Occupational Metal Exposure and Parkinsonism

W. Michael Caudle

Abstract Parkinsonism is comprised of a host of neurological disorders with an underlying clinical feature of movement disorder, which includes many shared features of bradykinesia, tremor, and rigidity. These clinical outcomes occur subsequent to pathological deficits focused on degeneration or dysfunction of the nigrostriatal dopamine system and accompanying pathological inclusions of alpha-synuclein and tau. The heterogeneity of parkinsonism is equally matched with the complex etiology of this syndrome. While a small percentage can be attributed to genetic alterations, the majority arise from an environmental exposure, generally composed of pesticides, industrial compounds, as well as metals. Of these, metals have received significant attention given their propensity to accumulate in the basal ganglia and participate in neurotoxic cascades, through the generation of reactive oxygen species as well as their pathogenic interaction with intracellular targets in the dopamine neuron. The association between metals and parkinsonism is of critical concern to subsets of the population that are occupationally exposed to metals, both through current practices, such as mining, and emerging settings, like E-waste and the manufacture of metal nanoparticles. This review will explore our current understanding of the molecular and pathological targets that mediate metal neurotoxicity and lead to parkinsonism and will highlight areas of critical research interests that need to be addressed.

Keywords Copper • E-Waste • Iron • Manganese • Manganism • Nanoparticles • Parkinsonism

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Introduction

The neurotoxicological outcomes related to metal exposure are varied, as metals are capable of migrating to many different brain regions and interacting with a catalogue of different neuronal populations, affecting a variety of intracellular targets and pathways within these cells. This promiscuity introduces a complexity to ascribing neurotoxicological effects to select metals. In light of these complexities, extensive work has highlighted the unique sensitivity of select brain regions to metal exposure and the neurological deficits that arise from these interactions. To this end, the basal ganglia, a region severely damaged in Parkinson disease (PD), appear to be a selective target for metal-induced neurotoxicity. Perhaps not surprising, as with other environmental factors, metal exposure has been suggested to be a risk factor for the development of PD and other parkinsonian-related movement disorders. Recent work has been focused on bringing to light a more specific understanding of how certain metals interact with neuronal targets and intracellular pathways in the basal ganglia to elicit neurological deficits. Thus, this section will present recent findings concerning the potential role and mechanisms of action of metal toxicity in Parkinson disease and parkinsonism and will introduce emerging exposure concerns that may have neurotoxicological implications for the future.

Clinical and Pathological Signs of Parkinsonism

Parkinsonism is a heterogeneous group of neurological disorders that share common pathological features of alteration to the nigrostriatal dopamine circuit, in addition to pathological accumulations of alpha-synuclein or tau, as determined at autopsy (Dickson 2012). These pathological signs give rise to a suite of clinical symptoms focused on the presence of disordered movement, predominantly described in terms of bradykinesia, tremor, and postural instability, in addition to other extrapyramidal deficits and neuropsychiatric signs. With this broad category of movement disorders, three specific disorders, Parkinson disease (PD), progressive supranuclear palsy (PSP), and multiple system atrophy (MSA), have been extensively investigated and used to demonstrate the clinical and pathological heterogeneity that defines parkinsonism. Of these, PD has been the most extensively characterized, with cardinal clinical signs including asymmetrical resting tremor, slowed movement, cogwheel rigidity, and postural instability (Fahn 2003). These motor signs are often accompanied by non-motor deficits in autonomic and neuropsychiatric function, ranging from gastrointestinal and cognitive deficits to olfactory and sleep disturbances (Langston 2006). These clinical manifestations appear to be extensively associated with pathological findings, including damage to the dopaminergic circuit that originates in the substantia nigra pars compacta (SNpc) and sends dopaminergic projections to the striatum (Fahn 2003). While these deficits appear to underlie many of the motor deficits observed in PD, pathological

alterations to other brain regions and neurotransmitter systems, including the noradrenergic and serotonergic circuits, have also been demonstrated to be involved in the plethora of non-motor symptoms that define the disease. In addition to alterations in neurotransmitter pathways, PD is pathologically defined by the presence of alpha-synuclein inclusions (Dickson 2012). Although the precise neuronal function of alpha-synuclein is still under investigation, it is well-established that conformational changes and misfolding of this protein are pathogenic mechanism involved in damage to the dopamine neurons in the SNpc.

