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The Role of Environmental Exposures in Neurodegeneration and Neurodegenerative Diseases

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Neurodegeneration describes the loss of neuronal structure and function. Numerous neurodegenerative diseases are associated with neurodegeneration. Many are rare and stem from purely genetic causes. However, the prevalence of major neurodegenerative diseases is increasing with improvements in treating major diseases such as cancers and cardiovascular diseases, resulting in an aging population. The neurological consequences of neurodegeneration in patients can have devastating effects on mental and physical functioning. The causes of most cases of prevalent neurodegenerative diseases are unknown. The role of neurotoxicant exposures in neurodegenerative disease has long been suspected, with much effort devoted to identifying causative agents. However, causative factors for a significant number of cases have yet to be identified. In this review, the role of environmental neurotoxicant exposures on neurodegeneration in selected major neurodegenerative diseases is discussed. Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis were chosen because of available data on environmental influences. The special sensitivity the nervous system exhibits to toxicant exposure and unifying mechanisms of neurodegeneration are explored.

Key Words: **neurodegeneration; Parkinson's disease; neurotoxicity; pesticides; neurotoxicology.**

The nervous system is a highly complex organ that, even in phylogenetically lower organisms, is responsible for a variety of tasks including receiving and processing sensory information and the control of highly complex behaviors that allow for survival. Major anatomical and physiological differences are apparent between mammals compared with lower species. Such differences account for increased behavioral complexity and a higher level of overall functioning. Even between humans and closely related primate species, there are major differences. For example, in the prefrontal cortex, major organizational differences are thought to result in our increased cognitive abilities (Semendeferi *et al.*, 2001).

In humans, highly adapted cognitive function is a direct result of evolutionary changes in neuroanatomy and neurophysiological functioning. The most obvious gross differences are increased prefrontal cortex volume and complexity (Semendeferi *et al.*, 2001). The complexity of the nervous and the energy requirements for normal function can render the system susceptible to a variety of insults. The behavioral and physiological manifestations of such insults can be influenced by numerous variables. With respect to environmental exposures, e.g., age, sex, route of exposure, dose, and genetic profile, all typically have major influences on the magnitude of the effects, the specificity of the lesion, and the phenotypic consequences (Spencer *et al.*, 2000).

The temporal development of anatomical and behavioral abnormalities following exposure to a neurotoxicant can broadly be divided into two categories. (1) Acute. Here, shortly after exposure—hours to days, a neurological phenotype presents. Such a phenotype may or may not be reversible and may or may not stem from cell loss. Exposure may interfere with neurophysiological functioning, without initiating permanent dysfunction or cell loss. For example, exposure to an industrial solvent may produce central nervous system (CNS) depression without overt neuron loss and when the exposure source is removed, the symptoms may disappear. (2) Chronic. Neurotoxicant exposure requires weeks to years and, in some cases, decades to produce cell dysfunction and cell death that result in detectable neurological alterations. Such neurotoxicant exposures may result in neurodegeneration, a broadly used term, etymologically meaning the loss of structure or function of neurons. The term is typically used to describe progressive neuronal loss and often used to describe a diverse group of neurological disorders known as neurodegenerative diseases (Przedborski *et al.*, 2003). Although there are hundreds of diseases that could be described as neurodegenerative

diseases, many are rare. However, a few are relatively common, with Alzheimer's (AD) and Parkinson's diseases (PD) affecting millions of Americans.

A common feature of virtually all neurodegenerative diseases is that the consequences are often devastating, with severe mental and physical effects. This is due in large part to the loss or dysfunction of neurons—a highly specialized cell type that is typically postmitotic—lost cells are not replaced. Bluntly put, once it is lost, a neuron is typically gone forever, along with its associated function.

The role of neurotoxicant exposures in neurodegeneration and neurodegenerative diseases is reviewed here. Unfortunately, most cases have unknown causes, although much research suggests specific environmental and genetic risk factors. The environmental risk factors for the selected prominent neurodegenerative diseases with suggested environmental links are discussed. The special sensitivity of the nervous system to toxicant exposures and shared mechanisms by which toxicants may act to disrupt neurological function are explored. Although human data bear the most direct relevance to human disease, interpretation is often difficult due to exposure to mixtures and variability of exposure levels between individuals. Thus, *in vivo* experiments, most often in rodents or primates, offer the ability to examine neurodegeneration elicited by single environmental neurotoxicant exposures. *In vitro* experiments in this context are only discussed when they add a specific mechanistic insight. Although such experiments have much reduced costs and the results are typically obtained much more rapidly, the complexity of the human nervous system is unable to adequately be modeled in cell culture experiments.

NEUROTOXICOLOGY: HISTORICAL PERSPECTIVES

Neurotoxicology can broadly be defined as the study of adverse effects on the nervous system resulting from chemical exposures, both synthetic and natural. In this context, hundreds of chemicals are suspected of having direct or indirect effects on the normal functioning of the human nervous system (Spencer *et al*., 2000). A basic understanding that exposure to certain substances may affect the nervous system functioning can be found in some of the earliest written records of human history. The posited relationship typically revolved around the notion that consumption or exposure of a specific substance will elicit a given behavioral consequence. The history of lead poisoning serves as an excellent example. For instance, the neurological effects of lead poisoning have been known for millennia. Written records by the Greek physician Nicander, describing ''gleaming, deadly white lead,'' and Nero's physician, Dioscorides, stating ''lead makes the mind give way,'' date from the second century B.C. and the first century A.D., respectively (Needleman, 2009). The effects of lead poisoning, including decreased fertility and psychosis arising from extensive use in aqueducts and as a sweetener in wine, have even been hypothesized to contribute to the fall of the Roman Empire (Gilfillan, 1965; Needleman, 2004). Although lead can affect all of the body's organ systems, the nervous system is particularly sensitive. Importantly, a safe threshold for lead has failed to be identified (Needleman, 2009). Thus, even though the neurological effects have been known for thousands of years, much more recent advances continue to illuminate the mechanisms behind such symptoms. Lead can affect both the peripheral nervous system and CNS, with children exhibiting heightened sensitivity (Bellinger, 2004). The best described effects of lead on neurons are myelin loss and axonal degeneration (Dart *et al*., 2004). More recent data suggest that the neurodevelopmental effects of lead may stem, in part, from inhibition of glutamate release, *N*-methyl-D-aspartate receptor function, or alterations in synapse formation (White *et al*., 2007). Thus, even a brief consideration of lead neurotoxicity research has illustrated the evolving focus of neurotoxicology. Although the first step in recognizing the effects of a neurotoxicant in humans is often a thorough patient history that results in correlating abnormal behavioral signs with specific exposures, the end goal of neurotoxicology research is to understand mechanisms of action and toxicity. Such an understanding is needed to best estimate the risks of a given exposure.

NEURODEGENERATION: HISTORICAL PERSPECTIVES

Neurodegeneration can cause a highly diverse group of neurological disorders. Neurological disorders have been described throughout human history and associated gross abnormalities in brain appearance known for several hundred years (Berchtold and Cotman, 1998). However, in roughly the past 100 years, the link between neurodegeneration and neurological disorders has been identified and described extensively. As early as 1892, Bloq and Marinesco used the recently discovered carmine stain and found abnormal accumulation of an unknown substance into plaques in an elderly epileptic patient (Berchtold and Cotman, 1998; Boller and Forette, 1989). Two key findings were made in the early 1900s linking the loss of neuronal structure and function to neurological disorders. In 1907, Fischer extensively described plaque formation, finding neuropathological alterations in 12 of 16 cases of senile dementia, but not in 45 cases of progressive paralysis, 19 cases of functional psychosis, and 10 normal control subjects (Berchtold and Cotman, 1998; Fischer, 1907). More famously, in the same year and in a single case, the German physician and pathologist, Alois Alzheimer, described in detail the presence of neurofibrillary tangles in neurons in the brain of a severely demented 51-year-old woman. Alzheimer also noted the plaques that had been observed by Fischer (Alzheimer, 1907; Berchtold and Cotman, 1998). Roughly a decade later, specific regional neuronal cell loss was attributed to neurological sequelae. In PD, in 1919, tremor and

rigidity in patients were found to be associated with cell loss in the substantia nigra (Tretiakoff, 1919).

NEUROTOXICANT EXPOSURES AND NEURODEGENERATION: HISTORICAL PERSPECTIVES

Although the effects of lead have long been known to disrupt neurological functioning, the role of neurotoxicant exposures in neurodegeneration and neurodegenerative diseases has only been much more recently understood. An excellent example of the coalescence of experimental neurotoxicology and neurodegeneration is the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) story. MPTP was produced as an accidental side product during the illicit chemical synthesis of 1-methyl-4-phenyl-4-propionoxypiperidine, an opioid analgesic drug. Drug users exposed to MPTP presented to the clinic with a behavioral phenotype strikingly similar to PD (Langston *et al*., 1983). This report directly led to the creation of one of the most prominent and important animal models of PD. A significant amount of mechanistic work led to the findings that MPTP crosses the blood-brain barrier (BBB), to be metabolized in astrocytes to its active metabolite (1-methyl-4-phenylpyridinium, MPP+), and to enter catecholamine neurons through the dopamine transporter (Javitch *et al*., 1985). Once in dopamine neurons, MPP+ concentrates in mitochondria and inhibits complex I. The resulting ATP depletion and oxidative stress are thought to be the main mechanisms that cause catecholaminergic cell dysfunction and death (Nicklas *et al*., 1985). The finding that an acute neurotoxicant exposure could lead to specific and ongoing neurodegeneration has led to numerous advances. Years after the initial exposure, there is evidence for active neurodegeneration in both monkeys and humans. Gliosis and microglia surrounding surviving dopamine neurons suggest ongoing neurodegeneration long after acute toxicant exposure (Langston *et al*., 1999; McGeer *et al*., 2003). To date, the monkey MPTP model remains the gold standard for testing novel therapeutics.

MAJOR NEURODEGENERATIVE DISEASES INFLUENCED BY ENVIRONMENTAL EXPOSURES

Although hundreds of human diseases may fit the definition of a neurodegenerative disease, many are rare and have been found to be caused by purely genetic factors. A small number of neurodegenerative diseases accounts for the prevalence of most cases. Most of the cases in this group of diseases stem from unknown causes. Cases are often divided into "genetic," those stemming from purely inherited factors or sporadic, and those caused by unknown factors, including environmental exposures. Most cases are now thought to arise from a combination of genetic risk factors and environmental influences. However, these interactions remain poorly understood. Unfortunately, most neurodegenerative diseases typically have no known cure, and in most cases, even slowing disease progression has proven to be enormously challenging. Thus, most current research on neurodegenerative diseases focuses on two broad aspects: (1) identifying and reducing causative factors and (2) finding and implementing novel treatments that are curative or at least reduce disease progression.

