Introduction

Parkinson’s disease (PD) is the most common neurodegenerative disorders in the elderly that impairs the sufferer's motor skills and cognitive processes (Parkinson, 1817). PD is affecting approximately 1-2% of people over the age of 65 worldwide. While there is widespread degeneration in the central and peripheral nervous systems in PD, the hallmark pathology remains the dopaminergic striatal insufficiency secondary to degeneration of dopaminergic neurons in the substantia nigra (SN). Most of PD are sporadic and age related and only approximately 5% is a familial disease (Stewart & William, 2008). With the progressive loss of the nigrostriatal dopaminergic neurons, there is a corresponding decrease of dopamine (DA) content in both the SN and striatum. It is the loss of these DA-producing projections that is thought to account for the majority of physical and motor deficits seen in PD. Although subject to intensive research, the etiology of PD is still enigmatic and the treatment is basically symptomatic. Many factors are speculated to operate in the mechanism of cell death of the nigrostriatal dopaminergic neurons in PD, including oxidative stress and cytotoxicity of reactive oxygen species (ROS), disturbances of intracellular calcium homeostasis, exogenous and endogenous toxins and mitochondrial dysfunction (Lev et al., 2003).

PD is a progressive neurodegenerative disorder clinically characterized by the cardinal symptoms of cogwheel rigidity, resting tremor, bradykinesia, stooped posture and shuffling gait (Thomas & Beal, 2007; Wu et al., 2011). As stated above, there is a loss of dopaminergic cells in the substantia nigra pars compacta (SNpc) that 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).

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). 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 hydrogen peroxide and free radicals. Ultimately these toxic molecules induce neuronal death through mitochondrial dysfunction (Soderstrom et al., 2009). 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 lesions model have served as an experimental basis to develop new antiparkinsonian drugs and treatment strategies, or surgical approaches, including transplantation of neural tissue.

The nigrostriatal dopaminergic and corticostriatal glutamatergic systems are anatomically and functionally connected playing antagonistic roles in the basal ganglia controlling spontaneous motor behaviour (Smith & Bolam, 1990; Ossowska et al., 1994; Danysz et al., 1995; Schmidt & Kretschmer, 1997). A DA-glutamate imbalance in the basal ganglia has been hypothesised to underlie the pathophysiology of parkinsonism (Greenamyre & O’Brien, 1991; Mitchell & Carroll, 1997; Starr et al., 1997). It is suspected that because neurons that are most vulnerable in PD are those that also receive strong input from glutamate pathways that glutamate must play some role in the events that lead to neuronal damage during 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). In fact, pharmacological treatments that reduce NMDA receptors activity limit the extent of nigro-striatal damage (Sonsalla et al., 1998), improve motor symptoms of PD (Chase & Oh, 2000) & prevent or reduce levodopa-induced dyskinesia (LIDs) (Papa & Chase, 1996; Blanchet et al., 1999; Hadj Tahar et al., 2004) in animal models of PD.

Cell transplantation to replace lost neurons is a novel approach to 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 cell replacement for the treatment of PD is based on two hypotheses: first, the predominant symptoms of PD are dependent on the dysfunction or loss of the dopaminergic neurons in the nigrostriatal pathway; and second, dopaminergic neurons grafted into the DA-deficient striatum can replace those neurons lost as a result of the disease process and can reverse, at least in part, the major symptoms of the disease. Cells are commonly grafted to the striatum because DA is required in the striatum and it is unlikely that the cells implanted into the adult degenerating SN will physically re-establish the long nigrostriatal pathway to innervate the striatum and supply it with DA (Alexi et al., 2000). The fetal brain tissue used in clinical transplantation studies is ethically challenging to obtain (Lindvall, 2001). Also, while under normal conditions the 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 also 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).

*Introduction*
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, serotonin (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 (Poewe, 2009). 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 (Muñoz et al., 2008). 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. GABA supplementation can help decrease the overstimulation of neurotransmitters such as acetylcholine and can possibly be used in Parkinson's disease help to inhibit acetylcholine (Nandhu et al., 2010). 5-HT and Gamma aminobutyric acid (GABA) can be also used as agents for cell proliferation and differentiation. Our earlier studies showed that 5HT and GABA acting through specific receptor subtypes 5HT₂ (Sudha & Paulose, 1998) and GABAB (Biju et al., 2002) respectively, control cell proliferation and act as co-mitogens.

In the present study a detailed investigation on the alterations of glutamate and its receptors in the brain regions of unilateral 6-OHDA infused rats were carried out. Glutamate receptor subtypes- NMDAR1, NMDA2B, mGluR5 and GLAST glutamate transporter gene expression in the 6-OHDA infused rats were also studied. In addition to that the possible linkage between the 6-OHDA induced changes in IP3,
cAMP and cGMP functional regulation and Bax, α-synuclein, TNF-α and CREB gene expression in the brain regions of PD rats has been elucidated. We also demonstrated the autologous differentiation of BMC to neurons using comitogenic 5-HT and GABA by confocal studies with PKH2GL cell membrane tracker dye, Nestin and GFAP. Our present study on 5-HT, GABA and BMC dependent regulation of glutamatergic receptors in the brain will certainly enlighten novel therapeutic possibilities for PD management.