Multiple system atrophy has also been extensively evaluated and is classified as a major parkinsonian syndrome. Like PD, MSA is clinically described as exhibiting alterations in movement involving the basal ganglia, as well as autonomic dysfunction that precedes the motoric deficits (Gilman et al. 1999). While MSA shares many of the clinical features as PD, a major divergence of these disorders is the responsiveness to the dopamine replacement drug, L-DOPA. Given the extensive loss of dopamine in the nigrostriatal pathway in PD, L-DOPA treatment has served as the "gold standard" of therapeutic intervention for well over 50 years. In contrast, MSA does not respond as robustly to L-DOPA treatment. The reasons for this discrepancy are not known. However, it is interesting to note that while PD and MSA share many clinical and pathological features, one striking difference is the localization of pathogenic alpha-synuclein inclusions in the brain. Such inclusions in MSA are predominantly localized to glia, specifically oligodendrocytes, rather than intraneuronally, as seen with PD (Lantos 1998).

Progressive supranuclear palsy is clinically defined by motor disturbances in addition to other neurological deficits, including dementia and a lack of autonomic participation (Williams et al. 2005). These clinical findings suggest the involvement of other brain regions and neural circuits that are independent of the nigrostriatal dopamine pathology. Indeed, the pathological findings in PSP are significantly more promiscuous than PD or MSA, encompassing a variety of other neuronal nuclei and regions. The involvement of these other brain regions and circuits may also underlie the attenuated response of PSP patients to L-DOPA therapy. Additional support for the pathological complexity of PSP is found in the presence of inclusions of the microtubule protein, tau, to create neurofibrillary tangles and glial inclusions, which are hallmark pathological signs in disorders like Alzheimer disease and dementia (Dickson et al. 2007). Taken in sum, the clinicopathological landscape of parkinsonian disorders comes with an extensive complexity that must be appreciated when discussing the etiology and pathogenic processes that may underlie observed clinical signs.

While parkinsonism clearly has underlying genetic etiology, the majority of cases are idiopathic, suggesting an exogenous contribution to disease etiopathogenesis. To this end, a variety of environmental factors have been associated with parkinsonism, including exposure to pesticides, solvents and other industrial chemicals, as well as metals (Caudle et al. 2012; Hatcher et al. 2008; Caudle 2015). Metal exposure represents an interesting etiological feature of the disease. In one hand, we rely extensively on specific metals to perform various biological functions in the body and the brain. However, if levels of metals are not tightly regulated, they can

have severe repercussions to the function of the nervous system. While metals comprise a naturally occurring element of our dietary intake, these exposures provide a relatively low level of exposure to these compounds. In contrast, the inclusion of metals in a variety of industrial and commercial applications has introduced an occupational exposure scenario that exposes subsets of the population to elevated levels of potentially neurotoxic metals. When in excess, metals can damage the brain through a variety of intracellular cascades, most notably through their ability to generate highly reactive molecular species that can target a variety of intracellular components, leading to dysfunction. Within the brain, the basal ganglia appear to be especially vulnerable to the neurotoxic effects of excess metal exposure and the development of parkinsonian disorders.

To specifically address these points, this review will focus on occupational exposures to select metals that have been demonstrated to have significant associations with damage to the basal ganglia and the dopamine circuit seen in parkinsonism. This discussion will appraise the current epidemiological evidence related to these exposures and disease and will further explore these findings, in the context of pathological, clinical, and mechanistic perspectives.

