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The neurotoxicity of iron, copper and cobalt in Parkinson's disease through ROS-mediated mechanisms

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Abstract Parkinson's disease (PD) is the second most common neurodegenerative disease with gradual loss of dopaminergic neurons. Despite extensive research in the past decades, the etiology of PD remains elusive. Nevertheless, multiple lines of evidence suggest that oxidative stress is one of the common causes in the pathogenesis of PD. It has also been suggested that heavy metal-associated oxidative stress may be implicated in the etiology and pathogenesis of PD. Here we review the roles of redox metals, including iron, copper and cobalt, in PD. Iron is a highly reactive element and deregulation of iron homeostasis is accompanied by concomitant oxidation processes in PD. Copper is a key metal in cell division process, and it has been shown to have an important role in neurodegenerative diseases such as PD. Cobalt induces the generation of reactive oxygen species (ROS) and DNA damage in brain tissues.

Keywords Parkinson's disease · Reactive oxygen species · Iron · Copper · Cobalt

Abbreviations

AP-1	Activator protein-1
CNS	Central nervous system
CSF	Cerebrospinal fluid
$CoCl_2$	Cobalt chloride
DMT1	Divalent metal transporter 1
GLT-1	Glutamate transporter-1
GSH	Glutathione
HIF-1α	Hypoxia inducible factor 1α
IL-6	Interleukin-6
IREs	Iron-responsive elements
MAPK	Mitogen-activated protein kinase
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mTOR	Mechanistic target of rapamycin
NAC	*N*-acetyl-L-cysteine
NO	Nitric oxide
NorSAL	Norsalsolinol
NOS	Nitric oxide synthase
6-OHDA	6-Hydroxydopamine
PD	Parkinson's disease
ROS	Reactive oxygen species
SAL	Salsolinol
SNpc	Substantia nigra pars compacta

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SOD	Superoxide dismutase
THP	Tetrahydropapaveroline

Introduction

Parkinson's disease (PD) is an age-associated chronic disease. It is the second most prevalent neurodegenerative disorder afflicting 1–2 % of the people over the age of 65 (Dauer and Przedborski 2003). It is estimated that the population aged 65 years and older will be as high as 80 million by 2040 in the US alone (Boland and Stacy 2012). The economic burden of PD on national health care system continues to rise (Boland and stacy 2012). In clinic, PD is characterized by tremor, rigidity, slowness of movement and changes in posture. The main pathological hallmark of PD is the gradual loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the presence of aggregates of misfolded proteins (mainly α-synuclein), known as Lewy bodies (Anderson and Maes 2014; Dexter and Jenner 2013; Schapira et al. 2014; Lin et al. 2012). Although PD has been heavily researched in the past decades, the etiology of the PD is poorly understood. Many genetic studies have reported that some gene mutations, including gene duplication/triplication, are highly correlated with PD (Moore et al. 2005; Hu and Tong 2010). However, the majority of PD cases identified so far are sporadic with no clear genetic cause. A casual link between aging, genetic factors, life styles and environmental exposure may exist for PD cases (Gao and Hong 2011). In recent years, evidence has accumulated that chronic exposure to heavy metals and its associated oxidative stress are implicated in PD (Gandhi and Wood 2005; Arodin et al. 2014).

Literally, oxidative stress is defined as a redox imbalance with a surplus of oxidants or a deficit in antioxidants (Sies and Cadenas 1985; Shulman et al. 2011). The brain which consists of a large number of neurons is prone to oxidative damage as it is metabolically active and consumes about 20 % of total body oxygen in the resting state (Ciccone et al. 2013; Herculano-Houzel 2011). PD, as a brain disease, is inevitably affected by the oxidative stress. The aim of this article is to briefly review a positive association of oxidative stress with PD pathogenesis and further discuss the transition metals-induced oxidative stress in PD.

