We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

154

Countries delivered to

Our authors are among the

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

CLARIVATE ANALYTICS

BOOK CITATION INDEX

INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Pesticides and Parkinson's Disease

Arthur G. Fitzmaurice and Jeff M. Bronstein
David Geffen School of Medicine at UCLA
United States of America

1. Introduction

1.1 Clinical and pathological aspects of Parkinson's disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, affecting millions of people worldwide (Dorsey, Constantinescu et al. 2007). While some cases of familial PD have been reported, the etiology of most cases is still unknown. Significant progress in understanding the pathophysiology of PD has been made from genetic and epidemiologic studies that have implicated defects in a few key biological processes as potential final common pathological pathways.

PD is a progressive motor disorder characterized by death of dopaminergic neurons in the region of the brain called the substantia nigra pars compacta although other areas of the central and peripheral nervous system are involved (Braak, Del Tredici et al. 2003). The loss of dopaminergic neurons in PD leads to motor symptoms that include akinesia (inability to initiate movement), bradykinesia (slowness of movement), resting tremor, and balance problems. Non-motor symptoms can include cognitive impairments, mood disturbances, sleep dysfunction, gastrointestinal problems, and dysautonomia. PD is a progressive disorder and despite several effective therapies that treat many of the symptoms, there are no treatments that alter disease progression. Uncovering the causes of PD is likely necessary to find effective disease modifying therapies.

The pathological hallmark of PD is the presence of Lewy bodies, which are cytosolic inclusions with several molecular components although α-synuclein (α-syn) is the predominant protein (Spillantini, Schmidt et al. 1997). Lewy bodies also contain ubiquitin, a polypeptide that targets proteins to the ubiquitin proteasome system (UPS) for degradation.

1.2 Genes versus environment

Despite the elucidation of approximately 18 genes in familial PD and the identification of multiple risk factor genes using genome wide association studies on thousands of patients, only a small fraction of PD risk has been accounted for (Hardy 2010). Thus, environmental factors almost certainly play a major role in the pathogenesis of PD.

One of the first important clues that the environment may contribute to the pathogenesis of PD came in 1982 from the observation that a street drug contained a contaminant called 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which caused almost overnight a clinical syndrome resembling PD. It was subsequently found that MPTP killed dopaminergic neurons by being converted enzymatically to MPP+, specifically entering dopamine neurons via the dopamine transporter, and inhibiting complex I in the

mitochondrial respiratory chain. Notably, the chemical structure of the MPTP metabolite MPP+ is similar to paraquat, a commonly used pesticide. These and other observations led to a series of epidemiologic studies probing pesticides as potential contributors to the etiology of PD.

Although genetics hasn't found the cause of 95% of PD cases, the identification of specific genes and their functions have provided important clues into pathological processes that appear to be involved in non-genetic forms of PD. For example, mutations in the α-syn gene led to the finding that α-syn is the major component of Lewy bodies. Mutations in other genes have identified dysfunction of protein degradation (the UPS and autophagy) as possibly being involved in the pathogenesis of PD. Since other PD genes are involved in mitochondrial function and MPTP inhibits oxidative respiration, mitochondrial dysfunction also has been implicated in the pathogenesis of PD. We believe that environmental toxins may increase the risk of PD by causing dysfunction in these cellular processes. Here, we will review the evidence that pesticides are associated with the development of PD and the mechanisms by which they might act.

2. Pathophysiology of Parkinson's disease

2.1 Lewy bodies and α-synuclein homeostasis

Lewy bodies are the pathological hallmark of PD and the major component of these intracytosolic inclusions is α-syn (Spillantini, Schmidt et al. 1997). α-Syn exists in multiple forms including soluble monomers, oligomers and fibrils. The multimeric forms appear to be the toxic species and their formation is dependent on several factors including amino acid substitutions due to mutations in its gene, α-syn concentration, and the presence of dopamine and dopamine adducts (Li, Lin et al. 2005; Mazzulli, Armakola et al. 2007; Burke, Kumar et al. 2008). Exogenous factors such as pesticides have also been reported to increase α-syn aggregation. Given that α-syn aggregation appears central to the pathogenesis of PD and pesticides appear to promote this process via a variety of mechanisms, we will briefly discuss α-syn homeostasis.

2.1.1 α-Synuclein

α-Syn is a predominantly neuronal protein that was first implicated in the development of Alzheimer's disease. The identification of three mutations—A53T, A30P, and G188A—in its gene in a few families with dominantly-inherited PD led to the finding that fibrillar α-syn is the major component of Lewy bodies not only in these patients but also in sporadic PD (Nussbaum and Polymeropoulos 1997; Spillantini, Schmidt et al. 1997; Kruger, Kuhn et al. 1998; Trojanowski, Goedert et al. 1998; Giasson, Jakes et al. 2000). Overexpression of normal α-syn by gene multiplication causes fairly typical PD (Farrer, Kachergus et al. 2004), and people who have an α-syn promoter that confers a higher level of expression are at higher risk of developing PD (Pals, Lincoln et al. 2004; Mueller, Fuchs et al. 2005). Thus, increased levels of normal α-syn increases one's risk of getting PD and if it is high enough, it causes it. Importantly with respect to this review, certain pesticides can cause α-syn levels to increase providing a theoretical mechanism to contribute to PD (see below for individual pesticides). Furthermore, pesticides can directly increase the rate of α-syn fibril formation adding another method they can contribute to the pathogenesis of PD (Uversky, Li et al. 2001).

2.1.2 Ubiquitin-proteasome system dysfunction in Parkinson's disease

α-Syn concentrations are determined by the relative amount of its expression and degradation, and the higher the concentration, the more likely it is to form aggregates. Both the ubiquitin-proteasome system (UPS) and autophagy have been shown to degrade α-syn. The soluble form appears to be degraded by the UPS while the lysosomal pathway appears to degrade aggregated forms of the protein (Liu, Corboy et al. 2003; Cuervo, Stefanis et al. 2004; Zhang, Tang et al. 2008; Mak, McCormack et al. 2010). The UPS is a highly regulated ATP-dependent degradative multi-subunit pathway that helps clear the cell of damaged, misfolded or otherwise unneeded proteins. Proteins are targeted to the UPS by ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin-protein ligases (E3). Once polyubiquitinated, proteins are recognized by the 19S regulatory complex of the 26S proteasome and translocated to the 20S complex for degradation. Finally, ubiquitin is recycled via thiol proteases called deubiquitinating enzymes, which fall into the ubiquitin carboxyl-terminal hydrolase (UCH) or ubiquitin-specific processing protease (UBP) families (Goldberg 2003).

Three known genetic causes of PD involve aspects of UPS function. Parkin gene mutations cause autosomal recessive PD and is an E3 ubiquitin ligase necessary for targeting proteins for degradation. UCH-L1 gene mutations cause autosomal dominant (AD) PD and UCH-L1 is necessary for the recycling of ubiquitin. Finally, α-syn is a substrate for the UPS and mutations and duplication of its gene cause AD PD. There is also evidence that UPS dysfunction is involved in sporadic PD. Reduced UPS activity has been found in brains of PD patients (McNaught and Jenner 2001) and some investigators have found that administration of UPS inhibitors to rodents can recreate some of the features of PD although these models remain controversial (Bove, Zhou et al. 2006; Kordower, Kanaan et al. 2006; Manning-Bog, Reaney et al. 2006; McNaught and Olanow 2006; Schapira, Cleeter et al. 2006; Zeng, Bukhatwa et al. 2006). Finally, we have found that several commonly used pesticides inhibit the UPS and are associated with an increased risk of developing PD (Wang, Li et al. 2006; Chou, Maidment et al. 2008).