Iron Exposure and Parkinsonism

Iron is one of the most prevalent metals and is utilized in a variety of biological functions, including its incorporation into hemoglobin for oxygen transport, and as a cofactor for enzymatic activity in cytochrome C and catalase. However, alterations in the regulation of iron levels in the basal ganglia leading to excess accumulation have been shown to result in parkinsonian deficits. For example, Friedreich's ataxia, which manifests as a host of neurological deficits including motor dysfunction, is defined by alterations in iron handling in the mitochondria by the protein, frataxin, leading to accumulation (Gomes and Santos 2013). While these findings point to deficits in iron homeostasis following biological levels of iron exposure, other occupational-based studies have evaluated the effect of excess iron exposure, via iron fumes generated by welding activities or iron dust from iron and steel production, as a risk factor for PD and parkinsonism (Gorell et al. 1997, 1999a, b; Rybicki et al. 1999). However, many of these studies were unable to demonstrate iron exposure, on its own, as a factor that underlies PD etiology. Rather, iron exposure that occurred in combination with other metals, including lead or copper, seemed to implicate iron as a risk factor. Interestingly, in many of these studies, copper alone was significantly associated with risk of PD, while iron + copper seemed to elevate this risk. While the occupational data may still be controversial, a more concise discussion of the role of iron in PD can be gleaned from pathological and imaging data. Indeed, a variety of studies have found significantly elevated levels of iron in the putamen and SNpc of PD patients, placing iron at the point source of PD pathology (Gerlach et al. 2006; Hare and Double 2016; Oakley et al. 2007; Sofic et al. 1988). Whether these excess levels arise from an explicit increase in occupational

exposure to iron is unclear, but evidence has shown that alteration in intracellular iron homeostasis in the brain and dopamine neurons may underlie iron accumulation and pathology in the basal ganglia. Several proteins are involved in mediating the intracellular dynamics of iron. Iron is predominantly transported into the brain and neurons by the divalent metal transporter 1 (DMT1) as well as through binding to transferrin, which is then trafficked across the neuronal membrane by the transferrin receptor. Once inside the neuron, iron can be stored by ferritin, which regulates the levels of free iron in the cytoplasm and reduces the ability of iron to generate reactive species (Honarmand Ebrahimi et al. 2015; Moos et al. 2007). Thus, alterations at various points in iron homeostasis could underlie iron-mediated neurotoxicity in dopamine neurons. Evidence to support these ideas has shown elevations in iron in the substantia nigra of PD patients that have increased expression of DMT1 and transferrin receptors on dopamine neurons. Additionally, reductions in ferritin also result in an increase of free cytosolic iron. In contrast to these findings, a polymorphism in the transferrin receptor that causes a reduction in its activity has been shown to limit the amount of iron transported into dopamine neurons, serving as a protective mechanism in PD (Dexter et al. 1991; Rhodes et al. 2014).

Dopamine neurons, as well as noradrenergic neurons in the locus coeruleus, have additional means to regulate cytosolic iron levels through the sequestration by neuromelanin (NM). Neuromelanin is a dark-colored pigment that is synthesized from the breakdown products of dopamine and other catecholamines in the midbrain (Sulzer et al. 2000). While the physiological role of NM is still being debated, evidence suggests that it acts as a "sink" for a variety of potentially neurotoxic exogenous and endogenous compounds in dopamine and norepinephrine neurons (Zecca et al. 2002). However, under cellular distress or damage, NM may become detrimental to the neuron by releasing its neurotoxic cargo back into the cell and into the extracellular environment. Additionally, it has been suggested that NM can become overwhelmed or saturated with such species, including iron, causing it to release excess amounts into the cell (Zucca et al. 2004).