Although environmental exposures have been linked to several neurodegenerative diseases, it should be noted that a single environmental factor accounting for a significant number of cases has not been identified. Given that humans are exposed to numerous environmental toxicants in the course of a life span, identifying such a factor has proven to be very difficult, if not impossible. However, epidemiology and laboratory-based science have identified factors that influence risk and reproduced the key pathological features using animal models of the major neurodegenerative diseases. These data are highly informative on the role that neurotoxicant exposures may play in neurodegeneration.

Alzheimer's Disease

AD is the most common neurodegenerative disease, affecting an estimated 5.4 million Americans (Hebert *et al*., 2003). Advances in medicine have increased the average life span, resulting in an aging population. Because AD and most neurodegenerative diseases are diseases of aging, the prevalence is expected to continue to increase in the future. The disease is expected to affect 1 in 85 people in the world by 2050 (Brookmeyer *et al*., 2007).

AD is a devastating disease with the most identifiable symptom being dementia. The mean life expectancy is 7 years and fewer than 3% survive 14 years after diagnoses (Molsa *et al*., 1986, 1995). AD is mostly thought to be a disease in aging, with most diagnosis occurring in those aged 65 years and older (Brookmeyer *et al*., 1998). However, early-onset cases do occur and typically arise from genetic causes.

AD is characterized pathologically by the presence of intracellular neurofibrillary tangles containing the protein tau in a hyperphosphorylated state and extracellular plaques containing amyloid beta (Aβ) (Tiraboschi *et al*., 2004). Gross brain atrophy in end-stage cases is overtly obvious in the temporal lobe, parietal lobe, cingulate gyrus, and portions of the frontal cortex (Wenk, 2003). The relative contributions of plaques and tangles to the AD phenotype remain an intensely debated topic. Much mechanistic work has illuminated mechanisms of protein accumulation and aggregation in the formation of plaques and tangles. However, the ultimate cause of most cases remains unknown, with roughly 0.1% arising from autosomal dominant factors (Blennow *et al*., 2006). These cases are typically early onset and linked to mutations in Aβ metabolism. However, genetic risk factors may be a major influence on the etiology. The best known risk factor is the inheritance of the ε4 allele of apolipoprotein, an important protein in CNS lipid homeostasis, with 40–80% of patients expressing at least one allele of

apolipoprotein E4 (Mahley *et al*., 2006; Strittmatter *et al*., 1993). Although geneticists believe that many genetic risk factors may have a role in AD etiology, it should be noted that over 400 genes have been tested specifically for a contribution to AD and the results have typically been null (Blennow *et al*., 2006; Waring and Rosenberg, 2008).

The identification of environmental risk factors for AD has been even more difficult than the elucidation of genetic risks. Much work has focused on exposure to metals; most notably, aluminum (Crapper *et al*., 1973) was linked to AD decades ago, with the metal being reported in plaques (Candy *et al*., 1986; Yumoto *et al*., 2009) and tangles (Perl and Brody, 1980), although more recent pathological, mechanistic, and epidemiological data have not always supported such a link (Frisardi *et al*., 2010; Landsberg *et al*., 1992). Although the current data have not proven aluminum exposure to be a causative factor, much ongoing research is focusing on metal exposures and AD. A key gap in our understanding of the role of aluminum in the pathological features of AD remains whether aluminum participates in the pathogenesis, or if plaques and tangles simply accumulate the metal due to increased affinity. Interestingly, serum aluminum is elevated two- to threefold in patients with dementia, including those diagnosed with AD, but not as high as in patients treated with aluminum-containing drugs, such as those with renal failure (Roberts *et al*., 1998). Small studies comparing aluminum consumption in cases and controls have found increases in odds ratios (about twofold) in those with a consumption history of high aluminum-containing foods (Rogers and Simon, 1999). Although the risk associated with consumption of aluminum seems to be higher from drinking water versus dietary consumption, interpreting such results is very difficult due to other metal ions contained in drinking water (Frisardi *et al*., 2010). Overall dietary balance may also influence aluminum accumulation, where an acid-forming diet, such as one high in dietary fat or total energy, can lead to increased serum and brain concentrations of aluminum and other metal ions (Grant *et al*., 2002). However, large, rigorously controlled epidemiological studies have yet to identify high aluminum exposure/consumption as a causative factor in AD (Forster *et al*., 1995; Gillette-Guyonnet *et al*., 2005; McLachlan *et al*., 1996). A recent systemic review of epidemiological reports on aluminum and AD found that 68% established a link, 23.5% were inconclusive, and 8.5% did not establish a relationship (Ferreira *et al*., 2008).

Aluminum exposure in rodents has recapitulated some of the key features of AD. However, the results have typically fallen short of reproducing the classic pathological features of the disease. For example, aluminum was found to produce tau aggregation *in vitro*, but not *in vivo* (Mizoroki *et al*., 2007). However, progressive cortical Aβ deposition after 12 months of aluminum exposure has been reported in the mouse, where accumulation in aged controls is not detected (Rodella *et al*., 2008). Interestingly, aluminum exposure in transgenic mouse models of AD has been found to potentiate Aβ deposition (Praticò *et al*., 2002b). In aged rats, aluminum administration altered levels of copper, zinc, and manganese in certain brain regions and resulted in an enlargement of hippocampal mossy fibers (Fattoretti *et al*., 2004). Rabbits have proven to be especially sensitive to aluminum exposure, with intracerebral and intravenous infusions reproducing some of the pathological features consistent with AD (Savory *et al*., 2006). However, oral administration has proven less successful in reproducing AD pathology.

The mechanism by which aluminum may participate in the pathogenesis of AD remains to be determined. Aluminum at concentrations found in human brains of some patients who had died of AD inhibits rat brain glycolysis. Inhibition of brain carbohydrate utilization is one potential mechanism by which aluminum may act as a neurotoxicant (Lai and Blass, 1984). Metal ions may play an important role in protein conformation. Aluminum, in particular, may affect Aβ aggregation, oligomerization, and toxicity (Bharathi *et al*., 2008). Aluminum may alter normal processing of Aβ precursor protein (Drago *et al*., 2008; Garruto and Brown, 1994).

There have also been several studies linking zinc to AD. Although aluminum is a nonessential element, zinc is an essential trace element required for normal human biological functioning (Cuajungco and Lees, 1997; Frisardi *et al*., 2010). Again, the role is controversial, with reports of zinc depletions in human brain regions affected by AD contradicting laboratory-based science showing that zinc could induce Aβ aggregation (Bush *et al*., 1994; Cuajungco and Lees, 1997). Some reports have indeed found increases in human brain of AD patients (Religa *et al*., 2006). Zinc overload also exacerbates Aβ deposition in transgenic mouse models (Wang *et al*., 2010).

Other metals, including copper, have been implicated. Alterations in brains of AD patients and in transgenic mouse models have been reported (White *et al*., 1999). Copper also has been found to bind to Aβ (Hou and Zagorski, 2006). Thus, aggregated protein in AD seems to bind and accumulate a diverse group of metals. However, copper and other metals have yet to be directly implicated in the pathogenesis of AD.

Developmental lead exposure has also been implicated, illustrating the now well-known phenomenon that environmental exposures during development may influence late-life neurodegeneration. In rodents, developmental lead exposure has been found to predetermine regulation of amyloid precursor protein and the accumulation of β-amyloid (Basha *et al*., 2005). In aged monkeys (23 years old) exposed to lead at infancy, elevations of AD-related genes were found. Importantly, AD-like pathology, including β-amyloid plaques in the frontal association cortex, was found (Wu *et al*., 2008).

Alterations in brain and peripheral metal concentrations remain a major topic of interest in AD research. Given how tightly the brain regulates essential metal ion concentrations, it is unlikely that dietary consumption differences alone play

a major role in the pathogenesis of AD. Results from large epidemiological studies support such a conclusion. However, disruptions in metal transport or regulation could result in significant shifts in brain metal ion concentrations, which could lead to neurological dysfunction and potentially AD-relevant neurodegeneration.

Parkinson's Disease

The second most common neurodegenerative disease is PD, estimated to affect nearly 5 million people worldwide (Dorsey *et al*., 2007). The primary motor phenotype of the disease consists of bradykinesia, resting tremor, and postural instability. Nonmotor symptoms are widespread and as treating dopaminergic symptoms has improved, are now in many cases becoming the chief patient complaints. The hallmark pathology of PD remains the loss of dopamine neurons in the substantia nigra and the occurrence of cytoplasmic inclusions known as Lewy bodies in surviving neurons (Braak *et al*., 2004; Forno, 1996; Spillantini *et al*., 1997). However, PD is now known to affect multiple brainstem nuclei, other brain regions, and to involve systemic pathology (Braak *et al*., 2004).

Roughly 10% of total cases are thought to stem from purely inherited genetic factors. However, as with AD, the majority of cases arise from unknown causes. PD, much more so than AD, has a long history of links to environmental exposures. The MPTP story showed that exposure of a drug analog able to cross the BBB and be metabolized into a toxicant that could enter and destroy dopaminergic neurons could reproduce the major behavioral and pathological features of PD (Javitch *et al*., 1985; Langston *et al*., 1983). This group of findings created a significant research emphasis on how environmental agents with similar properties/mechanisms may be responsible for a much greater number of PD cases. Given that MPTP enters dopamine neurons through the dopamine transporter and mutations in this transporter have been found to interact with pesticide exposure, increasing the risk for developing PD (Ritz *et al*., 2009), much current research is focused on environmental factors and gene–environment interactions.

Numerous chemical agents may induce a behavioral phenotype known as parkinsonism, which shares some of the behavioral features of PD, but often has differing mechanistic and pathological correlates. For example, compounds including industrial gases, organophosphate insecticides, and certain pharmaceuticals have been shown to elicit such a phenotype (Barbosa *et al*., 1992; Liou *et al*., 1997; Müller-Vahl *et al*., 1999). These findings are often presented in the form of case reports with limited pathological data, where much further validation would be required to establish relevance to PD. Behavioral features may arise from extrapyramidal dysfunction that does not share the pathological features of PD and additional neurological features that are not characteristic of PD also may be present. Environmental exposures that significantly alter dopaminergic neurotransmission in the substantia nigra and its projections could potentially result in movement abnormalities that share some features of PD. The majority of these exposures may actually bear limited relevance to the etiology of PD, and the establishment of specificity to PD pathogenesis requires a good deal of laboratory, clinical, and pathological investigation. For example, solvents such as methanol, ethanol, and industrial and home cleaners may induce parkinsonism in humans. These exposures may occur after large bolus doses or chronic exposures. Variable responses to L-3,4-dihydroxyphenylalanine (L-DOPA) and significant motor improvements after solvent exposure cessation question specificity and relevance to PD (Carlen *et al*., 1981; Davis and Adair, 1999; Hageman *et al*., 1999; Kuriwaka *et al*., 2002; Ley and Gali, 1983; McLean *et al*., 1980; Mozaz *et al*., 1991; Uitti *et al*., 1994). It should be noted that occupations involving hydrocarbon exposure have also been found to be a risk factor for earlier onset and increased severity of PD symptoms (Jaques *et al*., 2001). Thus, in addition to eliciting parkinsonism at high doses, chronic solvent exposures may influence the pathogenesis of PD.

