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Chapter 14

Occupational exposures and parkinsonism

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The term parkinsonism refers to a suite of neurologic disorders, such as Parkinson's disease (PD), multiple systems atrophy (MSA), and progressive supranuclear palsy (PSP), that share a diverse constellation of clinical features that include bradykinesisa, postural instability, rigidity, and tremor (Dickson, 2012). This heterogeneity is further observed in the pathologic manifestations of these disorders. For instance, while the presence of accumulations of the cytoplasmic protein α-synuclein is a common pathologic feature of PD and MSA, PSP is more aptly pathologically defined by inclusions of the micotubule protein, tau. However, a common unifying pathologic feature of many parkinsonian disorders is the loss of dopaminergic neurons in the substantia nigra that occurs following loss of dopaminergic projections to the basal ganglia, which seem to underlie many of the major clinical features associated with parkinsonism (Dickson, 2012). It can be appreciated that this spectrum of parkinsonian clinicopathologic presentations can significantly complicate the differential diagnosis of PD and other parkinsonian disorders.

Parkinsonian disorders have a varied etiology and may arise from defined genetic alterations or can be induced following exposure to a host of different chemicals, drugs, or toxicants that selectively damage the nervous system. The contribution of inherited and sporadic forms of parkinsonism has been best elucidated in PD, which has shown a clear influence of genetic mutations as well as exogenous factors involved in disease etiology. Indeed, mutations to several genes have been identified as genetic risk factors for the disease, yet these genetic alterations are only able to account for 5–10% of the cases of PD (Farrer, 2006). This would suggest that there are exogenous or environmental factors that influence the risk of development of PD, that either work independently or in conjunction with genetic predisposition to facilitate the onset of the disease (Gao and Hong, 2011). Epidemiologic evidence further supports the contribution of environmental factors in PD, showing the incidence of PD in monozygotic and dizygotic twins was almost identical, suggesting the heritability of PD was low (Tanner et al., 1999; Wirdefeldt et al., 2008, 2011b). More importantly, it provided evidence that an exogenous factor was significantly influencing the relative risk of PD.

Additional epidemiologic and laboratory work over the last several decades has provided extensive support for the idea that exposure to different environmental factors, including pesticides, metals, and solvents, as well as other toxicants found in industrial and commercial uses, could be a significant risk factor for the development of PD as well as other parkinsonian syndromes (Table 14.1) (Wirdefeldt et al., 2011a). The majority of these exposures occur in an occupational setting to individuals who are most likely to have direct interaction with the compound. Indeed, the highest level of pesticide exposure appears to occur with those who are using the chemicals, such as pesticide applicators, farmers, and gardeners. A similar concern is seen with workers highly exposed to solvents during metal manufacturing, as well as individuals exposed to metal dust and fumes during mining, smelting, or welding activities. Each of these settings, coupled with the potential for less than optimal personal protective equipment, leaves the individual vulnerable to prolonged, high-level exposure scenarios that can lead to significant damage of the nervous system. In the following sections I will provide a discussion of several classes of compounds and specific chemicals that have been shown in both epidemiologic and laboratory work to increase the risk of PD and parkinsonism.

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Table 14.1

Environmental toxicants associated with parkinsonism

Chemical	Exposure setting(s)	Mechanism(s) of action	Reference
Dieldrin	Occupational, diet	Dopamine mishandling, generation of reactive oxygen species (ROS)	Corrigan et al. (1996, 2000); Kitazawa et al. (2001); Kamel et al. (2007); Hatcher et al. (2008)
Chlorpyrifos	Occupational	Alteration in dopamine signaling	Dhillon et al. (2008); Gatto et al. (2009); Torres-Altoro et al. (2011)
Rotenone	Occupational	Inhibition of mitochondrial complex I	Betarbet et al. (2000); Dhillon et al. (2008); Tanner et al. (2011)
Paraquat	Occupational	Generation of ROS	Thiruchelvam et al. (2000b); Manning-Bog et al. (2002); McCormack et al. (2002); Kamel et al. (2007); Tanner et al. (2011)
Polychlorinated biphenyls (PCBs)	Occupational, diet	Dopamine mishandling	Seegal et al. (1994); Corrigan et al. (1998, 2000); Caudle et al. (2006); Steenland et al. (2006); Hatcher-Martin et al. (2012)
Iron	Occupational, diet	Generation of ROS	Gorell et al. (1997); Gerlach et al. (2006); Kaur et al. (2007)
Manganese	Occupational	Generation of ROS, NMDA-mediated excitotoxicity, mitochondrial inhibition	Gavin et al. (1999); Guilarte et al. (2006); Racette et al. (2012)
Trichloroethylene (TCE)	Occupational	Generation of ROS, inhibition of mitochondrial complex I	Gash et al. (2008); Liu et al. (2010); Goldman et al. (2012)

NMDA, *N*-methyl-D-aspartate.

PESTICIDES

Pesticides are a broad class of compounds used in both agricultural as well as household settings to control or eliminate various nuisance plants, insects, or animals that could impact human and crop health. Specifically, pesticides include compounds formulated to manage rodents (rodenticides), fungus (fumigants), plants (herbicides), and insects (insecticides) through various mechanisms of action that may be specifically formulated to target the central nervous system of pests, such as insecticides, or may affect the function of other cellular components, leading to demise. The most prominent route for human exposure to these pesticides is through their direct application by an individual, again, either in a large commercial agricultural setting, like a farm, or even on a smaller scale, such as a home garden or in an indoor setting. Less direct exposures can also occur to individuals who are working or living in close proximity to the area where these compounds are being applied as a consequence of off-target effects or by handling food that has been sprayed with pesticides. Over the last several decades a wealth of studies have been conducted that demonstrate a strong association between exposure to pesticides and risk or incidence of PD. However, because multiple pesticides are usually used it has been difficult to delineate specific classes of pesticides and even more cumbersome to identify specific compounds in each relevant class that that may underlie the risk for PD. In more recent years the use of novel techniques and technologies as well as better-defined study populations have allowed for a more focused investigation of the impact of individual pesticides on PD, providing a better understanding of the chemicals and potential mechanisms of action that contribute to PD pathogenesis. Although there are currently dozens of individual pesticides being used, I will narrow the following discussion in order to appraise the classes and individual chemicals that have demonstrated the strongest epidemiologic and laboratory support for an association between human exposure and PD risk.