The neurotoxicity of elevated iron in dopamine neurons is focused on the ability of cytosolic iron to catalyze the formation of reactive oxygen species, including hydroxyl radicals, through the Fenton reaction. Furthermore, iron in the cytosol can also interact with dopamine to metabolize dopamine into neurotoxic dopamine quinones and other neurotoxic species. These neurotoxic species are highly reactive and can interact with various intracellular components in the dopamine neuron, including DNA, membrane lipids, and proteins, leading to their dysfunction and decrement of the dopamine neuron (Hare and Double 2016). Moreover, iron may also participate in the formation of neurotoxic accumulations of the PD-relevant protein, alpha-synuclein (Uversky et al. 2001). Although the specific function of alpha-synuclein is still under investigation, it is clear that it plays a critical role in synaptic function in dopamine neurons. A key pathological feature of PD is accumulation of neurotoxic alpha-synuclein aggregates in dopamine neurons (Dickson 2012). Although the precise pathway that mediates the formation of these inclusions is vague, extensive work has described the interaction between intracellular metals and alpha-synuclein in accelerating its pathological misfolding into neurotoxic species (Carboni and

Lingor 2015; Lu et al. 2011). Such an interaction may be critical in delineating the role iron exposure plays in parkinsonism. While elevated iron levels and reduced ferritin are seen in the substantia nigra of PD patients, similar alterations in iron handling are not observed in the substantia nigra of patients with MSA. Although both PD and MSA display significant damage to the dopamine system and are pathologically defined by alpha-synuclein accumulations, the localization of these inclusions in these two disorders diverges. While they are exclusively seen in dopamine neurons in the SNpc of PD patients, neuronal inclusions are rarely seen in MSA, instead collecting in oligodendrocytes (Lantos 1998). Thus, these findings could give critical insight into the pathological mechanisms related to PD and MSA and the environmental contribution of iron exposure to each disorder.

Copper Exposure and Parkinsonism

Similar to iron, copper is a critical metal element for several biological functions in the human body. Copper serves as a cofactor for the antioxidant copper/zinc superoxide dismutase (Cu/ZnSOD), which functions to metabolize the reactive oxygen species, superoxide to limit its potential interaction with intracellular targets. Copper is also involved in neurotransmitter synthesis, specifically through its interaction with dopamine beta-hydroxylase, a key enzyme in the synthesis of norepinephrine from dopamine (Harris 2000). Like iron, exposure to elevated levels of copper can also occur in occupational settings, including mining. Indeed, epidemiological evidence supports such exposures as risk factors for the development of PD. Studies performed by Gorell et al. have evaluated workers occupationally exposed to elevated levels of copper over multiple decades. From these studies it was found that occupational exposure for greater than 20 years resulted in a 2.5-fold increased risk for PD. Interestingly, when copper was assessed in the context of combined exposure with other metals, including lead or iron, the risk increased to 5.3- and 3.7-fold, respectively (Gorell et al. 1997, 1999a).

Under physiological conditions copper is bound to ceruloplasmin in the blood. When copper is unbound, it can be transported across biological membranes, including the blood-brain barrier and neuronal membranes via the copper transporter 1 (CTR1) (Hellman and Gitlin 2002). Once inside the neuron, intracellular levels of copper are tightly regulated by additional transporters ATP7A and ATP7B, which function to efflux excess copper from the cell (Hellman and Gitlin 2002). Each of these transport mechanisms is highly expressed in the substantia nigra and targeted for dysfunction, leading to alterations in copper homeostasis. Indeed, Wilson disease is defined by an excess accumulation of copper in the brain and damage to the basal ganglia following a reduction in the expression and function of ATP7A (Bandmann et al. 2015).

In light of these findings, the contribution of copper to dopaminergic pathology is complex, with both elevations and reductions in copper concentrations suggested to contribute to pathogenesis of dopamine neurons. From the context of excess

accumulation of copper in the substantia nigra, it has been suggested that copper participates in the formation of reactive species, such as hydroxyl radicals, through the Fenton reaction, which can subsequently damage the dopamine neuron (Oder et al. 1993; Barbeau and Friesen 1970; Hitoshi et al. 1991; Barthel et al. 2003). While this certainly provides a possible mechanism, extensive work has also focused on the interaction of copper with alpha-synuclein and its contribution to conformational changes and protein misfolding leading to the acceleration of neurotoxic alpha-synuclein fibrils (Carboni and Lingor 2015; Dell'Acqua et al. 2016; Valensin et al. 2016). Interestingly, phosphorylation of alpha-synuclein, specifically at serine 129, has been shown to increase the binding affinity of copper with alpha-synuclein and further increase the neurotoxic accumulations of the protein (Lu et al. 2011). While alpha-synuclein has received the greatest attention, DJ-1, another PD-relevant protein, has also been shown to interact with copper (Bjorkblom et al. 2013; Girotto et al. 2014). Unlike alpha-synuclein, DJ-1 appears to serve as a copper-binding protein that participates in additional copper homeostasis. Indeed, mutation of specific residues abolishes this metal-binding function and increases copper-induced neurotoxicity. Interestingly, such an interaction with DJ-1 is independent of its endogenous antioxidant functions.

