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Oxidative Stress in Parkinson's Disease; Parallels Between Current Animal Models, Human Studies and Cells

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1. Introduction

Reactive oxygen species (ROS) are byproducts generated primarily from the breakdown of oxygen during aerobic metabolism. ROS can be found as free radicals containing highly reactive unpaired electrons (super oxide, nitric oxide, hydroxyl radical) or as other molecules (hydrogen peroxide, peroxynitrate). Under normal physiological conditions, ROS are neutralized by antioxidants. However, an increased production of ROS, namely, oxidative stress, can occur under pathophysiological conditions. Oxidative stress can be defined as an imbalance between oxidants and antioxidants where the oxidants are favoured, potentially leading to cellular damage (Sies 1985, Sies 1986, Sies 1991).

The brain is highly susceptible to oxidative stress due to its high metabolic rate and limited regeneration capability (Andersen 2004). Oxidative stress has been implicated in a variety of neurodegenerative disease, including Parkinson's disease (PD), Alzheimer's disease, and amyotrophic lateral sclerosis. However, presence of oxidative stress as a cause or consequence of neurodegeneration, remains to be determined.

This review focuses on the pathogenesis of PD in relation to oxidative stress and the current animal models used to mimic the pathophysiology of human PD. We will also compare the animal and human data for PD like neurodegeneration with cell models of PD. This will also include a review on current experimentation and antioxidant therapies for counteracting oxidative stress.

2. Parkinson's disease

PD was first described in the early 19th century in the monologue "An essay on the shaking palsy" (Parkinson 2002). The three cardinal symptoms of PD are bradykinesia, rigidity, and

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postural instability (Gash et al. 1996). The clinical diagnosis of PD is usually based on the United Kingdom Parkinson's Disease Society Brain Research Centre criteria (Gibb and Lees 1988), with the accuracy of this diagnosis being high (90%) (Hughes, Daniel and Lees 2001). During the first 10 years of the disease, patients usually exhibit slowness of movement, mild gait hypokinesia, resting tremor, micrographic handwriting and reduced speech volume (Morris 2000). During the latter stages of the disease, festination, dyskinesia, akinesia, marked hypokinesia, postural instability and falls are usually more pronounced (Morris 2000). The symptoms of this condition only show after 80% of the striatal innervations and 60% of the substantia nigra par compacta dopaminergic neurons are lost, suggestive of a pathological process initiated at the synaptic end of the nigral neurons, with neuronal death as a result from a 'dying back' process (Dauer and Przedborski 2003).

2.1 Parkinson's disease pathology

PD can be defined as a progressive neurodegenerative disorder characterised histopathologically by the degeneration of the dopaminergic nigrostriatal pathway (Watts et al. 1997). Post-mortem analyses of the substantia nigra in PD patients have shown effects of oxidative stress with a decrease in glutathione (GSH) levels, increased levels of iron, neuromelanin associated redox-active iron, lipid peroxidation, protein oxidation and DNA damage (Jenner and Olanow 1998, Faucheux et al. 2003, Dexter et al. 1989). These changes may directly induce nigral cell degeneration via oxidative stress or render neurons susceptible to the actions of toxins.

The neurotrophic factor milieu of the brain is affected in PD patients. A decrease in brain derived neurotrophic factor (BDNF) in the post-mortem brains of clinically and pathologically diagnosed PD patients, compared to normal controls (Mogi et al. 1999, Parain et al. 1999). A decrease in BDNF mRNA expression in the substantia nigra of PD patients has also been demonstrated (Howells et al. 2000). A decrease in glial cell derived neurotrophic factor (GDNF) and ciliary neurotrophic factor (CNTF) also occurs in the brains of PD patients (Chauhan, Siegel and Lee 2001). The resultant inability to up-regulate neurotrophic factors in response to injury or stress may compromised defence mechanisms of the brain, thus contributing to cell degeneration (Olanow and Tatton 1999).

2.2 Pathogenic role of host/exogenous factors

There is increasing evidence of host and /or exogenous factors playing a role in the pathogenesis of PD. Many of these factors negatively impact mitochondrial function.

2.2.1 Age

The incidence of PD is related to increasing age (de Rijk et al. 1997, Mayeux et al. 1992, Van Den Eeden et al. 2003). With age, high levels of mitochondrial DNA deletion (Bender et al. 2006); increase in α-synuclein (Chu and Kordower 2007); decrease in dopamine transporter mRNA (Bannon et al. 1992); decrease in neurotrophic factor gene expression (Lee, Weindruch and Prolla 2000); reduced response to growth factors (Smith 1996); decrease in brain peroxidase and catalase activity (Ambani, Van Woert and Murphy 1975); and a decrease in dopamine binding sites (Severson et al. 1982) are apparent in the neuronal population of the substantia nigra. The relationship between PD and aging includes a

superposition of a topographic gradient of neuronal loss in brainstem and basal forebrain structures related to the disease process and an age-related temporal gradient. Clinical progression of PD is determined by advancing age and not by disease duration; and a biological interaction is involved in the effects of the disease process and aging on non dopaminergic structures (Levy 2007).

2.2.2 Environmental toxins

Pesticide exposure is implicated as an environmental risk factor for PD (Herishanu et al. 2001, Le Couteur et al. 1999, Tanner 1989, Ho, Woo and Lee 1989). The susceptibility of humans to these pesticides has been reported to be linked to genetic factors (Menegon et al. 1998, Drozdzik et al. 2003). Many of these pesticides have a major site of action along the mitochondrial electron transport chain (Degli Esposti 1998), which results in increasing oxidative stress.

