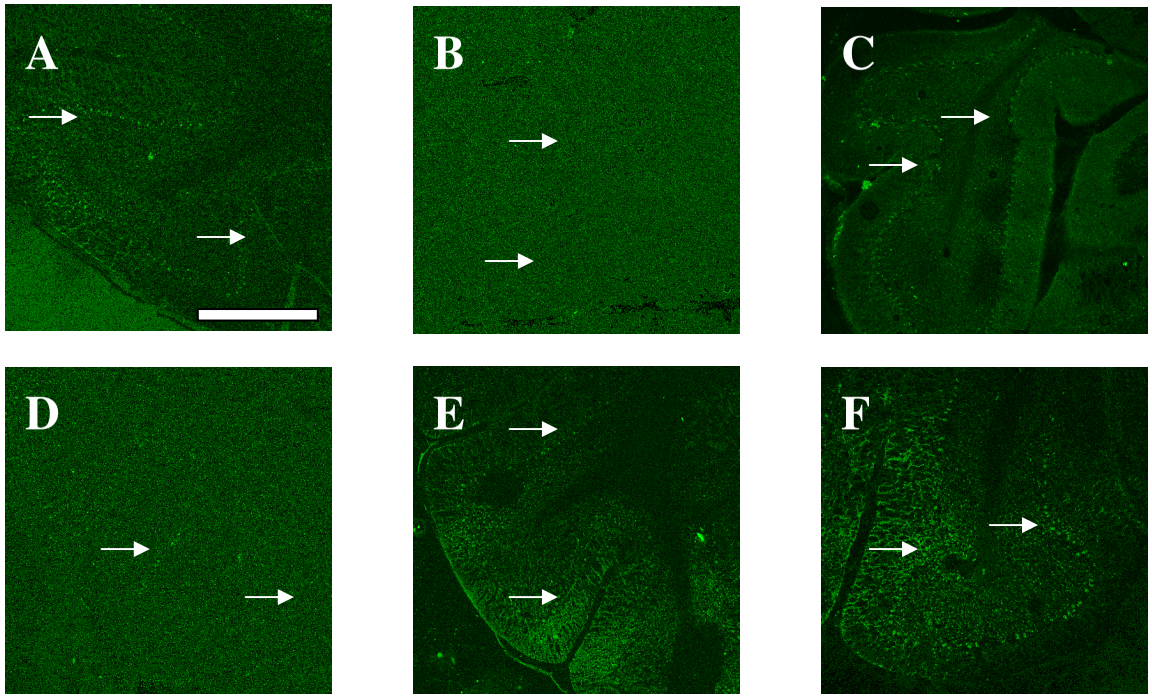
Experimental Groups	Mean Pixel Intensity
Control	21.33 ± 1.82
6-OHDA	55.85 ± 3.24[a]
6-OHDA + BMC	51.69 ± 3.19[a]
6-OHDA + 5-HT + BMC	37.27 ± 2.38[b,e]
6-OHDA + GABA + BMC	40.17 ± 2.26[b,e]
6-OHDA + 5-HT + GABA + BMC	24.89 ± 2.06[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 102
5-HT transporter expression in the Cerebellum of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 250 μm.

Table - 103
5-HT transporter expression in the Cerebellum of control and experimental rats

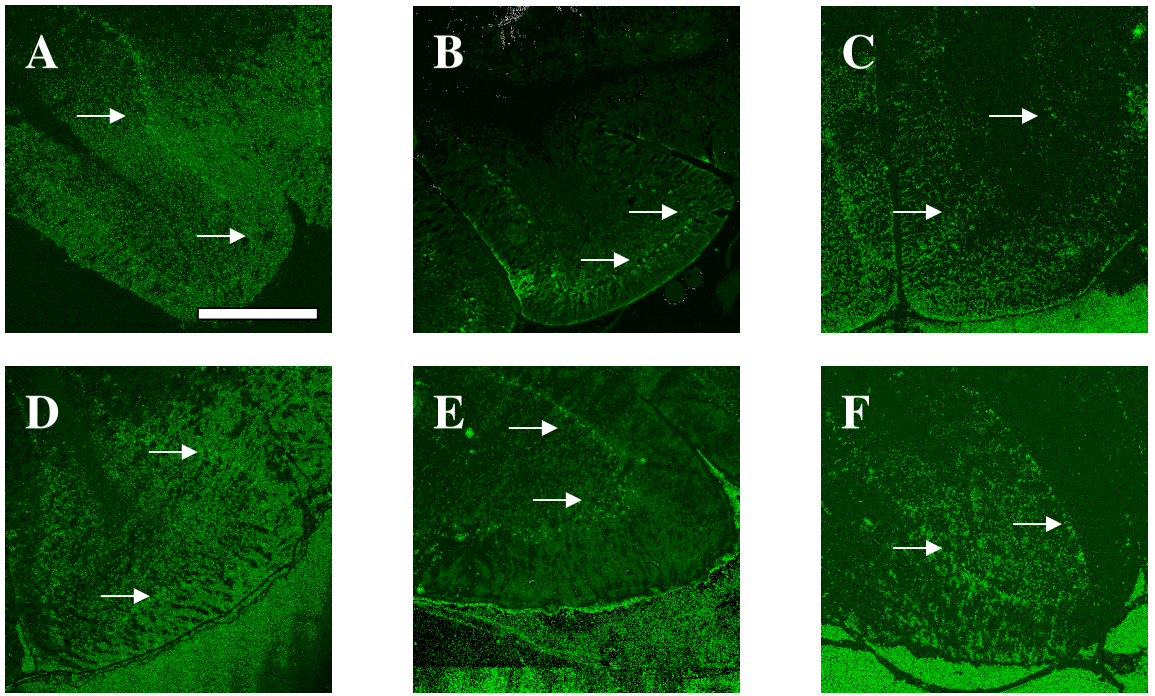
Experimental Groups	Mean Pixel Intensity
Control	44.84 ± 2.98
6-OHDA	14.83 ± 2.31[a]
6-OHDA + BMC	18.94 ± 2.24[a]
6-OHDA + 5-HT + BMC	35.87 ± 2.03[c,e]
6-OHDA + GABA + BMC	33.22 ± 2.96[c,e]
6-OHDA + 5-HT + GABA + BMC	39.27 ± 2.29[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 103
BDNF expression in the Cerebellum of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 250 μm.

Table - 104
BDNF expression in the Cerebellum of control and experimental rats

Experimental Groups	Mean Pixel Intensity
Control	42.25 ± 2.89
6-OHDA	19.36 ± 2.47[a]
6-OHDA + BMC	20.57 ± 2.21[a]
6-OHDA + 5-HT + BMC	35.47 ± 1.98[c,e]
6-OHDA + GABA + BMC	34.99 ± 2.09[c,e]
6-OHDA + 5-HT + GABA + BMC	38.27 ± 2.31[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Table - 105
Serotonin content in the Brain stem
of control and experimental rats

Experimental Groups	5-HT Content (nmoles/g wet wt.)
Control	**1.87 ± 0.10**
6-OHDA	**1.33 ± 0.05[a]**
6-OHDA + BMC	**1.34 ± 0.08[a]**
6-OHDA + 5-HT + BMC	**1.69 ± 0.08[c,e]**
6-OHDA + GABA + BMC	**1.66 ± 0.03[c,e]**
6-OHDA + 5-HT + GABA + BMC	**1.80 ± 0.08[d]**

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 104
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

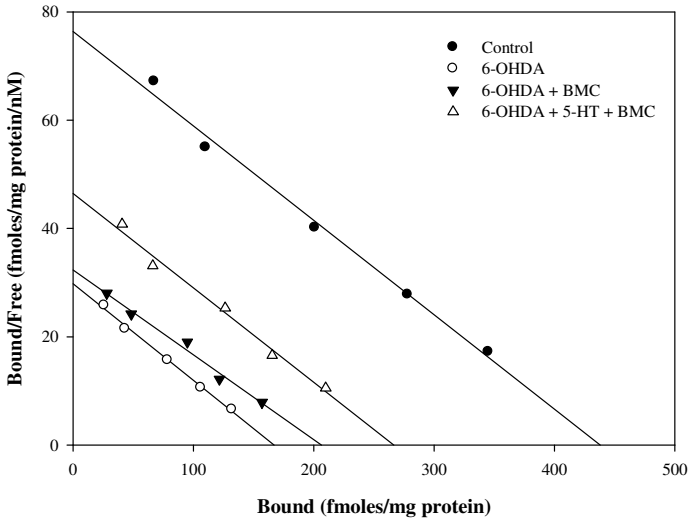


Table - 106
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	437.21 ± 40.28	5.73 ± 0.58
6-OHDA	167.14 ± 18.69[a]	5.65 ± 0.42
6-OHDA + BMC	202.70 ± 23.87[a]	6.10 ± 0.70
6-OHDA + 5-HT + BMC	266.21 ± 28.15[b,e]	5.75 ± 0.48

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 105
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Brain stem of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

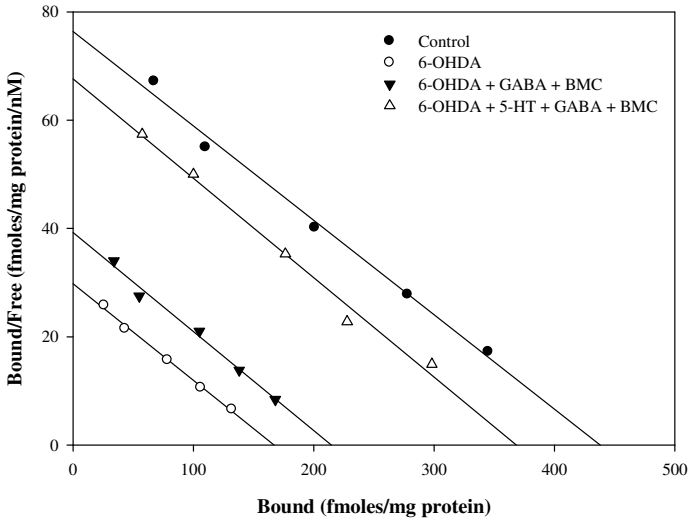


Table - 107
Scatchard analysis of [^{3}H]5-HT binding against 5-HT in the Brain stem of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	437.21 ± 40.28	5.73 ± 0.58
6-OHDA	167.14 ± 18.69[a]	5.65 ± 0.42
6-OHDA + GABA + BMC	213.68 ± 28.26[b,e]	5.50 ± 0.45
6-OHDA + 5-HT + GABA + BMC	368.62 ± 42.88[d]	5.47 ± 0.66

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 106
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

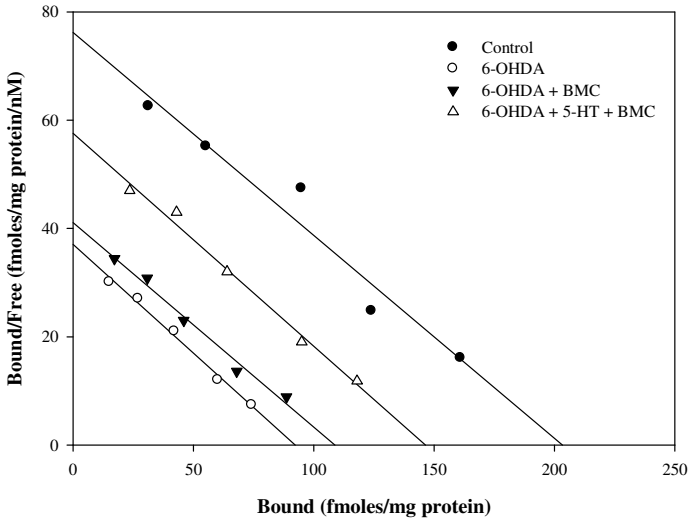


Table - 108
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	203.36 ± 19.45	2.68 ± 0.22
6-OHDA	92.05 ± 8.63[a]	2.52 ± 0.25
6-OHDA + BMC	108.97 ± 9.81[a]	2.66 ± 0.27
6-OHDA + 5-HT + BMC	146.66 ± 10.32[b,e]	2.55 ± 0.21

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure - 107
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Brain stem of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

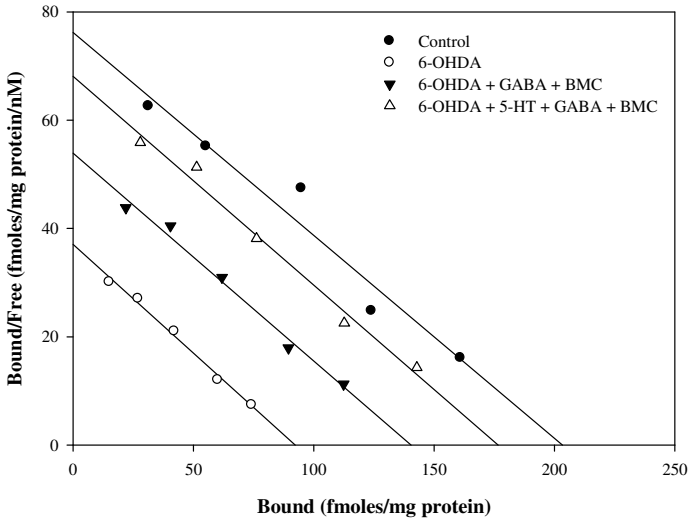


Table - 109
Scatchard analysis of [^{3}H]ketanserin binding against ketanserin in the Brain stem of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	203.36 ± 19.45	2.68 ± 0.22
6-OHDA	92.05 ± 8.63[a]	2.52 ± 0.25
6-OHDA + GABA + BMC	139.86 ± 9.55[b,e]	2.60 ± 0.24
6-OHDA + 5-HT + GABA + BMC	176.29 ± 12.74[d]	2.60 ± 0.28

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 108
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

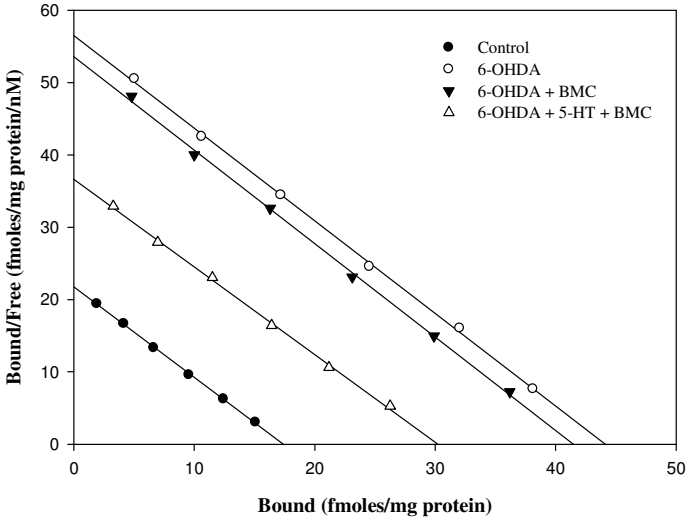


Table - 110
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC and 6-OHDA + 5-HT + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	17.30 ± 1.98	0.80 ± 0.08
6-OHDA	44.07 ± 4.73[a]	0.78 ± 0.05
6-OHDA + BMC	41.43 ± 4.08[a]	0.78 ± 0.08
6-OHDA + 5-HT + BMC	30.18 ± 2.94[c,e]	0.83 ± 0.07

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC

Figure – 109
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Brain stem of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

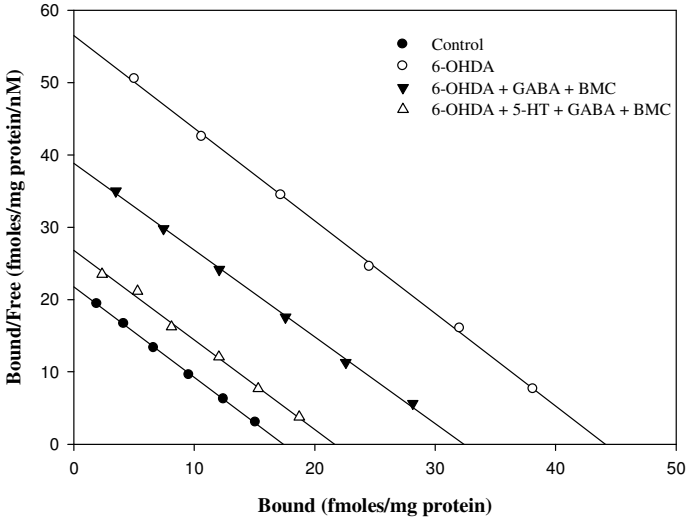


Table - 111
Scatchard analysis of [^{3}H]mesulergine binding against mesulergine in the Brain stem of Control, 6-OHDA infused, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	B_{max} (fmoles/mg protein)	K_d (nM)
Control	17.30 ± 1.98	0.80 ± 0.08
6-OHDA	44.07 ± 4.73[a]	0.78 ± 0.05
6-OHDA + GABA + BMC	32.21 ± 3.34[c,e]	0.83 ± 0.07
6-OHDA + 5-HT + GABA + BMC	21.71 ± 2.22[d]	0.81 ± 0.08

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
B_{max} – Maximal binding; K_d – Dissociation constant