Oxidative stress and PD

When the levels of reactive oxygen species (ROS) surpass the antioxidant capacity of a cell, it poses a stress condition on the cells. This oxidative stress condition causes irreversible damage to the cells and can ultimately lead to cell death. ROS can be produced in excess quantities such as superoxide free radical, hydrogen peroxide (H_2O_2), singlet oxygen, nitric oxide (NO), and peroxynitrite (Chong et al. 2012; Maiese et al. 2010, 2011). Overproduction of ROS can subsequently result in the loss of DNA integrity, mitochondrial dysfunction, lipid peroxidation and misfolding of proteins that could damage neuronal cells (Jayaram et al. 2011; Yang et al. 2011a). Several cellular antioxidant systems including catalase, superoxide dismutase (SOD), glutathione peroxidase and vitamin C, D, E and K can reduce toxic ROS to non-toxic levels (Muley et al. 2012; Sun et al. 2012; Suzen et al. 2012). It is noted that the brain is more vulnerable to deleterious ROS and oxidative damage when compared with other organs. In the brain, it consumes about 20 % of the oxygen supply of the body and a significant portion of oxygen is converted to ROS resulting from high oxygen metabolism of neurons (Marlatt et al. 2004; Matés et al. 2009; Johnson et al. 2012). Moreover, the brain has only a relatively modest antioxidant system and low levels of free radical-scavenging enzymes to cope with free ROS (Barnham et al. 2004; Mytilineou et al. 2002; Roberts et al. 2010). Furthermore, the sensitivity of neurons to oxidative damage, which accumulates in aging neurons, might also be due to their postmitotic nature (Crabtree and Zhang 2012). Under oxidative stress, high concentrations of readily oxidizable polyunsaturated fatty acids in the brain are peculiarly prone to lipid peroxidation and the generation of toxic radical species. Thus, oxidative stress may be a primary component that leads to the onset and pathogenesis of neurodegenerative disorders.

PD, as a progressive neurodegenerative movement disorder, is characterized by a selective loss of nigrostriatal dopaminergic neurons (Dawson and Dawson 2003). Accumulating experimental evidence

suggests that oxidative stress is involved in dopaminergic neuronal apoptosis in PD (Jenner and Olanow 2006; Zeng et al. 2014; Zhang et al. 2015). For example, H_2O_2, a major oxidant generated when oxidative stress occurs, could induce apoptosis of neuronal cells (Chen et al. 2010a). Rotenone, as a neurotoxin in PD models, could induce the overproduction of H_2O_2, leading to the apoptosis of neuronal cells (Zhou et al. 2015; Ojha et al. 2016). In addition, implication of oxidative stress in PD is further supported by postmortem analysis of the brains from patients with PD. Such evidence for oxidative stress in PD brains includes a dramatic depletion of the antioxidant glutathione (GSH), a reduction in mitochondrial complex I activity, DNA oxidation, augmented SOD activity and elevated free iron levels (Blum et al. 2001; Mythri et al. 2011). Moreover, some bio-markers related to oxidative stress are increased in the cerebrospinal fluid (CSF) (such as malondialdehyde content and superoxide radical production) and blood of patients with PD (Vinish et al. 2011; Buhmann et al. 2004).

It is believed that the generation of deleterious ROS and oxidative damage play a pivotal role in dopaminergic neuronal cell death (Zemlyak et al. 2006; Hu et al. 2011; Chong et al. 2014). As one of important sources of ROS, transition metals, such as copper and iron, have been found to be accumulated in brains of patients with PD (Andersen 2004) (Fig. 1). These findings suggest that transition metals might be involved in PD pathogenesis via ROS-generating pathways. Here we will further discuss ROS-mediated mechanisms underlying the neurotoxicity of iron, copper and cobalt in PD.

Metal ions and PD

Many metal ions are essential components of a wide variety of biological processes of living systems. In the nervous system, metals are involved in several important cellular functions and physiological activities. For example, iron is essential for DNA synthesis, neurotransmission, myelination, oxygen activation, mitochondrial electron transport and metabolism (Halliwell 2006; Benarroch 2009; Crichton et al. 2011). Besides iron, copper is required for biosynthesis of neurotransmitters and mitochondrial respiration (Schlief et al. 2006; Telianidis et al. 2013). In addition, cobalt is a critical component of Vitamin B12 which is oxygen-sensitive and important for the normal functions of the nervous system. Three classes of cobalt/B12-dependent enzymes, including isomerases, methyltransferases and reductive dehalogenases, participate in the reactions essential to DNA synthesis, fatty acid synthesis and energy production (Banerjee and Ragsdale 2003).