Insecticides

By far the most widely used pesticides in the USA and abroad are insecticides. Chemicals in this class of pesticide can be further stratified into different groups that are defined by their chemical structure and their specific mechanisms of action. In general, insecticides are formulated to directly target the central nervous system of insects, leading to neurologic dysfunction and death. The most prominent classes of insecticides are organochlorines, organophosphates, pyrethroids, and rotenoids. Of these compounds, the majority of epidemiologic

studies have focused on the risk of PD associated with exposure to organochlorines. However, more recent work has also begun to uncover the contribution of exposure to organophosphates and rotenoids as possible risk factors. While several laboratory studies have demonstrated the ability of pyrethroids to alter the function of the nigrostriatal dopamine system (Bloomquist et al., 2002; Elwan et al., 2006), these compounds have not been explicitly shown to impact the risk of PD in the human population.

Organochlorines

Organochlorine insecticides, including DDT, dieldrin, heptachlor, lindane, and β-hexachlorocyclohexane (β-HCH), were extensively used, beginning in the 1940s and continuing through the 1970s, when their manufacture and use were discontinued due to environmental and human health concerns. While the vast majority of these compounds have been phased out, many of these compounds are still used in other developing countries, while others, such as endosulfan, have only recently seen their applications and use reduced. Organochlorine insecticides have varied targets and mechanisms of action within the central nervous system that affect the function of sodium and calcium channels and transporters as well as interfering with γ-aminobutyric acid (GABA) neurotransmission by blocking specific GABA receptors, contributing to their neurotoxic effects (Narahashi et al., 1995). These compounds are of further concern as their physical and chemical properties confer a high degree of lipophilicity and resistance to breakdown and metabolism, both in the environment as well as the human body, which allows them to persist and bioaccumulate in these settings. Thus, although the use of many of these compounds has been discontinued for many years, their presence is still detectable in the environment and in human tissue, even in populations that never had a direct exposure, creating a continued health concern for the human population.

The impact of occupational exposure to organochlorine compounds on the nigrostriatal dopamine system and the risk of PD has been demonstrated in several studies in the last 15 years (Corrigan et al., 1996, 2000; Kamel and Hoppin, 2004; Kamel et al., 2007; Elbaz et al., 2009; Ross et al., 2012). Of these compounds, occupational exposure to dieldrin and β-HCH has received the most attention as possible risk factors for PD (Kamel et al., 2007; Weisskopf et al., 2010; Kamel, 2013; Rhodes et al., 2013). One of the first studies to show an association between exposure to dieldrin and PD was that by Corrigan et al. (1996, 2000), which showed an elevation of dieldrin in the caudate nucleus and substantia nigra of patients with PD compared with controls. Similar elevations in serum levels of β-HCH have been found in PD patients compared with both control as well as individuals diagnosed with Alzheimer's disease (Richardson et al., 2009, 2011), suggesting a link between exposure to these compounds and risk of PD. Several laboratory investigations utilizing cell- and animal-based models further support these findings, especially for dieldrin. Work by Hatcher et al. (2008) demonstrated a significant alteration in dopamine handling as well as an increase in oxidative stress and α-synuclein in mice exposed to dieldrin. Selective damage to dopamine neurons and elevations in oxidative stress, alterations to mitochondrial function and elevated expression of α-synuclein have also been shown in primary cultured and clonal cell models of dieldrin exposure (Sanchez-Ramos et al., 1998; Kitazawa et al., 2001). Furthermore, studies that utilized a developmental exposure to dieldrin also showed alterations in the expression of both the dopamine transporter (DAT) and the vesicular monoamine transporter 2 (VMAT2) in offspring. These same animals also demonstrated an increased vulnerability to dopaminergic damage following subsequent exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Richardson et al., 2006).

Organophosphates

Although developed in the 1940s, the use and application of organophosphate insecticides for agricultural and household use did not escalate until the late 1960s as a response to the restrictions placed on the use of organochlorine compounds. Similar to organochlorines, organophosphate insecticides have been formulated to target specific cellular components of the central nervous system. In contrast to the organochlorine compounds, organophosphates exert their neurotoxicity by interaction and inhibition of the acetylcholinesterase enzyme, which functions to degrade the neurotransmitter, acetylcholine, into choline and acetyl coenzyme A, thus terminating the action of acetylcholine at the postsynaptic receptors. In the presence of an organophosphate compound this degradation is inhibited and acetylcholine is allowed to remain in the synaptic cleft and continue to interact with and activate acetylcholine receptors, resulting in a suite of neurologic symptoms that can lead to death. The most common organophosphate compounds found in the environment are chlorpyrifos, malathion, and methyl parathion. Like organochlorines, the manufacture and use of organophosphate insecticides have been greatly restricted or completely discontinued due to their general toxicity to the human population; however some compounds are still in use, both in the USA as well as abroad.