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC

Figure - 110
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

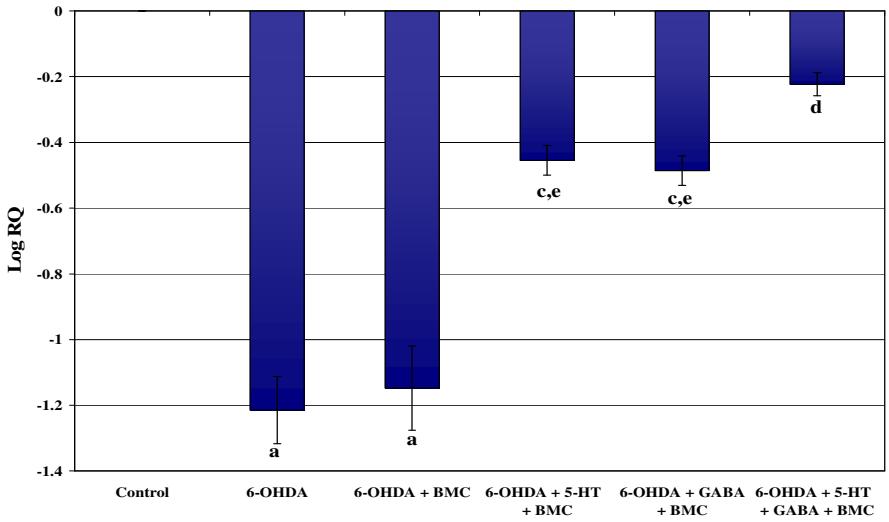


Table - 112
Real Time PCR amplification of 5-HT_{2A} receptor subunit mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-1.21 ± 0.10^{a}
6-OHDA + BMC	-1.15 ± 0.13^{a}
6-OHDA + 5-HT + BMC	$-0.45 \pm 0.05^{c,e}$
6-OHDA + GABA + BMC	$-0.49 \pm 0.05^{c,e}$
6-OHDA + 5-HT + GABA + BMC	-0.22 ± 0.03^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 111
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

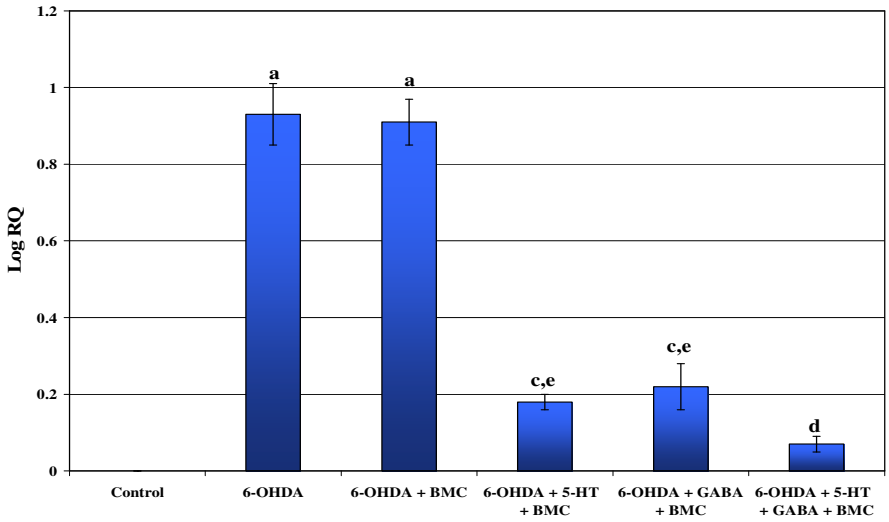


Table - 113
Real Time PCR amplification of 5-HT_{2C} receptor subunit mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	0.93 ± 0.08^{a}
6-OHDA + BMC	0.91 ± 0.06^{a}
6-OHDA + 5-HT + BMC	$0.18 \pm 0.02^{c,e}$
6-OHDA + GABA + BMC	$0.22 \pm 0.06^{c,e}$
6-OHDA + 5-HT + GABA + BMC	0.07 ± 0.02^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 112
Real Time PCR amplification of 5-HT transporter mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

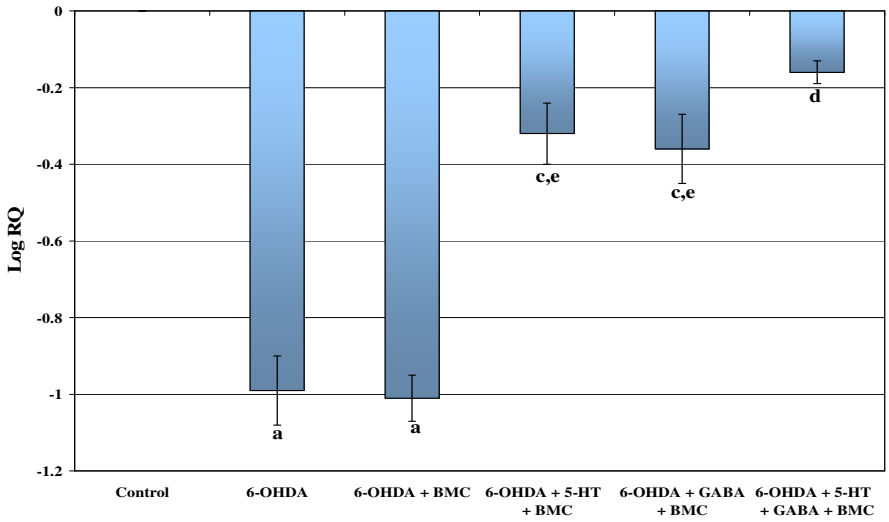


Table - 114
Real Time PCR amplification of 5-HT transporter mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-0.99 ± 0.09[a]
6-OHDA + BMC	-1.01 ± 0.06[a]
6-OHDA + 5-HT + BMC	-0.32 ± 0.08[c,e]
6-OHDA + GABA + BMC	-0.36 ± 0.09[c,e]
6-OHDA + 5-HT + GABA + BMC	-0.16 ± 0.03[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 113
Real Time PCR amplification of SOD mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

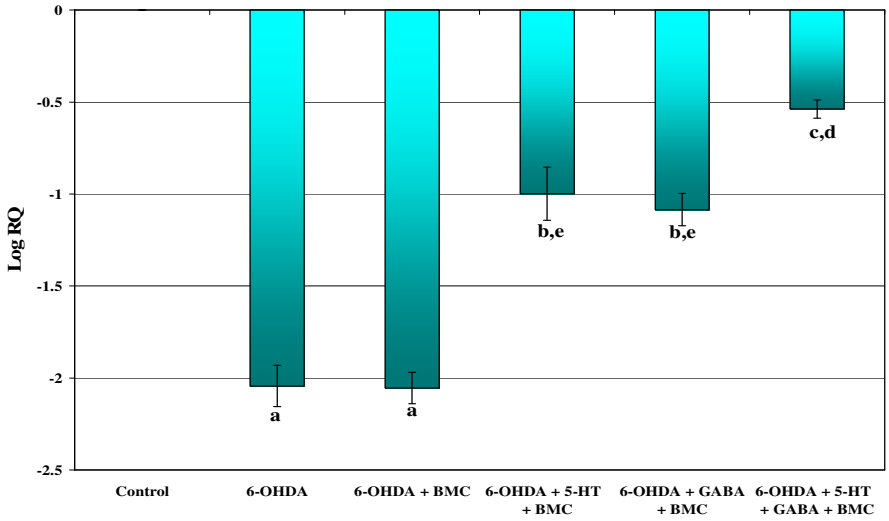


Table - 115
Real Time PCR amplification of SOD mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.04 ± 0.11[a]
6-OHDA + BMC	-2.05 ± 0.08[a]
6-OHDA + 5-HT + BMC	-0.99 ± 0.14[b,e]
6-OHDA + GABA + BMC	-1.08 ± 0.09[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.54 ± 0.05[c,d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 114
Real Time PCR amplification of GPx mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

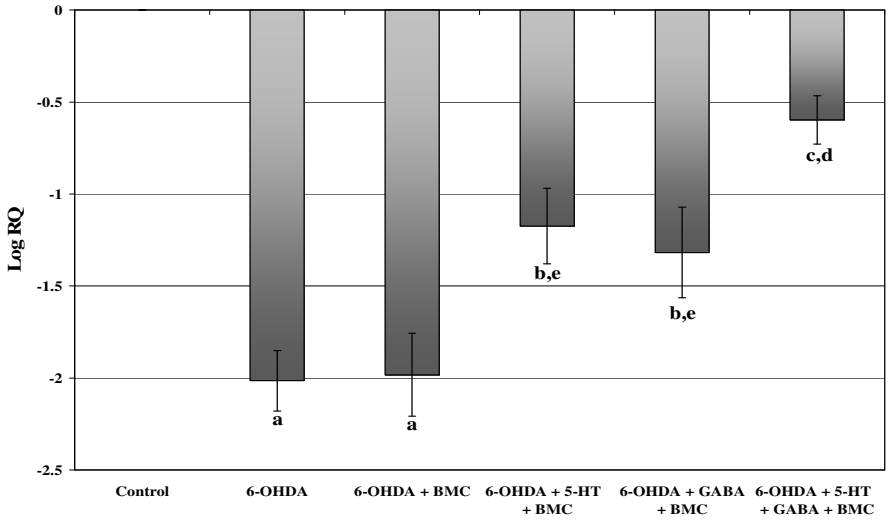


Table - 116
Real Time PCR amplification of GPx mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-2.01 ± 0.16[a]
6-OHDA + BMC	-1.98 ± 0.22[a]
6-OHDA + 5-HT + BMC	-1.17 ± 0.20[b,e]
6-OHDA + GABA + BMC	-1.32 ± 0.25[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.60 ± 0.13[c,d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 115
Real Time PCR amplification of Akt mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

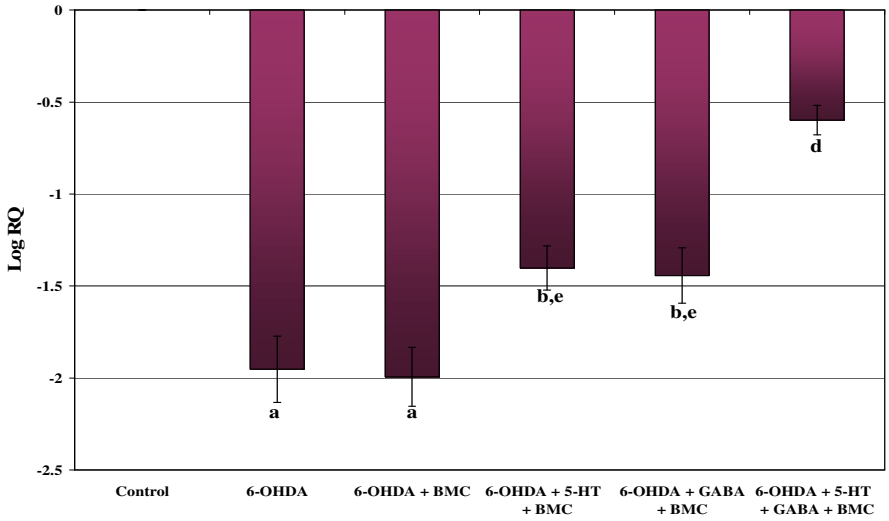


Table - 117
Real Time PCR amplification of Akt mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-1.95 ± 0.18[a]
6-OHDA + BMC	-1.99 ± 0.16[a]
6-OHDA + 5-HT + BMC	-1.40 ± 0.12[b,e]
6-OHDA + GABA + BMC	-1.44 ± 0.15[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.60 ± 0.08[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 116
Real Time PCR amplification of NF-κB mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

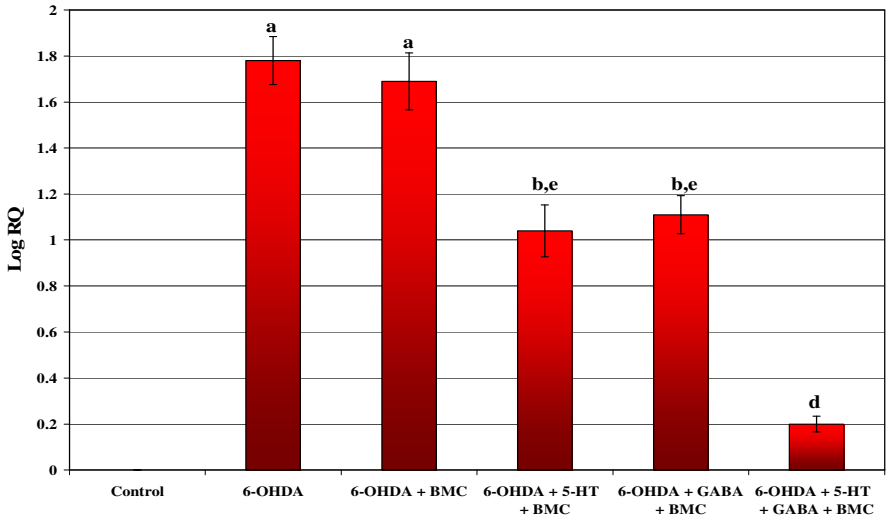


Table - 118
Real Time PCR amplification of NF-κB mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	1.78 ± 0.10^{a}
6-OHDA + BMC	1.69 ± 0.12^{a}
6-OHDA + 5-HT + BMC	$1.04 \pm 0.11^{b,e}$
6-OHDA + GABA + BMC	$1.11 \pm 0.08^{b,e}$
6-OHDA + 5-HT + GABA + BMC	0.20 ± 0.03^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 117
Real Time PCR amplification of Caspase-8 mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

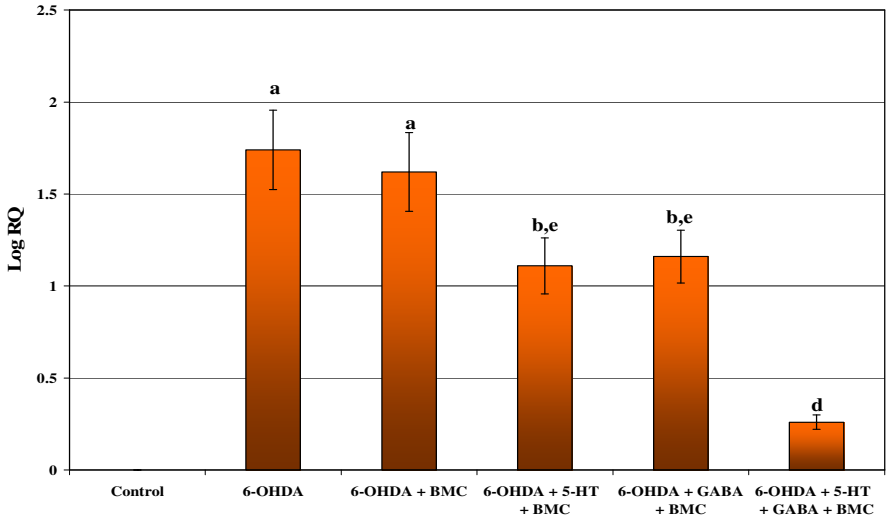


Table - 119
Real Time PCR amplification of Caspase-8 mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	1.74 ± 0.21^{a}
6-OHDA + BMC	1.62 ± 0.21^{a}
6-OHDA + 5-HT + BMC	$1.11 \pm 0.15^{b,e}$
6-OHDA + GABA + BMC	$1.16 \pm 0.14^{b,e}$
6-OHDA + 5-HT + GABA + BMC	0.26 ± 0.03^{d}

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 118
Real Time PCR amplification of BDNF mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

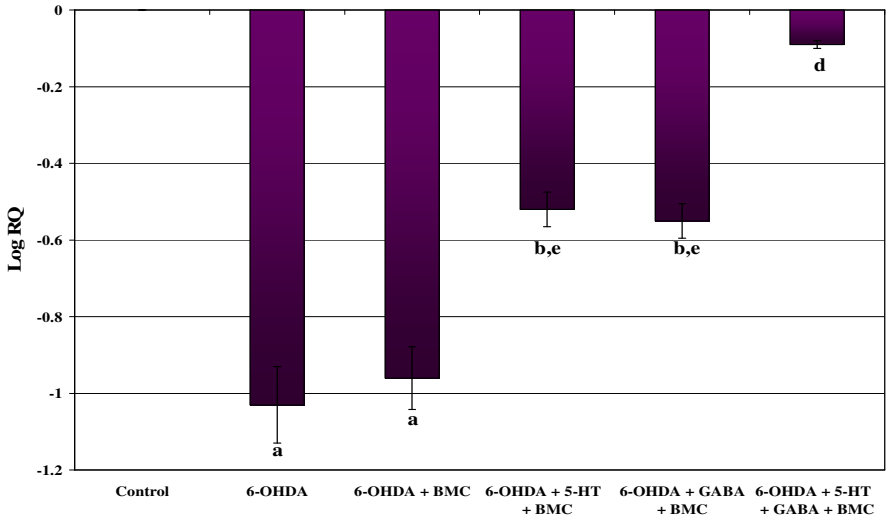


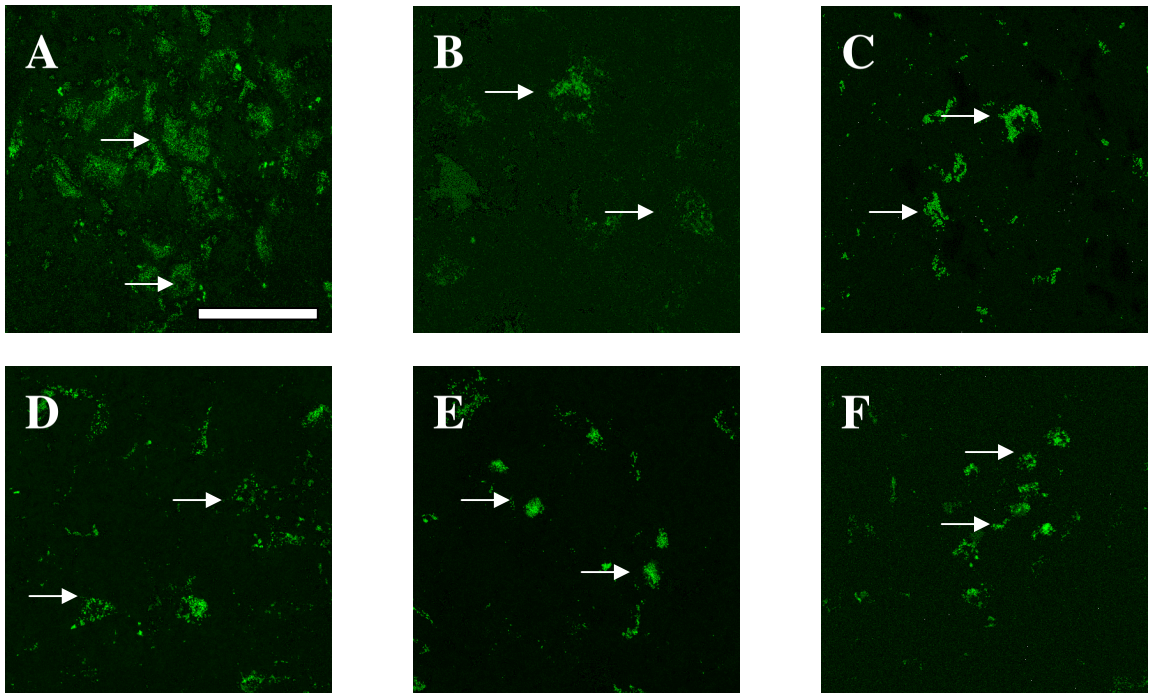
Table - 120
Real Time PCR amplification of BDNF mRNA in the Brain stem of Control, 6-OHDA infused, 6-OHDA + BMC, 6-OHDA + 5-HT + BMC, 6-OHDA + GABA + BMC and 6-OHDA + 5-HT + GABA + BMC treated rats

