Chapter 2
Parkinson's disease – a neurodegenerative disorder

2.1 Introduction

PD is the second most common neurodegenerative disease, with incidence sharply increasing with age (Yazdani *et al.,* 2006; Hart & Xu, 2009; Prediger *et al.,* 2012). This disease was first described in 1817 as "shaking palsy", in a ground-breaking monograph written by James Parkinson (Standaert & Young, 2001; Rezak, 2007). In this monograph he noted, "Until we are better informed regarding the nature of this disease the employment of internal medicines is scarcely warrantable" (Rezak, 2007). A short discussion will follow regarding the epidemiology, clinical presentation, pathophysiology and etiology of PD. In addition, an overview of experimental animal models used to study PD will be given.

2.2 Epidemiology

Over the past decades PD has attracted the interest of a vast number of scientists. This may be attributed to the occurrence of PD in approximately 1% of the adult population over the age of 65 (Beers *et al.,* 2006; Hart & Xu, 2009; Bossy-Wetzel *et al.,* 2004) and 0.4% of people over the age of 40 (Beers *et al.,* 2006). Since PD is an age-related neurological disorder, juvenile PD is very rare (Beers *et al.,* 2006).

2.3 Clinical overview

Clinically the symptoms of PD presents as four cardinal motor features (Prediger *et al.,* 2012) that include resting tremor, a slowing of physical movement (bradykinesia), postural rigidity (Henderson *et al.,* 2003; Yazdani *et al.,* 2006; Hart & Xu, 2009) and characteristic gait disturbances (Onofrj *et al.,* 2008). Patients diagnosed with PD may exhibit one or more of the aforementioned symptoms (LeWitt, 2008). Apart from the progressive clinical impairments, patients may also develop dementia, especially older patients (LeWitt, 2008; Onofrj *et al.,* 2008).

Additionally, PD is associated with non-motor symptoms that include sleep disturbances, olfactory deficits, memory impairment, anxiety, depression and gastrointestinal disturbances (Henderson *et al.,* 2003; Prediger *et al.,* 2012). It is speculated that the manifestation of these non-motor symptoms may already be identified preclinically (Henderson *et al.,* 2003; Prediger *et al.,* 2012). According to Hudry and co-workers (2003) olfactory deficits were found to be bilateral and independent of gender, disease duration, medication, motor disability and functions

related to cognitive, perceptivo-motor and memory skills. It is furthermore emphasized that the psychological symptoms, such as anxiety and depression, are under-diagnosed in PD patients (Prediger *et al.,* 2012).

2.4 Pathophysiology

The motor symptoms associated with PD are considered to be the result of the progressive loss of neuromelanin-containing dopaminergic neurons (Figure 2.1) in the substantia nigra pars compacta (SNpc) (Nagatsu & Sawada, 2006; Prediger *et al.,* 2012). These neurons project to the striatum of the brain and are known as the nigrostriatal pathway. The loss of the nigrostriatal neurons results in dopamine depletion in the striatum. Overall, the lack of dopamine in the striatum leads to the characteristic symptom of hypokinesia (decreased bodily movement) in PD (Hart & Xu, 2009). Onset of clinical PD occurs after approximately 70% of striatal dopamine reduction (Cookson, 2009).