2.2.3 Genetic determinants

The role of genetic factors in PD has been the subject of intense scrutiny. The first clue of familial PD was provided in 1907 when Gowers reported approximately 15% of his PD patients reported an affected family member (Gowers 1902) Since then many genes have been identified as causing familial PD (Schapira 2008). The products associated with the gene mutations are either mitochondrial proteins or are associated with mitochondria. Namely, proteins that interface with the pathways of oxidative stress and free radical damage.

Gene	Locus	Inheritance	Gene product
PARK1/4	4q21	Autosomal dominant	α-synuclein
PARK2	6q25	Autosomal recessive	Parkin
PARK3	2p13	Autosomal dominant	-
UCH-L1	4p15	Autosomal dominant	Ubiquitin thiolesterase
PINK1	1p35	Autosomal recessive	PTEN-induced putative kinase 1
PARK7	1p36	Autosomal recessive	DJ-1
LRRK2	12p	Autosomal dominant	Leucine-rich repeat kinase 2
ATP13A2	1p36	Autosomal recessive	ATPase type 13A2
PARK10	1p32	Autosomal recessive	-
PARK11	2q36-q37	-	-

Table 1. Genetic causes of PD (modified from Schapira, 2008)

2.2.4 Sporadic Parkinson's disease

The Braak hypothesis suggests that the initial event in sporadic PD may be an infectious assault on susceptible neuronal types in the olfactory or enteric nervous system (Braak et al. 2003a, Hawkes, Del Tredici and Braak 2007, Braak et al. 2003b). The Lewy neuritis and Lewy bodies' progress rostrally in stages into the lower brainstem region (medulla oblongata and pontine tegmentum; stages 1 and 2), followed by the midbrain (substantia nigra; stage 3) and the basal prosencephalon and mesocortex (stage 4), and eventually the neocortex (stage 5 and 6) (Braak et al. 2003a, Braak et al. 2003b). Stages 1 to 3 have been characterised as the

pre-symptomatic phase while stage 4 to 6 has been characterised as the symptomatic phase. The sequential ascending topography reported by Braak (2003b) has been reported to be only partially in line with the latest imaging of PD (Brooks 2010). It may instead reflect the more primitive regions of the nervous system (and perhaps the more active) showing a greater susceptibility.

3. Parkinson's disease animal models

There are both toxin and genetic animal models popularly used to represent PD. Both of these models increase ROS production directly or indirectly to induce the degeneration of the nigrostriatal pathway in laboratory animals.

3.1 Neurotoxins

There are four main toxin induced models popularly used to produce PD like symptoms in rodents. The neurotoxins used are 6-OHDA, MPTP, paraquat in combination with Maneb, and rotenone.

3.1.1 6-Hydroxydopamine (6-OHDA)

The neurotoxin 6-OHDA destroys catecholaminergic neurons by the combined effect of reactive oxygen species (ROS) and quinines (Cohen and Heikkila 1984). To specifically induce PD in an animal model, 6-OHDA is injected stereotaxically into the substantia nigra, the medial forebrain bundle, or the striatum (Javoy et al. 1976). 6-OHDA is delivered directly into the brain by stereotaxic means as 6-OHDA does not cross the blood-brain barrier, thus ruling out systemic injections (Bove et al. 2005). The administration of 6-OHDA into the substantia nigra or the medial forebrain bundle mediates its uptake anterogradely, while administration into the striatum causes the uptake of the chemical retrogradely. 6-OHDA is transported into dopaminergic neurons via their high-affinity catecholaminergic uptake system (Zigmond, Hastings and Abercrombie 1992). 6-OHDA is usually administered unilaterally to produce a unilateral lesion, allowing the unlesioned side to act as an internal control and to minimise morbidity and mortality (Betarbet, Sherer and Greenamyre 2002). The 6-OHDA lesioned rat has been extensively characterised behaviourally and pathologically, making it one of the models of choice when investigating PD (Schwarting and Huston 1996). However, the effects of 6-OHDA are acute and do not show the same cellular pathology (Lewy bodies) as seen in PD (Dawson and Dawson 2002).

3.1.2 1-Methyl-4-Phenyl-1,2,5,6-Tetrahydropyridine (MPTP)

MPTP was accidentally produced during the illegal production of 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP), a synthetic opioid drug, causing heroin addicts to display Parkinson-like symptoms (Langston 1996). MPTP readily crosses the blood-brain-barrier and is converted by the enzyme monoamine oxidase B (MAO-B) to 1-methyl-4-phenyl-2, 3-dihydropyridium (MPDP+) that then deprotonates to generate the corresponding pyridium species, MPP+ (Smeyne and Jackson-Lewis 2005). MPP+ has a high affinity to the dopamine transporter, thus it is highly selective to dopaminergic neurons (Javitch et al. 1985). Its selective uptake leads to severe damage to the nigrostriatal dopaminergic system, acting as a neurotoxin that inhibits mitochondrial complex I, producing oxidative stress and disturbing

intracellular calcium homeostasis (Sedelis, Schwarting and Huston 2001). When MPTP is delivered systemically, MPTP produces bilateral lesions of the dopamine neurons (Sedelis et al. 2001). Following systemic administration and collateral damage to the ventral tegmental area, an external source of dopamine is needed to stimulate adequate food and water uptake (Petzinger and Langston 1998). Bilateral lesions also have a high morbidity and mortality rate. The other difficulty with using MPTP lesioned animal models is that MPTP has varying effects on different animal models and strains due to differences in visceral functions (Betarbet et al. 2002). These drawbacks in mice are being looked at with the behavioural phenotyping of a MPTP mouse animal model for PD (Sedelis et al. 2001).