Animal Status	Log RQ
Control	0
6-OHDA	-1.03 ± 0.10[a]
6-OHDA + BMC	-0.96 ± 0.08[a]
6-OHDA + 5-HT + BMC	-0.52 ± 0.05[b,e]
6-OHDA + GABA + BMC	-0.55 ± 0.04[b,e]
6-OHDA + 5-HT + GABA + BMC	-0.09 ± 0.01[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.
[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 119
5-HT_{2A} receptor expression in the Brain stem of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 121
5-HT_{2A} receptor expression in the Brain stem of control and experimental rats

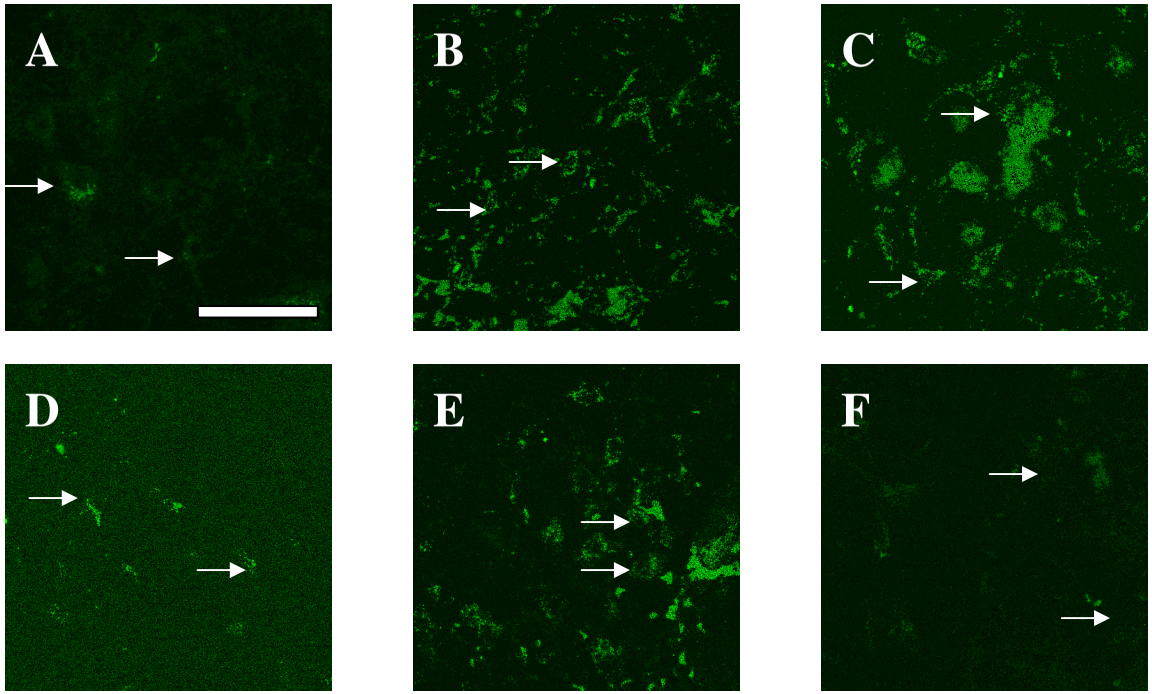
Experimental Groups	Mean Pixel Intensity
Control	48.47 ± 2.30
6-OHDA	27.97 ± 1.98[a]
6-OHDA + BMC	28.24 ± 2.33[a]
6-OHDA + 5-HT + BMC	41.87 ± 2.03[b,e]
6-OHDA + GABA + BMC	40.39 ± 1.49[b,e]
6-OHDA + 5-HT + GABA + BMC	45.38 ± 2.17[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 120
5-HT_{2C} receptor expression in the Brain stem of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 122
5-HT_{2C} receptor expression in the Brain stem of control and experimental rats

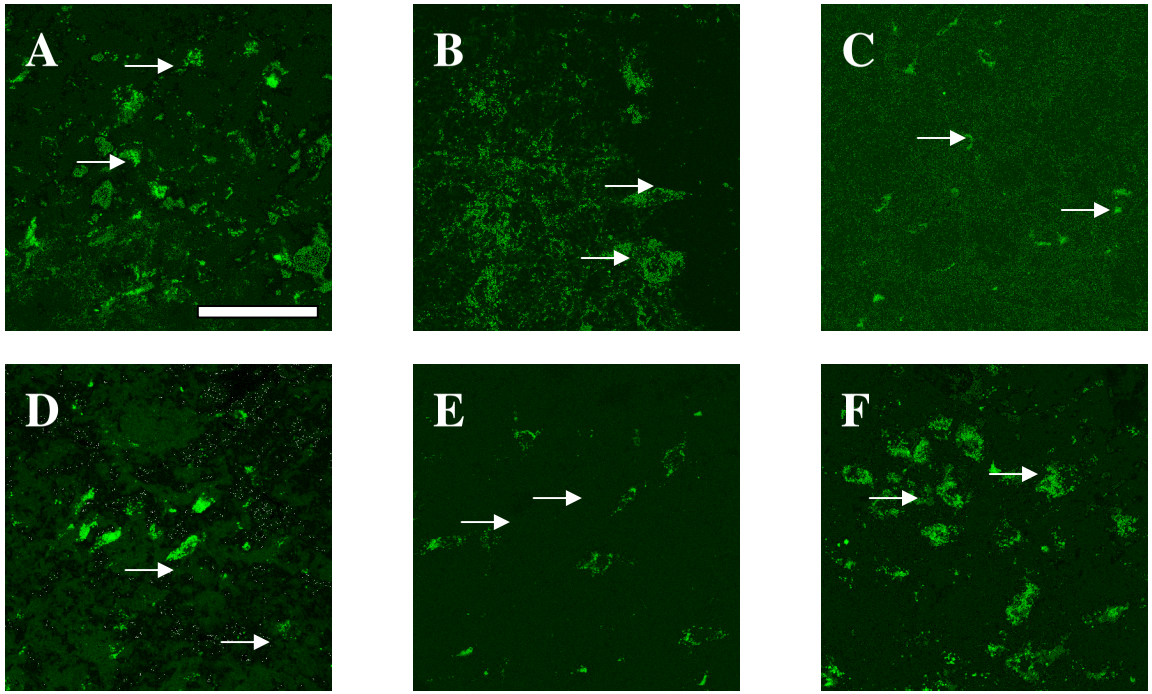
Experimental Groups	Mean Pixel Intensity
Control	22.25 ± 1.96
6-OHDA	47.38 ± 3.19[a]
6-OHDA + BMC	44.96 ± 2.93[a]
6-OHDA + 5-HT + BMC	29.18 ± 1.54[c,e]
6-OHDA + GABA + BMC	32.37 ± 3.08[c,e]
6-OHDA + 5-HT + GABA + BMC	23.86 ± 1.88[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 121
5-HT transporter expression in the Brain stem of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 123
5-HT transporter expression in the Brain stem of control and experimental rats

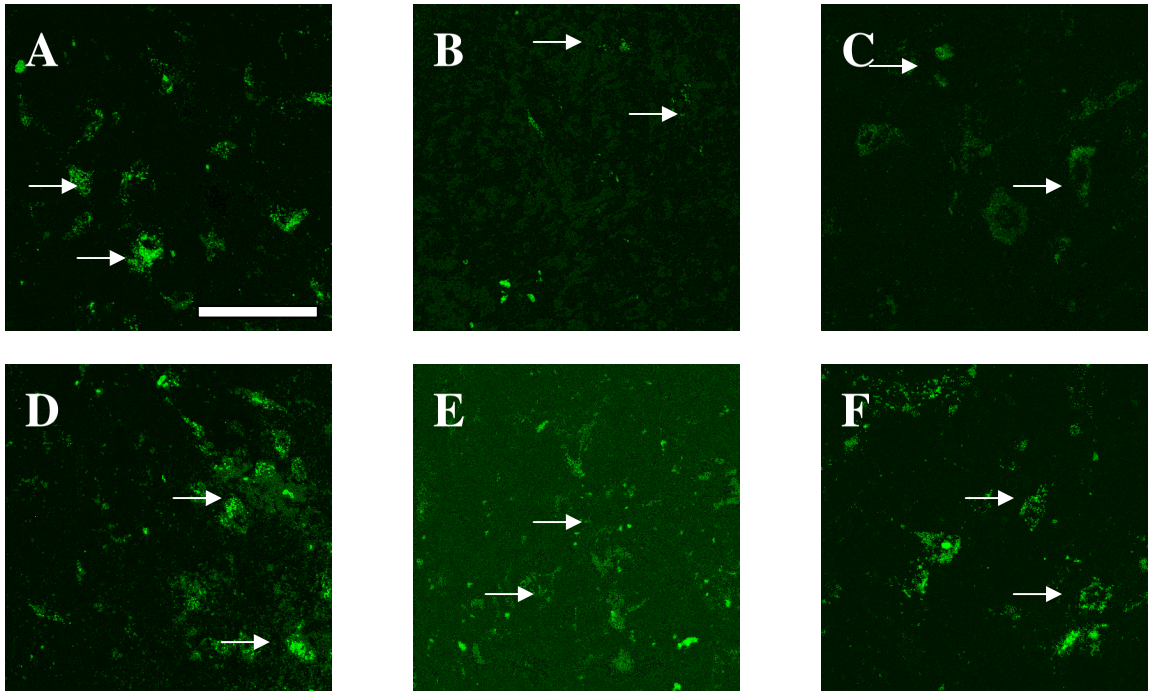
Experimental Groups	Mean Pixel Intensity
Control	53.47 ± 3.29
6-OHDA	23.81 ± 1.85[a]
6-OHDA + BMC	26.26 ± 2.65[a]
6-OHDA + 5-HT + BMC	42.91 ± 3.88[c,e]
6-OHDA + GABA + BMC	39.02 ± 3.23[c,e]
6-OHDA + 5-HT + GABA + BMC	51.28 ± 3.17[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Figure - 122
BDNF expression in the Brain stem of control and experimental rats



A – Control, B – 6-OHDA infused, C – 6-OHDA infused treated with BMC, D – 6-OHDA infused treated with Serotonin and BMC, E – 6-OHDA infused treated with GABA and BMC, F – 6-OHDA infused treated with Serotonin, GABA and BMC. The scale bars represent 75 μm.

Table - 124
BDNF expression in the Brain stem of control and experimental rats

Experimental Groups	Mean Pixel Intensity
Control	47.12 ± 2.20
6-OHDA	24.30 ± 1.94[a]
6-OHDA + BMC	27.18 ± 2.05[a]
6-OHDA + 5-HT + BMC	40.31 ± 2.94[c,e]
6-OHDA + GABA + BMC	35.14 ± 2.02[b,e]
6-OHDA + 5-HT + GABA + BMC	43.92 ± 2.18[d]

Values are Mean ± S.E.M of 4-6 separate experiments. Each group consist 4-6 rats.

[a] $p<0.001$, [b] $p<0.01$, [c] $p<0.05$ when compared to Control.
[d] $p<0.001$, [e] $p<0.01$ when compared to 6-OHDA group.

C – Control, 6-OHDA – 6-OHDA infused, 6-OHDA + BMC – 6-OHDA infused treated with BMC, 6-OHDA + 5-HT + BMC - 6-OHDA infused treated with Serotonin and BMC, 6-OHDA + GABA + BMC - 6-OHDA infused treated with GABA and BMC, 6-OHDA + 5-HT + GABA + BMC - 6-OHDA infused treated with Serotonin, GABA and BMC.

Discussion

Parkinson's disease (PD) is the second most common neurodegenerative disorder, afflicting approximately 6 million people worldwide. The cardinal features of PD include resting tremor, rigidity, bradykinesia and postural instability. These symptoms are a result of the degeneration of the dopaminergic nigrostriatal pathway originating in the SN*pc*. While SN*pc* neurons are preferentially lost in PD, they are by no means the only neuronal population affected. Degeneration in other areas namely, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem are likely to contribute many of the motor as well as non-motor symptoms of PD, such as depression, dementia and autonomic dysfunction. Current treatments address the dopaminergic deficit, providing symptomatic benefit to many of the motor deficits. However, there are many symptoms that do not respond to dopaminergic therapy. In addition, there are no proven interventions to slow down the underlying degenerative process.

There is increasing interest in the transplantation of stem cells as a means of recovering function in individuals with neurodegenerative disease. Although substantial improvements result from the systemic administration of L-DOPA or DA agonists, such pharmacological interventions do not address the etiology of the disease, provide a permanent remedy or prevent progression of the degenerative process (Snyder & Olanow, 2005). Implantation of stem cells will provide a more constitutive and relevant solution. This realisation has prompted a renewed interest in stem cells, which serves as a replenishable source of cells for the treatment of neurodegenerative disorders. The success of the cell transplantation will depend on the ability of the cells to replace those neurons lost as a result of the disease process in the DA-deficient striatum and reverse, at least in part, the major symptoms of the disease. Previous studies on PD animal models have examined functional recovery after cell implantation, employing behavioural testing followed by post-mortem histology to establish cellular efficacy (Lu *et al.*, 2005). A more recent study using MRI alone in PD rats, demonstrated the visualization of implanted neural stem cells for several weeks with improved post-

transplantation behavioural rotation (Yang *et al*., 2006). Other reports have shown implanted mesenchymal stem cells tracked by MRI for 50 days in a rodent model of stroke (Jendelova *et al*., 2004) and oligodendrocyte progenitors were tracked for six weeks in a rodent model of demyelination (Bulte *et al*., 2002). A clinically relevant strategy is to implant BMC that are constitutively capable of neural differentiation and cytokine secretion. Allowing the cells to develop within the PD-affected brains, yields cells whose phenotypes, numbers, locations and regulation are determined by the interplay of donor elements and the local host milieu. A consequence of such donor–host interaction would result in a more pertinent homeostasis. We hypothesized that the BMC-based approach might better mitigate some of the limitations of previous strategies, where pre-programmed partially differentiated cells did not provide functional recovery (Brederlau *et al*., 2006). To date, bone-marrow-derived cells, comprising both hematopoietic and mesenchymal stem cells (MSCs), represent a major source of exogenous adult progenitor cells capable to regenerate and repair tissues (Han *et al.*, 2006). Several reports have demonstrated that BMC's have the potential to directly differentiate into multiple cellular types, such as myogenic progenitors, neural cells and hepatocytes (Giordano *et al.*, 2007). Many data also suggest that the BMC-mediated restoration of injured tissues depend upon their capacity to release a broad spectrum of cytokines/growth factors inhibiting apoptosis, promoting angiogenesis and stimulating the host cells to regenerate the damaged tissues (Dezawa *et al.*, 2005). Another interesting and intriguing feature of BMC's relies on their capability to avoid immune system recognition and to establish immune response inhibition (Rasmusson, 2006). BMC holds potential as a readily available autologous cellular therapy for ameliorating the degeneration of DA and 5-HT neurons in PD (Glavaski-Joksimovic *et al.*, 2009). Bone marrow stromal cells (BMSC) promote survival and renders protection on progressive loss of DA neurons (Shintani *et al.*, 2007; Park *et al.*, 2008; Cova *et al.*, 2010). Graft of adult mesenchymal stem cells reduces behavioural effects induced by 6-OHDA lesion and partially recovers the dopaminergic pathway (Bouchez *et al.*, 2008). All the

above studies show that besides their ability to differentiate into neurons, BMC's also exert neuroprotective effect against the DA depletion.