The task of identifying a causative environmental agent that is responsible for a significant number of cases has proven to be enormously difficult. Unfortunately, such an agent has yet to be identified. Given the amount of research that has been conducted, the general conclusion that can be drawn is that outside of a few rare cases, it is highly unlikely that exposure to a single agent accounts for a significant number of cases. Much more likely, multiple hits over time from numerous compounds, in association with a background of genetic risk factors, are responsible for most cases.

Epidemiological studies have identified a number of diverse classes of risks and compounds that may have a role in the pathogenesis of human PD. For example, rural living, well water consumption, diet, and exposure to metals, solvents, and pesticides have been repeatedly implicated as risk factors for the development of PD (Di Monte, 2001; Fall *et al*., 1999; Gatto *et al*., 2009; Gorell *et al*., 1997, 1998; Hageman *et al*., 1999; Kuhn *et al*., 1998; Kuopio *et al*., 1999; Liou *et al*., 1997; Logroscino *et al*., 1996; Pezzoli *et al*., 1996; Semchuk *et al*., 1993; Smargiassi *et al*., 1998). Thus, the potential risk factors for PD include highly diverse classes of compounds.

Pesticides, herbicides, and fungicides have received the most attention as risk factors for PD. The identification of rural living, well water consumption, and exposure to agricultural chemicals have highlighted the risks of exposure to such compounds (Gatto *et al*., 2009; Gorell *et al*., 1998; Smargiassi *et al*., 1998). Recent work examining a large population and tracking specific pesticide use identified two pesticides that result in elevated risk for PD. Here, paraquat and rotenone exposure were identified as significant risk factors (Tanner *et al*., 2011). This recent report using advanced epidemiological techniques supports many previous epidemiological studies that have suggested a link (Dhillon *et al*., 2008; Hertzman *et al*., 1990; Liou *et al*., 1997) and laboratory-based research showing that exposure to these compounds elicits PD-like pathology in animals.

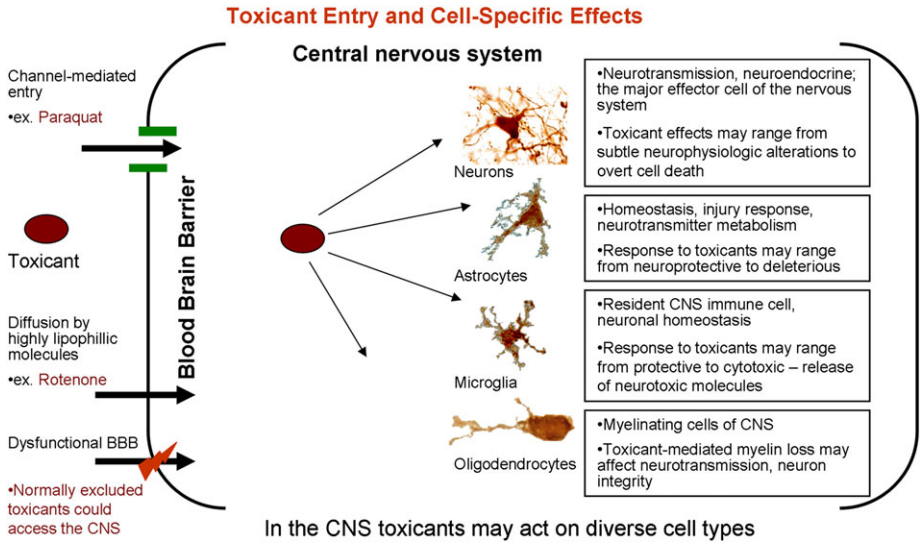

FIG. 1. Toxicant entry into the CNS and interactions with diverse cell types. To gain access to the CNS, a toxicant may enter through a specific transporter if it has structural similarities to endogenous molecules that are selectively transported across the BBB. Highly lipophilic molecules may pass directly through biological membranes gaining access to the CNS. A damaged or dysfunctional BBB could potentially allow toxicants that would normally be excluded to enter the CNS. Once in the CNS, toxicants may interact and influence the physiology of a variety of very different cell types, including neurons, astrocytes, microglia, and oligodendrocytes. Toxicant action on each of these cell types may adversely affect neurological function.

Paraquat is a bipyridal broad-spectrum herbicide used widely in developing countries. Although use in the United States is highly restricted, it remains one of the most commonly used herbicides worldwide (Wesseling *et al*., 2001). Paraquat was initially postulated to be a putative neurotoxicant because of its structural similarity to the active metabolite of MPTP, MPP+. Given its use as a pesticide, the possibility that this compound could be an environmental factor in the etiology of PD has received a great deal of attention.

The mechanism by which paraquat produces nigrostriatal damage *in vivo* appears to be somewhat different from MPTP. Paraquat is thought to enter the brain through a neutral amino acid carrier (McCormack and Di Monte, 2003, Fig. 1). However, it has been directly demonstrated that paraquat does not act by direct inhibition of complex I (Richardson *et al*., 2005). Paraquat has long been known to generate reactive oxygen species (ROS) by redox cycling and it is very likely that such a mechanism is responsible for effects on dopaminergic neurons (Fisher *et al*., 1973; Ilett *et al*., 1974).

Systemic paraquat injection in mice elicits dose-dependent (5–10 mg/kg) decreases in movement and dopamine cell counts in the substantia nigra (Brooks *et al*., 1999). Additionally, repeated paraquat administration produces selective loss of nigral dopamine neurons (McCormack *et al*., 2002). A model of PD combining paraquat and the fungicide maneb has also been developed (Thiruchelvam *et al*., 2000). This model was developed based on overlapping geographical use of the two compounds and its relevance is supported by epidemiological studies that suggest an interaction (Dhillon *et al*., 2008).

Rotenone has been used extensively as an insecticide and as a piscicide to kill fish. It is a naturally occurring compound that is found in the roots and leaves of several plant species. Rotenone is a well-known, high-affinity, selective inhibitor of mitochondrial complex I that has been used in biological experiments for decades (Ravanel *et al*., 1984). Interestingly, it has also been known for decades that systemic mitochondrial complex I inhibition occurs in PD patients (Parker *et al*., 1989; Schapira *et al*., 1989). The hypothesis that specific populations of neurons, and in particular nigral dopamine neurons (those lost in PD), are sensitive to systemic complex I inhibition lead to testing rotenone in animals.

Rotenone is a highly lipophilic compound that is easily able to cross the BBB rapidly (Talpade *et al*., 2000, Fig. 1). Early *in vivo* experiments that administered rotenone directly into the parenchyma at >500,000 times the IC_{50}, or systemically at 10–18 mg/kg/day, did not produce selective pathology consistent with PD (Ferrante *et al*., 1997; Heikkila *et al*., 1985; Rojas *et al*., 2009). However, chronic administration at much lower doses that achieved complex I inhibition, similar to that observed in platelets of PD patients, produced highly selective nigrostriatal degeneration in rats (Betarbet *et al*., 2000). Key pathological markers, including cytoplasmic alpha-synuclein-positive inclusions similar to Lewy bodies, were observed in surviving dopamine neurons. Thus, the rotenone model provided the first proof of concept that systemic mitochondrial impairment could produce selective loss of nigral dopamine neurons. These findings support the hypothesis that nigral dopamine neurons have a unique sensitivity to complex I inhibition. Thus, rotenone and other environmental toxins

with similar mechanisms may indeed be significant risk factors for PD.

Numerous other classes of environmental agents have been linked to PD, including organochlorines, organophosphates, and carbamates. However, currently, there is limited epidemiological evidence and chronic animal-based, laboratory-based research is mostly lacking.

Industrial exposures, particularly to solvents, are receiving much attention. Trichloroethylene (TCE) is a highly volatile organic chemical that has been used for many years as an industrial solvent, a dry cleaning agent, a grain fumigant, a caffeine extractant, and an anesthetic (Jollow *et al*., 2009). It is a major environmental contaminant in industrialized countries and is one of the most commonly identified groundwater contaminants at 1700 National Priorities List hazardous waste sites surveyed in the United States (ATSDR, 1997; Fay and Mumtaz, 1996; NRC, 2006).

The neurological effects of TCE have long been known, although the pathological correlates have been somewhat controversial in animals and humans (Schaumburg, 2000). More recent data have shown that inhalation of TCE in the rat after 60 days was found to elicit locomotor impairments (Waseem *et al*., 2001). Additionally, two recent reports have identified links between long-term TCE exposure and PD in humans and described the creation of a TCE animal model of PD. Factory workers with high-level exposure, working adjacent to the TCE source, were found to have PD. In this study, PD symptom severity was correlated with exposure level/duration (Gash *et al*., 2008). In rats, chronic administration caused specific loss of nigral dopamine neurons and alterations in dopamine levels (Gash *et al*., 2008; Liu *et al*., 2010). TCE crosses the BBB and induces oxidative stress (Khan *et al*., 2009; Liu *et al*., 2008a,b). The proposed mechanism is inhibition of mitochondrial complex I (Gash *et al*., 2008), which fits well with both human and animal data from other models, such as the rotenone model. However, more confirmatory data are needed to prove definitively that the mechanism of action is through complex I inhibition. Thus, there is now a preliminary link of prolonged TCE exposures to motor impairment and multiple reports of an animal model. Epidemiological studies have not yet identified TCE as a risk factor and more labs will need to replicate the animal studies.

Metals have long been thought to play a role in PD. In particular, iron accumulates in the substantia nigra of PD patients (Gerlach *et al*., 2006). Specifically, increased iron has been observed within nigral neurons of PD patients (Oakley *et al*., 2007). Thus, nigral iron accumulation is unlikely to be due solely to the contribution from proliferating and reactive glia as has occasionally been hypothesized. It remains unclear whether iron accumulation occurs in the substantia nigra as a result of PD or whether iron accumulation directly contributes to the pathogenesis of PD (Berg and Hochstrasser, 2006; Kaur and Andersen, 2004). However, a recent report utilizing data from both animal models and postmortem human brain tissue from PD patients suggests that iron is directly involved in the pathogenesis of PD. Here, a novel iron transport system specific to dopamine neurons was found to be disrupted in both human PD and rotenone-treated rats (Mastroberardino *et al*., 2009).