2.1.3 Autophagy and Parkinson's disease

Autophagy is a cellular process that involves protein and organelle degradation. Dysfunction of autophagy has long been known to be involved in disease but only recently has been implicated in the pathogenesis of PD. Gaucher's disease is an autosomal recessive lysosomal storage disease caused by mutations in its gene that lead to dysfunction of autophagy and are associated with a marked increased risk of developing typical PD with Lewy bodies (Aharon-Peretz, Rosenbaum et al. 2004; Neumann, Bras et al. 2009; Sun, Liou et al. 2010). Another autosomal recessive Parkinsonian disorder (PARK9) is caused by a mutation in another lysosomal gene, ATP13A2 (Ramirez, Heimbach et al. 2006). PINK1 has also been shown to be a modifier of autophagy and mutations in its gene cause PD with Lewy bodies (PARK6) (Narendra, Jin et al. 2010; Samaranch, Lorenzo-Betancor et al. 2010). Additional evidence for a role of autophagy in PD comes from studies of sporadic PD brains where increased numbers of autophasomes have been described (Anglade, Vyas et al. 1997).

α-Syn clearance is likely carried out by both the UPS and autophagy. Large aggregates of α-syn proteins are likely degraded by macroautophagy but soluble α-syn can undergo degradation via an alternate lysosomal pathway, chaperone-mediated autophagy (CMA)

(Massey, Zhang et al. 2006). α-Syn has also been found to inhibit lysosomal macroautopaghy and oligomers are resistant to CMA adding further support for a possible role of protein degradation dysfunction in the pathogenesis of PD (Martinez-Vicente, Talloczy et al. 2008).

2.2 Mitochondrial dysfunction and oxidative stress

The role of mitochondrial dysfunction in the pathophysiology of PD was first suggested by the discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin selective for nigral dopaminergic neurons, acts through inhibition of complex I of the electron transport chain. MPTP is converted by monoamine oxidase (MAO-B) to its toxic metabolite 1-methyl-4-phenylpyridinium (MPP+), which is rapidly concentrated by dopaminergic neurons into the mitochondria and produces cell death (Langston, Ballard et al. 1983; Chiba, Trevor et al. 1985; Javitch, D'Amato et al. 1985; Gainetdinov, Fumagalli et al. 1998). This discovery led to the findings that complex I activity is reduced not only in brains of PD patients but also in peripheral mitochondria (Schapira, Cooper et al. 1990; Haas, Nasirian et al. 1995). Furthermore, mutations in some genes that code for mitochondrial associated proteins can cause PD (e.g. DJ1 and PINK1) and chronic systemic administration of complex I inhibitor (rotenone) in rodents reproduces many of the clinical and pathological aspects of PD (Betarbet, Sherer et al. 2000).

It is still unclear what are the downstream targets of mitochondrial dysfunction. ATP depletion is not necessary in the rotenone rodent model for its toxicity but the generation of reactive oxygen species (ROS) appears to be essential. ROS are known to oxidize DNA, lipids and proteins to cause cellular damage. Interestingly, ROS from complex I inhibition leads to UPS inhibition (Chou, Li et al. 2010). Furthermore, the formation of ROS from complex I inhibition likely contributes to the Lewy-like bodies observed in the rotenone model (Betarbet, Canet-Aviles et al. 2006).

2.2.1 Aldehyde dehydrogenase (ALDH) inhibition

Another form of mitochondrial dysfunction implicated in PD involves the inhibition of aldehyde dehydrogenase 2 (ALDH2), a mitochondrial ALDH. This enzyme is responsible for the detoxification of aldehydes that could otherwise modify proteins. For example, the lipid peroxidation product 4-hydroxy-2-nonenal (HNE) is detoxified by ALDH2 and increased HNE has been reported in post mortem PD brains as adducts (Yoritaka, Hattori et al. 1996) and as a component of Lewy bodies (Castellani, Perry et al. 2002). Furthermore, HNE has been shown to prevent α-syn fibrillation and form α-syn oligomers, which are toxic to primary mesencephalic cultures (Qin, Hu et al. 2007). Another ALDH2 substrate, the dopamine metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL), has also been reported to induce α-syn aggregation and be toxic to dopaminergic neurons (Burke, Kumar et al. 2008). ALDH involvement in the pathogenesis of PD is not yet well established but preliminary *in vitro* and epidemiology studies have implicated this enzyme as a possible mediator of some pesticides' toxicity (see benomyl below).

2.3 Altered dopamine homeostasis

Conventional wisdom in the pathophysiology of PD is that dopaminergic neurons are selectively vulnerable, although more recent evidence suggests that neuronal loss is more widespread. One hypothesis for this possible vulnerability is via the metabolism of dopamine itself (Hastings 2009).

Dopamine and its metabolites are toxic and dopamine adducts have been shown to stabilize α-syn oligomers. DOPAL, a substrate for ALDH2, is particularly toxic. Interestingly, DOPAL is formed by the enzyme MAO-B and blocking this enzyme with specific drugs appears to alter the progression of PD (Olanow, Rascol et al. 2009). Thus, alterations in levels of dopamine or its metabolites might contribute to neuronal loss. Increased levels of VMAT2, a vesicular transporter that lowers cytosolic dopamine levels, lowers the risk of developing PD (Glatt, Wahner et al. 2006). Further support for altered dopamine homeostasis in PD comes from a recent report that polymorphisms in the dopamine transporter (DAT) gene in combination with pesticide exposure also increases the risk of PD (Ritz, Manthripragada et al. 2009).