3.1.3 Paraquat and Maneb

1,1-dimethyl-4,4-bipyridinium, better known as paraquat is a herbicide that has a similar structure to MPP+, making it a putative risk factor for PD (Dawson and Dawson 2002). Paraquat when delivered systemically can pass the blood brain barrier (Brooks et al. 1999). Paraquat has a high affinity to the nigrostriatal dopaminergic system (Thiruchelvam et al. 2000) and exposure in mice can cause up-regulation and aggregation of α-synuclein, a pathological sign of PD in humans (Manning-Bog et al. 2002). Due to its structural similarity to MPP+, paraquat's mechanism of action is believed to involve oxidative stress and its toxic effect via the mitochondria (Betarbet et al. 2002). A link between paraquat and other types of herbicide/pesticides with a increased incidence of PD has been demonstrated (Liou et al. 1997). The effects of paraquat on the dopaminergic system can be increased when mixed with Maneb (manganese ethylenebisdithiocarbamate) (Thiruchelvam et al. 2000). Maneb is a fungicide that has been implicated in an increased incidence of PD in humans (Ferraz et al. 1988, Meco et al. 1994). This animal model is of use when examining PD like syndromes due to environmental factors.

3.1.4 Rotenone

Rotenone is a naturally occurring root extract of *Lonchocarpus utilis* and *Lonchocarpus urucu* used as an insecticide as well as a piscicide (Caboni et al. 2004). Rotenone is a high-affinity inhibitor of complex 1 of the mitochondrial electron transport chain (Sherer et al. 2003b). Rotenone cytotoxicity is not dependent on the dopamine transporter (Hirata et al. 2008). Complex 1 inhibition by rotenone can cause the production of ROS that causes oxidative damage in dopaminergic neurons (Testa, Sherer and Greenamyre 2005).

When neurons are exposed to rotenone in cell culture, they produce ROS and superoxides, with dopaminergic neurons showing higher susceptibility to rotenone compared to other neurons (Radad, Rausch and Gille 2006, Ahmadi et al. 2003, Moon et al. 2005). Over time, the increase in ROS and superoxides produced by rotenone exposure leads to cell death (Ahmadi et al. 2003, Moon et al. 2005). Thus rotenone is a relevant toxin for developing a rat model of PD.

In general, rotenone blocks the electron transfer between the Complex I-associated iron-sulfur clusters and ubiquinone binding site (Grivennikova et al. 1997) (Figure 1). Specifically, rotenone acts as a semiquinone antagonist and displaces the ubisemiquinone intermediate at the ubiquinone binding site (Degli Esposti 1998). By inhibiting the ubiquinone binding site, rotenone alters the state of complex I, leading to higher superoxide