5-HT and GABA as therapeutic agents for cell proliferation and differentiation is a novel approach. 5-HT plays an important trophic role during neurogenesis (Lauder *et al.*, 1981; Hernández R, 1994) and has been reported to affect neuronal proliferation, differentiation, migration and synapatogenesis (Gaspar *et al.*, 2003). Lauder and Krebs (1978) reported that parachlorophenylalanine (PCPA), a 5-HT synthesis inhibitor, retarded neuronal maturation, while mild stress, a stimulant of 5-HT synthesis, accelerated neuronal differentiation. 5-HT can influence both biochemical and morphological differentiation of neurons and have an organizing function in the developing nervous system which involves effects on neurite outgrowth and other aspects of neuronal differentiation, including synaptogenesis (Lauder, 1990). GABA, the main inhibitory neurotransmitter in the mature CNS, was recently implicated in playing a complex role during neurogenesis. GABA acts as a chemoattractant and involves in the regulation of neural progenitor proliferation. GABA induces migration and motility of embryonic cortical neurons (Behar *et al.*, 1996, 2000; Haydar *et al.*, 2000). GABA acts as a trophic factor not solely during prenatal neurogenesis but also postnatally and promotes cell proliferation and NGF secretion (Ben-Yaakov & Golan, 2003). Our earlier studies showed that 5-HT and GABA acting through specific receptor subtypes $5HT_2$ (Sudha & Paulose, 1998) and $GABA_B$ (Biju *et al.*, 2002) respectively, control cell proliferation and act as co-mitogens. We have also previously established the DA and glutamate receptors functional regulation during PD by neurotransmitters 5-HT and GABA in combination with BMC (Nandhu *et al.*, 2011a, 2011b; Paul *et al.*, 2010, 2011). Individual and combined treatments with 5-HT and GABA did not show significant changes. Hence our present study evaluated the functional changes rendered by BMC alone and in combinations with 5-HT and GABA.

Loss of body weight in PD

Weight loss is common among PD patients. The frequency of weight loss among such patients is 52 % as reported by Abbott *et al*., (1992) and 65 % by Moroo *et al*., (1994). Weight loss is more prominent in women (average body weight loss 8.5 %) than in men (4.3 %) and becomes marked in patients with advanced disabilities. Weight loss in PD can be ascribed, primarily, to a loss of fat tissue. A variety of components contribute to weight loss, involving hyposmia, insufficient food ingestion, impaired hand–mouth coordination, difficulty in chewing, dysphagia, intestinal hypomotility, depression, decreased reward processing of dopaminergic mesolimbic regions and increased energy requirements due to muscular rigidity and increased involuntary movements such as dyskinesia and tremor (Bachmann & Trenkwalder, 2006; Aziz *et al.*, 2008).

We observed a significant weight loss in 6-OHDA infused PD rats. Weight loss postlesion has been reported previously following bilateral intrastriatal (Cousins *et al.*, 1993; Salamone *et al.*, 1993; Roedter *et al.*, 2001) and bilateral medial forebrain bundle (MFB) 6-OHDA-induced lesions (Dunnett *et al.*, 1983) and has been attributed to profound motor deficits interfering with drinking and feeding behaviour. During post lesion period, an increase in muscle rigidity and movement-induced reflex electromyographic activity has also been reported in rats with bilateral 6-OHDA-induced lesions of the SN (Wolfarth *et al.*, 1996).

Energy expenditure decreases due to motor impairment but increase in parallel with worsening of muscle rigidity and the development of LIDs. Disturbed motility and absorption of the gastrointestinal tract impair energy intake. Dysphagia occurs in the advanced stage of PD and anorexia caused by depression also could cause disturbed energy intake. Anti-Parkinsonian drugs accelerate anorexia and dysfunction of the gastrointestinal tract. Moreover, weight loss is also associated with insufficient nutrition, precipitating infection and decubitis and increasing the mortality rate (Kashihara, 2006).

Treatment with 5-HT, GABA and BMC in combinations significantly improved the body weight indicating restoration of the equilibrium between

intake, digestion and absorption of energy from nutrients on the one hand and energy expenditure on the other hand.

Behavioural alterations in PD rats

Unilateral lesion of the nigrostriatal projections in rats with 6-OHDA leads to the loss of DA cells in the SN, through retrograde axonal transport at the DA striatal terminals. 6-OHDA induces toxicity through intra or extracellular auto-oxidation, H_2O_2 formation induced by MAO-B activity or direct inhibition of the mitochondrial respiratory chain and consequent oxidative stress (Shim *et al*., 2009). These affiliated neurocellular changes leads to the representative Parkinsonian symptoms which show similarity to those observed in PD. Unilateral injections of 6-OHDA produce distinct motor impairments that include decreased rearing, akinesia, postural abnormalities and DA agonist-induced asymmetric rotating behaviours (Schwarting & Huston, 1996; Johnson *et al.*, 1999). Rats with depletions in the nigrostriatal system represent a successful tool for understanding the effects of selective dopaminergic lesions (Truong *et al.*, 2006) and as a reasonable model for replicating aspects of the human disease. Behavioural tests are widely used as important indices to measure the impairment of the movement in the PD models. This battery of sensorimotor tests can be used to characterize the extent of lesion in 6-OHDA-injected rats and assess the effectiveness of potential therapeutic approaches in the 6-OHDA rat model.

In PD, the progressive degeneration of nigral dopaminergic neurons results in motor deficits only after 80% of the nigrostriatal system has degenerated. Therefore behavioural studies preferentially involve unilateral destruction of the nigrostriatal pathway with 6-OHDA to avoid the debilitating consequences of a bilateral lesion (Hritcu *et al*., 2008). Depending on the dose and the site of infusion into the brain, unilateral 6-OHDA SN*pc*-lesioned rats present an almost complete loss of dopaminergic neurons in the SN*pc*, a proportional depletion of striatal DA and gross motor disturbances, like turning behaviour (e.g. after a challenge with DA receptor agonists) and reduced locomotion. Ungerstedt (1968) reported preliminary findings that injection of the neurotoxin 6-OHDA into

one nigrostriatal pathway of the rat produced an animal with loss of catecholamine histochemical fluorescence from the ipsilateral striatum and with marked motor asymmetry, turning spontaneously towards the side of the 6-OHDA injection. Unilateral injection of 6-OHDA into the SN caused degeneration of the ipsilateral nigrostriatal pathway and loss of DA from the ipsilateral striatum. Following injection of 6-OHDA into the nigrostriatal pathway, a rat exhibits rotational behaviour or a body asymmetry towards the lesioned side. This circling behaviour is exaggerated with systemic administration of amphetamine, which stimulates catecholamine release. Within a few weeks after 6-OHDA treatment, striatal denervation hypersensitivity to DA develops; it is demonstrated by circling behaviour in the opposite, away from the side of the injection site direction with administration of the DA agonist, apomorphine. Our studies with apomorphine showed a reversal in the rotational behaviour in rats treated with 5-HT, GABA and BMC compared to 6-OHDA infused rats. This indicates the reduction of DA receptor hypersensitivity after the BMC transplantation with 5-HT and GABA.

Although drug-induced rotational behaviour has conventionally been used for the analysis of lesioned animals, a pure behavioural test that can evaluate such animals in a drug-free state better reflect a more natural response following lesion. The unilateral damage of dopaminergic nigrostriatal system through intrastriatal injection of 6-OHDA is a well-established and widely used animal model of PD and is followed by a gradual reduction in striatal DA levels and up regulation of dopaminergic postsynaptic receptors. These changes produce a functional asymmetry that is conventionally measured by apomorphine and amphetamine dopaminergic agonists. However, the development of sensitivity due to repeated apomorphine administration in the long term might complicate the interpretation of drug-induced rotational behaviour (Klug & Norman, 1993), especially when assessing the efficacy of neural transplants. For example, in transplanted animals with hemiparkinsonism, a normalization of the drug-induced behaviour indicate a recovery from imbalance in DA contents and releasing capacity in the bilateral nigrostriatal pathway, but the observed behaviour is a pharmacological reaction

(Hattori *et al*., 1992). EBST can be used as a reliable behavioural parameter in 6-OHDA-induced hemiparkinsonian rats.

The present study demonstrated that rats with 6-OHDA lesions in the SN displayed a biased contralateral swing activity that correlated highly with the conventional apomorphine-induced rotational behaviour. Stress caused by handling the animal by its tail induces the biased swing behaviour. Past studies have reported that tail pinch and stressor effects result in changes in locomotor activity (Rouge-Pont *et al.*, 1993). The dopaminergic system is activated by stressful stimuli (Imperato *et al.*, 1991). Since DA exerts some tonic influence on the striatal neurons, an imbalance in striatal DA levels affect stress-evoked DA release and reuptake in the striatum which, in turn, alters the locomotor activity. The 6-OHDA induced contralateral body swinging preference was significantly reduced in animals receiving BMC implantation along with 5-HT and GABA. However, no significant improvement was observed in the rats implanted with BMC alone. The present results have shown that BMC implantation along with 5-HT and GABA reduced the nigrostriatal damages caused by 6-OHDA and significantly improved the behavioural deficits associated with 6-OHDA induced PD. Large and extended improvement in the EBST suggest that implantation of BMC in combination with 5-HT and GABA preferentially enhanced motor functional recovery.

The stepping test is a highly useful test to monitor lesion and transplant induced changes in forelimb akinesia, a behavioural parameter that is analogous to limb akinesia and gait problems seen in patients with PD. Patients with PD have difficulties in executing a movement efficiently and with maintaining gait (Lamberti *et al.*, 1997). The degree of akinesia is associated with the degree of depletion of DA neurons and therefore, it is expected that severe model is associated with more serious movement disorders, as also shown by Kirik *et al.* (1998). Consistent with the previous observations of Norton *et al.* (1992), Schallert *et al.* (1992) and Olsson *et al.* (1995), the 6-OHDA lesion induced marked deficits in forelimb stepping on the side contralateral to the lesion. After the 6-OHDA lesion, the performance of the left paw (contralateral to the lesion)

was significantly impaired compared to the intact controls. The 6-OHDA lesion profoundly affected the left paw performance which resulted in a dragging paw when the rat was moved sideways by the experimenter. Treatments with 5-HT, GABA and BMC in combinations significantly improved the performance with the left paw, whereas BMC administered alone were without effect. The most pronounced effect was seen after transplantation of BMC along with 5-HT and GABA together, which restored the number of adjusting steps to a level no longer different from that seen in the intact controls. The present observations strongly suggest that the 5-HT and GABA supplemented BMC induced effects on rotation and forelimb akinesia have similar underlying mechanisms, that is, tonic activation of DA receptors in SN and striatum by a sustained release of DA from the grafted BMC, which results in a normalization of the sensitivity of the initially denervated receptors. PD rats transplanted with BMC-derived dopaminergic neurons showed a substantial recovery of apomorphine-induced rotation as well as stepping tests (Dezawa *et al.*, 2004).

Hypokinesia of gait with reduced stride length is characteristic for many basal-ganglia-related disorders. Assessment of gait parameters is typically done from footprints made by rats running freely through a tunnel on a piece of paper after their paws are coloured. The analysis of footprint patterns and walking tracks permits assessment of motor function in a manner distinct from that of the rotarod test, in that the footprint analysis does not impose on the animal a requirement for either motor ability or coordination. The manual gait analysis has been used previously to reveal alterations in stride length in several rodent models of PD, including MPTP-lesioned mice and 6-OHDA-lesioned mice and rats (Kurz *et al.*, 2007). Fernagut *et al.* (2002) described stride-length performance in mice after pharmacological- and/or subacute neurotoxin-induced Parkinsonism. We observed a shorter stride length in 6-OHDA lesioned rats compared to control. The present data confirm previous evidence suggesting that pattern generating networks for locomotion in DA-depleted rats are functional and produce a rhythmic gait pattern (Pellis *et al.*, 1987). One possible explanation for these alterations in walking patterns of DA depleted rats is a change in spinal reflex pathways. Sensorimotor

assessments have previously shown that loss of DA affects cutaneous and proprioceptive perception in rats (Schallert *et al.*, 2000) and in humans (Abbruzzese & Berardelli, 2003). The unilateral DA depletion changed the sensory input and influenced the gait patterns produced by each side to a different extent (Metz *et al.*, 2005). Also, modulation of the output from the brain stem, particularly the reticular formation induces asymmetric stepping patterns in unilaterally DA depleted rats. The reticular formation gives rise to the reticulospinal tract that provides the excitatory drive for spinal pattern-generating networks (Grillner *et al.*, 1998; Prentice & Drew, 2001; Schucht *et al.*, 2002). The asymmetry in basal ganglia output results in an asymmetric reticulospinal tract activation, which in turn results in an asymmetric gait pattern (Metz *et al.*, 2005). Treatment with 5-HT, GABA and BMC in combination reversed the altered gait pattern observed by footprint analysis to near control.

Deteriorations in balance and posture have been reported at stage 2–3 (mild–moderate PD symptoms) using the Hoehn and Yahr scale (Hoehn & Yahr, 1967). Potentially advantageous over other motor tests, the beam-walking task has the ability to assess fine-motor initiation, coordination and postural balance of an individual animal. There was a significant and consistent difference in time to traverse the balance beam by 6-OHDA lesioned rats compared to control. This suggests that DA depletion in the SN*pc* resulted in both an increased delay in initiating movement and a reduced speed in crossing the beam, which would be consistent with akinesia and bradykinesia observed previously in animal models of PD.

Symptoms/behavioural changes in rat models of PD have been correlated with DA cell loss. In particular, behaviours that have been shown to correlate with cell loss include postural bias, reaction time, locomotion and cognition. In all our experimental behavioural tests, the results show that rats with 6-OHDA lesions displayed obvious difficulties in locomotion, balance and posture, all of which are well correlated to cell loss. In patients, these PD symptoms develop when DA cell loss reaches 68% (Fearnley & Lees, 1991). Non-motoric aspects of PD in humans such as cognition have been shown to decline with progression of motor

symptoms (Sawamoto *et al.*, 2002). The significance of our outcomes imply that use of neuroprotective and neuroregenerative therapy with BMC in combination with 5-HT and GABA in PD will leave patients mildly symptomatic (rather than experiencing greater deterioration long-term) by halting further cell loss and improving functional recovery.

Substantia nigra *pars compacta*

The SN is a division of the basal ganglia consisting of two major components, the SN*pr* and SN*pc*. The SN*pr* contains one of the populations of basal ganglia output neurons and the SN*pc* contains the dopaminergic nigrostriatal neurons which are involved in the modulation of the flow of cortical information through the basal ganglia. SN*pc* is one of the main output nuclei of the basal ganglia structures and as such plays an important role in the motor activity. DA neuronal systems, originating in the SN*pc* constitute one of the main actors of such an important role (Campusano *et al*., 2002). A pathologic hallmark feature of PD and essential for its pathologic diagnosis is loss of nigrostriatal DA neurons of the SN*pc*. It is this loss, in addition to possible dysfunction of the remaining neurons, that accounts for the approximately 80% loss of DA in the corpus striatum (Sonsalla *et al*., 2012). Neuropathologic studies of PD suggested that patients with the earliest signs of disease have already lost as much as 50% of the pigmented dopaminergic neurons in the SN*pc* (Marsden, 1990).

Growing lines of evidence suggest that PD is not solely a dopaminergic disease but that there is a more diffused pathology involving the serotonergic neurotransmitter system. 5-HT neurons in the DRN project mainly to the basal ganglia, particularly the SN*pc,* striatum, frontal cortex and the limbic system. The serotonergic system is involved in the modulation of various cognitive and physiological processes, such as, mood, emotion, sleep and appetite. Thus altered serotonergic neurotransmission results in both motor and nonmotor disturbances observed in PD (Navailles & De Deurwaerdère, 2011) and therefore, the modulation of 5-HT has obvious implications for the treatment of PD. In the present study, 5-HT content was observed to be decreased in PD rats. In PD, there

is loss of 5-HT cell bodies (Halliday *et al.*, 1990; Kim *et al.*, 2003). The ascending 5-HT system from the forebrain innervates each of the basal ganglia nuclei, which collectively malfunction due to loss of DA in the nigrostriatal pathway to generate the motor symptoms of PD (Di Matteo *et al.*, 2008). As a result, there is decreased production of 5-HT due to the degeneration of serotonergic neurons. Dysfunctional 5-HT neurotransmission is an important risk factor for depression (Tan *et al.*, 2011), which is a major symptom associated with PD.

There is tight functional interaction between DA and 5-HT receptors and regulation of dopaminergic neurotransmission by 5-HT_{2A} and 5-HT_{2C} receptor systems has been well established. Activation of 5-HT_{2A} receptors can facilitate stimulated DA release, whereas, 5-HT_{2C} inhibit dopaminergic neural activity and DA release (Berg *et al.*, 2008). We observed a decreased expression of 5-HT_{2A} receptors whereas the 5-HT_{2C} receptors showed an increased expression. It has been shown that 5-HT_{2A} receptors are coexpressed with DA 1–5 receptors in different brain regions, such as the SN*pc* and corpus striatum (Goldman-Rakic, 1999). Immunohistochemistry showed that 5-HT_{2A} receptors are colocalized with TH and are expressed on dopaminergic neurons within the A10 DA subnuclei (Nocjar *et al.*, 2002). The decreased expression of 5-HT_{2A} receptors results in the inhibition of DA release as can be observed from the levels of DA analysed in the present study. Intracortical infusion of the 5-HT_{2A} receptor antagonist M100907 profoundly attenuates DA release induced by systemic administration of the 5-HT agonist, suggesting that stimulation of cortical 5-HT_{2A} receptors increase DA release from the mesocortical system (Pehek *et al.*, 2006).

Increase in 5-HT_{2C} receptor expression was observed in 6-OHDA-lesioned rats, strictly in accordance with the evidence that 5-HT_{2C} receptor binding in the SN of age-matched control tissue was less than half that in the SN of patients with PD (Radja *et al.*, 1993; Fox & Brotchie, 2000). This evidence highlights a selective change in the 5-HT_{2C} receptor activity only in the output regions of the basal ganglia. 5-HT_{2C} receptors' up-regulation might be compensatory, being a consequence of a decreased level of 5-HT in these nuclei, thus indicating a role for them in the neuronal mechanisms involved in PD (Fox & Brotchie, 2000).