Iron, an essential metal that is obtained through the diet, has many important biological functions, most notably as a required component for oxygen to bind to heme. Given that iron accumulates in PD, high-iron diets have been explored as a potential risk factor. Some retrospective studies have reported an association between dietary iron and PD. However, a much more powerful prospective study of 47,406 men and 76,947 women failed to establish a link (Logroscino *et al*., 2008). Given that iron uptake through the gut is highly regulated, increased dietary consumption is unlikely to significantly alter brain levels. More likely, aberrant iron accumulation in the brain may result from disorders of transport and uptake. For example, patients with homozygous mutations for the highly penetrant C282Y in the hemochromatosis gene *HFE* were more likely to develop PD than controls (Dekker *et al*., 2003). Additionally, polymorphisms in transferrin have also been found to increase risk for PD (Borie *et al*., 2002). Therefore, the role of iron in PD is unlikely due directly to environmental or dietary factors. Environmental compounds that result in neuronal iron accumulation, e.g., rotenone, may ultimately lead to neurodegeneration (Mastroberardino *et al*., 2009). Additionally, genetic alterations in iron uptake or homeostasis could dramatically influence response to environmental toxins, given the well-known role of iron in oxidative stress.

Manganese exposure can also produce a form of parkinsonism (also known as manganism), although the behavioral and pathological features are typically distinct from typical PD. Manganese is the 12th most abundant element in the earth's crust and is an essential element for human biology (Chu *et al*., 2000). Elevated manganese exposures can occur in miners and welders, and during the chemical manufacture of maneb (Feldman, 1999; Santamaria and Sulsky, 2010). Excessive manganese exposure can produce striatal dopamine depletion and extrapyramidal dysfunction, including parkinsonism and chorea (Chu *et al*., 2000). There are many known variables that affect the neurological response to manganese exposure. The onset of symptoms depends on level of exposure, size of particles, and individual susceptibility (Mena, 1979).

Again, a common mechanistic theme in PD-related toxicants is mitochondrial dysfunction. Manganese has long been known to accumulate in mitochondria and impair oxidative metabolism (Maynard and Cotzias, 1955). Animal studies showed that manganese accumulates in the mitochondrial fraction of the striatum and causes dopamine depletion (Chu *et al*., 2000). However, there are several major differences in manganese-induced parkinsonism from typical PD. The nigrostriatal pathway is spared and the syndrome is typically unresponsive to L-DOPA (Chu *et al*., 2000; Olanow *et al*., 1996). Additionally, the neuropathological hallmark of manganism

is degeneration of the basal ganglia, particularly the globus pallidus, and the absence of Lewy bodies (Perl and Olanow, 2007; Yamada *et al*., 1986). Thus, although manganese exposure can produce motor abnormalities that may share behavioral features with PD, a distinct behavioral and pathological syndrome separate from typical PD occurs following manganese intoxication.

Although the biochemical and pathological features of manganism and PD are clearly different, multiple recent studies have examined gene–environment interactions in manganese exposure regimens. The majority of these studies examine PD-relevant genes. Treatment of rats with the manganese-based fungicide maneb has not been found to alter levels of α-synuclein, a key pathological event in PD (Nielsen *et al*., 2006). One study found that mice expressing two PD-causing α-synuclein mutations exposed to an enriched manganese diet did not exhibit gene–environment interactions relevant to PD (Peneder *et al*., 2011). Although some *in vitro* reports have shown that overexpression of normal or mutated human α-synuclein increases manganese toxicity and that manganese exposure itself increases α-synuclein levels, there is not sufficient *in vivo* evidence to show that such an interaction is currently important to either human manganism or PD (Peneder *et al*., 2011; Pifl *et al*., 2004). Given that the neuropathological characterization of human manganism cases does find evidence of Lewy body pathology (Perl and Olanow, 2007), human data also suggest that such an interaction may not be important.

Several *in vitro* studies have also suggested that Parkin—an E3 ligase that is important in PD—may influence manganese neurotoxicity (Higashi *et al*., 2004; Roth *et al*., 2010; Wang *et al*., 2009). A recent study in rats exposed to welding fumes containing manganese and manganese injections showed alterations in several genes that are important in both sporadic PD and genetic forms, including Parkin (Park2), Uchl1 (Park5), and DJ-1 (Sriram *et al*., 2010). Although a histological evaluation was not performed in this study, the result compels further evaluation of PD-related genes after *in vivo* manganese treatment. The evaluation of manganese neurotoxicity in transgenic models related to these genes would be of great interest.

Although a single causative toxicant has yet to be identified that accounts for a significant number of cases, the wealth of research studies suggests that environmental exposures play a significant role in sporadic PD. As the power of epidemiological studies increases, specific toxicants that serve as risk factors for PD are being identified. Ultimately, reducing exposures to such toxicants will hopefully reduce the risk of developing PD.

Multiple Sclerosis

Multiple sclerosis (MS) is a neuroinflammatory disease where the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, ultimately leading to demyelination, scarring, and axonal degeneration (Compston and Coles, 2008). The prevalence is highly variable based upon geographical, genetic, and ethnic variables. In the United States, more than 200,000 individuals are estimated to be affected (Noonan *et al*., 2002). The neurological symptoms are widespread and typically affect motor, sensory, visual, and autonomic function (Compston and Coles, 2008). These symptoms ultimately arise from subsequent difficulties with communication between neurons. The loss of myelin inhibits the neurons' ability to propagate action potentials (Compston and Coles, 2002). Overt loss of lower motor neurons may also occur (Vogt *et al*., 2009). The cause of MS remains unknown, although genetic, specific infections causing neuroinflammation and environmental factors have been implicated. A likely autoimmune mechanism is supported by the presence of antibodies to myelin antigens in the cerebrospinal fluid (CSF) and serum (Weiner, 1998). The prognosis is highly variable and is dependent on the disease subtype and individual susceptibility, though MS patients typically have a life expectancy of 5–10 years less than average (Compston and Coles, 2008).

The most well described environmental influence on MS is geography. The global distribution can be generalized as increasing incidence as the distance from the equator, both north and south, increases (Kurtzke, 1975; 1993). However, within this gross generalization, there are several areas with disproportionally low and high incidence rates (Compston and Coles, 2008). This has led to the hypothesis that low sunlight and vitamin D deficiency may play a role. Given the neuroinflammatory nature of MS, much work has also focused on the role of infections. MS patients have been reported to be infected with measles, mumps, rubella, and Epstein-Barr virus at later ages than matched controls (Martyn *et al*., 1993).

There are some data that toxicant exposure may have a role in MS. Roughly 20% of cases can be explained by purely genetic influences (Compston and Coles, 2008). Smoking, both active and passive (second hand), have been linked to increased MS risk (Hernan *et al*., 2005; Mikaeloff *et al*., 2007). However, there are some data showing that environmental exposures may influence MS, directly affecting oligodendrocytes. The majority of work has focused on solvent exposures, which can cause demyelination. For example, an elevated risk for MS in shoe and leather workers from Florence, who were likely exposed to organic solvents, was found (Amaducci *et al*., 1982). Case reports have implicated solvent exposures, e.g., chronic methanol ingestion can also produce clinical symptoms and histological features very similar to MS (Henzi, 1984). However, well-controlled epidemiological studies have produced conflicting results on a link between solvent exposures and MS (Marrie, 2004; Mortensen *et al*., 1998; Riise *et al*., 2002). Unfortunately, many of these studies are confounded by the use of prevalent cases and self-reported exposure assessments, potentially suffering from survivorship and recall bias (Marrie, 2004). A meta-analysis of case-controls produced

a pooled relative risk estimate of 1.7 (95% confidence interval 1.1–2.4) for solvent exposures and MS risk (Landtblom *et al.*, 1996).

Diverse environmental exposures such as fungal toxins have also been proposed as putative MS risk factors, although compelling support for such hypothesis remains lacking (Purzycki and Shain, 2010). From the available data, it is clear that much further work will be required to identify plausible risk factors, especially given the complexities of abnormal neuroimmune function that is present in MS.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a specific type of motor neuron disease characterized mainly by the degeneration of lower motor neurons in the brainstem and ventral horn of the spinal cord and degeneration of the afferent upper motor neurons in the cortex (Bento-Abreu *et al.*, 2010). Although the incidence of ALS is only 1–2 per 100,000, the lifetime risk may approach 1/400 to 1/700 (Johnston *et al.*, 2006). The main symptoms are muscle atrophy and weakness, fasciculations, and spasticity (Rowland and Shneider, 2001). The disease is progressive and fatal, with a 3- to 5-year survival time in most patients, most often due to bulbar dysfunction and respiratory dysfunction (Bento-Abreu *et al.*, 2010). Roughly 10% of cases are familial, with about 2% of total cases being accounted for by mutations in superoxide dismutase 1 (SOD1) (Rosen *et al.*, 1994).

The role of environmental exposures in ALS is poorly understood. Although many studies have been published on links between specific exposures and ALS, few have been confirmed (Bento-Abreu *et al.*, 2010). Similar to other prominent neurodegenerative diseases, inherited cases occur, but account for a small percent of total cases. Given that the most common mutation affects the protein SOD1, which is involved in the reduction of superoxide free radicals, it is plausible that environmental agents eliciting oxidative stress may have a role in ALS. However, the connection between SOD1 function and ALS is much more complicated than an increase in oxidative stress. Missense mutations in almost every amino acid residue of the protein can cause ALS, irrespective of their effect on dismutase activity (Borchelt *et al.*, 1994; Robberecht *et al.*, 1994; Rosen *et al.*, 1994). Unfortunately, attempts to identify specific classes of compounds important to this disease have been largely unsuccessful.

Exposure to lead, mercury, and pesticides have all been cited as potential risk factors for ALS (Johnson and Atchison, 2009). Accumulating data suggest that environmental exposures may influence the development of the ALS phenotype, suggesting that specific populations of neurons may be more sensitive to specific toxins. However, specific exposures have not yet been linked to precipitating ALS. Thus, the strength of the data is currently much less than the strength of PD data. Indeed, elevated blood lead levels are associated with and increase risk for ALS (Fang *et al.*, 2010). However, the association with heavy metal and pesticide exposures to ALS risk highlights the selective sensitivity of this group of neurons to environmental exposures. Although other neuronal populations are undoubtedly affected, neurons with very long axons and high energy requirements are prone to neurodegeneration.

Gulf War veterans may have an increased risk for developing ALS (Horner *et al.*, 2008; Miranda *et al.*, 2008). However, an elevation in risk remains controversial. Excluding a specific form of neurodegeneration in Guam (discussed below), environmental influences in ALS are very poorly understood.