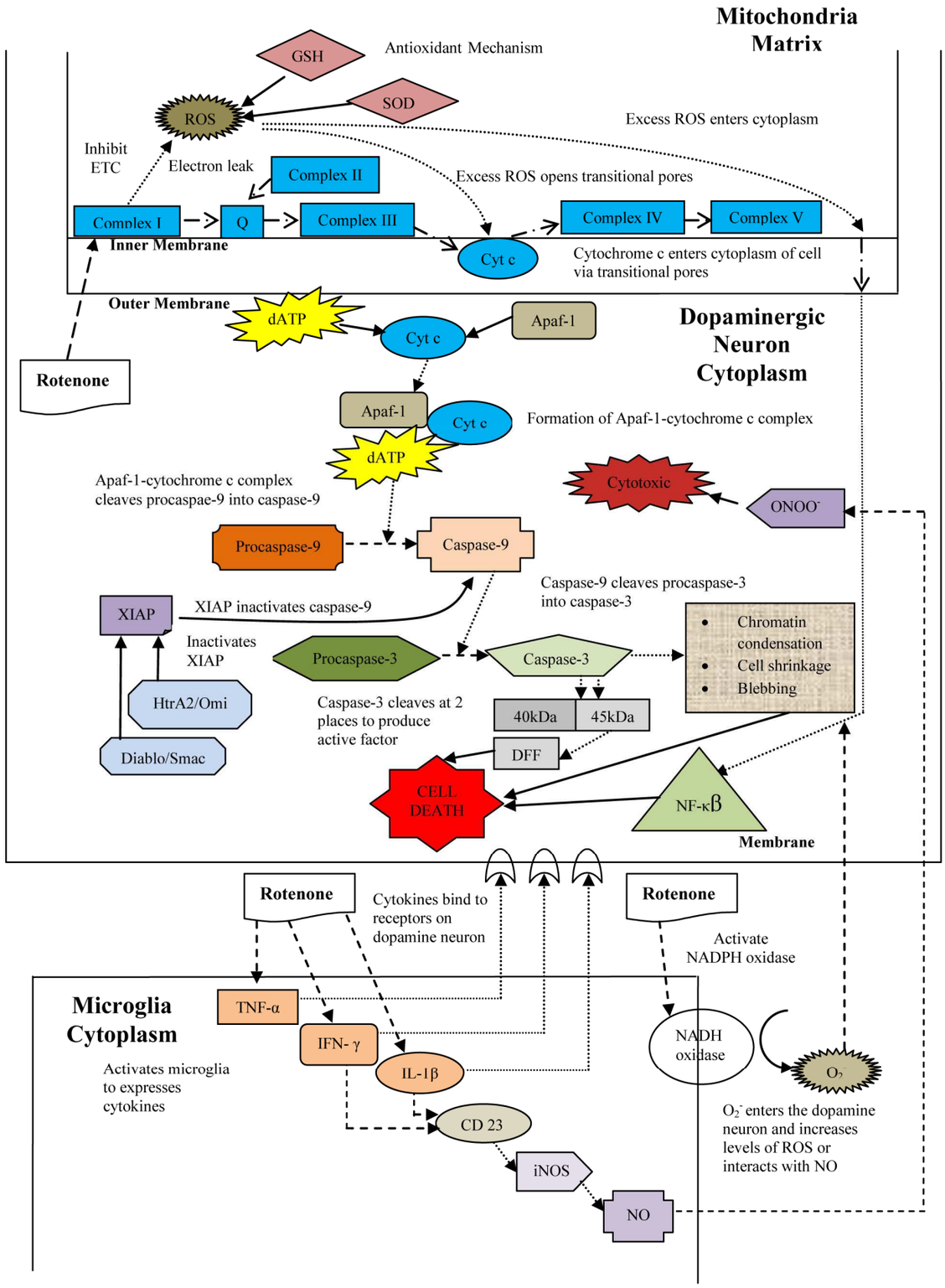

Fig. 1. Mechanism of action of rotenone

production at the same site (Lambert and Brand 2004). The inhibition of Complex I may overwhelm the mitochondria antioxidant system that consist of superoxide dismutase production with manganese (SOD) at the active site and GSH (Fridovich 1995, Betarbet et al. 2002), increasing the ROS concentration in the mitochondrial matrix. The increase of ROS activates the apoptotic intrinsic pathway, which increases the permeability of the outer membrane via the opening of transition pores (Turrens 2003). This allows cytochrome c to move from the intermembrane space into the cells cytoplasm, allowing it to bind with Apaf-1 (apoptopic protease activating factor) (Zou et al. 1997). In the presence of ATP or dATP, the Apaf-1 – cytochrome c complex changes its configuration, exposing the Apaf-1's CARD (caspase recruitment domain) to allow for the recruitment of procaspase-9 (Li et al. 1997). This interaction changes procaspase-9 into caspase-9 that in turn cleaves procaspase-3 into caspase-3. Cells contain an inhibitor of apoptosis (IAP) to prevent accidental caspase-9 activation. XIAP binds to the activated N terminus of caspase-9, making it inactive (Shiozaki et al. 2003). This process can be reversed by the mitochondrial proteins Diablo/Smac and HtrA2/Omi that are released during apoptosis (Vaux and Silke 2003), leading to caspase-3 activation. Caspase-3 cleaves the 45 kDa subunit of a two unit protein in two places producing a DNA Fragmentation Factor (DFF) (Liu et al. 1997). The increase in oxidative stress can also activate nuclear factor kappa β (NF-κβ) (Panet et al. 2001), which has been implicated in the beginning of a pro-apoptopic gene expression programme which may play a role in neurodegenerative disease (Qin et al. 1998, Panet et al. 2001).

Rotenone has the ability to activate microglia *in vivo* (Sherer et al. 2003a). This activation causes the release of tumour necrosis factor α (TNF- α), interleukin 1β (IL-1β), and interferon γ (IFN- γ). These cytokines can bind to their respective receptors and activate transduction pathways, leading to NF-κβ activation and ultimately, apoptosis (Gao, Liu and Hong 2003). It was reported that NF-κβ is present before caspase-3 (Wang et al. 2002), which suggests that superoxides and cytokines produced by the activation of microglia by rotenone play a role in the activation of NF-κβ before complex I inhibition initiates the activation of caspase-3 apoptosis. However, excess ROS from the cytoplasm due to the Complex I inhibition could result in ROS crossing over into the cytoplasm via voltage-dependent anion channels (Han et al. 2003), which could also help activate NF-κβ. Excess ROS in the cytoplasm could also be complemented by the superoxides produced by the activated microglia via NADPH oxidase (Gao et al. 2002). The superoxides produced by NADPH oxidase can also interact with nitric oxide (NO) to produce peroxinitrate (ONOO-), a potent oxidant (Gao et al. 2003) implicated with being cytotoxic and able to damage the neuron's cell membrane (Hirsch 2000, Imao et al. 1998). NO is produced via the inducible nitric oxide synthase that is activated by CD23 which in turn is induced by the presence of TNF- α and IFN- γ (Munoz-Fernandez and Fresno 1998, Hirsch 2000).

Initial studies of the effect of rotenone used systemically in the rat showed a decrease in brain dopamine levels, decreases in tyrosine hydroxylase immunoreactivity in the substantia nigra, and motor deficits similar to those seen in PD (Betarbet et al. 2000, Sherer et al. 2003c, Alam and Schmidt 2002). Rotenone treatment also leads to intracytoplasmic inclusions within dopaminergic neurons thereby mimicking some aspects of PD histopathology (Betarbet et al. 2002). Unfortunately, systemic delivery of rotenone results in high mortality due to the systemic toxicity resulting in liver failure and inconsistent lesions of the substantia nigra (Dawson and Dawson 2002). These problems were alleviated with intra-peritoneal

administration of rotenone in a specialised vehicle of a medium-chain triglyceride, although this model developed a debilitating behavioural phenotype in a relatively short time and is not appropriate as a slow onset chronic model (Cannon et al. 2009).