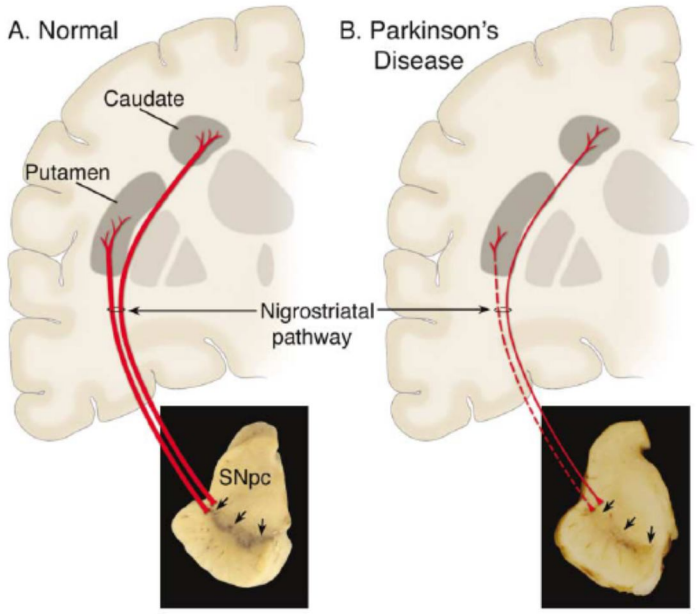


Figure 2.1: Schematic representation of the nigrostriatal pathway (red). Panel **A** demonstrates the normal state of the nigrostriatal pathway. From the SNpc, dopaminergic neurons project to the basal ganglia and synapse in the striatum (i.e., putamen and caudate nucleus). The photograph of the SNpc depicts the normal pigmentation of the SNpc (black arrows) that is produced via neuromelanin within the dopaminergic neurons. Panel **B** demonstrates the degeneration of the nigrostriatal pathway with PD. The dashed red line and thin solid red line indicates a loss of dopaminergic neurons that projects to the putamen and caudate nucleus, respectively. The photograph of the SNpc depicts the loss of dark–brown pigment neuromelanin (black arrows) of the SNpc due to the loss of dopaminergic neurons (Dauer & Przedborski, 2003).

The formation of fibrillar cytoplasmic inclusions, known as Lewy bodies (Figure 2.2), is another hallmark of PD (Betarbet *et al.,* 2000). Lewy body inclusions can be found in the SNpc dopaminergic neurons as well as other brain regions, namely, the cortex and magnocellular basal forebrain (Yazdani *et al.,* 2006). The exact composition of Lewy bodies is still unkown. However, it is believed that these intracytoplasmic eosinophilic inclusions (Schlossmacher *et al.,* 2002; Prediger *et al.,* 2012) predominantly contain ubiquitin and α-synuclein (Betarbet *et al.,* 2000; Schlossmacher *et al.,* 2002). Lewy bodies may also contain parkin, synphilin, neurofilaments and synaptic vesicle proteins (Bossy-Wetzel *et al.,* 2004).

Figure 2.2: Histology of brain sections of sporadic cases of PD, demonstrating Lewy bodies visualized by staining or immunocytochemistry using antibodies specific for ubiquitin and α-synuclein (Bossy-Wetzel *et al.,* 2004).

Overexpression of normal α-synuclein may increase a person's risk for developing PD (Saha *et al.,* 2004; Cookson, 2009). Even though the physiological functions of α-synuclein still remains to be determined, it is thought that the products of the mutant α-synuclein gene have a tendency to aggregate resulting in neurotoxicity with the formation of Lewy bodies (Ono *et al.,* 2009).

Furthermore, autosomal recessive juvenile PD (AR-JP) is associated with the accumulation of parkin-associated endothelin receptor-like receptor (Pael-R) (Yang *et al.,* 2003, Kubota *et al.,* 2006). Interestingly, the presence of Lewy bodies is usually not documented with AR-JP. The exact relationship between Pael-R and AR-JP is not understood yet. However, it has been documented that accumulation of Pael-R may cause neurotoxicity that result in dopamine neuronal death in AR-JP (Yang *et al.,* 2003).

2.5 Etiology

It is believed that idiopathic PD is the result of a loss of dopaminergic neurons in the SNpc (Montastruc *et al.,* 1994). PD may have numerous causes, one of which includes genetic mutations (LeWitt, 2008), especially in familial PD (Armentero *et al.,* 2011). It is generally believed that mutations in the gene coding for α-synuclein may be the cause of an inherited form of PD (Saha *et al.,* 2004; Cookson, 2009).