Taken together, dysfunction of several cellular processes appears to contribute to the pathogenesis of PD. Aggregation of α-syn (oligomerization and possibly fibril formation) is the leading candidate for the final common pathway for neurons to die in PD. There is evidence that pesticides cause dysfunction in many of these processes providing potential mechanisms for their toxicity (Figure 1).
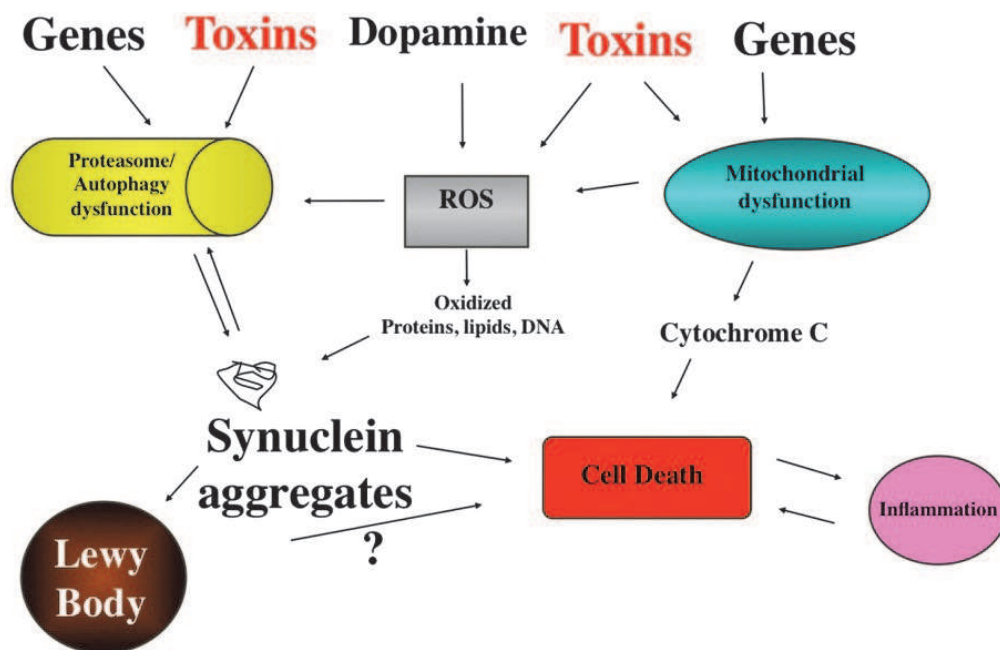

Fig. 1. Proposed pathophysiology of Parkinson's disease.

3. Epidemiology of Parkinson's disease

3.1 Environment and Parkinson's disease

Over the past two decades, several epidemiologic studies have identified a number of environmental factors that are associated with an altered risk of developing PD. Smoking tobacco is almost universally found to be associated with a lower risk of developing the disease (Ritz, Ascherio et al. 2007). Caffeine and alcohol consumption have also been associated with a reduced risk of PD (Hellenbrand, Seidler et al. 1996). Since all of these addictive behaviors are associated with reduced incidence, it has been proposed that they may be surrogate markers for a common behavioral phenotype of pre-clinical PD patients rather than these exposures all being protective. The use of nonsteroidal anti-inflammatory

drugs has also been found to reduce the risk of PD suggesting inflammation may be somehow involved in its pathogenesis (Wahner, Bronstein et al. 2007).

A number of studies have found strong associations between an increased risk of PD and rural living, well-water consumption, farm occupations, and pesticide exposure. These reports have been reviewed extensively by others so we will not review all the studies here (Le Couteur, McLean et al. 1999; Di Monte 2003; Alavanja, Hoppin et al. 2004; Kamel and Hoppin 2004; Li, Mink et al. 2005; Brown, Rumsby et al. 2006). The association with pesticide exposure has been the most provocative association with developing PD to date although almost all of these reports were based on self-reporting pesticide exposure (i.e. potential recall bias) and the diagnosis of PD was not confirmed (Gartner, Battistutta et al. 2005). Despite these weaknesses, a meta-analysis of case–control studies obtained a combined odds ratio (OR) for PD risk of 1.94 (95% CI, 1.49–2.53) (Priyadarshi, Khuder et al. 2000). Subsequent studies reported OR of up to 7.0 (Brown, Rumsby et al. 2006).

Recently, the issue of potential recall bias was mitigated by determining pesticide exposure in a prospective manner. Petrovitch et al reported an increased risk of developing PD in Japanese-American men who worked on a plantation and were exposed to pesticides (Petrovitch, Ross et al. 2002). Similarly, Ascherio et al found a 70% increased risk of developing PD in those who reported significant pesticide exposure (Ascherio, Chen et al. 2006). These reports add support for a true association between pesticides and PD but still are limited in that they did not identify individual toxins and dose response relationships could not be determined.

3.2 Specific pesticides as risk factors

There are a few ongoing studies that address both the issue of recall bias and are identifying specific pesticides that confer an altered risk of developing PD. The Agricultural Health Study (AHS) is a prospective study, including 84,740 private pesticide applicators (mostly farmers) and their spouses recruited in 1993-97 in Iowa and North Carolina. Pesticide exposure was self-reported but felt to be reliable. The diagnosis of PD was also self-reported but later confirmed by direct examination. The first report from this study found an association between PD with increasing lifetime days of use of any pesticide but no specific pesticide could be definitely implicated due to lack of statistical power (Kamel, Tanner et al. 2007). Recently, the investigators reported that PD was associated with rotenone (OR 2.5, 95% CI 1.3, 4.7) and paraquat use (OR 2.5, 95% CI 1.4, 4.7) (Tanner, Kamel et al. 2011). The strength of this study is that it is prospective, the diagnosis was confirmed by examination, and specific toxins were identified. The primary weakness of this study is that they have only 110 cases limiting their power to test a number of pesticides individually and in combinations. The small number of cases also limits their ability to test gene-environment interactions. One additional limitation was that quantitation of pesticide exposure, types of exposure and length of exposures were self-reported. Despite these shortcomings, this study adds strong epidemiological evidence that pesticides are associated with an increased risk of developing PD, especially for rotenone and paraquat.

Ritz and colleagues at UCLA have taken another approach to identifying specific pesticides that are associated with an altered risk of PD. We took advantage of the California Pesticide Use Reporting database and Geographic Information System land-use maps to estimate historical exposure. All commercial pesticide applications have been recorded by compound, quantity, and specific location since 1974. Thus, individual subject exposures

can be approximated by using their residential and occupational addresses for the past 37 years. In this Parkinson's Environment Gene (PEG) study, neurologists specializing in movement disorders went into the field to confirm the diagnosis in over 350 incident PD cases in the central California valley where pesticides are applied liberally and the risk of PD appears to be increased (Ritz and Yu 2000; Kang, Bronstein et al. 2005). A similar number of age and sex matched control subjects were also recruited from the same communities. In addition to several lifestyle and medical assessments, DNA and serum samples were also obtained.

Individual pesticides were investigated in the PEG study based on previous reports implicating the agents as possibly involved in the pathogenesis of PD based on previous epidemiologic and/or laboratory studies. Maneb and paraquat were investigated because administration of pesticides to rodents produces a nice model of PD (see below). Estimates for maneb and paraquat exposures incurred between 1974 and 1999 were generated based on their residence. Exposure to both pesticides within 500m of their homes increased PD risk by 75% (95% CI 1.13, 2.73). Subjects aged ≤ 60 yo were at much higher risk of developing PD when exposed to either maneb or paraquat alone (odds ratio (OR) = 2.27, 95% CI: 0.91, 5.70) or to both pesticides in combination (OR = 4.17, 95% CI: 1.15, 15.16) (Costello, Cockburn et al. 2009). PEG investigators have found similar associations with organophospate pesticides—diazinon (OR 1.73, CI 1.23, 2.45) and chlorpyrifos (OR 1.50, CI 1.04, 2.18) (Manthripragada, Costello et al. 2010)—and ziram (OR 3.01, CI 1.69, 5.38). In subjects ≤ 60 yo, exposure to both ziram and paraquat had a 6-fold increase in risk of PD (CI 1.94, 18.33) (Wang, Costello et al. 2011). It is important to note that all estimates of exposures were not dependent on subject recall for total exposure or duration of exposure. Recent exposure to pesticides (1990 to 1999) was not generally associated with an increased risk of PD consistent with the theory that PD pathology likely starts several years before it manifests itself clinically.