Interestingly, in our study, the 5-HT, GABA and BMC combination treatment group could significantly reverse the altered expression of 5-HT_{2A} and 5-HT_{2C} receptors to near control. It has been well established that 5-HT_{2A} receptors enhance both DA release and DA synthesis (Schmidt *et al.*, 1992; Navailles & De Deurwaerdère, 2011) whilst the activation of 5-HT_{2C} receptors participates in the tonic inhibitory control they exert on DA release in the rat SN*pc* (De Deurwaerdère *et al.*, 2004).

5-HT concentrations in neural tissue are controlled by a presynaptic 5-HT transporter protein that plays a pivotal role in the termination of serotonergic neurotransmission. The magnitude and duration of postsynaptic responses are mediated by the transporter; hence changes in the expression of this transporter would have critical implications for the fine tuning of serotonergic neurotransmission. 5-HTT gene expression in the present study showed a significant down regulation compared to control. Neurochemical studies have indicated a decrease in striatal and cortical 5-HT and a reduction in CSF 5-HT concentration in PD patients (D'Amato *et al.*, 1987; Toghi *et al.*, 1993). Furthermore, biochemical abnormalities of the serotonergic system associated with PD is a direct result of 5-HTT abnormalities. We also observed a decrease in 5-HT content in 6-OHDA lesioned PD rats. Consistent with the observation of reversal of decreased 5-HT content to near control, we found a reversal of 5-HTT gene expression in 6-OHDA + 5-HT + GABA + BMC group of rats which improves the impaired serotonergic transmission and in turn the DA transmission.

A consistent neurochemical abnormality in PD is degeneration of dopaminergic neurons in SN*pc*, leading to a reduction of DA levels. In our study, 6-OHDA infusion into the SN*pc* region leads to reduced DA content thus confirming Parkinsonism. The distribution of striatal 5-HT receptors and their restricted influence on DA neuron activity suggest that the endogenous 5-HT system exerts multiple and subtle influences on DA-mediated behaviours. Nigrostriatal infusions of exogenous 5-HT has been shown to enhance DA release in the rat SN (Thorré *et al*., 1998). *In vitro* studies have reported an excitatory influence of exogenous 5-HT on basal DA release in the striatum (Zhou *et al.*,

2005). For confirming whether the transplanted cells can reverse back the normal DA production, we analysed the DA content and expression of TH positive cells. TH catalyses the formation of L-DOPA, the rate-limiting step in the biosynthesis of DA. 6-OHDA infusion severely down regulated the TH gene expression as well as reduced the number of TH-immunopositive neurons compared to the control group. Treatment with 5-HT and GABA along with BMC reversed these alterations which imply that the differentiated BMC is able to synthesise DA. Thus the elevated levels of 5-HT observed in the combination treated group increases the DA release in the striatum, improving the motor deficits and related depressive illness occurring during PD.

Defects in several cellular systems including mitochondrial dysfunction, oxidative stress and dysregulated kinase signalling have been implicated as early triggers that start cells down the road towards neuronal death in PD. As dysfunction in these systems mounts, pathways that are more explicitly involved in cell death become recruited. Eventually, neurons become overwhelmed and degenerate. Because of the increased oxygen consumption by mitochondria, inhibition of complex I can result in accumulation of ROS and other powerful oxidants. These oxidants, including H_2O_2 and superoxide radicals, result in damage to the cell contents. A likely ROS target is the electron transport chain itself, thereby perpetuating the cycle resulting in further damage and injury to the cell (Cohen, 2000). Antioxidant enzymes – SOD and CAT showed a decreased level of activity while gene expression studies of SOD and GPx showed down regulation in 6-OHDA PD rats compared to control, in the present study. Free radicals induce lipid peroxidation in neuronal and glial cell membranes directly causing DNA damage in neuronal and glial cells. These cascades in membrane peroxidation and DNA damage can induce apoptotic neuronal and glial cell death (Lee *et al.*, 2005). Lipid peroxidation levels showed elevation in 6-OHDA infused rats in the present study. Mitochondrial dysfunction and subsequent oxidative stress participate directly in cell death through the activation of caspases and release of proapoptotic proteins, eventually resulting in DNA fragmentation, alterations in the cellular cytoskeleton and cell death (Elmore, 2007). The reversal

of all the above altered oxidative stress markers indicate that 5-HT, GABA and BMC in combinations renders neuroprotection to dopaminergic neurons against oxidative damage.

Recent studies implicate defective signalling by the serine threonine kinase Akt in the neurodegeneration of PD (Timmons *et al.*, 2009). Active Akt has vital roles in cell survival, metabolism and neuronal function. Akt expression was found to be down regulated in the present study. Akt and phospho^{Ser473}-Akt - containing dopaminergic neurons are severely depleted in the brain in PD (Timmons *et al.*, 2009). This causes the down regulation of Akt observed in the present study. Normalising defective Akt activity could be a viable treatment strategy for PD (Burke *et al.*, 2007). The activation of Akt by BMC in combination with 5-HT and GABA shows pro-neuronal survival capabilities.

6-OHDA induces death of nigral DA neurons by apoptotic mechanisms (Przedborski, 2005). The transcription factor NF-κB plays a proapoptotic role in excitotoxin-induced apoptotic death of nigral neurons through up regulation of p53 and c-Myc (Qin *et al.*, 1998, 1999). We observed an enhanced expression of NF-κB in SN*pc*. BMC in combination with 5-HT and GABA reversed this enhanced expression. 5-HT metabolises to the potential neuroprotective antioxidants, normelatonin and melatonin, which helps to prevent oxidative damage caused as a result of 6-OHDA administration. N-acetyl-serotonin (normelatonin) and melatonin protect neurons against oxidative challenges and suppress the activity of the transcription factor NF-κB (Lezoualc'h *et al.*, 1998).

The cell death machinery in 6-OHDA model follows apoptosis by the activation of caspase – 8 (Iwata *et al.*, 2004). Caspase - 8 activates effecter caspases such as caspase - 3, caspase - 6, and/or caspase - 7. Cutillas *et al.* (1999) using stereotaxic administration of zVAD.fmk, a caspase inhibitor, have shown that caspase – 8 mediated mechanism is involved in inducing dopaminergic cell death in the SN. The combination treatment group in the present study could bring down the increased expression of apoptotic effector caspase-8 thus halting neurodegeneration in the SN*pc*.

Extensive research has shown that small proteins called neurotrophins have profound influences upon the development, survival, regulation of function and plasticity of diverse neuronal populations in both the CNS and PNS (Lindsay *et al.*, 1994). The neurotrophins comprise a family of homologous proteins which includes NGF, BDNF, neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5). Despite the 50-55% similarity in the amino acid composition of these molecules (Hohn *et al.*, 1990), the different neurotrophins promote the survival of distinct, yet overlapping, sets of central and peripheral neurons. Reduced BDNF mRNA expression in PD substantia nigra contributes directly to the death of dopaminergic neurons and the development of PD (Porritt *et al.*, 2005). The increased BDNF production in the treatment group protects nigrostriatal dopaminergic neurons from 6-OHDA insult. BDNF is required for the establishment of proper number of dopaminergic neurons in the SN*pc* (Baquet *et al.*, 2005). Moreover, BDNF promotes the sprouting of mature, uninjured serotonergic axons and dramatically enhance the survival or sprouting of 5-HT axons normally damaged in PD (Mamounas *et al.*, 1995).

GDNF is a potent neurotrophic factor for survival of dopaminergic neurons (Xing *et al.*, 2010). GDNF has been shown to exert neuroprotective and restorative effect on the nigral DA system in 6-OHDA (Ding *et al.*, 2004) and MPTP-induced (Cheng *et al.*, 1998) animal PD models, in non-human primates (Eslamboli *et al.*, 2003) and by direct intraputamenal infusion in PD patients (Patel *et al.*, 2005). BMC when supplemented with 5-HT and GABA further elevated the nigral levels of GDNF as is evident from the up regulated mRNA expression of GDNF. The up regulated GDNF in our study further support our result that the BMC indeed have differentiated to dopaminergic neurons in the SN*pc* thus exerting its protective effect to counteract neurodegeneration and promote neuronal survival. Our treatment strategy has the advantage of endogenous GDNF production and stimulation which otherwise when administered exogenously has been shown to protect nigral dopaminergic neurons against neurotoxic models of PD as well as in clinical studies.

Using BrdU and NeuN co-labelling studies, we demonstrated the differentiation of implanted BMC to neurons with the aid of 5-HT and GABA. NeuN which is a mature neuronal marker is expressed by all the viable neurons in the brain. BrdU labels the proliferating BMC administered to the SN*pc*. We observed that in the SN*pc* of rats treated with BMC in combination with 5-HT and GABA, most of BrdU-positive cells were immunoreactive to NeuN, indicating that the implanted BMC have differentiated into mature neurons. The fact that we observed elevated levels of DA and TH expression in the same group confirms that the newly formed neurons are indeed secreting DA. BMC administered alone to 6-OHDA rats did not show immunoreaction to NeuN, rather the number of BrdU-positive cells was lower when compared to the groups administered along with 5-HT and GABA suggesting cell death by 6-OHDA toxicity in absence of proliferative factors. 5-HT and GABA are involved in a variety of cellular processes involved in regulating metabolism, proliferation and morphology. The fine integration of these dynamic events appears to involve multiple receptor action. A recent study evaluating long term effects of intrastriatal grafts of DA neurons in PD, points to the need for future cell-based therapies using fetal tissue or stem cells in PD patients requiring additional grafts of serotonergic neurons to relieve nonmotor symptoms by restoring serotonergic neurotransmission (Politis *et al.*, 2012). Our combination treatment in the present study, which reverses back the altered serotonergic neurotransmission, will serve as an ideal therapeutic strategy taking into account the problems associated with DA grafts alone.

Corpus Striatum

The chief pathological hallmark of PD is the progressive dopaminergic depletion, caused by the selective death of neuronal subpopulations, projecting to the corpus striatum, a basal ganglia structure necessary for voluntary movement control and action learning, from the SN*pc*. The corpus striatum is a large subcortical structure in the mammalian brain that is involved in motor coordination, cognitive functions and complex processes associated with adaptive behaviours (Lang & Lozano, 1998; Berke & Hyman, 2000; McClure *et al.*, 2003;

Schultz *et al.*, 2003; Zhou *et al.*, 2003). Several intrinsic neurotransmitters interact to regulate its function, including DA from the nigrostriatal pathway and 5-HT from afferent raphe projections (Walker *et al.*, 1991). A distinguishing feature of the striatum is its extremely dense DA innervation (Björklund & Lindvall, 1984). The dense DA axon terminals provide the strongest expression of DA transporters (DAT) in the brain (Sesack *et al.*, 1998). The striatum also receives more modest 5-HT innervation and those fibers express the 5-HT transporters (Steinbusch, 1981; Pickel & Chan, 1999). Ultrastructurally, 5-HT terminals are in close proximity to DA terminals (Van Bockstaele & Pickel, 1993), providing an anatomical basis for the two systems to interact with each other. Through its action on cognate receptors, DA modulates a variety of functions including striatal synaptic plasticity (Gerfen & Surmeier, 2011). The functional consequence of selective midbrain dopaminergic cell loss is a dramatic depletion of striatal DA content. The ensuing homeostatic changes in the striatum are thought to largely contribute to the cardinal PD motor symptoms of tremor, rigidity and bradykinesia. These symptoms are effectively treated by DA replacement therapy by means of administering L-DOPA. However, the efficacy of this therapy diminishes over time as complicating side effects emerge in the form of LID.

Several lines of evidence implicate serotonergic pathways in the etiology and treatment of PD. Patients' exhibit decreased levels of 5-HT and 5-HIAA reuptake sites. 6-OHDA reduces striatal levels of 5-HT (Pe´rez-Otano *et al.*, 1991) and participate in their influence upon the motor, mood and cognitive symptoms of PD. L-DOPA displaces 5-HT from serotonergic neurons innervating the striatum, wherein it is transformed into DA (Arai *et al.*, 1996; Kannari *et al.*, 2001). We observed a decrease in 5-HT content in the corpus striatum of 6-OHDA induced PD rats. This decrease is due to a decrease in the rate of 5-HT synthesis as a result of denervation of the nigrostriatum (Pe´rez-Otano *et al.*, 1991). Changes in 5-HT neurotransmission have demonstrated to alter 5-HT and 5-Hydroxyindoleacetic acid (5-HIAA) concentrations (Kwok & Juorio, 1987; Sandrini *et al.*, 1997). 5-HT is metabolised to 5-HIAA by the mitochondrial enzyme MAO. MAO levels have been found to be elevated during PD

(Mallajosyula *et al.*, 2008). The decrease in 5-HT content in corpus striatum of 6-OHDA treated groups is brought about by significant decrease in 5-HT synthesis and increase in its breakdown to 5-HIAA. 5-HT concentrations are known to be highly correlated with depressive illness which is the major mental disturbance in patients with PD (Murray, 1996). Combined treatment using BMC along with 5-HT and GABA reversed the altered 5-HT content to near control.

5-HT facilitates DA outflow and is released by DRN neurons into the striatum where it acts upon diverse 5-HT receptors that are expressed on various pre and post synaptic components (Mathur & Lovinger, 2012). Studies investigating 5-HT/DA receptor interactions within the intact striatum have consistently demonstrated that intrinsic 5-HT_2 receptors can modify DA function that in turn affects behaviour (Lucas & Spampinato, 2000; Porras *et al.*, 2002). Intrastriatal costimulation of DAD_1 and 5-HT_2 receptors synergistically enhances locomotor behaviour in 6-OHDA-lesioned rats (Bishop & Walker, 2003). At receptor subtype level a distinction can be made between 5-HT_2 receptor subtypes which either constitutes an excitatory (5-HT_{2A}) or inhibitory (5-HT_{2C}) influence on DA release in the striatum (Lucas & Spampinato, 2000; Navailles *et al.*, 2004). Clinical evidence indicates 5-HT_2 receptor antagonists as anti-parkinsonian (Henderson *et al.*, 1992). Our studies showed a significant decrease in the number of total 5-HT and 5-HT_{2A} receptors during PD. This is consistent with the findings of Li *et al.* (2010). This suggests that 6-OHDA lesion interfere with 5-HT_{2A} receptor expression and prevent [^{3}H]ketanserin binding to the receptors, or enhance the receptor degradation and desensitization. In addition, the down regulation of 5-HT_{2A} receptor binding in this study provides indirect evidence for the plasticity of the serotonergic systems in the rat brain.

5-HT_{2C} receptors showed up regulation in the corpus striatum of PD rats. 5-HT_{2C}-dependent modulation of striatal dopaminergic tone contributes to the reported antiparkinsonian effects of the 5-HT_2 antagonist ritanserin (Henderson *et al.*, 1992). Intrastriatal infusion of the 5-$HT_{2B/2C}$ receptor antagonist SB 206553 enhances striatal DA release *in vivo* (Alex *et al.*, 2005; Alex & Pehek 2007), suggesting that striatal 5-HT_{2C} receptors participate in the ability of peripheral

5-HT_{2C} antagonists to unmask the tonic inhibitory control of 5-HT_{2C} receptors on *in vivo* striatal DA release (Di Giovanni *et al.*, 1999; De Deurwaerdère *et al.*, 2004; Navailles & De Deurwaerdère, 2011). An inhibitory action of 5-HT_{2C} receptors is further supported by data reporting an excitatory effect of local infusion of the 5-HT_{2C} antagonist RS 102221 into the nucleus accumbens (Dremencov *et al.*, 2005).

Striatal 5-HT_{2A} and 5-HT_{2C} are therefore differently regulated in 6-OHDA-lesioned animals. Alterations of 5-HT binding constants in PD reflect an imbalance in serotonergic activity. The altered receptor activity observed from the Scatchard plot was supported by the gene expression and immunohistochemical studies of 5-HT_{2A} and 5-HT_{2C} receptor subtypes. Numerous studies reveal that 5-HT_{2A} agonists positively modulate DA release under basal conditions and that 5-HT_{2A} antagonism decreases evoked DA release (Lucas & Spampinato, 2000; Ball & Rebec, 2005; Alex & Pehek, 2007). 5-HT_2 receptor stimulation of the DA-depleted striatum with the 5-HT_2 receptor agonist DOI induces motor behaviours, as a consequence of increased 5-HT_{2A} receptor expression in the dorsal striatum (Basura & Walker, 2001; Bishop *et al.*, 2004). 5-HT_{2C} knockout mice have elevated striatal baseline DA concentrations (Abdallah *et al.*, 2009), underscoring an interaction between serotonergic and dopaminergic systems (Lee *et al.*, 2011).

Studies using L-DOPA treatment have revealed that the regulation of 5-HT_{2A} is highly dependent on alterations in DA levels. In contrast, striatal 5-HT_{2C} appears to be regulated by nigrostriatal cell loss and the reduced levels of factors, other than DA, such as BDNF which are normally expressed in nigrostriatal neurons (Zhang *et al.*, 2007). Thus pharmacological manipulations at both 5-HT_{2A} and 5-HT_{2C} receptors are useful for the treatment of motor complications of PD. Hitherto; no study has been conducted in either non-human primates or humans to address this issue. BMC along with 5-HT and GABA reversed both the decreased 5-HT_{2A} receptors and the increased 5-HT_{2C} receptors. Hence it is a valuable therapeutic approach.