The etiology of sporadic PD is still unknown, however, certain contributing factors that have been identified include oxidative stress (Schlossmacher *et al.,* 2002; Yazdani *et al.,* 2006; Yacoubian & Standaert, 2009), ubiquitin/proteosomal system dysfunction, mitochondrial dysfunction (Schlossmacher *et al.,* 2002; Yazdani *et al.,* 2006; Armentero *et al.,* 2011), increased MAO-A and MAO-B activity (Armentero *et al.,* 2011) and neuroinflammatory processes (Armentero *et al.,* 2011; Yacoubian & Standaert, 2009). Epidemiological studies also suggest that an association exists between chronic exposure to pesticides (such as rotenone) and neuropathological features of PD (Betarbet *et al.,* 2000). Generally, 95% of PD cases are sporadic (Bossy-Wetzel *et al.,* 2004) and overexpression of normal α-synuclein may increase a person's risk for developing PD (Cookson, 2009).

2.6 Animal models

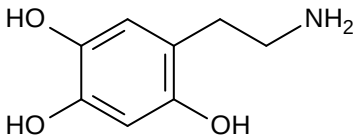
An ideal animal model of PD should be able to mimic the pathological and clinical features of PD. To date, none of the current animal models exhibit all of the PD-related features (Tieu, 2011). Despite these limitations, animal models have been studied extensively to elucidate the neuropathological mechanisms and to evaluate therapeutic strategies for PD (Tieu, 2011; Blesa *et al.*, 2012; Imai *et al.*, 2012).

To evaluate therapeutic strategies for PD, "symptomatic" or "pathophysiological" models are used to generate the PD associated motor symptoms (Dauer & Przedborski, 2003). Neurotoxins may be used to produce PD-related pathology and symptoms (Blesa *et al.*, 2012). The endogenous neurotoxin 6-hydroxydopamine (6-OHDA) and the exogenous neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are documented as the most used irreversible neurotoxins to create animal models of PD (Cleren *et al.*, 2003; Tieu, 2011; Blesa *et al.*, 2012).

6-OHDA (Figure 2.3) is a hydroxylated analogue of dopamine (Cleren *et al.*, 2003; Tieu, 2011) and was first described more than 50 years ago (Tieu, 2011). The uptake of 6-OHDA by dopamine and noradrenergic transporters may be explained by the common structural features 6-OHDA share with dopamine (Cleren *et al.*, 2003; Dauer & Przedborski, 2003). The neurotoxic action of 6-OHDA can be attributed to its ability to produce radical oxygen species (superoxide,

hydroxyl radicals) and H_2O_2 (Cleren *et al*., 2003), resulting in degeneration of both dopaminergic and noradrenergic neurons (Tieu, 2011).

Although various studies have documented the presence of 6-OHDA in both rat and human brains (Cleren *et al.*, 2003), 6-OHDA is unable to cross the blood-brain barrier (Dauer & Przedborski, 2003). Thus, 6-OHDA must be injected directly into the SNpc or striatum to target the nigrostriatal dopaminergic pathway (Dauer & Przedborski, 2003). Rats are the most frequently used species with the 6-OHDA model due to its replicability and stability (Emborg, 2004). The pathology of 6-OHDA animal models differs from the pathology of PD and represents one of the drawbacks of this experimental animal model (Dauer & Przedborski, 2003). Another disadvantage is that none of the 6-OHDA animal models have led to the formation of inclusions resembling Lewy bodies (Dauer & Przedborski, 2003).



6-OHDA

Figure 2.3: Chemical structure of the irreversible neurotoxin 6-OHDA.