The population is exposed to pesticides in a variety of ways, not just inhalation from spraying and crop dusters. Gatto et al. looked at five pesticides that were likely to be detected in well water (Gatto, Cockburn et al. 2009). Although local well water was not analyzed, these pesticides were identified based on their solubility, half-lives, and adsorptive properties. These included organophosphates (diazinon, dimethoate, chlorpyrifos), a carbamate (methomyl), and a sulfite ester (propargite). Excluding those who did not consume well water, potential inhalation and ingestion of each pesticide was associated with 23-57% increased risk of PD. Consuming well water potentiated this effect to a 41-75% increased risk. Up to a two-fold increase was observed for those who consumed water with the highest potential contamination of at least one of these pesticides. Finally, those with PD were found to have consumed well water an average of 4.3 years longer than controls. Because PEG has enrolled over 350 cases, we have statistical power to test gene-environment interactions. Not surprisingly, the risk of developing PD in pesticide-exposed subjects is clearly altered based on the subject's genetic background (see below).

3.3 Gene-environment interactions

Gene–environment interaction analyses for pesticides and PD have been rare due to small sample size and difficulty obtaining exposure data (Deng, Newman et al. 2004; Elbaz, Levecque et al. 2004; Kelada, Checkoway et al. 2006; Hancock, Martin et al. 2008). Elbaz et al found that pesticides had a modest effect in subjects who were not CYP2D6 poor

metabolizers, had an increased effect in poor metabolizers (approximately twofold), but poor metabolizers were not at increased PD risk in the absence of pesticide exposure (Elbaz, Levecque et al. 2004). Hancook et al found a gene-environment association in PD for pesticides and nitric oxide synthase 1 polymorphisms (Hancock, Martin et al. 2008). Kelada et al described a very modest risk of developing PD with specific dopamine transporter (DAT) alleles but a 5.7 fold increase (CI 1.73-18.53) in developing PD in subjects with occupational exposure to pesticides. These studies added proof of concept that the effect of environmental exposures on the risk of developing PD is at least partially dependent on one's genetic background (Kelada, Checkoway et al. 2006). Unfortunately, exposure assessments were very limited in all of these studies and individual toxins could not be determined.

Gene-environment analysis in Ritz's PEG study has only recently begun but has already revealed intriguing results. We replicated the DAT polymorphism's interaction with pesticide exposure described by Kelada et al for at least maneb and paraquat (Ritz, Manthripragada et al. 2009). Unexposed subjects with more susceptibility alleles had a 30% increased risk of developing PD whereas exposed subjects had an almost five-fold increased risk (OR = 4.53; 95% CI, 1.70-12.1). Importantly, there was a gene dose effect as well. In a similar manner, variations in PON1, the gene that encodes Paraoxonase 1 that metabolizes chlorpyrifos and diazinon, potentiated the increased PD risks associated with these organophosphates (Manthripragada, Costello et al. 2010).

For example, diazinon was associated with a 73% increased risk of PD (CI 1.23, 2.45) but the risk increases to 267% (CI 1.09, 6.55) in individuals who carry PON1 risk alleles. Variations in the dinucleotide repeat sequence (REP1) within the α-syn promoter appear to alter the risk to paraquat exposure (Gatto et al., 2010). Finally, we have preliminary evidence that variations in ALDH2 gene potentiate the increased risks associated with dithiocarbamates and other pesticides that inhibit ALDH activity (Fitzmaurice, Rhodes et al. 2010).

Clearly, the number of potential gene-environment interactions is enormous but we have clear proof of concept that these interactions need to be considered to truly understand environmental risks in PD. It will take very large sample sizes and good exposure analysis to obtain a better understanding of the many potential interactions that confer the bulk of PD risk factors. Alternatively, a candidate gene approach coupled with a better understanding of the pharmacokinetics and toxicity of specific pesticides may allow us to test gene-environment interactions using smaller sample sizes.

4. From association to causality - do pesticides cause PD and if so, how?

Epidemiological studies have clearly established the association between pesticide exposure and the development of PD. The possibility that this association represents causality has been strengthened by recent studies that addressed the problem of recall bias and have demonstrated a dose-effect relationship. Now that some individual pesticides have been implicated, mechanistic studies could be pursued. These studies are reviewed within the context of our current understanding of the pathophysiology of PD.

4.1 Rotenone

Rotenone is produced naturally in roots of certain plant species such as the jicama vine. It is a widely used domestic garden pesticide and because it is degraded by the sun in a matter of days, users tend to spray rotenone frequently. Rotenone is also a well-

characterized, high-affinity, specific inhibitor of complex I of the mitochondrial respiratory electron transport chain. Low complex I activity had been reported to be associated with PD both in brain and peripheral mitochondria but it wasn't known whether this is causal or a surrogate marker for something else. To further investigate this, Greenamyre and colleagues chronically administered the complex I inhibitor, rotenone, systemically into rodents. Some of these rats developed selective dopaminergic neuronal death as well as many of the motor features of PD. Importantly, neurons developed intracytoplasmic inclusions that were found to contain α-syn (Betarbet, Sherer et al. 2000). α-Syn pathology in the gastro-intestinal tract has also been described in the rotenone model similar to that seen in PD (Drolet, Cannon et al. 2009). Even small amounts of rotenone delivered intragastrically reproduces many of the same features described in rats given rotenone subcutaneously but in this model, the various stages of PD are reproduced in a progressive manner (Pan-Montojo, Anichtchik et al. 2010).

The mechanisms of rotenone toxicity are not completely clear but likely are more dependent on oxidative stress than energy failure (Sherer, Betarbet et al. 2002). The downstream targets of rotenone-induced oxidative damage are likely vast but the UPS appears to be one of them (Betarbet, Canet-Aviles et al. 2006; Wang, Li et al. 2006; Chou, Li et al. 2010).

Until recently, there have not been convincing epidemiologic reports linking rotenone exposure to PD. Dhillon et al reported an over 10 fold increase in risk although this study was limited because exposures were self-reported (Dhillon, Tarbutton et al. 2008). The Agricultural Health Study did find a 2.5 fold increased risk with prospective questionnaires adding further support for rotenone as a PD risk factor (Tanner, Kamel et al. 2011). Furthermore, many organic farmers in the 1970s used rotenone as a natural pesticide and a number of them have developed PD at a young age although scientific confirmation of these anecdotal reports is lacking. Other pesticides that are complex I inhibitors are used even less frequently than rotenone so little is known about associations with PD although one would predict a similar effect.

4.2 Paraquat

One of the first pesticides investigated for its potential link to PD was paraquat due to its structural similarity to MPTP, the drug that caused acute Parkinsonism in drug addicts. MPTP kills dopaminergic neurons by being metabolized to MPP+ by MAO-B, entering dopamine cells via the dopamine transporter and then inhibiting complex I in the mitochondrial respiratory chain. Paraquat is ubiquitously used as an herbicide to control weed growth and exposure to paraquat is associated with an increased risk of PD (Hertzman, Wiens et al. 1990; Semchuk, Love et al. 1992; Liou, Tsai et al. 1997).