The integrity of the 5-HT system can also be evaluated by measuring 5-HT transporter (5-HTT) availability. Our results showed decreased 5-HT

receptor and 5-HTT gene expression in the corpus striatum of 6-OHDA infused unilateral Parkinson's model rats. A loss of 5-HTT is thought to reflect a decrease of 5-HT terminals and loss of 5-HT neurons (Meyer, 2007). 5-HT and GABA along with BMC antagonized these effects. We conclude from our studies that 5-HT and GABA along with BMC potentiates a restorative effect by reversing the alterations in 5-HT receptor binding and gene expression that occur during PD. These neurofunctional deficits are one of the key contributors to impaired DA neurotransmission associated with PD. Previous studies showed that 6-OHDA induced damage increased the viability of transplanted BMC and attracts these cells (Hellmann *et al.*, 2005). But the BMC treated group of our studies did not show significant change as compared to the other groups which is due to slow differentiation of BMC when it is administrated alone. This was overcome by supplementing BMC along with neurotransmitters: 5-HT and GABA. Thus, it is evident that 5-HT and GABA along with BMC to 6-OHDA infused rats renders protection against altered serotonergic neurotransmission and related motor deficits which makes them clinically significant for functional reestablishment and recovering from PD symptoms.

Pathogenesis of PD involves strong oxidative stress, reduced antioxidant levels and mitochondrial defects all known to induce cell death in several cellular systems. In particular, free radicals and GSH depletion have been shown to trigger active cell death in neurons (Merad-Boudia *et al.*, 1998). The ratio between reduced and oxidized glutathione (GSH/GSSG) is decreased during degeneration thereby enhancing the formation of toxic hydroxyl radicals (Sofic *et al.*, 1992; Sian *et al.*, 1994). This represents one of the earliest biochemical defects in PD. The impairment of GSH-dependent detoxification is due to increased DA turnover that could itself increase basal production of H_2O_2 and then deplete GSH stocks (Riederer *et al.*, 1989). We observed a significant down regulation of GPx gene expression in 6-OHDA treated group of rats. This was significantly reversed to near control by treatment with BMC supplemented with 5-HT and GABA in combination. The loss of GSH and formation of protein glutathione mixed disulfide (PrSSG) in the brain result in various membrane dysfunction, such as

inhibition of Na^+/K^+-ATPase activity (Kish *et al.*, 1985). Neuroprotective strategies employing antioxidants aids to protect neurons and to diminish the progression of the disease. Decreased SOD activity can lead to an accumulation of H_2O_2. With an absence of a simultaneous increase of GPx activity, this could increase the stimulation of lipid peroxidation and protein oxidation, resulting in cellular damage. In the present study, we obtained a significant down regulation of SOD enzyme activity in the corpus striatum of 6-OHDA induced PD rats compared to control. These were in accordance with the results obtained for Real-time PCR amplification of SOD mRNA which was down regulated significantly. 5-HT and L-DOPA have been reported to exhibit protective effects on oxidative tissue damages (Park *et al.*, 2002). 5-HT is reported to scavenge superoxide anion and hypochlorous acid. GABA controls the activity of the DA-containing cells of the SN and loss of GABA and its synthesizing enzyme glutamic acid decarboxylase (GAD) have been observed in the basal ganglia of patients dying from PD (Haydar *et al.*, 2000). GABA is used as a supplement to help prevent the oxidation of L-DOPA and also as a method to inhibit ACh (Andrew *et al.*, 1993). The catalase detoxifies H_2O_2 to H_2O. CAT assay showed a decreased activity in the 6-OHDA treated rats compared to control. The decrease in activity of CAT enzyme results in accumulation of H_2O_2 formed in the brain and leads to neurodegeneration. 5-HT and GABA when supplemented in combination along with BMC reversed significantly the decreased SOD and CAT activity in 6-OHDA Parkinson's rats to control values. Similar results were obtained for the gene expression studies of SOD and CAT mRNA.

All these above phenomena give rise to increase in ROS levels and lead to damage of cellular macromolecules and their subsequent peroxidation. Our study on lipid peroxidation measured by thiobarbituic acid reactive material (TBARs) was elevated in 6-OHDA treated rats. PD brains showed a decrease in polyunsaturated fatty acid levels and increased levels of thiobarbituric acid-reactive compounds and the presence of 8-OHDG (Sanchez-Ramos *et al.*, 1994; Ebadi *et al.*, 1996). TBARs levels showed a significant reversal to control levels in response to treatment with 5-HT, GABA and BMC.

Activation of NF-κB is associated with DA and 6-OHDA induced neuronal injury in rat striatum (Lou *et al.*, 1999; Panet *et al.*, 2001; Tarabin & Schwaninger, 2004). NF-κB activation by 6-OHDA is prosurvival (Park *et al.*, 2004). The activation of NF-κB was found to be essential to DA induced apoptosis in PC12 cells (Panet *et al.*, 2001). Our observation of NF-κB expression showed an increased expression which was brought down by the combination treatment group. Blockage of NF-κB was found to correlate with anti-apoptotic effect of pioglitazone in PD (Dehmer *et al.*, 2004).

The mechanisms of catecholaminergic cell death induced by 6-OHDA neurotoxicity are explained in three main pathways: ROS generated by intra- or extracellular auto-oxidation, H_2O_2 formation induced by MAO and direct inhibition of the mitochondrial respiratory chain. Several reports have suggested that the excessive ROS generated by 6-OHDA leads to oxidative stress, which injures the cells and induces cell death *via* apoptosis (Blum *et al.*, 2001; Takata *et al.*, 2005). Apoptotic death of neurons was confirmed by the activation of caspase-8 in the present study. The process of 6-OHDA induced caspase activations by increased oxidative stress is mainly based on the striatal dopaminergic dysfunction (Tanaka *et al.*, 2006). The functional regulation of dopaminergic transmission by 5-HT, GABA and BMC hence results in lowering the caspase-8 expression thus protecting the neurons from apoptosis.

GDNF protects mesencephalic neurons by suppression of oxygen radical accumulation and caspase-dependent apoptosis in the MPP+ model, which are mediated by the PI3K/Akt pathway (Sawada *et al*., 2000; King *et al*., 2001; Ding *et al*., 2004). GDNF is up regulated following nerve regeneration and has been shown to have a role in the promotion of neuronal survival, migration of Schwann cells and to enhance myelination (Iwase *et al.*, 2005). GDNF, acts at least in part through Akt signalling and Akt activation increases GDNF expression (Cen *et al.*, 2006). Combination of 5-HT, GABA and BMC provided neuroprotection in the SN*pc* via Akt activation. Microdialysis studies performed on rat hippocampus demonstrated that GDNF significantly reduced free radical production and increased the activities of GPx and SOD (free radical scavengers) following

kainate-induced excitotoxicity (Cheng *et al.*, 2004). A similar mechanism operated in the SN since DA neurons are particularly susceptible to oxidative damage. In fact, endogenous DA metabolism generates several free radical species (Jenner & Olanow, 1996). When DA is metabolized to DOPAC, H_2O_2 is also formed, which then gets converted to hydroxyl radicals by the Fenton reaction. The Fenton reaction is fully dependent upon the availability of ferrous ions, which are found in abundance in the SN. Increased oxidative stress, coupled with diminished antioxidant stores, lead to lipid peroxidation and cell death. This suggests that supplementation of this growth factor restores this imbalance, decrease free radical production, increase antioxidant levels and ultimately arrest the progression of PD. This is precisely done by our treatment group of BMC, 5-HT and GABA in combinations.

Cerebral Cortex

The cerebral cortex is the seat of our highest forms of intelligence. It plays a central role in many complex brain functions including memory, attention, perceptual awareness, thought, language and consciousness. Changes in personality and moderate or mild cognitive debilitation are found in PD. Cerebral glucose metabolism is reduced in the cerebral cortex in PD patients suffering from cognitive impairment (Yong *et al*., 2007). Metabolic and neuroimaging observations have recently documented decreased prefrontal and parietal 18F-fluorodeoxyglucose uptake in PD cases with mild cognitive deficits (Huang *et al*., 2007, 2008). Studies have demonstrated complex I deficiency, abnormal ATP synthase and inner protein membrane prohibiting expression levels in the frontal cortex in PD (Parker *et al*., 2008). The cerebral cortex receives widespread inputs from subcortical areas involved in sensorimotor and limbic functions. Cerebral cortex activity is shaped by a number of neuromodulators, most notably monoamines. Among these, DA stands out as having an important role in cerebral cortex cognitive functions, including working memory, reward, and attention (Schultz, 2002). In fact, cognitive and executive deficits have been related, in part, to reduced dopaminergic innervation in the nigro-striatal and mesocortical

dopaminergic systems directly and indirectly compromising prefrontal cortical function *via* alteration of the basal ganglia (Cropley *et al.*, 2008; Marklund *et al.*, 2009). In addition to altered dopaminergic innervation, serotoninergic innervations derived from neurons of the raphe neurons are deficient in the neocortex in PD (Baloyannis *et al.*, 2006). This has been proposed as a concomitant factor in the pathogenesis of cognitive deficits in PD. The cerebral cortex, like all other motor structures, receives serotonergic innervations in the form of a plexus of fine varicose fibers (Dieudonné & Dumoulin, 2000). 5-HT content was observed to be reduced in the cerebral cortex of PD rats in the present study. 5-HT is a key modulatory neurotransmitter and has been implicated in the pathophysiology and treatment of anxiety and mood disorders (Neumeister *et al*., 2002).

Serotonergic responses to stress are mediated by different 5-HT receptor subtypes. 5-HT_{2A} receptor subtypes plays special role in serotonergic responses to stress and has been suggested to involve in affective disorders, anxiety disorders and depression (Hoyer *et al.,* 1986; Mikuni *et al.,* 1991). Total 5-HT and 5-HT_{2A} receptor binding was found to be decreased in the cerebral cortex of 6-OHDA infused PD rats. It has been shown that the DA neurons in the mesocortical pathway project from the VTA and the medial SN*pc* to the frontal lobe. Dopaminergic disruption in PD not only affects the nigrostriatal tract but also the mesocortical pathway (Jellinger, 2001). Because the brain serotonergic and monoamines dopaminergic systems have close interactions, PD reflects abnormalities in the cerebral cortex with the serotonergic system (Doder *et al.*, 2003). The down regulation of 5-HT_{2A} receptors binding in cerebral cortex in this study was confirmed by gene expression and immunohistochemical studies of 5-HT_{2A} receptor subtype and reflects 5-HT hypoinnervations following 6-OHDA lesion, because some studies have indicated that unilateral 6-OHDA lesion of the nigrostriatal dopaminergic system abolished increases in cortical–striatal 5-HT output (Mendlin *et al.*, 1999). This is in accordance with the reduced levels of 5-HT observed in the present study. Dysfunction of the nigrostriatal dopaminergic system and cortical–basal ganglionic circuits connecting the frontal lobe and the basal ganglia induce a series of impairment in cognitive functions like memory,

attention and executive function in Parkinson's patients (Tamaru, 1997). As one of the main 5-HT receptors, the dysfunction of 5-HT_{2A} receptors is recognized for their important roles and implications in a number of cognitive and stress-related disorders (Huang *et al.*, 2007). Abnormalities in 5-HT_{2A} receptor neurotransmission in the cortex are involved in the neural mechanisms underlying visual hallucinations associated with PD (Ballanger *et al.*, 2010). Global disruption of 5-HT_{2A} receptor signalling in mice significantly reduces inhibition in conflict anxiety indicating a specific role of cortical 5-HT_{2A} receptor function in the modulation of conflict anxiety (Weisstaub *et al.*, 2006). BMC along with 5-HT and GABA reversed the decreased 5-HT_{2A} receptor binding and gene expression to near control. Increase in expression of 5-HT_{2A} receptors in the rat brain is associated with reduced anxiety (Anseloni *et al.*, 2005).

5-HT_{2C} receptors are involved in a diversity of physiological functions such as the control of nociception, motor behaviour, endocrine secretion, thermoregulation, modulation of appetite and the control of exchanges between the CNS and the CSF (Tecott *et al*., 1995; Fone *et al*., 1998). Our findings report an increase in 5-HT_{2C} receptor function in the cerebral cortex with no significant change in K_d which is supported by the gene expression studies. Increased 5-HT_{2C} receptor function in cortical regions is implicated in mood disorders and anxiodepressive states (Millan, 2005). It has been reported that increased 5-HT_{2C} receptor contributes to the enhanced response to anxiety (Fone *et al*., 1996). 5-HT_{2C} receptor agonist 1-(m-chlorophenyl) piperazine has been reported to produce hypolocomtion, hypophagia and anxiogenesis (Samad *et al*., 2008) in rats. The changes in the receptors have been confirmed using immunofluorescent antibodies specific to 5-HT_{2C} receptors. Behavioural and neurochemical evidence for anxiogenic actions of 5-HT_{2C} agonists have been well documented in rodents (Hackler *et al*., 2007). The 5-HT_{2C} receptor subtype signals activate PLC, leading to the intracellular accumulation of inositol trisphosphate (IP_3) and subsequent Ca^{2+} release. Increased Ca^{2+} release triggers the oxidative damage and excitotoxicity (Bishnoi *et al*., 2008). Our earlier studies have shown an enhanced IP_3 and cAMP activity in the cerebral cortex of 6-OHDA induced PD rats (Nandhu

et al., 2011). The root cause for the enhanced IP_3 is the activation of 5-HT_{2C} receptors. Thus up regulated 5-HT_{2C} receptor function in PD cortex leads to excessive Ca^{2+} overload in cells leading to apoptosis. 5-HTT expression showed down regulation in the cerebral cortex in the present study. Our finding suggests that the density of 5-HTT is reduced in the cerebral cortex of rats with PD, presumably reflecting the loss of serotonergic innervation. Reduced levels of 5-HTT, as revealed by ^{123}I-FP-CIT SPECT, has been observed in PD (Roselli *et al.*, 2010). Fatigue has been associated with reduced 5-HTT binding in the amygdala (Pavese *et al.*, 2010). Since the 5-HT_{2A} and 5-HT_{2C} receptors localized in the cerebral cortex have been found to be important modulators of executive functions including memory and cognitive flexibility, evidences show that the modulation of these receptors can attenuate (Williams *et al.*, 2002) or enhance (Buhot, 1997) the learning and working memory. Considering PD obviously results in cognitive and memory impairment (Aarsland *et al.*, 2009), the treatment with 5-HT, GABA and BMC in combination which mediates its action through 5-HT_{2A} and 5-HT_{2C} receptors in the cerebral cortex has important clinical implications ameliorating the memory impairment and stress dysfunction in PD.

Brain cortex and mitochondrial O_2 uptake and complex I activity are significantly lowered in PD, whereas mitochondrial nitric oxide synthase activity, cytochrome content, mitochondrial mass and oxidative damage are significantly higher in the frontal cortex in PD. The decreases in tissue and mitochondrial 0_2 uptake and in complex I activity are considered the consequences of mitochondrial oxidative damage in the cerebral cortex in PD (Navarro & Boveris, 2009; Navarro *et al.*, 2009). Several key proteins are targets of oxidative damage in the cerebral cortex even at very early stages of PD-related pathology, including α-synuclein, β-synuclein and SOD (Ferrer, 2011). We observed a significant down regulation in gene expression of SOD in the cerebral cortex. In the same line of generalized oxidative stress and stress responses is the observation of decreased GPx, one of the main antioxidant enzymes inactivating H_2O_2, in microglial cells of the gray matter and white matter in PD (Power & Blumbergs, 2009). GPx was also

significantly down regulated in the cerebral cortex of PD rats. Our results indicate extensive cortical oxidative damage in PD.

Among its cellular effects in neurons, Akt not only suppresses apoptosis (Brunet *et al.*, 2001; Downward, 2004) but also regulates axon growth and sprouting (Markus *et al.*, 2002; Kwon *et al.*, 2006). Constitutively active form of Akt is capable of inducing sprouting of adult mesencephalic DA neurons *in vivo* (Ries *et al.*, 2006). Therefore reduced expression of Akt in cerebral cortex indicates possibility of apoptosis. The NF-κB activator, C2-ceramide induces NF-κB activation and apoptosis in cultured DA neurons through the production of free radicals (France-Lanord *et al.*, 1997; Hunot *et al.*, 1997). Mitochondrial dysfunction and oxidative stress "reset" the threshold for activation of apoptotic pathways in response to Caspase-8 and similar signals. Our analysis in the Caspase-8 gene expression gave an enhanced expression level which substantiates our observation. Endogenous BDNF is a trophic factor for cortical neurons (Ghosh *et al.*, 1994). While the endogenous BDNF was reduced in the PD cortex, it was elevated in the combination treatment group thus providing trophic support to cortical neurons.

Thus our results reveal the involvement of cerebral cortex in PD leading to altered behaviour and cognition resulting from impaired serotonergic cortical innervation and altered neuronal function due to oxidative stress ultimately leading to apoptosis. BMC along with 5-HT and GABA reversed these alterations, which is clinically significant.

Hippocampus

Hippocampus plays important roles in long-term memory and spatial navigation. A recent study showed that unilateral 6-OHDA lesion to the *SNpc* in rat significantly decreased cell proliferation in the subgranular zone (SGZ) suggesting that cell proliferation in the SGZ is under dopaminergic control from SN*pc* and ventral tegmental area (VTA) since the hippocampus receives dopaminergic input from both (Suzuki *et al.*, 2010). DA containing neurons participate in the regulation of certain cognitive processes (Prediger *et al*., 2011).