Although transition metals are important for life, well-documented evidence suggests that environmental and occupational exposure to toxic metals or metal-containing compounds leads to some serious health conditions, such as neurodegenerative diseases (Stohs and Bagchi 1995). Elevated levels of several metals (mainly iron and copper) have been found to be associated with the subjects with neurological diseases (Migliore and Coppedè 2009). In PD, high levels of iron have been observed in the degenerative dopaminergic neurons (Zhu et al. 2007), and lewy bodies contain reactive iron together with aggregated proteins such as α-synuclein (Castellani et al. 2000). The role of copper in the pathogenesis of PD is thought to be associated with its ability to form a complex with α-synuclein and promote α-synuclein into neurotoxic aggregates (Davies et al. 2011; Brown 2013). In addition, high levels of copper in PD have been observed in the cerebrospinal fluid (Hozumi et al. 2011), blood serum (Ahmed and Santosh 2010) and brain (Larner et al. 2013). Although there is no enough evidence to support the role of cobalt in PD, it is well established that cobalt-mediated free radical generation contributes to neuronal cell toxicity. Furthermore, previous studies suggested that cobalt ions could not only induce DNA damage and interfere with DNA repair, but also induce DNA–protein crosslinking and sister chromatid exchange (Hengstler et al. 2003). Importantly, low levels of cobalt can directly induce α-synuclein fibril formation (Uversky et al. 2001). Recent in vitro studies have shown that iron or copper interacting with mutant α-synuclein seems to aggravate the neurotoxicity elicited by α-synuclein (Chew et al. 2011; Wang et al. 2010). Here, it is worth noting that copper is a special case because, apart from the previously mentioned mechanism of neurotoxicity, it is also a co-factor of antioxidant enzymes such as ceruloplasmin. This duality makes copper interesting for

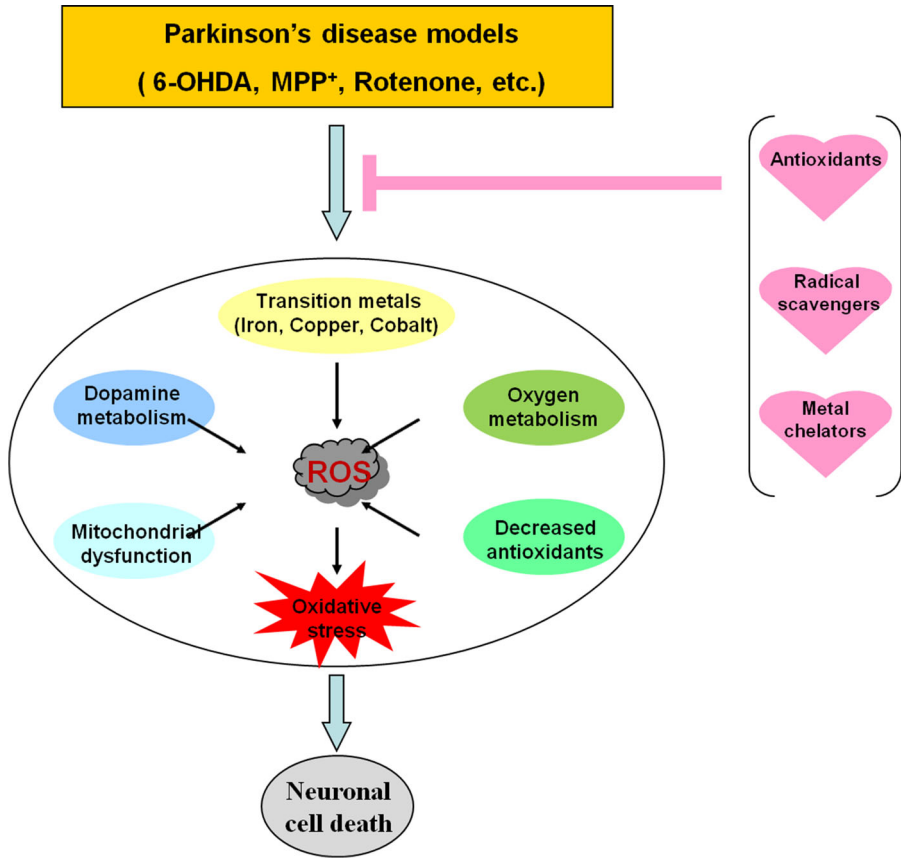

Fig. 1 Schematic illustration of main sources of ROS which ultimately cause neuronal cell death in PD models. Agents for potential therapeutic interventions, such as antioxidants, radical scavengers and metal chelators, are suggested to attenuate oxidative stress and prevent progressive loss of dopaminergic neurons in PD

the study of PD. In the following sections, we will mainly focus on three transition metals (i.e. iron, copper and cobalt) which are more relevant to PD.

Copper

Copper is an essential metal with an average concentration of 1.4–2.1 mg/kg in healthy individuals and it is readily absorbed from the diet through the small intestine (~2 mg/day). Under physiological conditions, copper can catalyze ROS formation via Fenton-like reaction (Wang et al. 2012). Disruptions in copper homeostasis are responsible for the neurological symptoms, such as PD (Tisato et al. 2010; Asthana et al. 2014). Some studies have indicated that long-term exposure (>20 years) to copper increases the risk of PD (Gorell et al. 1999). Other environmentally based studies within urban populations have also shown that the incidence of PD is greater in those areas with important emissions of copper or manganese (Willis et al. 2010). It has been reported that the copper level in PD is increased in the cerebrospinal fluid (Hozumi et al. 2011; Pall et al. 1987), blood serum (Ahmed and Santosh 2010) and brain (Larner et al. 2013). In addition, in the animal model of PD using 6-hydroxydopamine (6-OHDA), increased level of copper was observed in all regions along the dopaminergic pathways (Tarohda et al. 2005). Thus, copper excess may be an important factor for the onset or pathogenesis of PD.