Additional support for paraquat increasing the risk of PD comes from animal studies. Mice infused with paraquat for three consecutive weeks exhibit dopamine cell loss and cytosolic α-syn aggregates (Brooks, Chadwick et al. 1999; Manning-Bog, McCormack et al. 2002; McCormack, Thiruchelvam et al. 2002). The mechanism by which paraquat causes dopamine cell death is not clear. Since it is structurally very similar to MPTP, it was presumed that paraquat acted in a similar manner. Surprisingly, unlike MPP+, paraquat is not a substrate for the dopamine transporter and does not inhibit complex I except at very high concentrations (Richardson et al 2005). Paraquat toxicity does appear to be dependent on increasing oxidative stress and its action as a redox-cycler appears likely involved in its toxicity (McCormack, Atienza et al. 2005).

4.3 Dithiocarbamates (maneb and ziram)

Dithiocarbamates (DTCs) are a class of some of the most commonly used organic fungicides. They are classified into 2 groups based on whether there is a carbonyl (group 1) or hydrogen on the nitrogen carbamate. Most DTCs are complexed with metals including zinc (e.g. ziram and zineb), iron (e.g. ferbam) and manganese (e.g. maneb). DTCs first became relevant to PD researchers in 1985 when Corsini et al found that diethyldithiocarbamate pretreatment enhanced MPTP toxicity in mice (Corsini, Pintus et al. 1985). They proposed that diethyldithiocarbamate would potentiate MPTP toxicity by inhibiting superoxide dismutase since they believed at that time that MPTP acted primarily as a redox cycler. Thiruchelvam et al. later reported that maneb potentiated the toxicity of paraquat preferentially in the nigrostriatal dopaminergic system (Thiruchelvam, Brockel et al. 2000; Thiruchelvam, McCormack et al. 2003). Furthermore, maneb and paraquat exposure was found to exacerbate α-synucleinopathy in A53T transgenic mice (Norris, Uryu et al. 2007).

The animal models using maneb and paraquat were intriguing but it was only recently that an association between maneb and paraquat exposures and PD were reported (Costello, Cockburn et al. 2009). Similar to the animals studies, residential exposure to maneb and paraquat exposure together is associated with a 114% increased risk of newly diagnosed PD. Furthermore, the risk of PD was increased to 317% for cases ≤ 60 yo. Neither pesticide alone was associated with PD but there were few subjects with maneb only exposure so that the true effect for maneb alone could not be assessed. When both occupational and residential exposures are taken into account, subjects exposed to maneb and paraquat alone had a 126% and 50% increase in risk of developing PD respectively but for exposure to maneb and paraquat together, the risk increased to 8.75x (CI 2.3-33.2) in the younger group (Wang, Costello et al. 2011). These epidemiologic data taken together with the animal data are quite compelling that these pesticides truly increase the risk of PD.

As mentioned above, DTCs are a large group of fungicides with similar structures. We identified another DTC, ziram, in an unbiased screen to identify pesticides that inhibit the proteasome (Wang, Li et al. 2006). Maneb and some other DTCs were also found to inhibit the UPS but at higher concentrations (Chou, Maidment et al. 2008). Ziram selectively killed dopaminergic neurons in primary cultures and increased α-syn levels in the remaining neurons. Systemic administration of ziram alone into mice caused progressive motor dysfunction and dopaminergic neuronal damage (Chou et al 2008). Furthermore, subjects exposed to ziram alone had a 201% (CI 1.69, 5.38) increase of risk of developing PD and a 598% (CI 1.95, 18.3) increased risk when exposed with paraquat in subjects ≤ 60 yo (Wang, Costello et al. 2011). These data add further support for the role of DTCs as a causal risk factor for PD.

It is still not completely clear how DTCs act biologically. We have found that they do not increase oxidative stress and therefore are unlikely acting through the mitochondrial respiratory chain (Wang, Li et al. 2006). DTCs clearly inhibit the UPS and their potency depends on whether they contain a tertiary or a secondary amino group. Ziram was studied extensively given its high potency to inhibit the UPS and we found that it acts by interfering with the ubiquitin E1 ligase with an IC_{50} of 161 nM (Chou, Maidment et al. 2008). Zhou et al reported that maneb also inhibited the UPS but at higher concentrations (IC_{50} of approx. 6 μM) and increased protein carbonyls suggesting increased oxidative stress (Zhou, Shie et al. 2004). We also found that maneb inhibits the UPS at much higher concentrations than ziram but we did not find evidence of oxidative stress. Differences may very well be due to differences in the techniques used since we used an *in vitro* 26S UPS assay and DCF

fluorescence to detect ROS and Zhou et al used an *in vitro* 20S UPS assay and protein carbonyl immunohistochemistry for detection of oxidative stress. Recently, we have found that both maneb and ziram inhibit ALDH2 at environmentally-relevant concentrations, adding another potential mechanism of toxicity, especially to dopaminergic neurons (Fitzmaurice, Rhodes et al. 2010). Since ziram does not contain manganese, it is very unlikely that it is the manganese in maneb that confers its toxicity as some have suggested.

4.4 Benomyl

Another important fungicide implicated in PD pathogenesis is the benzimidazole compound benomyl. It was developed as a microtubule inhibitor and is sprayed on fruits, nuts, and leaves to prevent fungal growth. Preliminary findings from the PEG study revealed benomyl exposure increased PD risk by 138% (CI 1.33, 4.27) (Fitzmaurice, Rhodes et al. 2010).

Benomyl metabolizes spontaneously into another fungicide (carbendazim) and enzymatically into several thiocarbmate compounds. We have shown that benomyl and carbendazim are UPS inhibitors, although they are not as potent as ziram (Wang, Li et al. 2006; Fitzmaurice, Ackerman et al. 2010). Furthermore, benomyl has also been reported to inhibit mitochondrial ALDH (Staub, Quistad et al. 1998). Although these studies focused on hepatic ALDH, we recently reported that benomyl exposure reduced ALDH2 activity *ex vivo* in rat neuronal suspensions (Fitzmaurice, Ackerman et al. 2010). We have also found that exposure to benomyl or one of its ALDH2-inhibiting metabolites (S-methyl-N-butylthiocarbamate, or MBT) causes dopaminergic neuronal death *in vitro*, while the UPS-inhibiting metabolite (carbendazim) does not. These findings, combined with the observation that DTCs also inhibit ALDH2, suggest that ALDH2 inhibition may be an important mechanism in pesticide toxicity with respect to PD.

The toxicity of ALDH2 inhibition is likely due to the accumulation of toxic aldehydes. We would predict that ALDH2 inhibition would lead to increased levels of DOPAL and HNE adducts and preliminary studies in primary cultures support this hypothesis. Furthermore, the loss of dopaminergic neurons due to benomyl was attenuated by co-treatment with the MAO-B inhibitor pargyline which decreases DOPAL formation (Fitzmaurice, Ackerman et al. 2010). Since DOPAL and HNE accumulation have been reported to induce α-syn aggregation (Burke, Kumar et al. 2008), these findings support ALDH2 inhibition as an important mediator of pesticide toxicity in PD.