Although their use has been widespread, only a few studies have established a link between occupational exposure to organophosphate insecticides and the risk or incidence of PD. However, work in the last 5 years has begun to demonstrate significant associations between exposure to specific organophosphates and PD. Most notably, Hancock et al. (2008) showed an increased incidence of PD in patients occupationally exposed to organophosphate insecticides, while Dhillon et al. (2008) and Gatto et al. (2009) both specifically identified exposure to chlorpyrifos as a major contributor to PD risk. These findings are given further credence through laboratory investigations that suggest exposure to chlorpyrifos can significantly alter the normal functioning of the nigrostriatal dopamine pathway/circuit in rats (Torres-Altoro et al., 2011). One potential explanation for the lack of evidence relating exposure to organophosphates and PD could lie in the fact that, unlike their organochlorine predecessors, organophosphate compounds do not accumulate and persist in the environment to a similar extent as that seen with organochlorines. For example, the half-life of chlorpyrifos in soil is 10-fold less than that seen for an organochlorine insecticide such as dieldrin (Hatcher et al., 2008).

Interestingly, recent work has demonstrated an increased vulnerability to organophosphate neurotoxicity and risk for PD in individuals that carry one of several different mutations in their paraoxonase 1 (PON1) gene. PON1 serves an important function in the detoxication of specific organophosphate compounds, including chlorpyrifos and diazinon. Thus, alteration in the expression or function of PON1 would reduce the breakdown and elimination of these compounds, allowing them to persist and continue to affect acetylcholinesterase (Akhmedova et al., 2001; Manthripragada et al., 2010; Lee et al., 2013).

Rotenone

Rotenone is a naturally occurring compound extracted from the roots, leaves, and seeds of plants in the pea family and used for centuries by native Indians as a tool for hunting fish in rivers and streams. More recently, rotenone has been employed as a means to clear or manage nuisance fish in larger bodies of water as well as a small-scale pesticide on botanicals (Isman, 2006). As rotenone is highly hydrophobic, it is able to easily cross the cell membrane without the assistance of specific transport mechanisms. Unlike organochlorines and organophosphates, rotenone does not explicitly target the central nervous system. Rather, as a potent mitochondrial complex I inhibitor, it exerts its toxic and neurotoxic actions through disruption of adenosine triphosphate synthesis in the mitochondria and generation of oxidative stress (Degli Esposti, 1998). However, its reported specificity for damage to the nigrostriatal dopamine system may reside in the inherent vulnerability of the dopamine neurons to alteration in mitochondria function and oxidative stress and damage. Indeed, several reports have identified mitochondrial deficits in patients with PD (Schapira, 2008). While the interest in rotenone as a potential environmental risk factor for PD was initially bolstered by evidence demonstrating alterations in complex I in PD patients, it was previously believed that the short half-life in the environment and limited commercial use of rotenone reduced the potential exposure scenarios for the human population. However, recent epidemiologic findings suggest that, indeed, exposure to rotenone is a significant risk factor for development of PD in specific populations (Dhillon et al., 2008; Tanner et al., 2011).

Experimental support for these findings has been well established with findings that exposure of mice and rats to rotenone is capable of recapitulating many of the key pathologic features seen in human PD. The most prominent study, by Betarbet et al. (2000), found that treatment of rats with rotenone caused a significant reduction in dopamine in the striatum, loss of dopaminergic neurons and terminals in the substantia nigra pars compacta (SNpc) and striatum, respectively, in addition to elevated expression of oxidative stress and α-synuclein. Most interestingly, the rotenone-induced pathology was preferential for the dopamine system, sparing the GABA and glutamatergic neurotransmitter circuits in the basal ganglia. Since these studies, these findings have been repeated and expanded using various other model systems (Cannon and Greenamyre, 2010).

Herbicides

Herbicides are a broad class of pesticides that are used to remove nuisance plants, such as grasses and weeds, that may compromise the growth and yield of desired crops that are in close proximity. Herbicidal compounds are represented by numerous different formulations that target diverse cellular functions of plant cells, leading to their demise (Duke, 1990). Interestingly, many of these compounds are formulated to affect specific cellular components found only in plants and not in mammals, thus attempting to limit or reduce the potential for toxicity to the human population. For example, the widely used herbicide, 2,4-dichlorophenoxyacetic acid (2,4-D) targets auxin, which is a plant growth hormone. Although 2,4-D was synthesized to confer these specific mechanisms of action, there is still great concern regarding their toxic effects on the human population. Of the herbicides currently used, glyphosate, atrazine, 2,4-D, and paraquat are the most recognizable and have received the most attention related to their potential for toxic effects following occupational exposure. While

each compound has been extensively studied, only paraquat has been identified as a risk factor for PD.

Paraquat

Although the toxicologic properties of paraquat have been well known since the 1930s, paraquat has only been used as a herbicide since the 1960s. Like other herbicides, its primary function is to kill and control unwanted plants, weeds, and grasses both in commercial and private agricultural settings. Paraquat's primary mechanism of toxicity is through its ability to redox cycle within a cell, causing a massive production of reactive oxygen species, including superoxide anion (O_2^-) and hydroxyl radicals, which can subsequently damage the expression and function of multiple cellular components imperative for normal cell function (Bus and Gibson, 1984). Indeed, of the general class of herbicides, paraquat is deemed as one of the more toxic compounds.

Interest in the possible role of paraquat toxicity on the nigrostriatal dopamine system was stimulated in the 1980s when the chemical structure of paraquat was found to resemble that of the selective dopaminergic neurotoxin, l-methyl-4-phenylpyridinium (MPP+), which is taken up into the dopamine neurons by DAT (Snyder and D'Amato, 1985). Based upon these similarities it was suggested that paraquat may preferentially damage dopamine neurons and, like MPP+, may also target the mitochondria as a mitochondrial complex I inhibitor. However, laboratory studies focused on these concerns have found that paraquat does not enter dopamine neurons via the DAT and is not a potent complex I inhibitor, as compared with rotenone or MPP+ (Richardson et al., 2005). These findings suggest that paraquat's effects on dopamine neurons, as discussed below, may be mediated by the inherent vulnerability of the dopamine neuron to alteration in oxidative stress.