Cognitive impairments are observed in PD patients, especially on measures of memory, verbal fluency and other executive functions (McPherson & Cummings, 1996). Research suggests that the behavioural, motor and cognitive impairments found in PD patients reflect dysfunction of hippocampal neural circuitry (Saint-Cyr, 2003). Additionally, cognitive and motor problems contribute to the existence of depression in PD and conversely, symptoms of depression impact cognitive and motor deficits (Robinson & Manes, 2000). Potentiation, defined as an increase in synaptic efficacy, is readily induced by high frequency stimulation of the synapses between the Schaffer collaterals and the pyramidal cells in the hippocampus CA1 area (Malenka & Nicoll, 1999). The excitatory synapse in the stratum radiatum of the CA1 area of the hippocampus has a number of features that have been attributed to various aspects of memory encoding (Martin *et al.,* 2000). 5-HT has trophic effects during development (Gaspar *et al.*, 2003) and provides a rich innervation to the adult hippocampus (Azmitia & Whitaker-Azmitia, 1995) where it has been suggested to retain a trophic role (Gould, 1999; Djavadian, 2004). We observed a decrease in 5-HT content in the hippocampus of PD rats when compared to control. Levels of 5-HT (Taylor *et al.*, 2009) and the 5-HT metabolite 5-HIAA are found to be reduced in the hippocampus (Wilson *et al.*, 1996). The decline in 5-HT will result in a decrease in adult hippocampal neurogenesis and contribute to the depressive symptoms of PD. Studies of the serotonergic modulation of hippocampal function have been complicated by the marked heterogeneity of 5-HT receptor subtypes, with atleast 14 different subtypes expressed in the CNS. Psychological stress activates serotonergic neurons in the hippocampus and amygdale through cortical associated areas and through ascending catecholaminergic neurons from the brain stem (Feldman & Weidenfeld, 1998; Koob & Heinrichs, 1999). Serotonergic neurotransmission exerts a considerable influence on hippocampus. This structure is influenced powerfully by serotonergic projections from midbrain raphe nuclei (Tecott *et al.,* 1998) which modulate hippocampal electrical activity, hippocampal dependent behaviours and long term potentiation (LTP), a form of hippocampal plasticity that has been implicated in memory formation (Vanderwolf & Baker, 1986). The

level of 5-HT decreases the monoamine release from the hippocampus in PD rats. There is good evidence that noradrenaline and 5-HT interact to influence neuroplasticity in the brain (Delgado, 2004). In this study, we focused on the 5-HT_{2A} receptor which is expressed in the hippocampus. We observed a significant decrease in the B_{max} of 5-HT_{2A} receptors in the hippocampus of PD rats compared to control. 5-HT_{2A} receptor gene expression confirmed the receptor binding data. 5-HTT was also down regulated in PD rats. Chronic administration of 5-$HT_{2A/2C}$ antagonist enhances hippocampal progenitor proliferation on a faster time-scale than that reported for pharmacological antidepressants (Jha *et al.*, 2008). 5-HT_{2C} receptors are abundantly expressed throughout the hippocampal formation and the subiculum. An involvement of this receptor subtype is suggested in the regulation of neuronal plasticity. We observed a significant increase in 5-HT_{2C} receptors binding in the hippocampus of PD rats compared to control. 5-HT_{2C} receptors gene expression patterns were similar to the receptor binding studies. Combined treatment with 5-HT, GABA and BMC reversed the receptor alterations to near control. Anxiolytic like actions of 5-HT_{2C} receptor antagonists, transduced in the amygdala and hippocampus (Menard & Treit 1999; Campbell & Merchant 2003; Alves *et al*., 2004; Millan 2006) are expressed against certain forms of clinical anxiety. 5-HT_{2C} receptor antagonism has been reported to improve insomnia and sexual dysfunction comorbid to depression (Dekeyne *et al*., 2008). Treatment with combinations of 5-HT, GABA and BMC significantly reversed the receptor alterations to near control thus demonstrating the regulation of 5-HT levels, receptor alterations and reversed activity of 5-HTT in the hippocampus. The establishment of dopaminergic neuronal connections in the *SNpc* by 5-HT, GABA and BMC prevents the compensatory regulation of 5-HT_{2A} and 5-HT_{2C} receptors in the PD hippocampus and thus provide protection against the non motor symptoms associated with the hippocampus.

Oxidative stress reduces cellular antioxidative capabilities, impairs intracellular redox potential regulation and causes lipid peroxidation (Shiraga *et al.*, 1993; Kumar *et al.*, 1995). In the hippocampus also, SOD and GPx were down regulated. The loss of dopaminergic neurons in PD results in enhanced

metabolism of DA, augmenting the formation of H_20_2, thus leading to generation of highly neurotoxic hydroxyl radicals (OH*).

BDNF is a small dimeric protein that is extensively involved in synaptic plasticity and memory processes. BDNF in the hippocampus is involved in memory consolidation and activity-dependent neuronal reorganization that underlie memory formation. BDNF also exerts its role in long-term memory (LTM) formation in the CA1 region of the hippocampus (Alonso *et al.*, 2005). Exogenous BDNF has positive effects on synaptic strength and neuronal arborization of hippocampal neurons (Mamounas *et al.*, 2000). Endogenous hippocampal BDNF levels are decreased by stress, a precipitating factor in clinical depression and increased by antidepressant treatments (Nibuya *et al* 1995; Smith *et al.,* 1995). Gene expression studies of BDNF in 6-OHDA infused rats showed an increased expression which contributes to the depressive behaviour in PD. BDNF expression was reversed to control in the combination treatment group. Addition of exogenous BDNF to the hippocampus attenuates depression-related phenotypes (Shirayama *et al.*, 2002). Also, BDNF increases the production of antioxidant enzymes – SOD, GPx and CAT in hippocampal neurons (Mattson *et al.*, 1995). This additionally explains the neuroprotection in hippocampus delivered by the BMC, 5-HT and GABA combination treatment against oxidative stress.

Cerebellum

The basal ganglia and cerebellum are two groups of subcortical nuclei that have classically been regarded as motor structures. Damage to these brain regions produces well-described alterations in motor function. Cerebellar output abnormalities affects not only in the primary motor cortex but also subdivisions of premotor, oculomotor, prefrontal and infero temporal areas of cortex. In PD patients, increased activity was seen in the cerebellar vermis. Two distinct motivational systems in the brain have been described: the DA-dependent cortico-striatal-thalamocortical circuits and the DA independent brain stem pedunculopontine tegmental nucleus, which has strong interconnections to the

cerebellum. Parkinson's patients utilize the latter circuit when the former has been damaged (Weintraub & Potenza, 2006). Experimental evidence indicate the involvement of the cerebellum in variety of human mental activities including language (Fiez *et al*., 1996), attention (Allen *et al*., 1997), cognitive affective syndromes (Schmahmann & Sherman, 1998), fear and anxiety caused by threats of pain, thirst sensation and fear for air hunger and motor relearning (Imamizu *et al*., 2004; Marvel *et al*., 2004). There is also accumulating evidence to suggest that the cerebellum plays a role in more cognitive, social and emotional functions. Some of the most frequent signs of cerebellar hypoplasia include poor fine motor skills, hypotonia and autistic features (Wassmer *et al*., 2003). The cerebellar vermis integrates and processes the inputs from the vestibular, visual and proprioceptive systems to coordinate muscle timing as a result of which the centre of gravity stays within the limits of stable upright standing (Diener *et al*., 1989). Damage to the cerebellum, in particular the vermis (Baloh *et al*., 1998) results in more postural sway than in control subjects (Ho *et al*., 2004). Decreased postural stability would correspond with abnormalities of the vermis observed in autistic subjects (Gowen & Miall, 2005). Postural instability is an important aspect of PD. Electrophysiologists have reported that serotonergic agonists affect directly the firing of cerebellar neurons (Cumming-Hood *et al*., 1993) and are able to modulate the effect of excitatory amino acids.

5-HT_{2C} receptors exist in the rat cerebellum and they participate in the processing and integration of sensory information, regulation of the monoaminergic system modulation of neuroendocrine regulation, anxiety and feeding behaviour (Tecott *et al*., 1995). Our investigation revealed a decrease in the 5-HT content and an increase in 5-HT_{2C} receptor binding in the cerebellum of the PD rats compared to control.

5-HTT regulates the entire serotonergic system and its receptors *via* modulation of its expression and function. In brain, 5-HTT is present both in presynaptic membranes of nerve terminals in proximity to 5-HT containing cell bodies (Dennis *et al.,* 2004). 5-HTT mediates rapid removal and recycling of released 5-HT following neuronal stimulation. Thus, it has a critical role in the

homeostatic regulation of the signals reaching 5-HT receptors. 5-HTT is important in emotion regulation and social behaviour, drawing from an interdisciplinary perspective of behavioural genetics and cognitive neuroscience. Integration of these findings suggests that the impact of the 5-HTT gene on behaviour and have a role in social cognition (Turhan & Klaus-Peter, 2007). The decreased 5-HT levels decreased the expression of 5-HTT in cerebellum. 5-HT is packaged into vesicles for synaptic exocytosis. Extracellular 5-HT signals through 5-HT_{2A} receptors. We observed a decreased expression of 5-HT_{2A} receptors. Synaptic 5-HT signalling are terminated by uptake of 5-HT from the synapse by 5-HTT.

Free radicals arise from activated microglial cells present in degenerating SN*pc* (McGeer *et al.*, 1988), which produce nitric oxide (NO) and cytokines. Glial cell activation could also increase cytokine levels (e.g. TNFα) and ROS or directly activate the cell death pathway (Boka *et al.*, 1994; Mogi *et al.*, 1994; Hunot *et al.*, 1997). High ROS levels could induce secondary excitotoxicity, raising free cellular calcium in turn increasing intracellular NO levels. Relative GSH depletion is accompanied by a drop in GSH-peroxidase expression. We observed a decreased expression of SOD, GPx and Akt in the cerebellum followed by up regulation of NF-kB and caspase-8 thus showing that the high ROS levels generated as a result of oxidative stress activated the molecular cascade leading to apoptosis. The combination treatment group of 5-HT, GABA and BMC was seen to alleviate the above molecular events by modulation of BDNF activity.

Brain stem

There have been changes in our understanding of the pathology of PD, where it begins in the nervous system and how it progresses. Indeed, there is now evidence to suggest that PD does not affect the dopaminergic SN*pc* at the earliest stages but instead begins in the lower brain stem, olfactory bulb and anterior olfactory nucleus. The brain stem is a part of the brain located beneath the cerebrum and in front of the cerebellum. It connects the spinal cord to the rest of the brain. The brain stem controls involuntary muscles such as the stomach and the heart. The brain stem also acts as a relay station between the brain and the rest

of the body. Previous studies on deep brain stimulation at pedunculopontine nucleus (PPN) in the upper brain stem to the patients having PD with gait disturbance showed a significant improvement in gait, over 50%, which opens a whole new approach of the involvement of brain stem in PD (Plaha & Gill, 2005). Sections of the brain stem usually reveal loss of the normally dark black pigment in the locus coeruleus LC, pigmentation that correlates with neuronal cytoplasmic neuromelanin pigment that accumulates in an age-related manner. Loss of pigment correlates with neuronal loss and with the duration of Parkinsonism. Serotonergic cell bodies are located in the raphe nuclei of the brain stem (Parent *et al.*, 1981). Raphe nuclei provide 5-HT innervation to the entire brain, including the SN, corpus striatum and cerebral cortex, the core structures of the cortico-basal ganglia-thalamo-cortical loop, the physiology of which is disrupted in PD (DeLong & Wichmann, 2007; Parent *et al.*, 2011). Several studies have demonstrated neuronal loss and dystrophic neurites in the 5-HT-producing raphe nuclei in PD (Paulus & Jellinger, 1991; Gai *et al.*, 1995). The degenerative changes affecting raphe serotonergic neurons lead to a secondary reduction in 5-HT levels. 5-HT content was found to be significantly reduced in the present study. Decreased 5-HT function was found in untreated PD patients (Hegerl *et al.*, 2001), which was reversed 12 weeks after the initiation of L-DOPA therapy (Beucke *et al.*, 2010). In our study, total 5-HT and 5-HT_{2A} receptors of the brain stem are found to be decreased and 5-HT_{2C} receptors are found to be increased in 6-OHDA infused rats. 5-HT and GABA along with BMC treated PD rats reversed the binding parameters to near control values. Depletion in the DA content in the SN*pc* will decrease the 5-HT in the brain stem.

Electron transport chain complex activity seems to be significantly reduced in PD, which correlates with levels of coenzyme Q10 levels (ubiquinone) (Shults *et al.*, 1997). The generation of free radicals can also be produced by 6-OHDA which destroys striatal dopaminergic neurons causing Parkinsonism in experimental animals as well as human beings. Several studies reported the presence of 6-OHDA in both rat (Senoh *et al.*, 1959) and human brain (Curtius *et al.*, 1974) as well as in urine of L-DOPA treated PD patients (Andrew *et al.*,

1993). Manganese, an essential trace element, can also stimulate DA auto-oxidation and 6-OHDA generation (Garner & Nachtman, 1989). The combined occurrence of MAO activity, auto-oxidation and elevation in iron levels is responsible for the strong ROS production following 6-OHDA treatment. SOD and GPx mRNA was found to be down regulated in brain stem of 6-OHDA rats.

The activation of PI3K/Akt pathway has been generally accepted playing a critical role in neuronal survival (Brunet *et al.*, 2001; Frebel & Wiese, 2006) and the dysfunction of this pathway was observed in the PD patient midbrains (Malagelada *et al.*, 2008; Timmons *et al.*, 2009). We observed a down regulation of Akt expression in 6-OHDA infused rats, whereas this down regulation was reversed back to control in rats treated with BMC, 5-HT and GABA. Although the neuroprotective signalling mechanisms downstream of PI3K/Akt in dopaminergic neurons is not clear, increased activity of Akt promoted granule cell survival *via* phosphorylation of BCL-2 family member BAD on Ser-136 (Datta *et al.*, 1997).

NF-κB mediate neuro-protection against toxic insults (Chin *et al.*, 2004; Onyango *et al.*, 2005) or take part in proapoptotic pathways (Panet *et al.*, 2001; Dehmer *et al.*, 2004; Soos *et al.*, 2004). The elevation of NF-κB expression in brain stem of 6-OHDA rats in the present study is due to its neuroprotective role against 6-OHDA insult. However, the 5-HT, GABA and BMC regulation of 6-OHDA neurodegeneration resulted in bringing back the elevated expression of NF-κB to control levels.

In conclusion, the results from the present study demonstrate that BMC in combination with 5-HT and GABA proliferate and differentiate to dopaminergic neurons, functionally regulating 5-HT and its receptors in PD and renders neuroprotection against the oxidative stress mediated apoptotic death of neurons, thus alleviating the motor and non motor complications of PD. This will be of immense therapeutic impact in the clinical management of PD.

Summary

1. 6-OHDA infused unilateral Parkinson's disease rats were used as models to study the alterations in serotonergic neurotransmission resulting from oxidative stress mediated apoptosis and their regulation by 5-HT, GABA and BMC in combinations.

2. The body weight was analyzed to study the changes in body weight in 6-OHDA infused rats compared to control. Parkinson's disease induction in rats caused a reduction in the body weight and treatment combinations with 5-HT, GABA and BMC regained the body weight near to control and BMC supplemented alone showed no significant reversal in the body weight.

3. Behavioural studies: apomorphine induced rotational analysis, elevated body swing test, stepping test, footprint analysis test and beam-walk test were conducted to assess the motor function and coordination in control and experimental rats. 6-OHDA infused rats showed significant motor deficits. Rats treated with 5-HT, GABA and BMC in combinations reversed the behavioural response to near control. BMC treated alone showed no significant reversal in the behavioural deficits towards the control.

4. DA quantification and TH analysis using Real Time PCR and confocal microscopy were done to confirm the dopaminergic lesion in the SN*pc* resulting in PD and also to confirm the DA production after BMC differentiation. 6-OHDA infusion reduced DA production and TH expression in SN*pc*. Treatment with 5-HT, GABA and BMC in combinations reversed the DA content and TH expression near to control. BMC alone treated group did not show any significant reversal to control.

5. 5-HT content decreased in the SN*pc*, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of 6-OHDA infused rats compared to control. Treatment with 5-HT, GABA and BMC in combinations functionally reversed the alteration to near control. BMC alone treated group did not show any significant reversal to control.

6. Total serotonergic receptor functional status was analysed by Scatchard analysis using [^{3}H]5-HT. The total 5-HT receptors in corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of 6-OHDA infused rats were decreased compared to control with no significant change in the K_d representing the affinity. Treatment with 5-HT, GABA and BMC in combinations restored the total serotonergic receptors in brain regions near to control. There was no significant reversal in BMC alone treated rats.

7. 5-HT_{2A} receptor subtype functional status was analysed by Scatchard analysis using [^{3}H]ketanserin. The 5-HT_{2A} receptors in corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of 6-OHDA infused rats were decreased compared to control with no significant change in the K_d. Treatment with 5-HT, GABA and BMC in combinations functionally reversed the 5-HT_{2A} receptors to near control. BMC alone treated rats did not show any significant reversal to control.

8. 5-HT_{2C} receptor subtype functional status was analysed by Scatchard analysis using [^{3}H]mesulergine. The 5-HT_{2C} receptors in corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem showed a significant increase in 6-OHDA infused rats compared to control. 5-HT, GABA and BMC in combinations reversed the altered 5-HT_{2C} receptors to control. Rats administered with BMC alone did not show any significant reversal to control.

9. 5-HT receptor binding parameters were confirmed by studying the mRNA expression of the corresponding receptor subtype using Real Time PCR. 5-HT_{2A} receptors showed a decreased expression, whereas, 5-HT_{2C} receptors showed an increased expression in SN*pc*, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of 6-OHDA infused rats compared to control. Treatment with 5-HT, GABA and BMC in combinations reversed the 5-HT receptor subtypes gene expression status to control. The results showed an excitatory action by 5-HT_{2A} receptors and inhibitory action by 5-HT_{2C} receptors on DA release. There was no significant reversal in BMC alone treated rats.

10. The 5-HT transporter plays a key role in the termination of serotonergic neurotransmission and controls 5-HT concentrations in neural tissue. The gene expression of 5-HTT was studied in control and experimental rats. 5-HTT showed decreased expression in SN*pc*, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of 6-OHDA infused rats compared to control. Treatment combinations with 5-HT, GABA and BMC functionally reversed the alteration in 5-HTT gene expression to near control. BMC alone treated rats did not show any significant reversal of 5-HTT gene expression to control.