A syndrome similar to PD, namely parkinsonism, develops after administration of MPTP (Figure 2.4). Currently, the MPTP animal model is the most extensively studied PD animal model (Dauer & Przedborski, 2003) due to the ability of MPTP to generate PD-related features in both humans and non-human primates (Tieu, 2011). MPTP is lipophilic and crosses the blood-brain barrier rapidly (Dauer & Przedborski, 2003; Tieu, 2011). Once in the brain, MPTP is converted to 1-methyl-4-phenyl-2,3-dihydropyridinium ($MPDP^+$) by MAO-B in glial and serotonergic neurons (Williams, 1993; Cleren *et al.,* 2003; Dauer & Prezborski, 2003). $MPDP^+$ is subsequently converted to 1-methyl-4-phenylpyridinium (MPP^+) by an unknown mechanism (Dauer & Przedborksi, 2003), and MPP^+ is released into an extracellular space via another unknown mechanism (Dauer & Przeborski, 2003). MPP^+ is subsequently selectively taken up into dopaminergic neurons by means of the membrane bound dopamine transporter (Matusch *et al.,* 2010). Figure 2.5 represents the metabolism of MPTP after systemic administration. In the dopaminergic neurons the accumulation of MPP^+ in mitochondria interferes with complex I, resulting in the depletion of adenosine triphosphate (ATP) content in the striatum and consequently increase of oxidative stress and cell death (Cleren *et al.,* 2003; Dauer & Przeborski, 2003; Tieu, 2011). A major advantage of the MPTP animal model may be attributed to the ability of MPTP to damage the nigrostriatal dopaminergic pathway (Tieu, 2011). The ease of administrating MPTP via intraperitoneal injection leads to reproducibility of the experimental MPTP animal model and is another advantage (Tieu, 2011). Some of the

antiparkinsonian agents that have been evaluated in the MPTP model include MAO-B inhibitors (Shapira, 2011) and adenosine A_{2A} receptor antagonists (Armentero *et al.,* 2011).

Interestingly, the protoxin, MPTP, was accidentally synthesized in the 1980's (Przedborski & Vila, 2001). A group of drug addicts selfadministered this protoxin as part of their opioid habit. Dr. Langston and his team, who treated these drug addicts, observed that their symptoms exhibited a likeness to PD. These patients were treated with 3,4-dihydroxy-L-phenylalanine (L-DOPA) with great success (Przedborski & Vila, 2001; Dauer & Przedborski, 2003). This discovery opened new doors for research in PD.

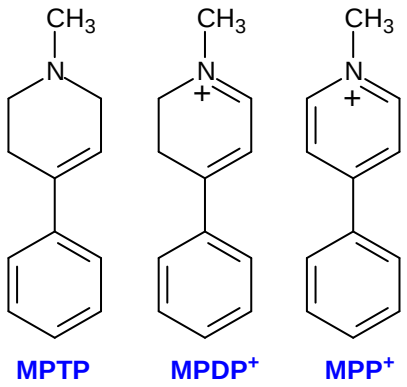


Figure 2.4: Chemical structures of MPTP, $MPDP^+$ and MPP^+.

Generally, PD models are based on toxins which produce dopaminergic nigral cell death. Other parkinsonian models used to disrupt or destroy the catecholaminergic system include reserpine and methamphetamine (Luthra *et al.,* 2009).

The aforementioned PD models are generally used to study animal behaviour such as catalepsy and akinesia (loss of physical movement). Unfortunately, the neurotoxins used to create PD animal models display an irreversible neurotoxic effect. In recent research the use of haloperidol, an antipsychotic drug, has been described as a pre-clinical model to study PD. This model produces extrapyrimidal PD symptoms and can also be used to study animal behaviour (Luthra *et al.,* 2009).