Guam ALS-Parkinsonism-Dementia

A high incidence of neurological disorders characterized by a combination of ALS plus parkinsonism and dementia, known as ALS-Parkinson's dementia complex (ALS-PDC) in indigenous Chamorro people of Guam and other Mariana Islands, has been known since a National Institutes of Health survey in the early 1950's (Karamyan and Speth, 2008). There is a long and rich literature focused on the role of cycad seed consumption and its relevance to this neurological disease. There was much difficulty creating an animal model of ALS-PDC and the cycad hypothesis was repeatedly abandoned. However, in the late 1980's, it was demonstrated that an amino acid component of the cycad seed, β-methylamino-L-alanine (BMAA), was neurotoxic *in vitro* and *in vivo* in both mice and nonhuman primates, reproducing several of the key features of the disease (Nunn *et al.*, 1987; Ross and Spencer, 1987; Spencer *et al.*, 1986; Spencer *et al.*, 1987). Human doses extrapolated from animal studies represented daily consumption of cycad flour equivalent to the entire body weight (Karamyan and Speth, 2008). Thus, the relationship was intensely criticized. Work that is more recent has identified other sources of BMAA, most notably bioaccumulation in animals, such as flying foxes that consume cycad seeds, and are eaten in significant quantities by the indigenous population (Karamyan and Speth, 2008). The effects of BMAA in animals are highly variable and are dependent on dose, route, time course, and species. Nonetheless, many of the key features of ALS-PDC have been reproduced in certain animals (Karamyan and Speth, 2008). Interestingly, a recent report found cycad seed treatments in the rat to induce a predominantly PD phenotype (Shen *et al.*, 2010). Thus, a naturally occurring amino acid able to gain access to the CNS may serve as a neurodegenerative agent if consumed in high enough quantities.

Other Neurodegenerative Diseases

Additional neurodegenerative diseases without a known purely genetic etiology exist. Notable examples with a potential environmental component to the etiology include multiple system atrophy (MSA) and progressive supranuclear palsy. Each of these diseases is considerably rarer than AD and PD, and each receives much less effort and research

dollars, although the symptoms are often devastating. Thus, unfortunately, the etiology of these diseases is very poorly understood. In these diseases, environmental links are suspected, but there is currently a lack of credible evidence. Data on MSA serve as an example. Here, transgenic animals designed to reproduce the key pathological features of the disease—an oligodendroglial synucleinopathy—suggest that further stressors, potentially environmental, may be required for development of MSA (Wenning *et al*., 2008). Specific environmental links remain very weak, with an older study finding an association with metal dusts and fumes, plastic monomers and additives, organic solvents, and pesticides when compared with controls (Brown *et al*., 2005; Nee *et al*., 1991). Because these diseases share features with more prominent neurodegenerative diseases, it is hoped that an increased understanding of the etiopathogenesis of more prominent diseases will provide an increase in the broad understanding of the role of neurotoxicant influences on neurodegeneration.

SENSITIVITY OF THE NERVOUS SYSTEM TO TOXICANT EXPOSURE

The signs and symptoms resulting from a neurotoxicant exposure are highly variable and depend on factors such as the specific area region of the nervous system affects. Manifestations of neurotoxicant exposure may include cognitive effects, movement abnormalities, mental effects, neuroendocrine alterations, and sensory deficits. The mammalian nervous system is highly unique in terms of the diversity in the functions and the demands of the system. These features render the system especially sensitive to the effects of numerous toxicants.

Anatomical Limitations

The CNS is anatomically limited by the skull and spinal cord. In other organ systems of the body, changes in organ size may be tolerated to an extent. However, particularly in the brain, such changes can be highly detrimental or fatal. Increases in intracranial pressure can arise from a variety of causes. Well-known causes include tumors, hematomas, edema, encephalitis, and obstructions of CSF flow. Changes in pressure can dramatically affect neuronal function and potentially be fatal. Toxins produced by viruses (producing viral meningitis), bacteria (producing bacterial meningitis), or endogenous toxins (elevated in liver failure) (Frontera and Kalb, 2011; Koedel *et al*., 2002; Kumar *et al*., 2009) can all result in life-threatening changes in intracranial pressure.

Energy Requirements

The task of receiving, processing, and transmitting signaling information requires an enormous amount of energy. In fact, many neuronal populations must transmit signals, conduct antero- and retrograde transport, and maintain cellular homeostasis at distances of >1 m due to long axon bundles. The brain, while only accounting for 2% of the body weight, receives 15% of the cardiac output, and consumes 20% of total body oxygen and 25% of total body glucose (Clark and Sokoloff, 1999). In addition to these requirements, the nervous system has little energy reserve capacity, having extremely low anaerobic activity. Thus, toxicants disrupting energy production have devastating consequences to the nervous system. The classic example is cyanide, a highly toxic natural compound produced by bacteria, fungi, algae, and certain plants. Cyanide is a well-known inhibitor of cytochrome oxidase (mitochondrial complex IV). The primary target organ is the CNS, with neurological effects appearing within seconds of administration (Dawson *et al*., 1995; Way, 1984). The high toxicity and neurological effects resulting from exposure to toxicants that inhibit cellular respiration illustrates the limited ability and selective sensitivity of neurons to energy depletion.

Chemical Transmission across the Extracellular Space

Much of the communication between cells in the nervous system occurs by the release of chemical signals across the extracellular space—neurotransmission. The release, reuptake, and metabolism of neurotransmitters are highly regulated. Perturbations to neurotransmitter systems may affect neuronal function and contribute to neurodegeneration. Furthermore, neurotransmitters themselves may be highly reactive and are thought to participate in the pathogenesis of neurodegenerative diseases, especially dopamine (Fig. 1). Toxicants may also utilize transporters to gain access to neurons, where there are significant structural similarities to the native neurotransmitter; for example, MPP+ entry through the dopamine transporter (Javitch *et al*., 1985).

Limited Ability to Replace Lost Cells

With a few notable exceptions, neurons in the human CNS lost after developments are not replaced. In the human brain, there is significant evidence for neurogenesis in the subventricular zone (migration to the olfactory bulb) and subgranular zone (migration to the dentate gyrus of the hippocampus) (Eriksson *et al*., 1998; Whitman and Greer, 2009). Neurogenesis in other mammalian brain regions remains controversial (Gould, 2007). Thus, the dogma proposed by Cajal, who stated, "Once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, ended, and immutable. Everything may die, nothing may be regenerated" remains relevant to most neuronal populations (Cajal, 1913–1914; Whitman and Greer, 2009). Functional compensation for the loss of a small number of neurons can typically be achieved by redundancy in the system of adaptive plasticity. However, there is a certain magnitude of loss that precipitates functional consequences. Thus, the ability of the

brain to compensate for cell loss is much lower than other organ systems, rendering it especially sensitive to toxicant exposure, with the potential for permanent consequences.

Maintenance of a Lipid-Rich Environment

A high lipid content is of major importance to myelination and neurotransmission of the CNS. Myelination is carried out by specialized cells (oligodendrocytes in the CNS and Schwann cells in the peripheral nervous system). Damage to lipids is a common feature of neurodegenerative diseases. Indeed, lipid peroxidation is a major pathological feature of PD, AD, ALS, and other prominent neurodegenerative diseases (Reed, 2011). Thus, neurotoxicants that directly or indirectly produce lipid peroxidation in the nervous system could alter neuronal function and be a risk factor for neurodegeneration. For example, brain pathways that are poorly myelinated are especially sensitive to PD and environmentally relevant mitochondrial complex I inhibitors, such as rotenone, that induce oxidative stress (Betarbet *et al.*, 2000; Braak *et al.*, 2004, Fig. 2A).

Cellular Diversity

Many organ systems have multiple cell types. However, the diversity of cell types and function in the nervous system is unmatched. The CNS consists of neurons, astrocytes, oligodendrocytes, and microglia, with endothelial cells lining blood vessels. In the peripheral nervous system, Schwann cells are present instead of oligodendrocytes. Toxicants may elicit neurodegeneration by directly affecting neuronal function or eliciting neuronal cell death. Additionally, neurons may be affected indirectly by other cells present in the nervous system. In the brain, extraneuronal cells as a group are referred to glia. In the past few decades, it has become clear that these cells have much more important roles than simply supporting neuronal homeostasis and function. With respect to neurotoxicant exposures, glia may play important roles in toxicant metabolism and their response to toxicant exposure may range from neuroprotective to the initiation of a harmful response to neurons.

Neurons. Neuronal diversity both morphologically and biochemically has a major role in sensitivity to specific toxic insults. Dopaminergic neurons of the substantia nigra are particularly vulnerable to oxidative stress. This population of neurons under basal conditions is burdened by high energy requirements, maintaining signaling to long, poorly myelinated processes (Fig. 2A). Projections exhibit extensive arborization, with a recent study finding total axon lengths of individual rat dopamine neurons approaching 1 m (average 500 μm) (Matsuda *et al.*, 2009). Additionally, this study found that

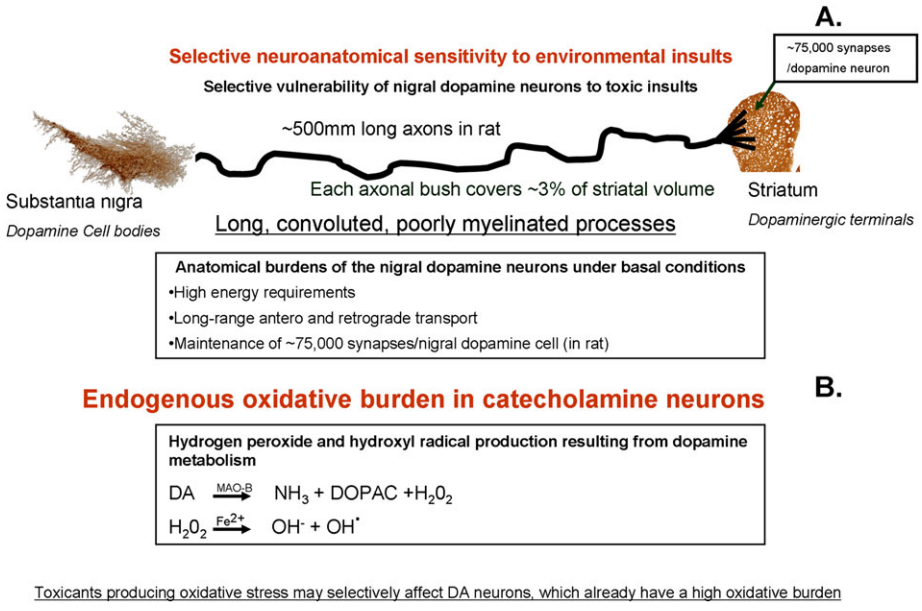

FIG. 2. Selective sensitivity of the nigrostriatal dopamine system to toxicant insults. (A) Neuronal morphology and physiology vary dramatically based on the anatomical region and neurotransmitter system. Specific populations of neurons may exhibit selective or heightened sensitivity to environmental insults based upon their anatomical features. As an example, the nigrostriatal dopamine system is selectively sensitive to several environmental toxicants. Long, poorly myelinated processes (average ~500 mm in rat—due to convolution) terminating in ~75,000 synapses result in a system with enormous energy and transport (antero- and retrograde) requirements (Braak *et al.*, 2004; Matsuda *et al.*, 2009). Such a system may be particularly sensitive to specific toxic insults. (B) Specific neurotransmitter systems may produce endogenous oxidative stress. These cell populations have an inherent oxidative burden and may be especially sensitive to additional oxidative insults elicited by exposure to environmental toxicants. Dopamine metabolism mediated by monoamine oxidase-B (MAO-B) produces hydrogen peroxide. The Fenton reaction occurring in the presence of Fe2+ may then result in the production of the highly reactive hydroxyl radical. This population is especially sensitive to additional oxidative stress insults.