5. Summary

The causes of PD are not completely understood but both genetic and epidemiologic studies suggest that dysfunction of one or more biological processes lead to α-syn aggregation and neuronal death. Epidemiologic studies have clearly shown PD to be associated with pesticide exposure and specific pesticides conferring at least some of this increased risk have recently been identified. The fact that administration of pesticides to animals recapitulates many of the behavioral and pathological features of PD provides evidence that the associations found in epidemiologic studies are causal. Elucidating the mechanisms of pesticide toxicity in mammals not only strengthens the hypothesis that exposure to these toxins can increase the risk of developing PD, but also furthers our understanding of the pathophysiology of the disease in general. It is clear that the list of pesticides discussed in this chapter is not complete and that pesticides are not the only environmental toxins that

alter the risk of PD, but the preponderance of evidence taken together supports an important role of pesticides in the pathogenesis of PD. A better understanding of these issues will take us one step closer to a cure.

6. References

Aharon-Peretz, J., H. Rosenbaum, et al. (2004). "Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews." N Engl J Med 351(19): 1972-1977.

Alavanja, M. C., J. A. Hoppin, et al. (2004). "Health effects of chronic pesticide exposure: cancer and neurotoxicity." Annu Rev Public Health 25: 155-197.

Anglade, P., S. Vyas, et al. (1997). "Apoptosis and autophagy in nigral neurons of patients with Parkinson's disease." Histol Histopathol 12(1): 25-31.

Ascherio, A., H. Chen, et al. (2006). "Pesticide exposure and risk for Parkinson's disease." Annals of Neurology 60(2): 197-203.

Betarbet, R., R. M. Canet-Aviles, et al. (2006). "Intersecting pathways to neurodegeneration in Parkinson's disease: Effects of the pesticide rotenone on DJ-1, [alpha]-synuclein, and the ubiquitin-proteasome system." Neurobiology of Disease 22(2): 404-420.

Betarbet, R., R. M. Canet-Aviles, et al. (2006). "Intersecting pathways to neurodegeneration in Parkinson's disease: effects of the pesticide rotenone on DJ-1, alpha-synuclein, and the ubiquitin-proteasome system." Neurobiol Dis 22(2): 404-420.

Betarbet, R., T. B. Sherer, et al. (2000). "Chronic systemic pesticide exposure reproduces features of Parkinson's disease." Nat Neurosci 3(12): 1301-1306.

Bove, J., C. Zhou, et al. (2006). "Proteasome inhibition and Parkinson's disease modeling." Annals of neurology 60(2): 260-264.

Braak, H., K. Del Tredici, et al. (2003). "Staging of brain pathology related to sporadic Parkinson's disease." Neurobiol Aging 24(2): 197-211.

Brooks, A. I., C. A. Chadwick, et al. (1999). "Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss." Brain Res 823(1-2): 1-10.

Brown, T. P., P. C. Rumsby, et al. (2006). "Pesticides and Parkinson's disease--is there a link?" Environ Health Perspect 114(2): 156-164.

Burke, W. J., V. B. Kumar, et al. (2008). "Aggregation of alpha-synuclein by DOPAL, the monoamine oxidase metabolite of dopamine." Acta Neuropathol 115(2): 193-203.

Castellani, R. J., G. Perry, et al. (2002). "Hydroxynonenal adducts indicate a role for lipid peroxidation in neocortical and brainstem Lewy bodies in humans." Neurosci Lett 319(1): 25-28.

Chiba, K., A. J. Trevor, et al. (1985). "Active uptake of MPP+, a metabolite of MPTP, by brain synaptosomes." Biochemical and biophysical research communications 128(3): 1228-1232.

Chou, A. P., S. Li, et al. (2010). "Mechanisms of rotenone-induced proteasome inhibition." NeuroToxicology 31(4): 367-372.

Chou, A. P., N. Maidment, et al. (2008). "Ziram causes dopaminergic cell damage by inhibiting E1 ligase of the proteasome." J Biol Chem 283(50): 34696-34703.

Corsini, G. U., S. Pintus, et al. (1985). "1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity in mice is enhanced by pretreatment with diethyldithiocarbamate." Eur J Pharmacol 119(1-2): 127-128.

Costello, S., M. Cockburn, et al. (2009). "Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California." Am J Epidemiol 169(8): 919-926.

Cuervo, A. M., L. Stefanis, et al. (2004). "Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy." Science 305(5688): 1292-1295.

Deng, Y., B. Newman, et al. (2004). "Further evidence that interactions between CYP2D6 and pesticide exposure increase risk for Parkinson's disease." Ann Neurol 55(6): 897.

Dhillon, A. S., G. L. Tarbutton, et al. (2008). "Pesticide/environmental exposures and Parkinson's disease in East Texas." J Agromedicine 13(1): 37-48.

Di Monte, D. A. (2003). "The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins?" Lancet Neurol 2(9): 531-538.

Dorsey, E. R., R. Constantinescu, et al. (2007). "Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030." Neurology 68(5): 384-386.

Drolet, R. E., J. R. Cannon, et al. (2009). "Chronic rotenone exposure reproduces Parkinson's disease gastrointestinal neuropathology." Neurobiol Dis 36(1): 96-102.

Elbaz, A., C. Levecque, et al. (2004). "CYP2D6 polymorphism, pesticide exposure, and Parkinson's disease." Ann Neurol 55(3): 430-434.

Farrer, M., J. Kachergus, et al. (2004). "Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications." Ann Neurol 55(2): 174-179.

Fitzmaurice, A. G., L. C. Ackerman, et al. (2010). "Aldehyde dehydrogenase inhibition by the fungicide benomyl leads to dopaminergic cell death: Relevance of dopamine metabolism to Parkinson's disease." Soc Neurosci (abstract): 655.24.

Fitzmaurice, A. G., S. L. Rhodes, et al. (2010). "Biochemical and epidemiologic screens link pesticide exposure, aldehyde dehydrogenase inhibition, and Parkinson's disease." Soc Neurosci (abstract): 752.3.

Gainetdinov, R. R., F. Fumagalli, et al. (1998). "Increased MPTP neurotoxicity in vesicular monoamine transporter 2 heterozygote knockout mice." Journal of neurochemistry 70(5): 1973-1978.

Gartner, C. E., D. Battistutta, et al. (2005). "Test-retest repeatability of self-reported environmental exposures in Parkinson's disease cases and healthy controls." Parkinsonism & Related Disorders 11(5): 287-295.

Gatto, N. M., M. Cockburn, et al. (2009). "Well-water consumption and Parkinson's disease in rural California." Environ Health Perspect 117(12): 1912-1918.

Giasson, B. I., R. Jakes, et al. (2000). "A panel of epitope-specific antibodies detects protein domains distributed throughout human alpha-synuclein in Lewy bodies of Parkinson's disease." J Neurosci Res 59(4): 528-533.

Glatt, C. E., A. D. Wahner, et al. (2006). "Gain-of-function haplotypes in the vesicular monoamine transporter promoter are protective for Parkinson disease in women." Hum Mol Genet 15(2): 299-305.

Goldberg, A. L. (2003). "Protein degradation and protection against misfolded or damaged proteins." Nature 426(6968): 895-899.