While each of these studies provides strong evidence for a mechanistic pathway leading to copper-induced dopaminergic neurotoxicity, it is predicated on the idea of excess copper, either due to elevated exposure or dysfunction in proteins that regulate intracellular levels of copper. However, to date, elevated tissue levels of copper have not been observed in PD. In contrast, copper has been found to be reduced or unchanged in both the substantia nigra and serum of patients with PD (Davies et al. 2014, 2016; Montes et al. 2014; Torsdottir et al. 1999, 2006). Additionally, alterations in the expression or function of copper-handling proteins have not been previously associated with PD incidence. This evidence seems to suggest another potential mechanism, by which copper could participate in neurotoxicity. As discussed above, copper is necessary for the enzymatic activity of the antioxidant Cu/ZnSOD, which functions to degrade superoxide that is generated in the neuron. Thus, a reduction in copper in the substantia nigra may increase the vulnerability of these dopamine neurons to oxidative damage that is constantly taking place through the normal biosynthesis and metabolic processes in the dopamine neuron. Moreover, as the transport of iron is tightly mediated by copper transport, a reduction in copper could elicit an accelerated transport of iron into the dopamine neurons (Ayton et al. 2013). In contrast to copper, iron is found to be elevated in the substantia nigra of PD patients (Jin et al. 2011).

Manganese Exposure and Parkinsonism

By far, one of the more interesting discussions related to metal toxicity and parkinsonism relates to the contribution excess exposure to manganese makes to basal ganglia pathology and clinical manifestations related to this pathology. As with

other metals already discussed, manganese is an essential cofactor for several enzymes, including superoxide dismutase (SOD), and plays a role in the synthesis and metabolism of neurotransmitters (Schroeder et al. 1966; Hurley et al. 1984; Golub et al. 2005). Similarly, manganese can have detrimental effects on this system through its accumulation and generation of reactive species among other mechanisms (Graham et al. 1978; Cohen 1984). At the root of this argument is whether or not excess manganese exposure results in damage to the nigrostriatal dopamine system similarly to that seen in idiopathic PD, suggesting that it is a possible causative environmental risk factor for PD, or whether such exposures generate a pathologically distinct parkinsonian syndrome, usually referred to as manganism. Work in recent years has addressed these concerns using a spectrum of epidemiological and lab-based studies to delineate the key pathological and clinical features of excess manganese exposure and contrast them with those seen in PD.

Manganism was originally described in 1837 by Dr. James Couper following his examination of patients who had been exposed to excess amount of manganese through the mining of manganese ore. In his clinical assessment, Dr. Couper noted extensive neurological deficits that initially manifested as deficits in neuropsychiatric and cognitive endpoints. Only after these symptoms were expressed did the more familiar motoric dysfunction so often associated with PD, including bradykinesia, tremor, and cogwheel rigidity, present (Gibbs et al. 1999; Huang et al. 1993). Interestingly, excess manganese deposits prominently in the basal ganglia, specifically within the globus pallidus, which is enriched in GABAergic neurons (Erikson and Aschner 2006; Bouabid et al. 2015; Kwakye et al. 2015).

