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](image)

**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 unknown. 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$_2$O$_2$ (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](image)

**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 & Przedborski, 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 & Przedborski, 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 self-administered 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⁺.](image)

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).
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.
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2.8 References