Haas, R. H., F. Nasirian, et al. (1995). "Low platelet mitochondrial complex I and complex II/III activity in early untreated Parkinson's disease." Ann Neurol 37(6): 714-722.

Hancock, D. B., E. R. Martin, et al. (2008). "Nitric oxide synthase genes and their interactions with environmental factors in Parkinson's disease." Neurogenetics 9(4): 249-262.

Hardy, J. (2010). "Genetic analysis of pathways to Parkinson disease." Neuron 68(2): 201-206.

Hastings, T. G. (2009). "The role of dopamine oxidation in mitochondrial dysfunction: implications for Parkinson's disease." J Bioenerg Biomembr 41(6): 469-472.

Hellenbrand, W., A. Seidler, et al. (1996). "Diet and Parkinson's disease. I: A possible role for the past intake of specific foods and food groups. Results from a self-administered food-frequency questionnaire in a case-control study." Neurology 47(3): 636-643.

Hertzman, C., M. Wiens, et al. (1990). "Parkinson's disease: a case-control study of occupational and environmental risk factors." Am J Ind Med 17(3): 349-355.

Javitch, J. A., R. J. D'Amato, et al. (1985). "Parkinsonism-inducing neurotoxin, N-methyl-4-phenyl-1,2,3,6 -tetrahydropyridine: uptake of the metabolite N-methyl-4-phenylpyridine by dopamine neurons explains selective toxicity." Proceedings of the National Academy of Sciences of the United States of America 82(7): 2173-2177.

Kamel, F. and J. A. Hoppin (2004). "Association of pesticide exposure with neurologic dysfunction and disease." Environ Health Perspect 112(9): 950-958.

Kamel, F., C. Tanner, et al. (2007). "Pesticide exposure and self-reported Parkinson's disease in the agricultural health study." Am J Epidemiol 165(4): 364-374.

Kang, G. A., J. M. Bronstein, et al. (2005). "Clinical characteristics in early Parkinson's disease in a central California population-based study." Mov Disord 20(9): 1133-1142.

Kelada, S. N., H. Checkoway, et al. (2006). "5' and 3' region variability in the dopamine transporter gene (SLC6A3), pesticide exposure and Parkinson's disease risk: a hypothesis-generating study." Hum Mol Genet 15(20): 3055-3062.

Kordower, J. H., N. M. Kanaan, et al. (2006). "Failure of proteasome inhibitor administration to provide a model of Parkinson's disease in rats and monkeys." Annals of neurology 60(2): 264-268.

Kruger, R., W. Kuhn, et al. (1998). "Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease." Nat Genet 18(2): 106-108.

Langston, J. W., P. Ballard, et al. (1983). "Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis." Science 219(4587): 979-980.

Le Couteur, D. G., A. J. McLean, et al. (1999). "Pesticides and Parkinson's disease." Biomedecine & Pharmacotherapy 53(3): 122-130.

Li, A. A., P. J. Mink, et al. (2005). "Evaluation of epidemiologic and animal data associating pesticides with Parkinson's disease." J Occup Environ Med 47(10): 1059-1087.

Li, H. T., D. H. Lin, et al. (2005). "Inhibition of alpha-synuclein fibrillization by dopamine analogs via reaction with the amino groups of alpha-synuclein. Implication for dopaminergic neurodegeneration." The FEBS journal 272(14): 3661-3672.

Liou, H. H., M. C. Tsai, et al. (1997). "Environmental risk factors and Parkinson's disease: a case-control study in Taiwan." Neurology 48(6): 1583-1588.

Liu, C. W., M. J. Corboy, et al. (2003). "Endoproteolytic activity of the proteasome." Science 299(5605): 408-411.

Mak, S. K., A. L. McCormack, et al. (2010). "Lysosomal degradation of alpha-synuclein in vivo." Journal of Biological Chemistry 285(18): 13621-13629.

Manning-Bog, A. B., A. L. McCormack, et al. (2002). "The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: paraquat and alpha-synuclein." J Biol Chem 277(3): 1641-1644.

Manning-Bog, A. B., S. H. Reaney, et al. (2006). "Lack of nigrostriatal pathology in a rat model of proteasome inhibition." Annals of neurology 60(2): 256-260.

Manthripragada, A. D., S. Costello, et al. (2010). "Paraoxonase 1, agricultural organophosphate exposure, and Parkinson disease." Epidemiology 21(1): 87-94.

Martinez-Vicente, M., Z. Talloczy, et al. (2008). "Dopamine-modified alpha-synuclein blocks chaperone-mediated autophagy." J Clin Invest 118(2): 777-788.

Massey, A. C., C. Zhang, et al. (2006). "Chaperone-mediated autophagy in aging and disease." Curr Top Dev Biol 73: 205-235.

Mazzulli, J. R., M. Armakola, et al. (2007). "Cellular oligomerization of alpha-synuclein is determined by the interaction of oxidized catechols with a C-terminal sequence." The Journal of biological chemistry 282(43): 31621-31630.

McCormack, A. L., J. G. Atienza, et al. (2005). "Role of oxidative stress in paraquat-induced dopaminergic cell degeneration." J Neurochem 93(4): 1030-1037.

McCormack, A. L., M. Thiruchelvam, et al. (2002). "Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat." Neurobiol Dis 10(2): 119-127.

McNaught, K. S. and P. Jenner (2001). "Proteasomal function is impaired in substantia nigra in Parkinson's disease." Neurosci Lett 297(3): 191-194.

McNaught, K. S. and C. W. Olanow (2006). "Proteasome inhibitor-induced model of Parkinson's disease." Annals of neurology 60(2): 243-247.

Mueller, J. C., J. Fuchs, et al. (2005). "Multiple regions of α-synuclein are associated with Parkinson's disease." Annals of Neurology 57(4): 535-541.

Narendra, D. P., S. M. Jin, et al. (2010). "PINK1 is selectively stabilized on impaired mitochondria to activate Parkin." PLoS Biol 8(1): e1000298.

Neumann, J., J. Bras, et al. (2009). "Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease." Brain : a journal of neurology 132(Pt 7): 1783-1794.

Norris, E. H., K. Uryu, et al. (2007). "Pesticide exposure exacerbates alpha-synucleinopathy in an A53T transgenic mouse model." Am J Pathol 170(2): 658-666.

Nussbaum, R. L. and M. H. Polymeropoulos (1997). "Genetics of Parkinson's disease." Hum Mol Genet 6(10): 1687-1691.

Olanow, C. W., O. Rascol, et al. (2009). "A double-blind, delayed-start trial of rasagiline in Parkinson's disease." The New England journal of medicine 361(13): 1268-1278.

Pals, P., S. Lincoln, et al. (2004). "α-Synuclein promoter confers susceptibility to Parkinson's disease." Annals of Neurology 56(4): 591-595.

Pan-Montojo, F., O. Anichtchik, et al. (2010). "Progression of Parkinson's disease pathology is reproduced by intragastric administration of rotenone in mice." PloS one 5(1): e8762.

Petrovitch, H., G. W. Ross, et al. (2002). "Plantation work and risk of Parkinson disease in a population-based longitudinal study." Arch Neurol 59(11): 1787-1792.