Epidemiologic support for the association between exposure to paraquat and the incidence or risk of PD is limited, but significant links have been identified in studies of occupationally exposed individuals (Kamel et al., 2007; Tanner et al., 2011; Wang et al., 2011; Freire and Koifman, 2012). Interestingly, the effect of paraquat on PD risk is often evaluated in the presence of additional pesticidal compounds, including fungicides, such as ziram and maneb. Indeed, in many studies, the risk of PD is elevated in individuals who reported exposures to a mixture of paraquat and maneb and/or ziram, suggesting a potential synergistic pathology between the two classes of pesticide (Costello et al., 2009).

While the epidemiologic support for paraquat as a risk factor for PD has gained ground in more recent years, the role for paraquat as a dopaminergic neurotoxin and its effects on the nigrostriatal dopamine circuit have been extensively studied in the laboratory. Consistent findings demonstrate that exposure of mice to paraquat routinely causes a selective loss of dopamine neurons in the SNpc in addition to a significant influx in reactive oxygen species and aggregation of α-synuclein protein (Thiruchelvam et al., 2000b; Manning-Bog et al., 2002; McCormack et al., 2002). These effects appear to be mediated by the redox cycling capability of paraquat in the dopamine neurons, as mice overexpressing superoxide dismutase, a scavenger of superoxide, are protected from the dopaminergic effects of paraquat (Peng et al., 2005). As discussed above, experimental data appear to mimic the epidemiologic findings, suggesting that exposure to a mixture of paraquat and maneb exacerbates many of the dopaminergic effects seen by paraquat alone (Thiruchelvam et al., 2000a).

Fungicides

Fungicidal compounds are used to combat fungal diseases in plants, either prior to the incidence of infection, or they can be applied to treat plants already infected with fungi or mold. Fungicides are comprised of a broad group of compounds, characterized by their diverse chemical structures and mechanisms of action. The most widely used class of fungicides is dithiocarbamates, which include compounds such as maneb, ziram, and mancozeb. In addition, other fungicidal compounds, like captan, folpet, and benomyl, which have a similar structure to the dithiocarbamates, have been extensively used. A significant amount of data has shown generalized, yet severe, toxicity of these compounds following exposure, including tumor development, dermal irritation, endocrine disruption, and some effects on the central nervous system. Of these compounds, the neurotoxic effects of the dithiocarbamate compounds, maneb and ziram, have been extensively studied, either as singular exposures or in conjunction with other pesticides, such as paraquat. As benomyl contains a carbamate moiety, similar to that seen with maneb and ziram, these compounds will be discussed as a group.

Carbamate fungicides

Although the dopaminergic neurotoxicity of exposure to carbamate fungicides has been well documented, the specific mechanisms of action are still being elucidated. Reports using cell-based models suggest that carbamate fungicides may exert their neurotoxicity on the dopamine system through several different pathways. Specifically, maneb has been shown to cause mitochondrial dysfunction through inhibition of the mitochondrial complex III, while ziram appears to affect dopamine neurons by inhibiting the function of the ubiquitin-proteasomal system

(UPS) (Zhang et al., 2003; Chou et al., 2008). Furthermore, in addition to affecting the UPS, benomyl has been shown to damage microtubule formation and inhibit the enzyme aldehyde dehydrogenase, which is involved in the metabolism of dopamine to nontoxic metabolites (Fitzmaurice et al., 2013). The majority of interest involving exposure to fungicides and PD has focused on the ability of maneb to augment the neurotoxic effects of paraquat on the nigrostriatal dopamine system. As discussed in the section on paraquat, maneb alone does not appear to cause overt dopaminergic neurotoxicity. Only when administered simultaneously with paraquat are its potential neurotoxic effects observed. These findings are further supported in epidemiologic studies that have identified a co-exposure to paraquat and maneb as a risk factor for PD, while a single exposure to only maneb does not appear to affect PD incidence (Costello et al., 2009). Similar epidemiologic studies have also found that concomitant occupational exposure to ziram and paraquat is a significant risk factor for PD, while exposure to ziram on its own is not (Wang et al., 2011). More recently, occupational exposure to benomyl was also suggested to be a risk factor for PD (Fitzmaurice et al., 2013).

Halogenated industrial compounds

Halogenated compounds are a class of chemicals characterized by varying degrees of halogen substitution on carbon atoms. Of these, substitutions with chlorine, bromine, or fluorine are the most commonly occurring and produce organochlorine, organobromine, and organofluorine compounds, respectively. The utility of these compounds in industrial as well as commercial settings is varied and can range from electric insulating coatings, flame-retardant oils, and in adhesives and plastics. The same physical and chemical properties that have made these compounds so attractive for use, including being highly stable and resistant to degradation, have also made them extremely dangerous to the environment and the human population, as they tend to have very long half-lives, thus allowing them to persist in the environment and in human tissue. Of the numerous compounds that can be categorized as organohalogens, our discussion will be focused on polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs), as these have received the most attention given their effects on the nigrostriatal dopamine system and as a risk factor for PD.

Polychlorinated biphenyls

PCBs are composed of biphenyl rings with varying amounts and positions of chlorine substitutions located around them, allowing for the formation of 209 different chemical conformations, also known as congeners. Their use in industrial and commercial settings began in the 1930s in the USA, where they were manufactured as mixtures of various congeners and sold under the trade name Aroclor. Of these mixtures, Aroclor 1242, 1254, and 1260, which contain 42%, 54%, and 60% chlorine, respectively, were the major mixtures produced. Due to their thermal stability, PCBs have been extensively utilized as lubricants and coolants to attenuate the generation of heat in transformers and capacitors, in hydraulic fluids, as well as other electric equipment (Erickson, 1986). Health concerns related to PCB exposure resulted in a discontinuation of their manufacturing and use in 1977. Even almost 40 years following this ban, significant levels of PCBs are still present in our environment and continue to impact human exposure and health (Safe, 1993; Kamrin et al., 1994).