The intensive production of ROS are widely seen in PD (Nikam et al. 2009; Reddy and Reddy 2011; Chakrabarti et al. 2011; Jomova et al. 2010), as indicated by an increase in the contents of lipid peroxidation in blood samples of patients with PD (Serra et al. 2009). Copper ions are very likely involved in this process (Greenough et al. 2013).

For example, in the rats exposed to copper in the drinking water for four weeks, the levels of the lipid oxidation marker malondialdehyde are increased, and the SOD activity is diminished in the brain (Ozcelik and Uzun 2009). Another study reported that copper sulfate directly injected into the substantia nigra of rodents could elicit dopaminergic cell toxicity such as decreased dopamine, increased oxidative stress and apoptosis (Yu et al. 2008). In addition, similarities between copper treatment and treatment with other commonly used oxidants have been found in human brain cells (Merker et al. 2005). Increased extracellular copper levels contribute to neuronal cell death by increasing the production of deleterious ROS (Huang et al. 2015). Particularly, copper affects the secretion of molecules involved in the protection of neurons against oxidative stress, such as cyclophilin A, or molecules capable of shifting neural cells toward a proinflammatory state, such as IL-1 (Spisni et al. 2009). It has been reported that treatment of PC12 cells (a common neural cell model) with dopamine-derived salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, SAL) causes decreased cell viability, which is exacerbated by copper (Kim et al. 2001). Moreover, cells exposed to both SAL and copper exhibit high levels of intracellular ROS. By contrast, copper chelator bathocuproinedisulfonic acid and the antioxidants *N*-acetyl-L-cysteine (NAC) or GSH ameliorate cytotoxicity induced by SAL and copper. All these findings suggest that copper facilitates the redox cycling of SAL (Kim et al. 2001). Besides SAL, another dopamine metabolite, norsalsolinol (NorSAL) reduces cell viability and induces apoptosis via cytochrome c release and caspase-3 activation in SH-SY5Y neuroblastoma cells (Kobayashi et al. 2009). Cytochrome c release, caspase-3 activation and apoptosis induction are all inhibited by the antioxidant NAC, suggesting that ROS contributes to the apoptosis induced by NorSAL. Treatment with NorSAL also increased levels of oxidative damage to DNA, a stimulus for apoptosis, in SH-SY5Y cells. It is worthy of note that NorSAL induced DNA damage is enhanced by Cu (II). Bathocuproine and catalase, as Cu (I) chelators, inhibit the DNA damage, implying that ROS generated from the reaction of H_2O_2 with Cu (I) mediates the DNA damage by NorSAL. These findings suggest that NorSAL- and copper-generated ROS induces oxidative DNA damage, which leads to caspase-dependent apoptosis in neuronal cells (Kobayashi et al. 2009). In other experiments, tetrahydropapaveroline (THP), a dopamine-derived tetrahydroisoquinoline alkaloid, has been reported to inhibit mitochondrial respiration and is considered to contribute to neurodegeneration implicated in PD. Because THP bears two catechol moieties, the compound may readily undergo redox cycling to produce ROS as well as toxic quinoids. Of particular significance, copper can also promote THP-mediated oxidative DNA damage (Soh et al. 2003). On the other hand, ROS may also enhance the copper accumulation in the brain. For instance, 6-OHDA, a dopaminergic neuron-specific ROS generator, induces an increase of copper in the brain regions related to dopaminergic pathways in a rat model of PD (Tarohda et al. 2005). Taken together, the neurotoxicity of copper might be through a ROS-mediated mechanism. It is yet to be known which one, ROS or copper, comes first to initiate dopaminergic neuron degeneration. In our laboratory, we have also found that copper overload induced apoptosis in SH-SY5Y cells, where AMPK and ROS may be involved in this process (unpublished data). The precise mechanisms in this process need to be further explored. Although copper excess contributes to neurodegeneration, deficiencies in copper absorption could also have a number of detrimental effects. For example, insufficient copper uptake during development interferes with the activity of copper-containing enzymes and results in dysregulation of protein crosslinking in the extracellular matrix and altered cell signaling (Uriu-Adams et al. 2010). The toxic effects of low level of copper may be related to reduced SOD activity. Therefore, the homeostasis of copper in body is very important.