Exposure to manganese is still a critical concern in occupational settings, as elevated exposures can most often occur via mining activities, steel manufacturing, and the inhalation of welding fumes (Hudnell 1999; Huang et al. 1989). While numerous studies have been conducted to address the neurological impacts of manganese exposure in these settings, its role in PD etiology is still controversial, with some suggesting a definitive association and others unable to equate exposure and disease (Santamaria et al. 2007). Similar to iron and copper, manganese is easily transported across biological membranes by the DMT1 as well as transferrin and transferrin receptor. In addition to these transporters, intracellular regulation of manganese is mediated by the SLC30A10 transporter which is critical to maintaining manganese homeostasis (DeWitt et al. 2013). Indeed, studies have found mutation in the SLC30A10 transporter that results in a significant reduction in expression causes an excess buildup of manganese in the basal ganglia, leading to parkinsonism (Quadri et al. 2012). Of note, while patients with this mutation demonstrate clinical manifestations of parkinsonism, this does not appear to be due to loss of the dopamine terminal in the striatum or damage to other aspects of dopaminergic function (Olanow et al. 1996; Shinotoh et al. 1995; Pal et al. 1999; Olanow 2004). This lack of dopamine terminal pathology may explain the lack of response to dopamine replacement with L-DOPA in these patients, suggesting the motor alterations associated with manganese accumulation are independent of dopaminergic losses.

In an effort to better define and delineate manganism, extensive characterization of the pathological and clinical signs has been undertaken. Using a variety of exper-

imental models, including human subjects that have been exposed to manganese and nonhuman primate imaging data, a clearer picture has begun to emerge. As discussed in previous sections, the pathological manifestations of idiopathic PD are well-established, showing extensive damage within the nigrostriatal dopamine system. While this pathology is often highlighted by severe losses in dopamine neurons in the SNpc and accompanied by reduction in dopamine terminals and dopamine content in the striatum, additional pathological features, including loss of VMAT2 and increased D2 receptor expression, provide further evidence for alterations in the integrity of the pre- and postsynaptic dopamine landscape. Subsequent to such dramatic dysfunction of the dopamine circuit, treatment with L-DOPA, which provides dopamine replacement, is key to restoring motor function to PD patients (Dickson 2012; Fahn 2003).

In stark contrast to these alterations, the nigrostriatal dopamine system is relatively spared in patients with elevated manganese exposure (Bouabid et al. 2015; Kwakye et al. 2015; Pal et al. 1999; Guilarte 2010, 2013; Perl and Olanow 2007). Indeed, for the most part, dopamine terminals appear to be intact, showing normal expression and function of DAT and VMAT2, unchanged striatal dopamine content, and a slight reduction in D2 receptors. Perhaps a more telling indictment of the effect manganese has on the dopamine system is the lack of response to L-DOPA, which, again, tends to be used to highlight clinical symptoms that emerge from alterations to the nigrostriatal dopamine system. In light of a paucity of overt dopaminergic pathology, dopamine neurotransmission within this circuit may still be dysfunctional (Guilarte and Gonzales 2015). Work from nonhuman primates exposed to manganese has demonstrated a significant reduction in dopamine release from the presynaptic terminals in the striatum (Guilarte et al. 2006). Although tissue content of dopamine may be unchanged, the ability of the dopamine neuron to release it and utilize it may be compromised through a yet-to-be discovered pathway. Indeed, while critical to the function of the dopamine circuit, dopamine transporters (DAT and VMAT2) comprise a very small sample of proteins involved in mediating normal dopamine neurotransmission. Thus, the alterations in this function could be occurring through a variety of intracellular cascades in the dopamine terminal that remain to be identified.

Further evidence for the delineation between PD and manganism resides in the presence and localization of alpha-synuclein or tau inclusions within the CNS. To date, few studies have evaluated alpha-synuclein expression following manganese exposure in human patients. However, studies using rodent and nonhuman primate models have identified an increase in the expression of alpha-synuclein oligomers in organotypic brain slices acutely treated with manganese. Moreover, alpha-synuclein inclusions were observed in neurons as well as glia in the frontal cortex of nonhuman primates treated with manganese (Cai et al. 2010; Verina et al. 2013; Xu et al. 2014). Interestingly, these findings seem to follow pathological signs routinely observed in MSA and that are used as to delineate MSA from PD. While the impact of these inclusions is still being formulated, current work has found under circumstances of elevated manganese exposure, manganese can facilitate the formation of alpha-synuclein aggregates, suggesting a possible mechanism of action for manganese in the neurotoxicity.