Coupled with the persistence of PCBs in the environment, they also display a high degree of lipophilicity, which allows them to deposit in lipid-rich areas of the body, including the brain. Just as in the environment, degradation or metabolism of PCBs and elimination from the body is also difficult, presenting a situation for PCBs to accumulate within the body and create a toxic setting of constant exposure to these compounds over several years. This type of exposure is of serious concern as PCBs have been shown to be detrimental to the central nervous system (Faroon et al., 2001). While exposure to PCBs has been linked with several neurobehavioral deficits (Park et al., 2010), exposure to and deposition of PCBs in the brain have been associated with the incidence of PD. Work by Corrigan et al. (1998, 2000) found significantly elevated concentrations of PCBs, as well as specific PCB congeners in the brains of PD patients compared with controls. An additional study by Hatcher-Martin et al. (2012) also identified a greater deposition of PCBs and congeners in the brains of PD patients versus controls. The association between PCB exposure and risk for PD was also demonstrated in a cohort who had been occupationally exposed to high levels of PCBs while working in a factory that manufactured electric capacitors. Interestingly, while an increased incidence of PD was observed, it was only seen in female employees and not in males (Steenland et al., 2006). A cohort of these workers was further studied by [$^{123}\beta$] CIT single-photon emission computed tomography imaging to determine if occupational exposure to PCBs altered DAT in the striatum. As before, female workers were found to show an inverse relationship between serum PCB levels and DAT densities in the striatum, suggesting that PCB exposure can specifically alter the nigrostriatal dopamine system (Seegal et al., 2010). Interestingly, these reductions in DAT are similar to those

observed in animal studies (discussed below). Furthermore, the relevance of gender in the above findings warrants additional research as it may provide important information regarding the cellular and molecular mechanisms involved in PCB-mediated neurologic disease.

The effects of PCBs on the nigrostriatal dopamine system in laboratory animals have been well recognized for many years. Indeed, numerous studies have used various experimental models, including dopaminergic cell lines or brain slices, as well as mice, rats, and nonhuman primates to demonstrate PCB-mediated reductions in dopamine and dopamine neurotransmission (Seegal et al., 1986, 1989, 1990, 1991, 1994, 1998; Shain et al., 1991; Lee and Opanashuk, 2004; Richardson and Miller, 2004). The mechanisms leading to the reduction in dopamine levels are varied as exposure has been demonstrated to inhibit tyrosine hydroxylase and aromatic acid decarboylase, which are both enzymes involved in the synthesis of dopamine. Additionally, PCBs have been shown to alter the expression and function of the plasmalemmal DAT as well as VMAT2 to sequester dopamine, both of which are known to tightly regulate dopamine levels in the neuron (Giros et al., 1996; Richardson and Miller, 2004; Bemis and Seegal, 2004; Caudle et al., 2006, 2008; Fonnum et al., 2006; Lee et al., 2012). The implication of alterations to dopamine handling via disruption of DAT and VMAT2 as contributors to damage to the nigrostriatal dopamine system by PCBs is still under investigation. However, it should be noted that deficits in the ability of VMAT2 to sequester cytosolic dopamine can result in elevated levels of oxidative stress in the striatum, subsequent loss of striatal dopamine and DAT, degeneration of dopamine neurons in the SNpc as well as behavioral alterations reminiscent of those found in PD (Caudle et al., 2007; Taylor et al., 2009). It has been postulated that this dopaminergic degeneration is a result of the accumulation of dopamine in the cytosol and its subsequent oxidation to neurotoxic species and the formation of reactive oxygen and nitrogen species (Caudle et al., 2008).

Polybrominated diphenyl ethers

Structurally similar to PCBs, PBDEs are composed of two aromatic rings, with each ring decorated with varying degrees of bromine substitutions, allowing for 209 different congeners. PBDEs were introduced and quickly utilized in a similar fashion to PCBs in the 1970s following their phase-out. PBDEs are additive flame retardants primarily used in the manufacture and insulation of electronic equipment, as well as reduction of flammability in polyurethane foam used in carpeting, furniture cushions, and home insulation (Darnerud et al., 2001; de Wit, 2002). The physical and chemical properties of PBDEs that also make them highly lipophilic, resistant to breakdown, persistent in the environment, as well as able to bioaccumulate and biomagnify in the environment and the human body make them a relevant neurologic concern, especially given the effects on the nigrostriatal dopamine system seen with PCBs (Norstrom et al., 2002).

While data concerning the effects of PBDEs on the nigrostriatal dopamine system are minimal, recent work in the last few years has begun to highlight some concerning findings. Initial work with these compounds found the PBDE mixture DE-71 appeared to target the DAT and VMAT2 proteins, causing a significant inhibition of their ability to sequester dopamine (Mariussen and Fonnum, 2003). More recently, these findings have been elaborated in an *in vivo* model of PBDE exposure. Mice treated with DE-71 demonstrated a loss of DAT and VMAT2 expression in the striatum as well as a reduction in striatal dopamine and a subsequent decrease in locomotor activity (Bradner et al., 2013). Interestingly, when PBDEs were administered to mice with a 90% reduction in VMAT2 expression and function, many of these dopaminergic findings were exacerbated (Bradner et al., 2013).