a single nigral dopamine neuron is estimated to innervate ~75,000 striatal interneurons. Dopamine metabolism itself produces oxidative stress (Hastings and Zigmond, 1994, Fig. 2B). Thus, this system is extremely sensitive to additional insults that elicit oxidative stress. In addition to anatomical and metabolic susceptibilities, nigrostriatal dopamine neurons have specific signaling properties that may contribute to their selective susceptibility to neurodegeneration. The ventral tegmental area (VTA) lies directly medial to the substantia nigra and contains dopaminergic neurons. However, in PD and in neurotoxicant-based PD models, VTA dopaminergic neurons are relatively spared. Much recent mechanist work suggests that reliance on L-type Ca(v)1.3 Ca2+ channels contributes to selective sensitivity to neurodegeneration (Chan *et al*., 2007). Thus, nigral dopamine neurons exemplify how anatomical, metabolic, and physiological features likely are major factors in selective sensitivity to neurotoxicant exposure and neurodegeneration.

An additional example of selective neuronal sensitivity occurs in motor neurons. ALS is characterized by the degeneration of motor neurons, which also have long axons and high energy requirements. Specifically, in ALS, the lower motor neurons in the brainstem and ventral horn of the spinal cord and afferent upper motor neurons in the cortex undergo neurodegeneration (Bento-Abreu *et al*. 2010).

Astrocytes. Astrocytes are present in both the brain and the spinal cord and have a typical star-shaped morphology. Differences in morphology and physiology between astrocytes throughout the nervous system, based upon anatomical location, are becoming much more appreciated. Astrocytes were long thought to serve roles as structural and homeostatic support to neurons. However, extensive research in the past several decades has shown that their functions are much more complex, with important roles in neurotransmitter uptake and release, regulation of ion concentrations in the extracellular space, modulation of synaptic transmission, vasomodulation, myelination promotion of oligodendrocytes, nervous system repair, and long-term potentiation (Moore *et al*., 2011; Pascual *et al*., 2005; Santello and Volterra, 2009; Simard and Nedergaard, 2004; Suzuki *et al*., 2011). Many of these functions have been investigated for a role in neurodegeneration, and there is a wealth of published studies showing that astrocytes participate in the process, with effects ranging from neuroprotective to potentiation of neurodegeneration. More specifically, astrocytes also likely have a major influence on neurotoxicant-induced neurodegeneration. Neurotoxicant administration in the CNS typically invokes some level of astrocytic response, such as migration to the site of injury and proliferation (Ogawa *et al*., 1989). A classic example of a role for astrocytes in neurotoxicant-induced neurodegeneration is from the MPTP literature, where astrocytes were found to metabolize the protoxin MPTP to the toxicant MPP+, which ultimately leads to degeneration of dopaminergic neurons (Javitch *et al*., 1985). Additionally, reactive astrocytes are thought to play a pathogenic role in ALS as they are observed surrounding remaining motor neurons (Kamo *et al*., 1987; Kushner *et al*., 1991). *In vitro* experiments replicate this, where brief exposure of rat astrocyte monolayers to peroxynitrite results in a persistent reactive morphology and promotion of apoptosis in motor neurons plated on top of the astrocyte monolayer (Cassina *et al*., 2002).

Astrocytes may also provide protection in PD, as evidenced by the fact that mutations in *DJ-1*, a gene thought to be involved in oxidative stress, causes early-onset PD in humans (Bonifati *et al*., 2003). Knockdown of astrocytic DJ-1 *in vitro* has been found to decrease the astrocytes ability to protect against neuron loss elicited by dopaminergic neurotoxicants (Mullett and Hinkle, 2009). Mice lacking *DJ-1* exhibit increased sensitivity to MPTP (Kim *et al*., 2005).

Trimethyltin-induced neurodegeneration is well characterized in the brain, where the loss of neurons is preceded by a neuroinflammatory response. *In vitro* mechanistic studies have revealed that the neuroinflammatory response, and the subsequent production of oxidative stress, is mediated by astrocytes (Rohl and Sievers, 2005).

Much data also show that astrocytes play an important role in neurotoxicity of metal exposures. Astrocytes have long been known to be of major importance in the neurotoxic response in lead neurotoxicity, both as an accumulator (lead sink) and as a direct target for cellular toxicity (Tiffany-Castiglioni, 1993; Tiffany-Castiglioni *et al*., 1986, 1987). One major mechanism by which astrocytes likely contribute to the neurotoxicity of lead is through glutamatergic toxicity. Lead-induced alterations in the ability of astrocytes to regulate glutamate levels are thought to be a major mechanism leading to excitotoxicity (Struzynska, 2009). Manganese is also known to affect astrocytes. Again, astrocytes serve as an accumulation site for the metal (Aschner *et al*., 1999). Nasal exposure—a major route of exposure in humans—was not found to cause overt neuronal damage in rats, but was found to elevate astrocyte proteins indicative of increased astrocyte reactivity (Henriksson and Tjalve, 2000). Such changes could be detrimental to neuronal function. Manganese exposure can also affect the role of astrocytes in regulating the major inhibitory neurotransmitter, γ-aminobutyric acid (GABA). Manganese was recently found to inhibit the GABA transporter, thereby resulting in increased extracellular GABA (Fordahl *et al*., 2010). Thus, the range of responses to neurotoxicants by astrocytes in the CNS is highly diverse.

Microglia. Microglia are the resident immune cells in the CNS. They originate in bone from hematopoietic stem cells, differentiating into monocytes. They then travel to the brain and further differentiate into specialized macrophages (Ritter *et al*., 2006). In the "resting" state, microglia typically have long thin processes and a small cell body. However, in response to insults to the nervous system, microglia undergo

major morphological and physiological alterations. The branches typically retract and the processes thicken and the cell may begin to produce proinflammatory factors (Aloisi, 2001; Gehrmann *et al*., 1995; Ritter *et al*., 2006). Similar to macrophages, microglia may use cytotoxic or phagocytic functions to destroy or remove both foreign material and damaged cells. Microglial activation is a common component of many neurodegenerative diseases. In AD, activated microglia are found in numbers and in the activity states above that of age-matched controls. Some reports have linked microglial activation directly with Aβ plaques and neurofibrillary tangles, the pathological hallmark of the disease (DiPatre and Gelman, 1997; Kobayashi *et al*., 1998). Similarly, in PD, microglial activation clearly occurs (McGeer *et al*., 1987, 1988). Microglial activation also occurs in the major neurotoxicant animal models of PD, including MPTP, 6-hydroxydopamine (6-OHDA), and rotenone (Cicchetti *et al*., 2002; Czlonkowska *et al*., 1996; Depino *et al*., 2003; Sherer *et al*., 2003). In these studies, importantly, microglial activation occurred before neuronal cell loss was observed. Furthermore, *in vivo* mechanistic work using rotenone showed that neurons cultured alone are much less sensitive to this dopaminergic neurotoxin than when cultured in the presence of microglia (Gao *et al*., 2002). In this report, rotenone was found to elicit superoxide release that was attenuated by NADPH oxidase inhibitors. These data suggest that microglia play an active role in the pathogenesis of neurodegenerative diseases and can be activated by neurotoxicant exposures.

Myelinating cells. Oligodendrocytes and Schwann cells are the myelinating cells of the CNS and PNS, respectively. Although these cells have now been found to have many important functions, it is their role in myelination that directly impacts neurons. Cell loss or dysfunction can negatively impact the ability of neurons to propagate axon potentials. Schwann cells typically myelinate up to 100 μm of an axon, with a single Schwann cell myelinating a portion of one neuronal axon (Kalat, 2008). Thus, for a 1-m axon of a motor neuron, 10,000 Schwann cells would be responsible for myelination. An individual oligodendrocyte, however, can extend its processes to up to 50 neurons (Kalat, 2008). In MS, oligodendrocyte dysfunction and cell loss occurs; myelin sheaths around axons in the brain and spinal cord are damaged leading to demyelination and scarring, ultimately inhibiting neuronal signaling (Brück *et al*., 1994). Although MS is often thought of as purely a demyelinating disease, mounting data suggest that there is a major overt loss of lower motor neurons (Vogt *et al*., 2009). Thus, loss of myelin has a very detrimental effect on neuronal function and may in turn result in neuronal cell death. This process is complex, involving the redistribution of sodium channels along the axon, at formerly myelinated sites, followed by the development of a persistent current that leads to ion imbalances, and subsequently calpain-mediated axon digestion, nitric oxide and free radical production, and mitochondrial dysfunction (Craner *et al*., 2004; Smith, 2007; Stys, 2005). It remains to be determined whether environmental toxicants can elicit neurodegeneration by acting directly on oligodendrocytes and elicit downstream neurodegeneration.

COMMON MECHANISMS OF NEUROTOXICANT-INDUCED NEURODEGENERATION IN NEURODEGENERATIVE DISEASES

Although the causes of the majority of neurodegenerative diseases are unknown, the pathogenic processes and mechanisms are much more understood. In fact, major mechanisms are shared between virtually all neurodegenerative diseases. BBB disruption, protein aggregation, oxidative stress, and mitochondrial dysfunction are major shared pathogenic processes. Neurotoxicants may either initiate or potentiate such processes, ultimately leading to neurodegeneration.