The side effects of peripheral rotenone treatment can be reduced or avoided by the infusion of a lower dose directly into the striatum, medial forebrain bundle or substantia nigra (Ravenstijn et al. 2008, Xiong et al. 2009). Bilateral infusion of rotenone into the medial forebrain bundle causes reductions in striatal dopamine and disruptions in motor behaviours (Alam, Mayerhofer and Schmidt 2004). However, bilateral infusions lead to weight loss and require specialised diets to maintain the animals (Betarbet et al. 2000, Sherer et al. 2003c), possibly due to bilateral lesioning of the ventral tegmental area. These problems are ameliorated by unilateral lesions which reduce dopamine signalling, dopamine level, DOPAC (3,4-dihydroxyphenylacetic acid) level and dopaminergic innervation, while increasing oxidative stress (hydroxyl radicals, GSH level, superoxide dismutase levels), as well as up-regulating α-synuclein expression in the ipsilateral substantia nigra (Sindhu et al. 2006, Antkiewicz-Michaluk et al. 2004, Saravanan, Sindhu and Mohanakumar 2005, Sindhu, Saravanan and Mohanakumar 2005, Ravenstijn et al. 2008, Xiong et al. 2009). Unilateral rotenone lesioned animals have shown differences in several behavioural indices, including rotarod and amphetamine or apomorphine-induced rotation, demonstrating the unilateral functional motor deficits associated with substantia nigra dopamine neuron loss (Sindhu et al. 2006, Sindhu et al. 2005, Ravenstijn et al. 2008, Xiong et al. 2009). Behavioural indices are also influenced by the lesion of the ventral tegmental area, as can occur with larger doses of rotenone in the medial forebrain bundle (Sindhu et al. 2005, Xiong et al. 2009, Thomas et al. 1994).

Our laboratory has recently reported that a low dose of rotenone injected into the medial forebrain pathway in adult rats caused progressive loss of dopaminergic neurons with the remaining neurons displaying pathophysiological hallmark of human PD (Norazit et al. 2010)(Figure 2). Unlike the complete lesion of dopaminergic neurons induced by focal 6-OHDA injection, rotenone injection into the medial forebrain bundle induced the up-regulation of markers of oxidative stress and markers of cell stress in dopaminergic neurons (Sindhu et al. 2005, Norazit et al. 2010). 0.5 µg of rotenone caused negligible necrosis, inflammation and a diffused glial response. A progressive loss of dopaminergic neurons in the substantia nigra and loss of striatal innervation was shown. The low dose of rotenone mediated dopaminergic cell death by oxidative stress as previously demonstrated (Rodrigues, Gomide and Chadi 2004). An increase in astrocytes and microglia occurs in human PD, where they have been ascribed both a neuroprotective and deleterious role (Imamura et al. 2003, Ishida et al. 2006, Vila et al. 2001). The study presented direct support for the hypothesis that rotenone induces a chronic state of oxidative stress in dopaminergic neurons. Rotenone exposure increased SOD2 immunoreactivity within surviving tyrosine hydroxylase positive neurons. The toxin leads to high super-oxide production, activating the apoptotic pathway as shown in the study with increased caspase-3 immunoreactivity (Esposti 1998, Lambert and Brand 2004, Turrens 2003). Under oxidative stress, cells generate G3BP positive cytoplasmic stress granules (Cande et al. 2004, Kedersha and Anderson 2002). This proposal was further validated by the presence of α-synuclein in tyrosine hydroxylase positive neurons 60 days following rotenone exposure (Norazit et al. 2010). α-synuclein is up-regulated in neurons subject to chronic oxidative stress, and plays a neuroprotective role and is expressed sporadically in the substantia nigra 28 days after rotenone infusion into the

medial forebrain bundle (Hashimoto et al. 2002, Quilty et al. 2006). This model has now been successfully used to test the neuroprotective properties of chronic exposure to neurotrophic factors (unpublished data).