METALS

Since the beginnings of cellular life, metals, including copper, zinc, iron, and manganese, have been a critical part of numerous biologic processes, especially enzymes. The use of these metals as enzymes arises from their efficient catalytic properties as they significantly increase the rates of enzymatic reactions owing to their ability to transfer electrons. In addition to their biologic use, metals have been used for centuries in commerce and industry. As a result, metals are recognized as some of the earliest toxicants in history, with reports of metal toxicity by Hippocrates around 370 BC. While the toxic effects of metal exposure on the human body have been well documented, the last 20–30 years have seen an increase in the recognition and appreciation for the neurotoxicologic impacts metal exposure can have on the human population. Indeed, the brain appears to be exquisitely vulnerable to metal toxicity as metals target various aspects of the neuron through generation of oxidative stress. These oxidants are extremely reactive and can readily interact with and modify various intraneuronal components, including proteins, lipids, and DNA, causing disruption in their normal function and expression and leading to more widespread alterations in neuronal processes. These effects are especially detrimental when they occur in the basal ganglia. As with other environmental factors, metal exposure has been suggested to be a risk factor for the development of PD and other

parkinsonian-related movement disorders. For instance, manganese, iron, copper, and lead have all been shown to alter the function of the dopamine system and increase the risk for parkinsonism. This section will present recent findings concerning the potential role and mechanisms of action of metal toxicity in PD and parkinsonism.

Iron

Iron is an essential metal for proper functioning of many biologic species through its extensive use by mitochondrial enzymes involved in the electron transport chain and oxygen transport by hemoglobin. Our exposure to iron occurs via the diet, especially meat, poultry, and fish, as well as iron supplementation. In addition, occupational exposure to iron, predominantly from metal fumes or metal dust generated during welding and in iron and steel production, can contribute to our body burdens of iron. Once inside the body, iron is transported across cell membranes by the divalent metal transporter 1 (DMT1) prior to being bound by proteins, such as transferrin, which traffics iron into tissues, and ferritin (H- and L-ferritin), which serves as a storage depot for free iron. These mechanisms are critical for regulating and maintaining iron homeostasis in the cell. As a consequence, alterations to these functions or overwhelming of their capacities can cause an elevation in free iron, which is highly susceptible to free radical generation via the Fenton reaction, which catalyzes the conversion of hydrogen peroxide to the highly reactive hydroxyl radical. These hydroxyl radicals easily react with various components of the cell, including DNA, membrane lipids, and protein, leading to their dysfunction. Dopamine neurons within the SNpc are highly susceptible to disruptions in iron homeostasis as a readily available supply of hydrogen peroxide is present as a normal byproduct of the production and metabolism of dopamine within the neuron. This suggests that a decrement in iron homeostasis could facilitate the further production of reactive species that could subsequently damage various aspects of the dopamine neuron. Indeed, a genetic form of iron mishandling in pantothenate kinase-associated neurodegeneration leads to iron accumulation in the basal ganglia, resulting in neuronal damage and parkinsonian symptomatology (Thomas et al., 2004).

In addition to these two disorders, several epidemiologic studies have established exposure to iron, most notably through occupational settings, as a risk factor for parkinsonism (Gorell et al., 1997, 1999a; Rybicki et al., 1999). Related to these findings, an increased accumulation of iron has been found in the serum and SNpc of PD patients compared with controls (Sofic et al., 1988; Gerlach et al., 2006; Oakley et al., 2007; Zhao et al., 2013). While the cause for this accumulation is suggested to be due to excessive exposure in an occupational setting, there is evidence that other molecular factors within the nigrostriatal dopamine system may exacerbate the neurotoxic effects of iron. For example, studies have shown elevated levels of the lactoferrin receptors and DMT1 on dopaminergic neurons in the SNpc of patients with PD, which could facilitate the transport of iron into the dopamine neurons. In a similar study, Friedman et al. (2011) found a decrease in the amount of L-ferritin, which serves to sequester and store free cytosolic iron, in PD patients versus controls. Taken in concert, coupling occupational exposure to iron with an increase in iron transport mechanisms as well as a reduction in the ability of the dopamine neurons to store free iron could provide an advantageous environment for the generation of oxidative stress.

The deleterious effects of iron mishandling have also been demonstrated in several animal models of PD. In a study by Kaur et al. (2007), exposure of neonatal mice to levels of iron routinely found in baby formula resulted in an age-dependent reduction in TH+ neurons in the SNpc and a loss of dopamine in the striatum of older animals. Additionally, unilateral injection of $FeCl_3$ into the SNpc of adult rats resulted in a significant reduction in striatal dopamine and other dopaminergic markers and a concomitant deficit in dopamine-related behaviors (Sengstock et al., 1994; Junxia et al., 2003). Given the broad and far-reaching cellular effects of iron-mediated oxidative stress, it is difficult to assign a precise cause or neuronal cascade that is affected by these events. However, studies have identified α-synuclein as a key target. In addition to acting directly on α-synuclein, the formation of oxidative species has been shown to facilitate the fibrilization and aggregation of this protein. Indeed, it is this aggregated and fibrillar conformation that is considered to the predominant toxic form of α-synuclein and involved in the degenerative process of dopaminergic neurons (Giasson et al., 2000; Uversky et al., 2001).