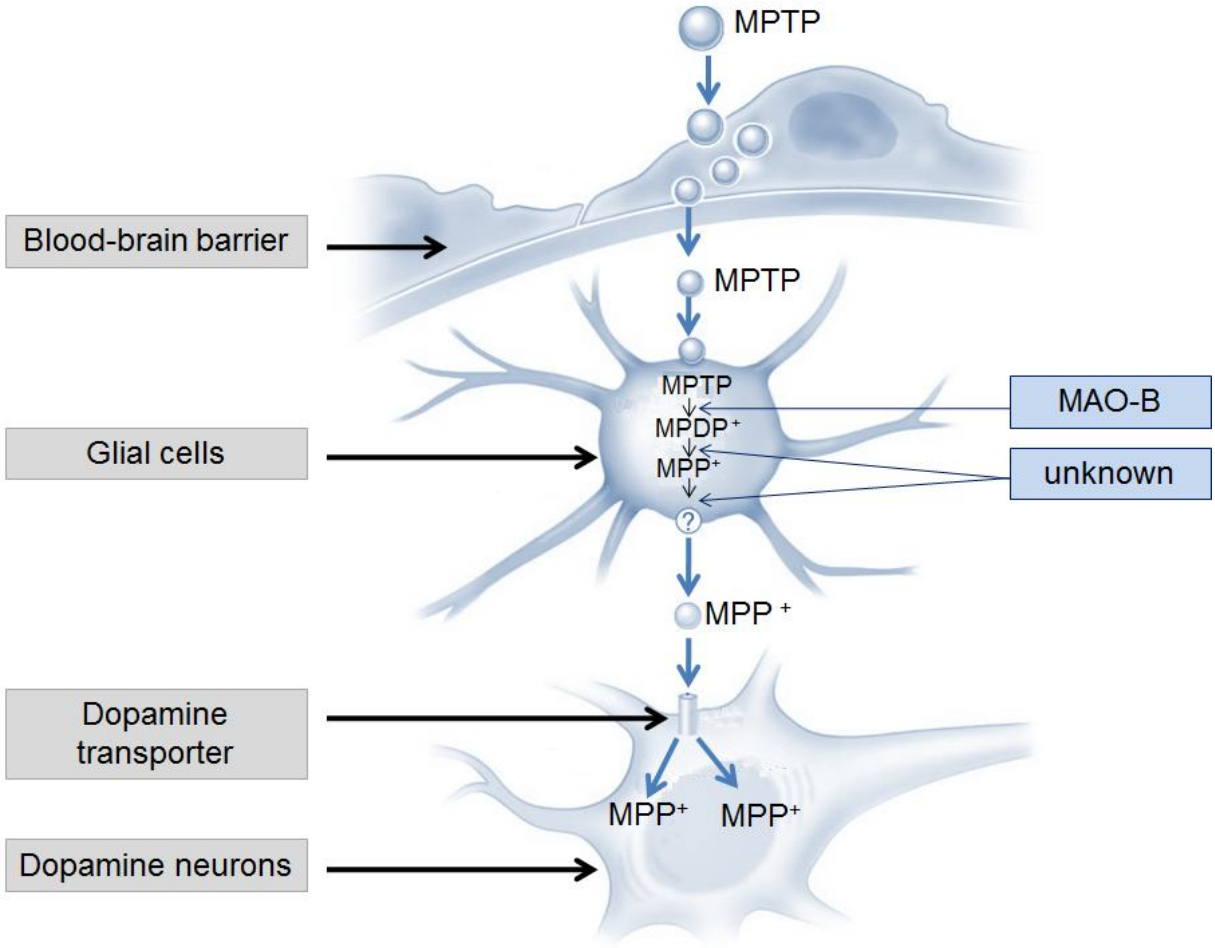


Figure 2.5: Representation of the metabolism of MPTP after systemic administration (Dauer & Przedborski, 2003).

2.7 Conclusion

PD is an age-related neurodegenerative disorder. The symptoms associated with PD are the result of a loss of dopaminergic neurons from the SNpc and generally include motor features such as resting tremor, bradykinesia, postural rigidity and gait disturbances. The role of dopamine depletion in PD and current strategies to treat PD will be discussed in Chapter 3.

Over the years different animal models have been used to study PD. The 6-OHDA and MPTP animal models are toxin-induced models and cause dopaminergic neuronal cell death to mimic PD (Blesa *et al.*, 2012). Unfortunately these chemicals display irreversible neurotoxic effects. Recently the use of haloperidol, an antipsychotic drug, was suggested as an alternative to study PD pre-clinically.

2.8 References

ARMENTERO, M.T., PINNA, A., FERRÉ, S., LANCIEGO, J.L., MÜLLER, C.E. & FRANCO, R. 2011. Past, present and future of A_{2A} adenosine receptor antagonists in the therapy of Parkinson's disease. *Pharmacology and therapeutics*, 132: 280–299.

BEERS, M.H., PORTER. R.S., JONES, T.V., KAPLAN, J.L. & BERKWITS, M. eds. 2006. The Merck manual. 18thed. New York: Merck research laboratories. 2291p.