Priyadarshi, A., S. A. Khuder, et al. (2000). "A meta-analysis of Parkinson's disease and exposure to pesticides." Neurotoxicology 21(4): 435-440.

Qin, Z., D. Hu, et al. (2007). "Effect of 4-hydroxy-2-nonenal modification on alpha-synuclein aggregation." J Biol Chem 282(8): 5862-5870.

Ramirez, A., A. Heimbach, et al. (2006). "Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase." Nat Genet 38(10): 1184-1191.

Ritz, B., A. Ascherio, et al. (2007). "Pooled analysis of tobacco use and risk of Parkinson disease." Archives of neurology 64(7): 990-997.

Ritz, B. and F. Yu (2000). "Parkinson's disease mortality and pesticide exposure in California 1984-1994." Int J Epidemiol 29(2): 323-329.

Ritz, B. R., A. D. Manthripragada, et al. (2009). "Dopamine transporter genetic variants and pesticides in Parkinson's disease." Environ Health Perspect 117(6): 964-969.

Samaranch, L., O. Lorenzo-Betancor, et al. (2010). "PINK1-linked parkinsonism is associated with Lewy body pathology." Brain 133(Pt 4): 1128-1142.

Schapira, A. H., M. W. Cleeter, et al. (2006). "Proteasomal inhibition causes loss of nigral tyrosine hydroxylase neurons." Annals of neurology 60(2): 253-255.

Schapira, A. H., J. M. Cooper, et al. (1990). "Mitochondrial complex I deficiency in Parkinson's disease." J Neurochem 54(3): 823-827.

Semchuk, K. M., E. J. Love, et al. (1992). "Parkinson's disease and exposure to agricultural work and pesticide chemicals." Neurology 42(7): 1328-1335.

Sherer, T. B., R. Betarbet, et al. (2002). "An in vitro model of Parkinson's disease: linking mitochondrial impairment to altered alpha-synuclein metabolism and oxidative damage." J Neurosci 22(16): 7006-7015.

Spillantini, M. G., M. L. Schmidt, et al. (1997). "Alpha-synuclein in Lewy bodies." Nature 388(6645): 839-840.

Staub, R. E., G. B. Quistad, et al. (1998). "Mechanism for Benomyl Action as a Mitochondrial Aldehyde Dehydrogenase Inhibitor in Mice." Chemical Research in Toxicology 11(5): 535-543.

Sun, Y., B. Liou, et al. (2010). "Neuronopathic Gaucher disease in the mouse: viable combined selective saposin C deficiency and mutant glucocerebrosidase (V394L) mice with glucosylsphingosine and glucosylceramide accumulation and progressive neurological deficits." Human molecular genetics 19(6): 1088-1097.

Tanner, C. M., F. Kamel, et al. (2011). "Rotenone, Paraquat and Parkinson's Disease." Environ Health Perspect.

Thiruchelvam, M., B. J. Brockel, et al. (2000). "Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: environmental risk factors for Parkinson's disease?" Brain Res 873(2): 225-234.

Thiruchelvam, M., A. McCormack, et al. (2003). "Age-related irreversible progressive nigrostriatal dopaminergic neurotoxicity in the paraquat and maneb model of the Parkinson's disease phenotype." Eur J Neurosci 18(3): 589-600.

Trojanowski, J. Q., M. Goedert, et al. (1998). "Fatal attractions: abnormal protein aggregation and neuron death in Parkinson's disease and Lewy body dementia." Cell Death Differ 5(10): 832-837.

Uversky, V. N., J. Li, et al. (2001). "Pesticides directly accelerate the rate of [alpha]-synuclein fibril formation: a possible factor in Parkinson's disease." FEBS Letters 500(3): 105-108.

Wahner, A. D., J. M. Bronstein, et al. (2007). "Nonsteroidal anti-inflammatory drugs may protect against Parkinson disease." Neurology 69(19): 1836-1842.

Wang, A., S. Costello, et al. (2011). "Parkinson's Disease Risk from Ambient Exposure to Maneb, Ziram,. And Paraquat at Work and Home." European Journal of Epidemiology in press.

Wang, X.-F., S. Li, et al. (2006). "Inhibitory effects of pesticides on proteasome activity: Implication in Parkinson's disease." Neurobiology of Disease 23(1): 198-205.

Yoritaka, A., N. Hattori, et al. (1996). "Immunohistochemical detection of 4-hydroxynonenal protein adducts in Parkinson disease." Proceedings of the National Academy of Sciences of the United States of America 93(7): 2696-2701.

Zeng, B. Y., S. Bukhatwa, et al. (2006). "Reproducible nigral cell loss after systemic proteasomal inhibitor administration to rats." Annals of neurology 60(2): 248-252.

Zhang, N. Y., Z. Tang, et al. (2008). "alpha-Synuclein protofibrils inhibit 26 S proteasome-mediated protein degradation: understanding the cytotoxicity of protein protofibrils in neurodegenerative disease pathogenesis." J Biol Chem 283(29): 20288-20298.

Zhou, Y., F. S. Shie, et al. (2004). "Proteasomal inhibition induced by manganese ethylene-bis-dithiocarbamate: relevance to Parkinson's disease." Neuroscience 128(2): 281-291.
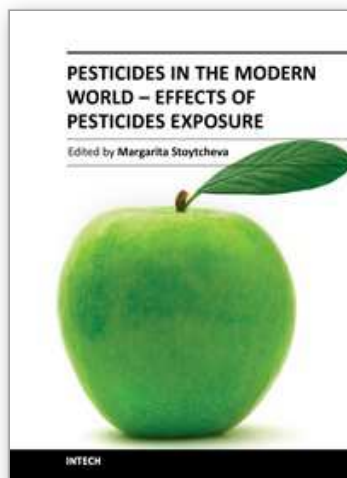
Pesticides in the Modern World - Effects of Pesticides Exposure

Edited by Dr. Margarita Stoytcheva

ISBN 978-953-307-454-2

Hard cover, 376 pages

Publisher InTech

Published online 12, September, 2011

Published in print edition September, 2011

The introduction of the synthetic organochlorine, organophosphate, carbamate and pyrethroid pesticides by 1950's marked the beginning of the modern pesticides era and a new stage in the agriculture development. Evolved from the chemicals designed originally as warfare agents, the synthetic pesticides demonstrated a high effectiveness in preventing, destroying or controlling any pest. Therefore, their application in the agriculture practices made it possible enhancing crops and livestock's yields and obtaining higher-quality products, to satisfy the food demand of the continuously rising world's population. Nevertheless, the increase of the pesticide use estimated to 2.5 million tons annually worldwide since 1950., created a number of public and environment concerns. This book, organized in two sections, addresses the various aspects of the pesticides exposure and the related health effects. It offers a large amount of practical information to the professionals interested in pesticides issues.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Arthur G. Fitzmaurice and Jeff M. Bronstein (2011). Pesticides and Parkinson's Disease, Pesticides in the Modern World - Effects of Pesticides Exposure, Dr. Margarita Stoytcheva (Ed.), ISBN: 978-953-307-454-2, InTech, Available from: http://www.intechopen.com/books/pesticides-in-the-modern-world-effects-of-pesticides-exposure/pesticides-and-parkinsons-disease

INTECH
open science | open minds