Copper

Like iron, copper is an essential metal that serves several important biologic functions in the body, including an important component of cytochrome c oxidase in mitochondrial respiration, as well as being an integral part of key enzymes, such as superoxide dismutase and dopamine ß-hydroxylase (Harris, 2000). Similar to iron, copper is very reactive and can exploit the Fenton reaction in order to generate hydroxyl radicals from hydrogen peroxide in the dopamine neurons. Thus, regulation and maintenance of manageable levels of copper are

imperative to normal neuronal function. The primary routes of occupational exposure to copper occur through the inhalation of fumes generated from welding, as well as metal mining and smelting activities. Copper in the blood is usually bound to ceruloplasmin prior to being transported into cells via the copper transporter ATPase (ATP7A), which serves to maintain copper homeostasis in the cell (Hellman and Gitlin, 2002). Indeed, mutation of this gene, as seen in Wilson's disease, results in accumulation of copper in several body tissues and damage to the basal ganglia and substantia nigra (Barbeau and Friesen, 1970; Hitoshi et al., 1991; Oder et al., 1993; Barthel et al., 2003). Further studies by Gorell et al. (1999b) have identified occupational exposures to copper as a risk factor for PD (Gorell et al., 1997, 1999a). These studies showed an almost 2.5-fold increase in risk for PD following a 20-year occupational exposure to copper. More recently, further evidence for copper exposure as a risk factor for PD has been demonstrated following intranigral injection of copper into rats. Investigators noted a significant reduction in several indices of dopaminergic neurodegeneration, including reduced striatal dopamine and loss of tyrosine hydroxylase projections and neurons in the striatum and substantia nigra, respectively (Yu et al., 2008).

The purported mechanisms of action that underlie copper-induced neuropathology are still tentative and somewhat contrasting, given our current understanding of copper levels in PD brains. It could be assumed that a persistent occupational exposure would result in an elevated deposition of copper in the brain and the ability of copper to generate neurotoxic reactive species, facilitating the neurodegenerative process, similar to iron. Related to this, recent reports have suggested that mitochondria are preferentially damaged following exposure to copper (Paris et al., 2009). Alteration to mitochondria function has long been appreciated as a potential pathogenic cascade in PD, most notably, through the aberrant generation of oxidative species following damage (Schapira, 2008). Additionally, like iron, copper has been shown to accelerate the oligomerization of α-synuclein monomers into neurotoxic fibrils, which can impair mitochondrial function, as well as other aspects of the dopamine neuron (Uversky et al., 2001). However, these speculated cascades would appear to be in contrast to previous studies that have reported unchanged or even reduced levels of copper in the SN of PD patients versus control (Davies et al., 2014). Given these findings, it has been suggested that dopaminergic pathology may arise from a reduction in the activity of the superoxide dismutase 1, a key cellular antioxidant in dopamine neurons, that results from the reduction in neuronal copper levels. Whether or not this interaction underlies dopaminergic loss is still unclear.

Manganese

Manganese is another essential metal with important functions in multiple biologic processes, including serving as cofactors for enzymes, including superoxide dismutase, as well as participating in neurotransmitter metabolism (Schroeder et al., 1966; Hurley et al., 1984; Golub et al., 2005). Although manganese exposure can occur through several different forms, including ingestion of food and exposure to manganese-containing products, exposure in an occupational setting such as mining, smelting, and welding appears to be a major contributor to these toxicants. The majority of these exposures are via inhalation of manganese dust, as in mining, or volatilization and inhalation of manganese fumes from manganese substrates during smelting and welding (Huang et al., 1989; Hudnell, 1999). Our current understanding suggests that inhalation of particulate manganese is able to bypass the blood–brain barrier where it is taken up directly by presynaptic nerve endings in the olfactory bulb. After being taken up, manganese is retrogradely transported to the cell body, where it can be released into the interstitial space (Tjalve and Henriksson, 1999; Vitarella et al., 2000; Fechter et al., 2002; Normandin et al., 2004). However, these pathways have been suggested based upon rodent studies and their relevance to human exposure is still being investigated (Brenneman et al., 2000; Aschner et al., 2005). Exposure to high levels of airborne manganese has been associated with several neurologic symptoms, including reduced neurobehavioral performance and neuropsychologic impairment (Huang et al., 1993; Gibbs et al., 1999). However, the most significant consequence of manganese toxicity appears to be impaired motor function, which manifests as a constellation of parkinsonian features, including muscular rigidity, tremor, reduced motor movement, and a "cock-walk" gait. Given these findings, a significant amount of attention has been focused on the neurologic effects of elevated occupational exposure to manganese, as they share several characteristic features of PD.

The association between elevated occupational exposure to manganese and neurobehavioral and motor dysfunction has been understood since the 1830s, when James Couper first described a neurologic dysfunction that shared many similarities to PD in workers exposed to manganese ore. Interestingly, at this time, Couper was able to delineate the symptomology related to manganese exposure that was distinct from typical PD. Since these findings, reports relating manganese exposure with parkinsonism have been mixed, with some studies identifying a clear association with occupational exposure (Gorell et al., 1999a, b; Racette et al., 2012), while others have not identified a similar link (Semchuk

et al., 1993; Seidler et al., 1996; Marsh and Gula, 2006). The reasons for this controversy are varied, suggesting that this is an area that needs further investigation.

Regardless of the controversy, several reports have confirmed the effects of manganese exposure on the brain, particularly nuclei of the basal ganglia. Of these nuclei, Criswell et al. (2011, 2012) found the pallidal nuclei to be more susceptible to manganese accumulation compared with the caudate and putamen in welders with high occupational exposure to manganese. These data are further aligned with pathologic findings that symptoms related to elevated manganese exposure are attributed primarily to damage to neurons in the globus pallidus (internal and external segments), while largely sparing the caudate, putamen, and SNpc. Further studies using imaging techniques have identified significant reductions in the dopaminergic D2 receptor in the basal ganglia. However, while most studies report the preservation of dopaminergic regions, such as the caudate, putamen, and substantia nigra (Shinotoh et al., 1995; Olanow et al., 1996; Pal et al., 1999; Olanow, 2004), others suggest a mild damage to these regions as well as a general alteration in their function following manganese exposure (Suzuki et al., 1975; Eriksson et al., 1992; Kim et al., 2002; Chen et al., 2006; Wright et al., 2004; Guilarte et al., 2006; Criswell et al., 2011).