Emerging Metal Exposures and Neurotoxicological Concerns

Metal Nanoparticles and Parkinsonism

The manufacture and use of metal-containing nanoparticles has significantly increased over the last several decades and seemingly integrated into various aspects of our daily lives. Consumer products, such as clothing and cosmetics, structure materials used in building, as well as biomedical imaging and drug delivery have all found extensive use for nanoparticles. Nanoparticles vary in size from 1 to 100 nm and can be covered with metallic coatings, ranging from titanium (Ti), aluminum (Al), iron (Fe), manganese (Mn), copper, (Cu), and gold (Au), among others (Win-Shwe and Fujimaki 2011). Because of their small size, they are able to easily move across biological membranes and deposit in tissue. Indeed, this property makes them ideally suited for therapeutic approaches that target the CNS, which would not otherwise be able to access the brain via conventional delivery systems. While these capabilities have provided new and exciting opportunities, evaluation of the health effects and, more specifically, the neurotoxicological impact of these compounds have not kept pace (Feng et al. 2015; Heusinkveld et al. 2016; Oberdorster et al. 2009).

Indeed, a critical area of research related to nanoparticles is health effects arising from occupational exposures during the manufacturing process. Unfortunately, the use of nanoparticles is still relatively new, and the identification of a highly exposed cohort does not currently exist. However, our understanding of the potential neurotoxic effects of metal nanoparticles has been significantly enhanced through in vitro and in vivo laboratory models. Indeed, given their size, nanoparticles are quickly taken up by the olfactory bulb and transported to the CNS by way of the olfactory nerve, following inhalational exposure. Via this route, nanoparticles have been shown to deposit throughout the brain, including the frontal cortex, striatum, hippocampus, and cerebellum (Elder et al. 2006; Imam et al. 2015). Although inhalational exposure represents the major route of access to the brain, nanoparticles can also be ingested or absorbed across the skin, making their way into the general circulation, and then transported across the blood-brain barrier. Similar to inhalational exposure, ingested nanoparticles have been found to accumulate in specific brain regions. And aligning with our discussion of general metal transport, nanoparticles appear to use redundant mechanisms, including transferrin and the transferrin receptor to gain access to the brain tissue. Once in the brain, nanoparticles are able to access a variety of neural cells, including neurons, astrocytes, and microglia. These targets provide a platform for interesting discussions related to the possible neurotoxic mechanisms, including the generation of reactive oxygen species and neuroinflammation that may underlie nanoparticle interactions with the brain.

Our current understanding of the impact metal nanoparticles may have on the human nervous system has extensively focused on a select group of molecules that utilize metals in the form of iron oxide, manganese oxide, or titanium dioxide for their function. Of these, the neurotoxicity of iron oxide nanoparticles has been

established. These nanoparticles are most commonly found in biomedical applications related to brain imaging as well as drug delivery of therapeutic compounds. The iron oxide coating allows them to bind to transferrin and be easily trafficked across the blood-brain barrier via the transferrin receptor. Once inside a biological tissue, these polymers can lose their iron coating, leading to accumulation of iron in the brain. Following an inhalational exposure, these nanoparticles were found to extensively accumulate in the olfactory bulb, hippocampus, striatum, and cortex (Imam et al. 2015). Interestingly, while the striatum is a critical part of the basal ganglia and is enriched in dopaminergic projections from the SNpc, alteration to olfactory function is appreciated as one of the earliest clinical indicators of PD. Thus, these findings suggest that inhalation of metal nanoparticles can deposit in brain regions associated with PD pathology. Additional studies highlighted iron oxide-induced reduction in dopamine using both in vitro and in vivo models of exposure (Imam et al. 2015; Wu et al. 2013). While the mechanisms related to these deficits are not clear, the same groups also identified an increase in reactive oxygen species, in addition to elevations in alpha-synuclein. Another potential neurotoxic mechanism, by which metal nanoparticles could induce damage, is via the activation of neuroinflammation. Findings from a study using inhalational exposure to manganese oxide nanoparticles found the greatest deposition of manganese oxide in the olfactory bulbs and the striatum. In these same brain regions, investigators recorded elevations in markers or neuroinflammation, including glial fibrillary-associated protein and tumor necrosis factor-alpha (Elder et al. 2006). As in many neurodegenerative disorders, inflammation plays a critical role in the pathogenesis of PD. While it has proven difficult to define inflammation as a cause or consequence of dopaminergic neurodegeneration, it is clear that neuroinflammation can participate in both sides of this neurotoxicological equation, resulting in a cyclical, self-propagating cascade that leaves a persistent inflammatory mark on PD (McGeer and McGeer 2004).