BBB Disruption

Unlike any other organ, retaining constancy of the internal biochemical environment is of utmost importance to the brain. The BBB and blood-CSF barriers serve to regulate transport in and out of the CNS as well as maintain ion concentrations in the fluid that bathes the CNS (cerebrospinal fluid) that are significantly different from the rest of the body (Laterra *et al*., 1999). Molecular movement across biological membranes, including the BBB, may occur through diffusion, pinocytosis, carrier-mediated transport, and transcellular transport (Kotyk and Janacek, 1975; Laterra *et al*., 1999). Specialized endothelial cells in brain capillaries are the site of the BBB, forming continuous tight junctions that create the specialized barrier. Neurotoxicants that are highly lipid soluble may easily move across biological membranes and thus cross the BBB by simple diffusion, gaining access to the brain (Fig. 1). However, biological substances such as glucose and neutral L-amino acids that are required by the brain but have low lipid solubility typically enter through carrier-mediated transport (Kotyk and Janacek, 1975; Laterra *et al*., 1999, Fig. 1). Neurotoxicants sharing similar chemical structures to endogenous molecules may also enter the brain by this mechanism. For example, the dopaminergic neurotoxicant paraquat has a similar structure to MPTP, which is highly lipophilic and able to cross biological membranes. However, in the human body, paraquat is thought to be in a charged state, a polar molecule unable to cross membranes. Paraquat is thought to gain access to the brain due to its structural similarity to amino acids, entering through a neutral amino acid carrier (McCormack and Di Monte, 2003).

The BBB is important in both neurotoxicology and neurodegeneration. Many toxicants would likely have a major effect on the brain but are unable to cross the BBB. 6-OHDA shares a structural similarity to dopamine. However, it

contains an extra hydroxyl group (Senoh *et al.*, 1959; Senoh and Witkop, 1959). It may enter dopamine neurons through the dopamine transporter because of its structural similarity to dopamine, where it undergoes auto-oxidation and leads to the damage and destruction of catecholamine neurons (Porter *et al.*, 1963, 1965; Sachs and Jonsson, 1975; Ungerstedt, 1968). However, given it is a polar molecule, it is unable to cross the BBB. For many decades, it has served as one of the most prominent models of PD; however, it must be directly infused into the parenchyma to elicit a selective lesion (Schwarting and Huston, 1996a, b). Many environmentally relevant compounds injected into the brain would likely have major deleterious effects. However, the BBB provides protection from those that are not highly lipophilic or that are unable to mimic a biological entity and gain access to the CNS.

In the majority of neurodegenerative diseases, the BBB is affected. Whether or not BBB dysfunction directly contributes to the pathogenesis of neurodegenerative diseases or is part of the pathology remains to be determined. However, it is certainly plausible that BBB dysfunction as a primary pathogenic event, or in the early stages of disease, could allow both endogenous molecules and environmental toxicants to enter the brain that under normal circumstances would be excluded. Such compounds may then actively elicit neurodegeneration.

Neurovascular changes occur as a normal part of aging. Changes may be much more prominent in chronic neurodegenerative diseases (Zlokovic, 2008). Broadly, modest, ~20% decreases in cerebral blood flow may be observed in the aging brain in association with decreased protein synthesis (Hossmann, 1994). More severe reductions, observed in neurodegenerative diseases, can lead to shifts in intracellular pH and water, and accumulation of glutamate and lactate and interstitial fluid (Drake and Iadecola, 2007; Zlokovic, 2008). Such decreases in resting cerebral blood flow may be observed in certain regions in AD, PD, MS, or other CNS disorders (Drake and Iadecola, 2007; Hu *et al.*, 2010; Lo *et al.*, 2003; Lok *et al.*, 2007; Melzer *et al.*, 2011). Additionally, changes in the brain capillary unit, loss of brain capillaries, or alterations in resting cerebral blood flow may be among the first signs of the disease process, occurring before overt neuronal changes or neurodegeneration, are apparent (Zlokovic, 2008).

In AD, neurovascular dysfunction is associated with progressive cognitive decline (Iadecola, 2004; Zlokovic, 2005). Accumulation of toxic Aβ occurs in both blood vessels and the parenchyma (Deane and Zlokovic, 2007; Hardy, 2006; Rovelet-Lecrux *et al.*, 2006). Additionally, major alterations in microvasculature occur, including reduced microvascular density, increased fragmented vessels, changes in vessel diameter, and capillary basement membrane thickening (Bailey *et al.*, 2004; Farkas and Luiten, 2001; Zlokovic, 2008). Ultimately, BBB alterations are thought to be major factors, affecting the accumulation and clearance of Aβ in AD. Interestingly, exposure to metals in the rat such as aluminum has been found to increase the permeability of the BBB to small peptides (Banks and Kastin, 1983). Lead exposure in rodents also elicits Aβ accumulation in the choroid plexus, likely through transport alterations at the blood-CSF barrier (Behl *et al.*, 2009, 2010; Crossgrove *et al.*, 2005). Thus, metals may affect BBB and blood-CSF barriers and potentially contribute to the pathogenesis of AD.

In PD, BBB disruption has also been proposed as part of the pathogenesis. The CSF/plasma ratio of several amino acids in PD patients in altered compared with controls suggesting dysfunction in amino acid transport across the BBB (Molina *et al.*, 1997). Some studies have linked polymorphism of the BBB component P-glycoprotein to risk for PD. Interestingly, although the risk associated with the mutation alone did not reach significance, those with the mutation and pesticide exposure exhibited a significant interaction in the form of increased risk (Drozdzik *et al.*, 2003; Furuno *et al.*, 2002). Thus, PD patients are more likely to have P-glycoprotein-mediated BBB dysfunction. Therefore, BBB dysfunction at various stages of the disease could allow access of chemicals to the brain, such as pesticides that would normally be excluded.

The presence of immune cells not normally found in the CNS, such as high numbers of leukocytes in the CNS, suggests a role of the BBB in MS. Here, cells normally excluded by the BBB enter the CNS under disease conditions. Autoaggressive CD4+ T lymphocytes are activated outside the CNS and enter the brain by crossing the BBB or blood-CSF barrier (Zlokovic, 2008). Leukocyte entry into the CNS is an early event in MS and the event itself may trigger BBB disruption (Engelhardt, 2006; Raine *et al.*, 1990). Such disruption may allow additional endogenous toxins or environmental exposures to enter the CNS and potentiate the disease process.

BBB disruption also occurs in ALS, where the total protein concentration in CSF of patients is considerably higher than that of controls (Leonardi *et al.*, 1984). Ultrastructural damage to the BBB is observed in both early and late stages of genetic animal models of ALS (Garbuzova-Davis *et al.*, 2007). Additionally, a disrupted blood–spinal cord barrier has been reported in mice SOD1 mutant mice. This occurred through a reduction in the levels of the tight junction proteins ZO-1, occludin, and claudin-5 between endothelial cells. These changes resulted in microhemorrhages, release of neurotoxic hemoglobin-derived products, reductions in microcirculation, and hypoperfusion. Furthermore, SOD1 mutant–mediated endothelial damage occurred before motor neuron degeneration (Zhong *et al.*, 2008). These findings suggest that these factors are central to the early stages of the disease pathogenesis.

Oxidative Stress

Oxidative stress is a major mechanism by which many neurotoxins act. Simply defined, oxidative stress is having too

many reactive species for available antioxidants, where oxidative damage is the biomolecular damage caused by attack of reactive species upon the constituents in living organisms (Halliwell and Gutteridge, 2007). There are an enormous amount of published studies on the role of oxidative stress and damage in neurodegenerative diseases. Most human studies assess signs of oxidative damage, and reports of oxidative modifications to the major biomolecules such as DNA, proteins, and lipids are numerous. Animal studies using neurotoxicant-based models to reproduce the key features of neurodegenerative diseases have supported the general role of oxidative stress in neurodegeneration.

An outstanding coverage of the diverse biochemical and cellular responses to oxidative stress can be found in the text by Halliwell and Gutteridge (2007). Here, the authors also summarize direct evidence (measurement of oxidative damage or biomarkers, such as oxidative damage to DNA, protein, and lipids) and indirect evidence (e.g., response, such as increases in detoxification enzymes) to oxidative stress in neurodegenerative diseases, including PD. For example, elevations in SOD activity in the CNS in human PD patients likely indicate a potential attempt to detoxify oxidative stress (Saggu *et al.*, 1989).

Oxidative stress and damage clearly occurs in AD. Lipid peroxidation, nitrotyrosine, reactive carbonyls, and nucleic acid oxidation are increased in vulnerable neurons of AD patients compared with control, regardless of whether individual neurons contain AD pathology (Castellani *et al.*, 2001; Nunomura *et al.*, 1999, 2001). Thus, signs of oxidative damage precede other pathological events in AD and is an early event in the disease pathogenesis (Bonda *et al.*, 2010). Additionally, patients with prodromal AD, mild cognitive impairment, have increased levels of isoprostanes, which are products of polyunsaturated fatty acid oxidation (Praticò *et al.*, 2000, 2001, 2002a). Furthermore, 4-hydroxynonenal, produced by lipid peroxidation, is found in plaques and promotes protofibril formation (Ando *et al.*, 1998; Siegel *et al.*, 2007). Finally, in transgenic mouse models, oxidative stress precedes Aβ deposition (Odetti *et al.*, 1998). Thus, oxidative stress and damage occurs in human AD and in animal models and is an early event. There are not yet significant data supporting neurotoxicant-induced oxidative stress as a primary event in AD. However, such toxicants could potentiate the disease process.

Broad examples of oxidative damage in human PD include increased total iron content in the substantia nigra (thought to be a contributor to oxidative stress), superoxide dismutase (involved in cellular response to oxidative stress), lipid peroxidation (a marker for oxidative damage to lipids), protein oxidation, and DNA oxidation versus age-matched controls (Alam *et al.*, 1997; Dexter *et al.*, 1989; Floor and Wetzel, 1998; Saggu *et al.*, 1989; Sofic *et al.*, 1988). The major neurotoxicant-based models of PD, including MPTP, 6-OHDA, paraquat, and rotenone, are all thought to produce oxidative stress and ultimately lesion dopamine neurons through oxidative stress, although the primary mechanisms of action differ significantly. Mitochondrial complex I inhibition elicits oxidative stress and is a major mechanism of MPTP (only in catecholamine neurons) and rotenone (systemically inhibits activity in all cells). Paraquat is thought to affect dopamine neurons through redox cycling, and 6-OHDA likely auto-oxidizes after selective uptake into dopamine neurons through the dopamine transporter (Cannon and Greenamyre, 2010). Given that paraquat and rotenone are thought to act through oxidative stress and have been identified as environmental risk factors for PD, it is very likely that oxidative stress is a common downstream mechanism by which neurotoxicants can damage the highly susceptible nigral dopamine neurons. Ultimately, any toxicant capable of entering dopamine neurons, either by diffusion or through carrier-mediated transport (commonly the dopamine transporter) and eliciting oxidative stress, could potentially be a risk factor for PD.