Similar findings have been observed in laboratory studies using nonhuman primates. Using an exposure paradigm that closely mimics that seen in humans, pathology appeared to be preferential for the globus pallidus, while leaving the dopaminergic inputs relatively untouched. In general, no change in DAT expression, striatal dopamine levels, with minimal reductions in the dopamine D2 receptor expression, and nonresponse to L-DOPA treatment was seen (Guilarte, 2013).

The mechanisms by which manganese mediates neurotoxicity are not wholly understood. It is known that manganese is predominantly transported into neurons by DMT1. Manganese, when in excess, can inhibit mitochondrial function, reduce glutathione levels, increase *N*-methyl-D-aspartate-mediated neurotoxicity and alter calcium homeostasis, all of which culminate in cellular dysfunction (Maynard and Cotzias, 1955; Brouillet et al., 1993; Gavin et al., 1999). Furthermore, manganese is a potent mediator of pro-oxidant activities, through its production of reactive species, particularly superoxides, peroxide, and hydroxyl radical (Graham et al., 1978; Cohen, 1984). More recently, the role of astrocytes in manganese-mediated neurotoxicity has been investigated. Manganese has been found to accumulate in significantly higher concentrations in astrocytes compared with other neuronal cells, and alter the antioxidant functions of astrocytes by altering glutathione synthesis (Dukhande et al., 2006; Erikson et al., 2008), which may further contribute to neuronal demise.

SOLVENTS

Solvents represent a broad range of chemicals with the common utility of dissolving one substance into another. The most common solvents in use today include trichloroethylene (TCE), toluene, acetone, hexane, and carbon disulfide, which all serve multiple purposes in industrial and home uses. Exposure to solvents can occur through several different routes, with the most prevalent route being occupational exposure via inhalation or dermal exposure. However, nonoccupational exposure can also occur through ingestion of contaminated water as well as inhalation exposure, both following improper waste disposal or accidental release of solvents. In general, solvents are lipophilic, allowing them to be amenable to quick and easy absorption into the body and to target organs following exposure. Over the years, several neurologic deficits have been associated with solvent exposure. Yet, the strongest support for solvent exposure as a risk factor for parkinsonism is found with TCE.

Trichloroethylene

TCE is a chlorinated hydrocarbon that has proved to be very versatile in its uses and applications, including its early use as an anesthetic given its properties as a central nervous system depressant. However, TCE is also extensively used in other industrial settings, including as a solvent in printing inks, paints, lacquers, varnishes, adhesives, and paint strippers. While the use of TCE in many of these applications has been reduced or replaced with other compounds, TCE is still widely used in the degreasing of metals and as an intermediate for hydrofluorocarbon production, highlighting its continued status as a potential health risk to those highly exposed.

The toxicity of TCE can be attributed to several mechanisms, including damage to cellular membrane integrity, formation of oxidative free radicals resulting in lipid peroxidation, as well as disruption of calcium transport. This membrane disruption leads to demyelination, with TCE exposure having been shown to result in loss of sensory nerve function (Huber, 1969; Feldman et al., 1970, 1985). As the potential neurotoxic effects of TCE exposure have become better recognized, an increased interest in the possible link between chronic exposure to TCE and parkinsonism has been explored. Indeed, over the last several years, multiple case reports have identified populations highly exposed to TCE exhibiting a potential increased risk incidence of PD and PD pathology (Bringmann et al., 1992; Guehl et al., 1999; Kochen et al., 2003; Gash et al., 2008; Goldman, 2010). Most recently a study of twins discordant for PD

identified exposure to TCE as having a sixfold increased risk for PD (Goldman et al., 2012). These epidemiologic findings are largely supported by the experimental literature, utilizing animal models of TCE exposure. Specifically, Gash et al. (2008) found TCE exposure to cause significant damage to the nigrostriatal dopamine system, as shown by loss of dopamine neurons in the SNpc as well as a subsequent loss of dopamine in the striatum and midbrain. While the exact mechanisms of action of TCE that led to dopaminergic neurotoxicity are not known, the authors were able to determine that TCE inhibits mitochondrial complex I, similar to other parkinsonian mimetics, such as MPTP and rotenone. Similar dopaminergic damage was also seen by Liu et al. (2010), as they found treatment of rats with TCE resulted in dopamine neuron degeneration in the SNpc as well as accumulation of α-synuclein and an increase in reactive oxygen species. Interestingly, neuronal damage appeared to be preferential to the dopamine neurons in the SNpc as no loss of GABAergic or cholinergic neurons was observed in this area and the dopaminergic neurons of the ventral tegmental area were similarly spared, as seen in PD.

CONCLUSIONS

Appreciation of the role of the environment in neurologic disease has made great strides in the last several decades, providing an enriched understanding of the relative contributions and interplay between environmental and genetic factors in parkinsonism. As described in this chapter, the nigrostriatal dopamine system appears to be uniquely vulnerable to toxic insults, containing a multitude of targets that can be taken advantage of to elicit a neurotoxic cascade. Identification of specific chemicals and compounds has served to elaborate our general understanding of which chemicals are impacting the central nervous system (Table 14.1). However, these compounds may simply be "scratching the surface" of the chemicals that can harm the dopamine system and that have not been identified yet. Thus, a rigorous approach, which seems to already be in place, needs to continue in order to delineate environmental factors that may be involved in parkinsonism risk. Beyond this identification, investigations should also be focused on elucidating the specific cellular and molecular targets and mechanisms of these chemicals that may underlie their neurotoxic properties. In doing so, not only will our understanding grow of how these toxicants are damaging the dopamine system, but we will achieve a greater appreciation of the cellular processes of the dopamine circuit and the aspects that may make it especially vulnerable to toxic insult. Finally, this knowledge could be utilized to identify molecular targets of the dopamine neuron and pathway that could be exploited for therapeutic interventions aimed at attenuating or abrogating the neurotoxic consequences.

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