BETARBET, R., SHERER, T.B., MACKENZIE, G., GARCIA-OSUNA, M., PANOV, A.V. & GREENAMYRE, J.T. 2000. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nature neuroscience*, 3: 1301-1306.

BLESA, J., PHANI, S., JACKSON-LEWIS, V. & PRZEDBORSKI, S. 2012. Classic and new animal models of Parkinson's disease. *Journal of biomedicine and biotechnology,* 2012: Article ID845618, 10 pages, doi:10.1155/2012/845618 (in press).

BOSSY-WETZEL, E., SCHWARZENBACHER, R. & LIPTON, S.A. 2004. Molecular pathways to neurodegeneration. *Nature medicine (Supplement),* 10: S2–S9.

CLEREN, C., NAUDIN, B. & COSTENTIN, J. 2003. Apparent opposite effects of tetrabenazine and reserpine on the toxic effects of 1-methyl-4-phenylpyridinium or 6-hydroxydopamine on nigro-striatal dopaminergic neurons. *Brain research*, 989: 187–195.

COOKSON, M.R. 2009. α-Synuclein and neuronal cell death. *Molecular neurodegeneration*, 4:9.

DAUER, W. & PRZEDBORSKI, S. 2003. Parkinson's disease: mechanisms and models. *Neuron*, 39: 889–909.

EMBORG, M.E. 2004. Evaluation of animal models of Parkinson's disease for neuroprotective strategies. *Journal of neuroscience methods*, 139: 121–143.

HART, M.P. & XU, A. 2009. Mice expressing mutant parkin exhibit hallmark features of Parkinson's disease. *Journal of neuroscience*, 29: 7392–7394.

HENDERSON, J.M., LU, Y., WANG, S., CARTWRIGHT, H. & HALLIDAY, G.M. 2003. Olfactory deficits and sleep disturbances in Parkinson's disease: a case – control survey. *Journal of neurology, neurosurgery and psychiatry*, 74: 956–958.

HUDRY, J., THOBOIS, S., BROUSSOLLE, E., ROYET, P.A. & ROYET, J.P. 2003. Evidence for deficiencies in perceptual and semantic olfactory processes in Parkinson's disease. *Chemical senses*, 28: 537–543.

IMAI, Y., VENDEROVA, K. & LIM, K.-L. 2012. Animal models of Parkinson's disease 2012. *Parkinson's disease*, 2012: Article ID729428, 2 pages, doi:10.115/2012/729428 (in press).

KUBOTA, K., NIINUMA, Y., KANEKO, M., OKUMA, Y., SUGAI, M., OMURA, T., UESUGI, M., UEHARA, T., HOSOI, T. & NOMURA, Y. 2006. Suppressive effects of 4-phenylbutyrate on the aggregation of Pael receptors and endoplasmic reticulum stress. *Journal of neurochemistry*, 97: 1259–1268.

LEWITT, P.A. 2008. Levodopa for the treatment of Parkinson's disease. *The new England journal of medicine*, 359: 2468–2476.

LUTHRA, P.M., BARODIA, S.K. & RAGHUBIR, R. 2009. Antagonism of haloperidol-induced swim impairment in L-dopa and caffeine treated mice: A pre-clinical model to study Parkinson's disease. *Journal of neuroscience methods*, 178: 284–290.

MATUSCH, A., DEPBOYLU, C., PALM, C., WU, B., HÖGLINGER, G.U., SCHÄFER, M.K.H. & BECKER, J.S. 2010. Cerebral bioimaging of Cu, Fe, Zn, and Mn in the MPTP mouse model of Parkinson's disease using laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS). *Journal of American society for mass spectrometry*, 21: 161–171.

MONTASTRUC, J.L., LLAU, M.E., RASCOL, O. & SENARD, J.M. 1994. Drug-induced parkinsonism: a review. *Fundamental and clinical pharmacology*, 8: 293–306.