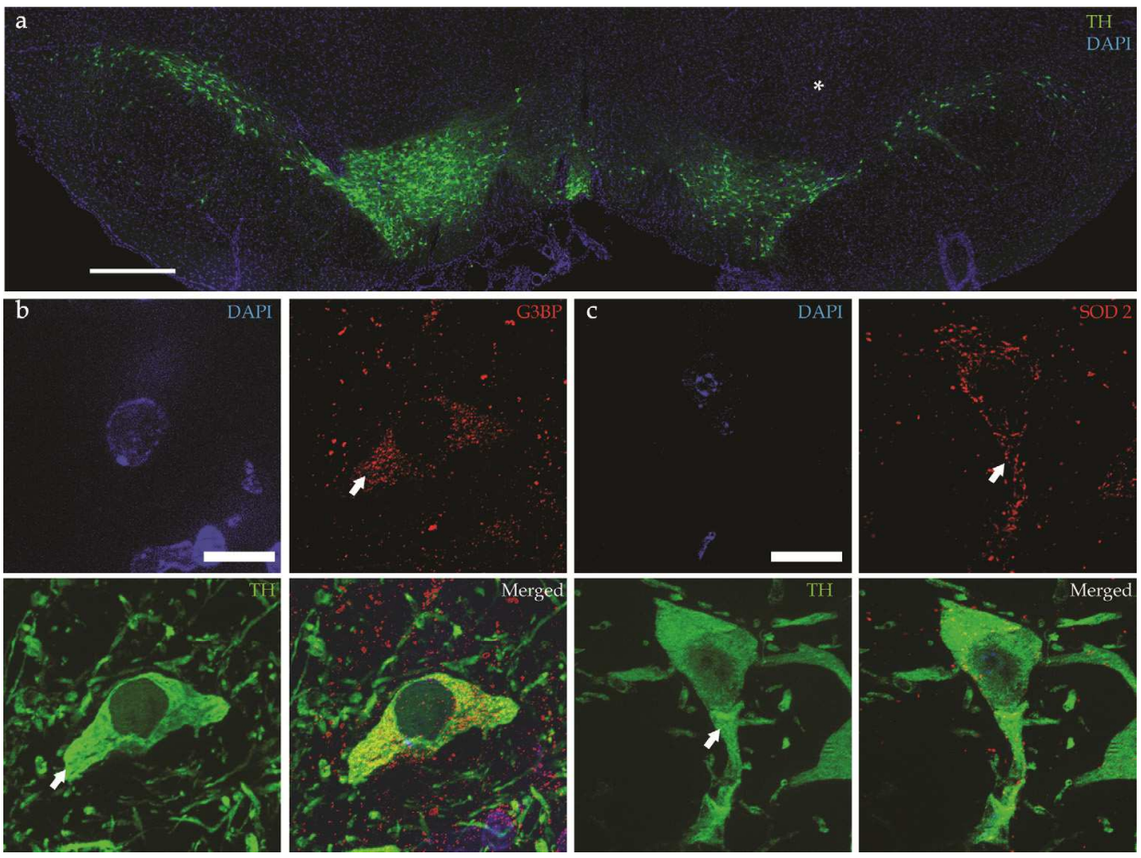

Fig. 2. Dopamine cell pathophysiology of the substantia nigra, induced by 0.5-µg rotenone delivered focally into the medial forebrain bundle and harvested after 14 days. a) The unilateral lesion is manifest as a subtle yet significant reduction in the number of dopaminergic neurons and dendritic arbour within the substantia nigra (asterisk) and a reduction in the dopaminergic innervation of the striatum (data not shown). The nigrostriatal circuitry contralateral to the lesion is uneffected by the rotenone treatment. b) Ras-GAP SH3 domain binding protein (G3BP) immunoreactivity (red, filled arrowhead) was expressed in tyrosine hydroxylase immunoreactive (green, filled arrowhead) dopaminergic neurons located in the rotenone exposed substantia nigra. c) Superoxide dismutase (SOD2) immunoreactivity (red, filled arrowhead) was also expressed in the rotenone exposed tyrosine hydroxylase immunoreactive (green, filled arrowhead) dopaminergic neurons. Nuclei for all sections are counterstained with the nuclear marker DAPI (blue) (scale bar=10 µm)

3.2 Cellular based models

Complete human disease phenotype is rarely observed in animal models introduced with human gene mutations. Thus, relevant human tissue is required to study the disease process

and potential therapies for neurodegenerative disorders such as PD. Pathological human samples are often confounded by difficult-to-control artefacts resulting from the disease process itself (Sutherland et al. 2009), biased sampling, and the necessity to process tissue in a timely manner following death (Atz et al. 2007, Marcotte, Srivastava and Quirion 2003, Preece and Cairns 2003). Together with rare foetal derived tissue, patient derived olfactory stem cells and induced pluripotent stem cells are currently used as models for PD.

3.2.1 Patient derived olfactory stem cells

Procuring relevant neural cells from patients with central nervous system disorders is difficult. Therefore, we have developed olfactory stem cells as a model for PD. Neural stem cells from adult human olfactory mucosa may be harvested and expanded to enrich for the stem cells, which are then frozen, banked, thawed, and regrown in quantity for gene and protein expression analyses and functional investigations. Assays on olfactory stem cell function have shown a reduction in gluthathione while pathway analysis has demonstrated significantly dysregulated pathways associated with mitochondrial function and oxidative stress (Matigian et al. 2010). The ease of patient derived olfactory stem cells propagation and banking allows them to be used for extended genomic, proteomic, and functional studies, including drug and biomarker discovery.

3.2.2 Patient derived induced pluripotent stem cells

Induced pluripotent stem (iPS) cells are pluripotent cells derived from differentiated cells, for example by introducing key transcription factor genes, as demonstrated in adult mouse fibroblasts (Takahashi and Yamanaka 2006). iPS cells have successfully been used to generate neurons from patients with sporadic PD (Soldner et al. 2009). Notably, despite these iPS cells being derived from LRRK2 mutation carriers, no phenotypic differences between sporadic PD iPS and control iPS cells were demonstrated (Nguyen et al. 2011). Patient-derived iPS cells have the potential to be used to identify changes in neural cell biology associated with the identified mutations.

3.3 Genetic animal models

Transgenic models have been developed as genetic factors linked to PD have been identified. Several autosomal dominant and recessive genes linked to mitochondrial dysfunction have been identified in humans as reviewed by Schapira (Schapira 2008). This created an opportunity for transgenic animals to mimic familial forms of PD (Fleming, Fernagut and Chesselet 2005).