E-Waste, Metal Exposure, and Parkinsonism

An emerging health risk that has extensive relevance to our discussion of metal-induced parkinsonism is the contribution of occupational exposure to metals through the recycling or reclamation of electronic waste (E-waste) (Breivik et al. 2014; Ogunseitan et al. 2009; Heacock et al. 2016). In general, E-waste can be simply defined as discarded electronic equipment, including computers, televisions, copiers, cell phones, circuit boards, and semiconductor chips, among other unwanted electronic products. A critical health concern arises when it is appreciated that these products contain a variety of heavy metals, including iron, manganese, copper, and cadmium that, as discussed, can enact severe neurological deficits (Luo et al. 2011; Tsydenova and Bengtsson 2011; Xue et al. 2012). Moreover, the neurological concerns are amplified when the conditions under which these metals are extracted may not endorse health of the workers that have direct inhalational and dermal

interactions with these materials. While E-waste disposal and recycling does occur domestically, a vast majority of these products are transported, globally, most often to Africa, Asia, and South America. In many of these settings, there is a lack of environmental health infrastructure in place to instill the appropriate policies and regulations necessary to ensure worker safety and reduce exposure to neurotoxic metals (LaDou and Lovegrove 2008; Leung et al. 2008; Zhang et al. 2012).

With these issues in mind, a critical gap exists in our understanding of the neurotoxicological issues that may arise in workers that are involved in E-waste. In this context, we are missing important exposure assessments of both the work environment and the workers themselves to gain a better understanding of the metals that are being exposed to, the concentrations they are being exposed at, and the potential body burdens of these compounds. While some data does exist that provides evidence that E-waste workers are being exposed to excess levels of metals, these data are minimal and do not provide a comprehensive picture of the exposure landscape (Asante et al. 2012; Julander et al. 2014). Further assessment that needs to evaluate the possible neurotoxicological effects of these exposures has also not been performed. While it is easy to present these shortcomings and resolutions in a simplistic manner, such approaches are far from straightforward, as several considerations need to be appreciated. For example, similar to other occupational settings, workers are not exposed to just one metal. Rather, their exposures most likely represent a mixture of metals. Thus, it becomes necessary to evaluate how these metals may interact to elicit neurological impacts and delineate the biological pathways that may underlie neurotoxicity. Related to this, a variety of other neurotoxic compounds are also part of E-waste, including several persistent organic pollutants, such as brominated flame retardants and dioxins, among others. Teasing out the relative contributions of these other compounds to neurotoxic endpoints will also be critical to elaborating our understanding of metal-mediated neurotoxicity in E-waste workers.

Conclusion

Although the contribution of metal exposure to parkinsonism has been appreciated for decades, our understanding of the various occupational settings of exposure as well as more specific pathological and clinical outcomes has allowed for an enriched discussion of these topics. Significant progress has been made in delineating the molecular targets and cascades of metal exposure that facilitate neurotoxicity in the basal ganglia. This data can now be integrated with epidemiological data being generated from emerging exposure scenarios, such as metal nanoparticles and metals in E-waste to elaborate the landscape of metal neurotoxicity and parkinsonism.

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