NAGATSU, T. & SAWADA, M. 2006. Molecular mechanism of the relation of monoamine oxidase B and its inhibitors to Parkinson's disease: possible implications of glial cells. *Journal of neural transmissions supplement*, 71: 53–65.

ONO, K., IKEMOTO, M., KAWARABAYASHI, T., IKEDA, M., NISHINAKAGAWA, T., HOSOKAWA, M., SHOJI, M., TAKAHASHI, M. & NAKASHIMA, M. 2009. A chemical chaperone, sodium 4-phenylbutyric acid, attenuates the pathogenic potency in human α-synuclein A30P + A53T transgenic mice. *Parkinsonism and related disorders*, 15: 649–654.

ONOFRJ, M., BONANNI, L. & THOMAS, A. 2008. An expert opinion on safinamide in Parkinson's disease. *Expert opinion on investigational drugs*, 17: 1115–1125.

PREDIGER, R.D.S., MATHEUS, F.C., SCHWARZBOLD, M.L., LIMA, M.M.S. & VITAL, M.A.B.F. 2012. Anxiety in Parkinson's disease: a critical review of experimental and clinical studies. *Neuropharmacology*, 62: 115–124.

PRZEDBORSKI, S. & VILA, M. 2001. MPTP: a review of its mechanisms of neurotoxicity. *Clinical neuroscience research*, 1: 407–418.

REZAK , M. 2007. Current pharmacotherapeutic treatment options in Parkinson's disease. *Disease-a-Month*, 53: 214–222.

SAHA, A.R., HILL, J., UTTON, M.A., ASUNI, A.A., ACKERLEY, S., GRIERSON, A.J., MILLER, C.C., DAVIES, A.M., BUCHMAN, V.L., ANDERTON, B.H. & HANGER, D.P. 2004. Parkonson's disease α-synuclein mutations exhibit defective axonal transport in cultured neurons. *Journal of cell science*, 117: 1017–1024.

SCHAPIRA, A.H.V. 2011. Monoamine oxidase B inhibitors for the treatment of Parkinson's disease. A review of symptomatic and potential disease-modifying effects. *CNS Drugs*, 26: 1061–1071.

SCHLOSSMACHER, M.G., FROSCH, M.P., PING GAI, W., MEDINA, M., SHARMA, N., FORNO, L., OCHIISHI, T., SHIMURA, H., SHARON, R., HATTORI, N., LANGSTON, J.W., MIZUNO, Y., HYMAN, B.T., SELKOE, D.J. & KOSIK, K.S. 2002. Parkin localizes to the Lewy bodies of Parkinson disease and Dementia with Lewy bodies. *American journal of pathology*, 160: 1655–1667.

STANDAERT, D.G. & YOUNG, A.B. 2001. Treatment of central nervous system degenerative disorders. (*In:* HARDMAN, J.G., LIMBIRD, L.E. & GOODMAN GILMAN, A., eds. Goodman and Gilman's the pharmacological basis of therapeutics. 10thed. New York : McGraw-Hill. p549–568).

TIEU, K. 2011. A guide to neurotoxic animal models of Parkinson's disease. *Cold spring harbor perspectives in medicine*, 1: a009316.

WILLIAMS, A. 1993. Hyper susceptibility to chemicals: risk factors for neurological disease? *Journal of neurology, neurosurgery and psychiatry*, 56: 943–946.

YACOUBIAN, T.A. & STANDAERT, D.G. 2009. Targets for neuroprotection in Parkinson's disease. *Biochimica et biophysica acta,* 1792: 676–687.

YANG, Y., NISHIMURA, I., IMAI, Y., TAKAHASHI, R. & LU, B. 2003. Parkin suppresses dopaminergic neuron-selective neurotoxicity induced by Pael-R in *Drosophila. Neuron*, 37: 911–924.

YAZDANI, U., GERMAN, D.C., LIANG, C.-L., MANZINO, L., SONSALLA, P.K. & ZEEVALK, G.D. 2006. Rat model of Parkinson's disease: chronic central delivery of 1-methyl-4-phenylpyridinium (MPP^+). *Experimental neurology,* 200: 172–183.