11. The extent of oxidative damage by 6-OHDA insult was assessed by studying the antioxidant enzyme activities of SOD and CAT in SN*pc* and corpus striatum and gene expression of SOD and GPx in SN*pc*, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of 6-OHDA infused rats. 6-OHDA infused rats showed decreased free radical scavenging capability whereas combinations of 5-HT, GABA and BMC reversed the condition to control. The 6-OHDA infused rats also showed an increase in the level of lipid peroxidation which was brought to near control by BMC in combination with 5-HT and GABA.

12. A significant down regulation of anti-apoptotic factor Akt was observed in the SN*pc*, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem which indicated the vulnerability of neurons in 6-OHDA infused rats to apoptosis. 5-HT, GABA and BMC in combinations reversed the gene expression to near control. BMC alone treated group did not show any significant reversal to control.

13. The transcription factor NF-κB showed a significant increase in expression in the SN*pc*, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of 6-OHDA infused rats. Treatment with 5-HT, GABA and BMC in combination reversed NF-κB gene expression status towards control. There was no significant reversal in BMC alone treated rats.

14. Increased gene expression of Caspase-8 in the SN*pc*, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of 6-OHDA infused rats advanced the neurodegeneration by apoptosis. Treatment with 5-HT, GABA and BMC in combination reversed Caspase-8 gene expression near to control. There was no significant reversal in BMC alone treated rats.

15. Neurotrophic factor BDNF showed significant down regulation in the SN*pc*, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem of 6-OHDA infused rats. Combined treatments with 5-HT, GABA and BMC reversed the BDNF gene expression near to control thus promoting the survival and sprouting of neurons. BMC alone treated rats showed no significant reversal in BDNF expression.

16. Increased expression of GDNF in SN*pc* and corpus striatum of 6-OHDA infused rats showed neuroprotection for the surviving dopaminergic neurons. All the treatment groups showed increased expression of GDNF and the maximum expression was observed in rats treated with 5-HT, GABA and BMC in combination thus exerting its neuroprotective and restorative effect for DA neurons.

17. The differential expression of 5-HT_{2A}, 5-HT_{2C} receptors, 5-HTT and BDNF in 6-OHDA infused rats observed from the receptor binding analysis and Real Time PCR was confirmed by confocal studies using specific antibodies in the brain slices. Treatment with 5-HT, GABA and BMC in combinations reversed the mean pixel value towards the control. Expression of GDNF was also in agreement with the gene expression studies. BMC alone treated group did not show any significant reversal to control.

18. We demonstrated the autologous differentiation of BMC to neurons using BrdU-NeuN co-labelling studies. BMC injected into the SN*pc* were tagged by proliferative marker BrdU and was seen to express NeuN which indicated neuronal cells. The BMC division and differentiation was increased when it was infused along with 5-HT and GABA. The most prominent expression was seen in rats treated with 5-HT, GABA and BMC in combination. However, BMC injected alone did not express any NeuN.

Our results thus showed that 5-HT receptor functional regulation and modulation of oxidative stress mediated apoptosis plays a critical role in the management of PD. Gene expression studies of 5-HT_{2A} and 5-HT_{2C} receptor subunits and 5-HTT serotonin transporter showed a prominent serotonergic dysregulation of neurotransmission in brain regions of 6-OHDA infused rats. The

findings from this study gives insight on understanding the molecular mechanisms underlying motor and non motor complications of PD resulting from neurodegeneration mediated by antioxidant enzymes, Akt, NF-κB and caspase-8. The altered 5-HT receptor activity will inhibit dopaminergic neural activity and DA release thereby affecting the motor control, cognition and memory in PD rats. Enhanced receptor activation increases Ca^{2+} overload triggering oxidative damage and apoptosis. Our results showed the autologous BMC differentiation to neurons in SN*pc* when infused along with 5-HT and GABA. BMC in combination with 5-HT and GABA showed functional recovery that is of immense therapeutic significance in the management of PD.

Conclusion

Parkinson's disease is a chronic progressive neurodegenerative disorder characterized by the selective loss of dopaminergic neurons in the SN*pc* resulting in severe motor impairments. Serotonergic system plays an important regulatory role in the pathophysiology of PD in rats, the evaluation of which provides valuable insight on the underlying mechanisms of motor, cognitive and memory deficits in PD. We observed a decrease in 5-HT content in the brain regions of 6-OHDA infused rat compared to control. The decreased 5-HT content resulted in a decrease of total 5-HT, 5-HT_{2A} receptors and 5-HTT function and an increase of 5-HT_{2C} receptor function. 5-HT receptor subtypes - 5-HT_{2A} and 5-HT_{2C} receptors have differential regulatory role on the modulation of DA neurotransmission in different brain regions during PD. Our observation of impaired serotonergic neurotransmission in SN*pc*, corpus striatum, cerebral cortex, hippocampus, cerebellum and brain stem demonstrate that although PD primarily results from neurodegeneration in the SN*pc*, the associated neurochemical changes in other areas of the brain significantly contributes to the different motor and non motor symptoms of PD. The antioxidant enzymes – SOD, CAT and GPx showed significant down regulation which indicates increased oxidative damage resulting in neurodegeneration. We also observed an increase in the level of lipid peroxidation. Reduced expression of anti-apoptotic Akt and enhanced expression of NF-κB resulting from oxidative stress caused an activation of caspase-8 thus leading the cells to neurodegeneration by apoptosis. BMC administration in combination with 5-HT and GABA to PD rats showed reversal of the impaired serotonergic neurotransmission and oxidative stress mediated apoptosis. The transplanted BMC expressed NeuN confirming that 5-HT and GABA induced the differentiation and proliferation of BMC to neurons in the SN*pc* along with an increase in DA content and an enhanced expression of TH. Neurotrophic factors – BDNF and GDNF rendered neuroprotective effects accompanied by improvement in behavioural deficits indicating a significant reversal of altered dopaminergic and serotonergic neurotransmission in PD. The restorative and neuroprotective effects of BMC in combination with 5-HT and GABA are of immense therapeutic significance in the clinical management of PD.

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16. **Korah PK**, Jes P, Nandhu MS, Paulose CS. Oxidative stress mediated neuronal damage in the corpus striatum of 6-hydroxydopamine lesioned Parkinson's rats: Neuroprotection by Serotonin, GABA and Bone Marrow Cells Supplementation. *Free Radical Biology & Medicine*. (Under review).
17. Pretty MA, **Korah PK**, Anitha M, Shilpa J, Paulose CS. (2011). Cerebellar BAX - induced Glutamate receptor gene expression impairs calcium homeostasis in Pancreatic islets of streptozotocin induced Diabetic rats: Neuroprotective role of pyridoxine and Aegle marmelose leaf extract. *Mol Cell Endocrinol.*, (Under review).
18. Amee K, **Korah PK**, Paulose CS. NMDA and mGlu5 receptors functional regulation in Hippocampus of pilocarpine- induced epileptic rats: Antagonism by *Bacopa monnieri*. *Epilepsia*. (Under review)
19. Chinthu R, Nandhu MS, **Korah PK**, Jayanarayanan S, Paulose CS. Cholinergic receptor subtypes decreased regulation in cerebellum of spinal cord injured rats: Functional recovery with Serotonin, GABA and Bone marrow cells. *Experimental Brain Research*. (Under review)

Awards

1. **Travel Grant** from Melvin Yahr International Parkinson's Disease Foundation to attend The XIX World Congress on Parkinson's Disease and Related Disorders, Shanghai, China (December 2011).
2. **Travel Grant** from APSN to attend The ISN/APSN School 2010 and the 10th Biennial Meeting of the Asia-Pacific Society for Neurochemistry (APSN) 2010, Mahidol University, Thailand (October 2010).

Abstracts Presented

1. Pretty Mary Abraham, **Korah P Kuruvilla**, CS Paulose. Altered 5HT2a receptor gene expression in the brain stem of diabetic rats: supplementation of pyridoxine and aegle marmelose leaf extract. International Conference on Advances in neuroscience & XXXVI Annual Meeting of Indian academy of neuroscience. Department of Biotechnology, Cochin University of Science and Technology (December 2008).
2. **Korah P Kuruvilla**, Jes Paul, Nandhu M S and C S Paulose. Up Regulation of Dopamine D1 Receptor in Cerebellum and Brain Stem in Unilateral Rotenone Lesioned Parkinson's Rat Model: Effect of Serotonin, Dopamine and Norepinephrine. 78th Annual Meeting of the Society of Biological Chemists, (India), Pune. (October 2009).
3. Nandhu. M. S**,** Jes Paul, **Korah P Kuruvilla** and C S Paulose. Dopamine D1 Receptor Up Regulation In Cerebellum and Brain Stem In Unilateral 6-Hydroxy Dopamine Rat Model: Antagonism By Serotonin And Gamma Amino Butyric Acid. Conference of Association of Clinical Biochemists of India, Amritha University, Cochin (November 2009)
4. Jes Paul, Nandhu M S, **Korah P Kuruvilla** and C.S.Paulose. Serotonin, Dopamine and Norepinephrine functional regulation of DA D1 receptors in Unilateral Rotenone lesioned Parkinson's rat model. 36th National Conference of Association of Clinical Biochemists of India, Amritha University, Cochin (November 2009)
5. Nandhu. M. S**,** Jes Paul, **Korah P Kuruvilla** and C S Paulose. Glutamate Receptor Up Regulation In Cerebellum of Unilateral 6-Hydroxy Dopamine Rat Model: Effect Serotonin, Gamma Amino Butyric Acid And Bone Marrow Cell Supplementation. International Conference on Neurosciences updates & ISN, APSN, IBRO & SNCI school, Cochin (December 2009).

6. Jes Paul, Nandhu M S, **Korah P Kuruvilla** and C.S.Paulose. Dopamine Receptor Subtypes Functional Regulation in Brain stem of Unilateral Rotenone Lesioned Parkinson's rat model: effect of serotonin, gamma amino butyric acid and bone marrow cell supplementation. International Conference on Neurosciences updates & ISN, APSN, IBRO & SNCI school, Cochin (December 2009).
7. Nandhu. M. S**,** Jes Paul, **Korah P Kuruvilla** and C S Paulose. Enhanced NMDAR1, NMDA2B and mGluR5 receptors gene expression in corpus striatum of unilateral 6-hydroxy dopamine rat model: effect of serotonin, gamma amino butyric acid and bone marrow cell supplementation. 2010 Canadian Neuroscience Meeting (CAN & CCNP) and 4th Canadian IBRO School, Ottawa (May 2010).
8. Chinthu Romeo, Anitha Malat, Jayanarayanan S, **Korah P Kuruvilla**, Smijin Soman and C S Paulose. Enhanced Malate dehydrogenase, Glutamate dehydrogenase, Arginase and Cholesterol in herbal formulation treated rats: A molecular study. Modern methods in herbal drug development, Bharata Mata College, Cochin (October 2010).
9. **Korah P Kuruvilla**, Jes Paul, Nandhu M. S., Smijin Soman and C. S. Paulose. Altered $5HT_{2A}$ receptor and 5HTT gene expression in the corpus striatum of unilateral 6-hydroxydopamine-induced Parkinsonian rats: Effect of serotonin, gamma amino butyric acid and bone marrow cell supplementation. The ISN/APSN School 2010 and The 10th Biennial Meeting of the Asia-Pacific Society for Neurochemistry (APSN) 2010, Mahidol University, Thailand (October 2010).
10. Jes Paul, **Korah P Kuruvilla**, Nandhu M S, and C. S. Paulose. Dopamine Receptor Subtypes Functional Regulation in Cerebellum of Unilateral Rotenone Lesioned Parkinson's Rat Model: Effect of Serotonin, Gamma Amino Butyric Acid and Bone Marrow Cells Supplementation. The ISN/APSN School 2010 and The 10th Biennial Meeting of the Asia-Pacific Society for Neurochemistry (APSN) 2010, Mahidol University, Thailand (October 2010).

11. **Korah P Kuruvilla,** Jes Paul, Nandhu. M. S**,** Anju TR and C S Paulose. Oxidative Stress mediated apoptosis leading to neuronal damage in the corpus striatum of 6-hydroxydopamine lesioned Parkinson's rats: Neuroprotection by Serotonin, GABA and bone marrow cells supplementation. 5th Congress of FAONS & XXVIII Annual Meeting of Indian Academy of Neurosciences, Lucknow (November 2010).
12. Naijil George, Anitha Malat, **Korah P Kuruvilla** and C. S. Paulose. Novel Role of Vitamin D_3 in the Prevention of Diabetogenesis in Rats. National Conference on Emerging Trends in Biotechnology & Annual Meeting of Society for Biotechnologists (India), Acharya Nagarjuna University, Guntur. (September 2011).
13. **Korah P Kuruvilla**, C. S. Paulose. Decreased Serotonergic receptors regulation in 6-hydroxydopamine lesioned rats: Neuroprotection by co-mitogenic Serotonin and GABA in combination with Bone Marrows Cells. XIX World Congress on Parkinson's Disease and Related Disorders, Shanghai, China (December 2011).

Figure Legends

Figure - 7

Confocal image of TH expression in the SN*pc* of control and experimental rats using immunofluorescent TH specific primary antibody and rhodamine tagged secondary antibody. ⟶ in white shows TH+ cells.

Figure – 21a, 21b, 21c

Confocal image of BrdU-NeuN co-labelling studies in the SN*pc* of control and experimental rats using immunofluorescent BrdU and NeuN primary antibodies and secondary antibodies of Alexa Fluor 594 and Alexa Fluor 488 respectively. ⟶ in white shows NeuN, BrdU and NeuN-BrdU co-labelled cells. BrdU positive BMC are red, NeuN labelled neurons are green and BrdU-NeuN co-labelled cells are yellow in colour.

Figure - 42

Confocal image of 5-HT_{2A} receptor expression in the corpus striatum of control and experimental rats using immunofluorescent 5-HT_{2A} receptor specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT_{2A} receptors.

Figure - 43

Confocal image of 5-HT_{2C} receptor expression in the corpus striatum of control and experimental rats using immunofluorescent 5-HT_{2C} receptor specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT_{2C} receptors.

Figure - 44

Confocal image of 5-HT transporter expression in the corpus striatum of control and experimental rats using immunofluorescent 5-HT transporter specific

primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT transporters.

Figure - 45

Confocal image of BDNF expression in the corpus striatum of control and experimental rats using immunofluorescent BDNF specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows BDNF expressing neurons.

Figure - 46

Confocal image of GDNF expression in the corpus striatum of control and experimental rats using immunofluorescent GDNF specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows GDNF expressing neurons.

Figure - 62

Confocal image of 5-HT_{2A} receptor expression in the cerebral cortex of control and experimental rats using immunofluorescent 5-HT_{2A} receptor specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT_{2A} receptors.

Figure - 63

Confocal image of 5-HT_{2C} receptor expression in the cerebral cortex of control and experimental rats using immunofluorescent 5-HT_{2C} receptor specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT_{2C} receptors.

Figure - 64

Confocal image of 5-HT transporter expression in the cerebral cortex of control and experimental rats using immunofluorescent 5-HT transporter specific

primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT transporters.

Figure - 65

Confocal image of BDNF expression in the cerebral cortex of control and experimental rats using immunofluorescent BDNF specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows BDNF expressing neurons.

Figure - 81

Confocal image of 5-HT_{2A} receptor expression in the hippocampus of control and experimental rats using immunofluorescent 5-HT_{2A} receptor specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT_{2A} receptors.

Figure - 82

Confocal image of 5-HT_{2C} receptor expression in the hippocampus of control and experimental rats using immunofluorescent 5-HT_{2C} receptor specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT_{2C} receptors.

Figure - 83

Confocal image of 5-HT transporter expression in the hippocampus of control and experimental rats using immunofluorescent 5-HT transporter specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT transporters.

Figure - 84

Confocal image of BDNF expression in the hippocampus of control and experimental rats using immunofluorescent BDNF specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows BDNF expressing neurons.

Figure - 100

Confocal image of 5-HT_{2A} receptor expression in the cerebellum of control and experimental rats using immunofluorescent 5-HT_{2A} receptor specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT_{2A} receptors.

Figure - 101

Confocal image of 5-HT_{2C} receptor expression in the cerebellum of control and experimental rats using immunofluorescent 5-HT_{2C} receptor specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT_{2C} receptors.

Figure - 102

Confocal image of 5-HT transporter expression in the cerebellum of control and experimental rats using immunofluorescent 5-HT transporter specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT transporters.

Figure - 103

Confocal image of BDNF expression in the cerebellum of control and experimental rats using immunofluorescent BDNF specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows BDNF expressing neurons.

Figure - 119

Confocal image of 5-HT_{2A} receptor expression in the brain stem of control and experimental rats using immunofluorescent 5-HT_{2A} receptor specific primary antibody and FITC tagged secondary antibody. ⟶ in white shows 5-HT_{2A} receptors.

Figure - 120

Confocal image of 5-HT_{2C} receptor expression in the brain stem of control and experimental rats using immunofluorescent 5-HT_{2C} receptor specific primary antibody and FITC tagged secondary antibody. → in white shows 5-HT_{2C} receptors.

Figure - 121

Confocal image of 5-HT transporter expression in the brain stem of control and experimental rats using immunofluorescent 5-HT transporter specific primary antibody and FITC tagged secondary antibody. → in white shows 5-HT transporters.

Figure - 122

Confocal image of BDNF expression in the brain stem of control and experimental rats using immunofluorescent BDNF specific primary antibody and FITC tagged secondary antibody. → in white shows BDNF expressing neurons.