The focus on MS as purely a demyelinating disease has been shifting. Disease progression is now known to depend on axonal degeneration, not repeated demyelination alone (Compston and Coles, 2008). Oxidative stress and damage are invariably part of the inflammatory and neurodegenerative processes. The presence of the reactive peroxynitrite has been consistently proven in acute and chronic active MS lesions (Cross *et al.*, 1998; Liu *et al.*, 2001; Oleszak *et al.*, 1998). In the serum of patients with MS, nitric oxide metabolites (nitrates/nitrites), lipid peroxidation products (malondialdehyde plus 4-hydroxyalkenals), and glutathione peroxidase activity were significantly increased (Koch *et al.*, 2006; Ortiz *et al.*, 2009).

Given that mutations in SOD1 are the most common genetic cause of ALS, aberrant redox status has long been a focus of ALS research. Oxidative damage to proteins, lipids, or DNA has been repeatedly reported in humans with ALS and genetic animal models (Barber and Shaw, 2010). Interestingly, SOD1 itself is found to be heavily oxidized in ALS, which may lead to a toxic gain of function (Andrus *et al.*, 1998; Ezzi *et al.*, 2007).

Oxidative stress remains a key focus of much neurodegenerative disease research. Neurotoxicants that are able to elicit oxidative stress in neurons are candidate risk factors for neurodegeneration. Antioxidant therapies also represent a major research focus, even though clinical trials utilizing antioxidants have been largely unsuccessful.

Protein Aggregation

Protein aggregation is a major unifying mechanistic theme in neurodegenerative diseases. Although each disease produces characteristic aggregation patterns—different specific proteins accumulating in different types of neurons—many of the mechanisms overlap. It should be noted that there is much overlap between diseases and ‘‘typical’’ cases—those

containing a specific aggregation pattern distinct from other neurodegenerative diseases are probably not as common as thought. In PD, e.g., the major pathological hallmark is the presence of cytoplasmic inclusions in surviving nigral dopamine neurons known as Lewy bodies, of which a major component is aggregated α-synuclein (Spillantini *et al*., 1997). However, PD is often accompanied with dementia, and in these cases, Aβ deposition has been observed (Burack *et al*., 2010; Kalaitzakis *et al*., 2008). Aggregated tau, the characteristic of neurofibrillary tangles in AD, is present in a host of neurodegenerative diseases known as tauopathies (Iqbal *et al*., 2010). Many of these "tauopathies" also cause parkinsonism (Ludolph *et al*., 2009). Hyperphosphorylated and insoluble tau also occur in areas of demyelination in MS (Anderson *et al*., 2008). In ALS, the propensity of SOD1 to aggregate may be more important to the pathophysiology than alterations in dismutase activity (Shaw and Valentine, 2007).

Environmental neurotoxicants that disrupt protein processing could potentially contribute to neurodegeneration. Animal studies support such a mechanism. A prominent example is the pesticide rotenone, which was the first neurotoxicant-based model to accurately reproduce the aggregation of α-synuclein characteristic of human PD (Betarbet *et al*., 2000). The rotenone model in particular has been found to replicate several intersecting pathways in neurodegeneration, including mitochondrial dysfunction, oxidative stress, and proteasomal dysfunction/protein aggregation (Betarbet *et al*., 2006). More recently, the organochlorine dieldrin has been linked to PD and was recently found to induce proteasomal dysfunction in cultured neurons leading to aberrant histone acetylation and cell death (Song *et al*., 2010).

A pathological hallmark of surviving motor neurons in ALS is the formation of filamentous "spheroid" bodies in proximal processes that may result from inappropriate NF subunit stoichiometry and/or hyperphosphorylation (Bruijn *et al*., 2004; Brune *et al*., 2003; Julien, 1999; Julien and Mushynski, 1998; Miller *et al*., 2002; Rao and Nixon, 2003). Cytoplasmic protein aggregation is a pathological feature observed in many neurodegenerative diseases. Thus, the induction of abnormal protein processing leading to aggregation may be a major mechanism by which environmental neurotoxicants are able to elicit neurodegeneration.

Mitochondrial Dysfunction

Mitochondrial dysfunction is another major feature of neurodegenerative diseases. Much research indicates that mitochondrial dysfunction may be an early or primary event in multiple neurodegenerative diseases. Mitochondrial dysfunction is a putative primary mechanism by which environmental toxicants may induce neurodegeneration.

Several publications have shown that mitochondrial dysfunction is a prominent and early event in AD (Pagani and Eckert, 2011). Mitochondrial accumulation of Aβ has been shown in both AD patients and transgenic mouse models (Caspersen *et al*., 2005; Lustbader *et al*., 2004; Manczak *et al*., 2006). Such accumulation has been postulated to affect mitochondrial import, fusion/fission, membrane potential, ROS production, and the integrity of mitochondrial DNA (Pagani and Eckert, 2011).

Systemic mitochondrial complex I inhibition has been known to occur in PD patients for decades (Parker *et al*., 1989; Schapira *et al*., 1989). Two major models of PD, MPTP and rotenone, act through complex I inhibition. MPTP selectively inhibits complex I in catecholamine neurons, whereas rotenone inhibits activity in all cells, producing a selective lesion in nigral dopamine neurons (Cannon and Greenamyre, 2010). The rotenone model has shown that nigral dopamine neurons are particularly sensitive to complex I inhibition. Rotenone exposure has now been implicated as a risk factor for human PD (Tanner *et al*., 2011). TCE, a solvent with a dramatically different structure has also been linked to PD, with a proposed mechanism of complex I inhibition (Gash *et al*., 2008). Thus, diverse environmental toxicants that are able to gain access to dopaminergic neurons may produce a lesion to the nigrostriatal dopamine system characteristic of PD.

Mitochondrial dysfunction is an emerging topic of interest in MS. Ultimately, the energy required to maintain intra-axonal ionic balance in axons lacking healthy myelin sheaths is likely to be greater than in healthy neurons (Waxman, 2006). Indeed, mitochondrial density and complex IV activity are increased compared with myelinated control spinal cord (Andrews *et al*., 2006; Boiko *et al*., 2001). In addition to proliferation and increased activity, signs of mitochondrial dysfunction occur in MS. Tissue complex I activity in chronic active lesions is reduced, whereas complex III activities on non-lesioned motor cortex are reduced, compared with control (Dutta *et al*., 2006; Lu *et al*., 2000). Interestingly, mitochondrial DNA deletions have been reported in cerebral grey matter, including neurons lacking mitochondrial DNA-encoded catalytic subunits of complex IV (Campbell *et al*., 2011). Specific defects in the main catalytic subunit of complex IV have been identified in MS (Mahad *et al*., 2008b). Whether mitochondrial dysfunction occurs because of inflammation or is a separate event is undetermined (Mahad *et al*., 2008a). It is notable that injections of potassium cyanide, a potent complex IV inhibitor in monkeys, produce progressive demyelination (Mahad *et al*., 2008a; McAlpine, 1946).

The role of mitochondria in ALS is very interesting. SOD1 is a soluble cytosolic protein that in ALS has been found to accumulate in the intermembrane space, matrix, and outer membrane of mitochondria (Higgins *et al*., 2002; Kawamata and Manfredi, 2008; Vande Velde *et al*., 2008; Vijayvergiya *et al*., 2005). In transgenic animal models, increased mutant SOD1 mitochondrial localization caused mitochondrial pathology and an accelerated disease course (Son *et al*., 2007). Mutant aggregated SOD1 localized to the mitochondria has

been proposed to cause multiple perturbations to mitochondrial function, including impaired respiration, disrupted redox homeostasis, reduced ATP production, altered calcium homeostasis, and initiation of apoptotic cascade (Shi *et al*., 2010).

Mitochondrial dysfunction is a major pathogenic event in neurodegeneration. In fact, it is typically an early event in the disease process. Environmental toxins that affect mitochondrial function have been linked epidemiologically to neurodegenerative diseases and shown in animals to elicit neurodegeneration. Therefore, toxicants with suspected links to neurodegenerative diseases should be explored for a potential effect on mitochondrial function.

SUMMARY

Neurodegenerative diseases are often highly debilitating to both mental and physical functioning. Most are strongly associated with aging; risk dramatically increasing in the later stages of life. Advances in medicine have resulted in dramatic increases in the average life span. Thus, with an aging population, the prevalence of neurodegenerative diseases is expected to continue to rise. For most of these diseases, two enormous challenges remain: (1) to determine the cause for most cases and (2) to discover disease modifying or curative treatments. Unfortunately, much research effort has yet to adequately address either of these challenges. However, our understanding of the pathogenic mechanisms has increased dramatically, and this knowledge will be essential for determining both the causes and the creation of novel treatments.

Environmental influences have long been suspected to play a role in neurodegenerative diseases. This is particularly true with PD, where there is a wealth of epidemiological studies linking environmental exposures to the disease. Additionally, multiple relevant environmentally linked neurotoxicants produce behavioral and pathological features of human PD. However, no neurotoxicant has been definitively linked as a causative agent in PD or other neurodegenerative diseases. Making such links will remain very difficult due to the number of compounds and exposure variability in humans over the course of a life span. Ultimately, the major goal in conducting research on the role of neurotoxicant exposures in neurodegenerative disease remains to identify potential risk factors. The reduction of newly identified risk factors would hopefully reduce the incidence rate and the burden of neurodegenerative diseases on human health. The linkage of neurotoxicants to human neurodegenerative diseases also provides the opportunities to create new animal models, and increase our understanding of the pathogenic mechanisms of human diseases. The development of better and more relevant animal models is crucial to the design and testing of novel therapeutics that hopefully will be developed in the future to treat this devastating group of diseases.

FINALLY, HOW CAN TOXICOLOGISTS HELP?

Neuroscientists and toxicologists clearly do not always agree on how best to model and investigate the role of neurotoxicant exposures in neurodegenerative diseases. A major issue is often the route and dose of a compound required to elicit a neurological phenotype, consistent with a specific human neurodegenerative disorder. Unfortunately, such high doses are often required to model years of human exposures in rodents with a comparatively much lower life span—even though they may appear to have little environmental relevance.

An emerging major need is the study of the preclinical features of neurodegeneration, particularly the biochemical and pathological features that occur before patients exhibit the cardinal disease signs. Having such data in hand is very important for the discovery of biomarkers and testing new therapeutics in a model, at the stage where therapeutic target would be disease modifying. Unfortunately, administering a therapeutic agent immediately before a bolus dose of a neurotoxicant that causes acute, major neurodegeneration is not that informative for the assessment of potential therapies. However, this approach is commonly employed in neuroscience research. Help from toxicologists is greatly needed in this area. What are the relevant doses of a given environmental compound that neuroscientists should be using to assess the role a specific toxicant may play in neurodegeneration? Given that humans are exposed to myriad compounds, which mixtures should we be testing? Neuroscientists understand that we must move beyond simply testing late-stage models of neurodegenerative disease, and we now have many endpoints that can be assessed prior to neuronal loss. It is strongly believed that toxicologists can help accomplish this endeavor in a way that is meaningful to human health and exposures.

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