3.3.1 PARK2 (PARKIN)

PARK 2 (Parkin) is transcribed in the mitochondria (Schapira 2008). The function of parkin remains to be elucidated; however the direct association between parkin and the mitochondria is of interest and warrants further study. In the knockout transgenic mouse model, animals had a decrease in mitochondrial respiratory chain function in the striatum and reductions in specific respiratory chain and antioxidant proteins (Palacino et al. 2004). Midbrain neuronal cultures obtained from PARK2 knockout mice had an increased sensitivity to rotenone, suggesting an effect on the mitochondrial respiratory chain

(Casarejos et al. 2006). In some of the mouse knockout models, subtle abnormalities of the nigrostriatal pathway or the locus coeruleus noradrenergic system have been observed (Goldberg et al. 2003, von Coelln et al. 2006). Conversely, over-expression of mutant parkin produces a progressive loss of dopaminergic neurons in the nigrostriatal pathway in both mice and drosophila (Lu et al. 2009, Sang et al. 2007, Wang et al. 2007). This suggests that some parkin mutants may act in a dominant negative fashion. The parkin animal model exhibits several movement indices in both drosophila and mice (Greene et al. 2003, Whitworth et al. 2005).

3.3.2 PINK1

Similar to parkin knockouts, PINK1 knockouts also have mild mitochondrial defects (Gautier, Kitada and Shen 2008, Palacino et al. 2004).The PINK1 product is transcribed in the nucleus, translated in the cytoplasm, and imported intact into the mitochondria, with subsequent processing and intra mitochondrial sorting (Schapira 2008). The lack of PINK1 in transgenic mice causes enlargement of mitochondria as well as a decrease in mitochondrial numbers in dopaminergic neurons of the nigrostriatal pathway (Gautier et al. 2008, Gispert et al. 2009, Kitada et al. 2007). Although these animals do not exhibit any changes in the nigrostriatal pathway, a deficit in dopamine neurotransmission has been observed (Kitada et al. 2007). Changes in several behavioral indices have also been shown in the PINK1 knockout drosophila animal model (Clark et al. 2006, Park et al. 2006).

It is interesting to point out that while both the knockdown of parkin and PINK1 have been linked to mitochondrial dysfunction, the expression of parkin ameliorates PINK1-related abnormalities but not vice versa (Clark et al. 2006, Park et al. 2006). This suggests that parkin and PINK1 are part of a common pathway with PINK1 functioning upstream from parkin.

3.3.3 α -Synuclein

α -synuclein is a protein aggregate that is the main part of Lewy bodies in human PD. The function of α-synuclein is as yet unclear, however, there appears to be a reciprocal relationship between this protein and oxidative stress (Henchcliffe and Beal 2008). α-synuclein is up-regulated in neurons subject to chronic oxidative stress and expressed sporadically in the substantia nigra (Hashimoto et al. 2002, Quilty et al. 2006, Norazit et al. 2010). The association between the presence of α-synuclein and PD has led to the development of a variety of animal models (Table 1). The over-expression of α-synuclein increased the loss in dopaminergic neurons in both drosophila and C. elegans models. (Feany and Bender 2000, Kuwahara et al. 2006, Lakso et al. 2003). However, only the dopaminergic loss in the drosophila model is progressive. A loss of dopaminergic neurons with the over-expression of α-synuclein has been demonstrated in mice; however the phenotypic outcome depends on the promoters used to drive transgene expression (Chesselet 2008). Transgenic mice presented with several functional abnormalities in the nigrostriatal system, some of which are dopamine responsive (Chesselet 2008). However, the loss of dopaminergic neurons is not progressive. α-synuclein toxicity is induced though mitochondrial dysfunction, proteasomal and lysosomal impairments, and disruption of ER-Golgi trafficking (Cooper et al. 2006, Cuervo et al. 2004, Martin et al. 2006, Tanaka et al. 2001). The link between mitochondrial dysfunction and α-synuclein aggregation suggests a

feed-forward loop that has the potential to initiate the progressive loss of dopaminergic neurons in the nigrostriatal system due to oxidative stress.

3.3.4 LRRK2

The LRRK2 protein functions as a serine-thereonine kinase, a known affector of mitochondrial function. A small percentage (10%) of LRRK2 is located in the outer mitochondrial membrane (West et al. 2005). Although the precise function of mitochondrial-located LRRK2 is not known, it has been suggested that it interacts with parkin. The current transgenic LRRK2 animal models are not robust enough to be used as a PD animal model due to the lack of loss of dopaminergic neurons of the nigrostriatal pathway (Li et al. 2010, Li et al. 2009, Lin et al. 2009, Wang et al. 2008, Tong et al. 2009). However, these animals do show several abnormalities in DA neurotransmission or in dopamine responsive behavior. It has been suggested that the mouse LRRK2 transgenic models do not exhibit more substantial pathology as LRRK2 mutations in humans are only partially penetrant, with further genetic and/or environmental insult required to induce the degeneration of dopaminergic neurons (Dawson, Ko and Dawson 2010).

4. Experimental therapies

4.1 Metal chelation therapy

Increased iron levels have been detected in the midbrain of PD patients suggesting that the increased levels of iron may be part of the disease pathology (Andersen 2004). Notably, iron participates as a catalyst to produce ROS.

4.1.1 8-Hydroxyquinolines

Previously the hydroxyquinoline clioquinol had been examined as a metal chelator in a clinical trial for Alzeimer's disease (Ritchie et al. 2003). The use of a variety of hydroxyquinolines to chelate iron into a form that does not catalyze ROS has shown promise in both *in vivo* and *in vitro* models (Table 2).

Hydroxyquinoline	Model	Reference
Clioquinol	MPTP mouse model	(Kaur et al. 2003)
HLA20	P19 cells exposuded to 6-OHDA	(Zheng et al. 2005)
VK-28	6-OHDA rat model	(Tsubaki, Honma and Hoshi 1971)
M30	MPTP mouse model In vitro	(Gal et al. 2005, Gal et al. 2006)
M98 and M99	SH-SY5Y and PC12 exposed to 6-OHDA	(Gal et al. 2006, Zheng, Blat and Fridkin 2006)
M10	PC12 cells exposed to 6-OHDA	(Ritchie et al. 2003)

Table 2. Hydroxyquinolines shown to chelate iron in both *in vivo* and *in vitro* models

Hydroxyquinolines are able to cross the blood brain barrier, allowing for oral administration. Hydroxyquinolines have also shown inhibitory effect on the activity of enzyme MAO-B (Yassin et al. 2000, Youdim, Fridkin and Zheng 2005).

4.1.2 Desferrioxamine

Previously, desferrioxamine was used to treat iron overload disease (Mandel et al. 2007). The use of Desferrioxamine has been reported to be neuroprotective *in vivo* and *in vitro* (Ben-Shachar et al. 1991, Jiang et al. 2006, Sangchot et al. 2002, Youdim, Stephenson and Ben Shachar 2004). Unlike hydroxyquinolines, desferrioxamine does not cross the blood brain barrier, thus removing the option of oral administration (Aouad et al. 2002).

4.2 Plant polyphenols

Polyphenols have been reported to have antioxidant properties, thus making them a candidate for antioxidant therapies (Malesev and Kuntic 2007). Green tea, cranberry, traditional chinese tea, and tumeric are sources of a variety of polyphenols (Reto et al. 2007, Ramassamy 2006, Perez, Wei and Guo 2009, Tan, Meng and Hostettmann 2000). Neuroprotective and neurorescue properties of plant polyphenols have been demonstrated *in vivo* and *in vitro* (Mandel, Maor and Youdim 2004, Mercer et al. 2005, Chen et al. 2006, Zbarsky et al. 2005, Mandel et al. 2006). Polyphenols exert their antioxidant effect via scavenging of free radicals and inhibition of the Fenton reaction (Perez et al. 2009, Pan, Jankovic and Le 2003).

4.3 Antioxidant therapy

The effects of oxidative stress are demonstrated in PD patients who have decreased GSH levels, increased levels of iron, neuromelanin associated redox-active iron, lipid peroxidation, protein oxidation and DNA damage in the substantia nigra (Jenner and Olanow 1998, Faucheux et al. 2003, Dexter et al. 1989). Antioxidant therapy has been suggested to ameliorate these effects.

4.4 Coenzyme Q_{10} (CoQ_{10})

CoQ_{10}, also known as ubiquinone is a cofactor that accepts electrons from Complex I and II of the electron transport chain in the mitochiondria (Beyer 1992, Dallner and Sindelar 2000). CoQ_{10} mediates its antioxidant effect via its interaction with *a*-tocopherol (Beyer 1992, Noack, Kube and Augustin 1994), inhibiting the activation of mitochondrial permeability, and acting independently of its free radical scavenging activity. Thus it blocks apoptosis (Papucci *et al.*, 2003), acting as a co-factor of mitochondrial uncoupling proteins which reduces mitochondrial-free radical generation (Echtay, Winkler and Klingenberg 2000, Echtay et al. 2002). Neuroprotection has been associated with the ability of CoQ_{10} to induce mitochondrial uncoupling in the substantia nigra of primates, after MPTP toxicity (Horvath et al. 2003). The use of CoQ_{10} as an antioxidant has been translated into phase II clinical trials (Shults et al. 2002) which showed a slowing of disease progression following 16 months of treatment.

4.5 Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP)

Deprenyl and tocopherol antioxidative therapy have been clinically trialed to explore its potential as therapy for PD (Shoulson et al. 2002). Deprenyl treatment delayed the initiation of levodopa therapy. Continued deprenyl treated subjects exhibited slower motor decline

and lower likelihood of developing freezing of gait. However, this treatment increased the likelihood of developing dyskinesia.

5. Conclusion

There is increasing evidence that many factors including age, environmental toxins, genetic determinants, and lifestyle factors influence the risk for PD. Many of these impact on oxidative stress related pathways. Animal and cellular models have been developed to mimic the disease pathology in humans. Currently, antioxidant therapies are being investigated in both animals and human clinical trials, with promising outcomes. Notably, antioxidant therapies appear to delay the onset of disease and disease progression, although they do not prevent or reverse disease progression.

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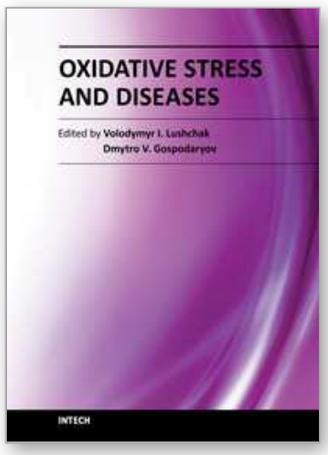

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The development of hypothesis of oxidative stress in the 1980s stimulated the interest of biological and biomedical sciences that extends to this day. The contributions in this book provide the reader with the knowledge accumulated to date on the involvement of reactive oxygen species in different pathologies in humans and animals. The chapters are organized into sections based on specific groups of pathologies such as cardiovascular diseases, diabetes, cancer, neuronal, hormonal, and systemic ones. A special section highlights potential of antioxidants to protect organisms against deleterious effects of reactive species. This book should appeal to many researchers, who should find its information useful for advancing their fields.

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