It is worthy to note that the role of copper in the pathogenesis of PD is also thought to be associated with its ability to form a complex with α-synuclein, which is a protein of unknown function and enriched at the presynaptic terminals of many neurons. α-synuclein aggregation is considered as a key event in PD pathogenesis (Olanow and Brundin 2013). It has been reported that copper is able to facilitate the formation of aggregated α-synuclein (Ahmad et al. 2012; Wright et al. 2009). Wang et al. (2010) used a cellular model of α-synuclein aggregation to investigate the association between metals and aggregate formation. Their findings suggest that copper plays an important role in α-synuclein aggregation and reduction in cellular copper results in a significant decrease in aggregate formation. They also showed that reduction in copper results in a change in localization of α-synuclein, which is more intensely localized to the plasma membrane with low copper, and this change is reversed when copper is restored to the cells (Wang et al. 2010). Furthermore, mutations of the copper

binding domains in α-synuclein alter the response of the protein to copper, whereas increased expression of wild-type α-synuclein increases cell sensitivity to the toxicity of copper (Wang et al. 2010). These results suggest that the potential pathological role of α-synuclein aggregates is dependent upon the copper binding capacity of the protein. This notion is supported by a recent study suggesting that overexpression of α-synuclein at non-toxic levels increases dopaminergic cell death induced by copper exposure via modulation of protein degradation pathways (Anandhan et al. 2015).

In addition, there is another protein to note. Ceruloplasmin is a multicopper—containing glycoprotein that is mainly bio-synthesized in the liver (Healy and Tipton 2007). Copper is a component of ceruloplasmin which contains up to 95 % of circulating copper (Larner et al. 2013). Ceruloplasmin acts as an iron oxidase, copper transporter, as well as many other functions (Vashchenko and MacGillivray 2013). The modification of ceruloplasmin with hydrogen peroxide can release copper and mediate α-synuclein aggregation (Gaggelli et al. 2006). Other than copper, ceruloplasmin may also modulate iron levels in the nervous systems. In ceruloplasmin-knockout mice, iron is deposited in the cerebellum and brain stem, leading to dopaminergic neuron loss and compromised motor coordination (Patel et al. 2002). Ceruloplasmin remains an attractive target for new therapeutic method in PD because of its antioxidant properties and its role as an iron regulator in the brain.

The current therapeutic strategies, such as supplying a dopamine precursor (L-DOPA), dopamine agonists (e.g., pramipexole, bromocriptine) and antioxidants, only provide symptomatic relief (Hung et al. 2012). As mentioned above, the role of copper in PD is complicated. Thus, there is still an imperative need to develop an appropriate copper ion chelator for moving from symptom-alleviating to disease-modifying therapies.

Iron

Iron, similar to copper,is one of the first-row transition metals in the periodic table. In the central nervous system (CNS), iron is essential for a variety of vital biochemical and metabolic functions, including neurotransmission, myelination, oxygen activation and mitochondrial electron transport. Although iron is very important for physiological processes in several organs including the brain, a wide body of evidence showing the neurotoxic effects of iron has been reported (Castellanos et al. 2002; Cheah et al. 2006; Double et al. 2003), especially on tyrosine hydroxylase-positive neurons (Double et al. 2003).

It has been shown that iron concentrations are significantly elevated in melanized dopaminergic neurons of patients with PD (Gerlach et al. 2006; Götz et al. 2004; Riederer et al. 1989; Youdim and Riederer 1993; Shoham and Youdim 2002; Hirsch et al. 1991), which has also been confirmed by magnetic resonance imaging (MRI) and ultrasound studies (Gorell et al. 1995; Berg et al. 1999). More specifically, neuromelanin granules with iron overload were observed around the neurons in SN of patients with PD (Jellinger et al. 1992). In animal models, an increase in iron levels was also observed in SN of 6-OHDA, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Gerlach et al. 2000; Youdim and Riederer 2004), lactacystin (Zhu et al. 2010) and rotenone (Mastroberardino et al. 2009) models of PD. PD is an age-associated disease, aging can regulate iron neurotoxicity. For example, adult mice (12–24 months old) fed with iron during the neonatal period show a decrease in striatal DA content, while their young counterparts (2 months old) with the same treatment have unchanged DA levels (Barlow et al. 2007; Kaur et al. 2007). Similar to PD, iron dysregulation also occurs in Huntington's disease (HD) (Dexter et al. 1991; Rosas et al. 2012). However, the locus of iron accumulation in PD seems to be different from that in HD (Bartzokis et al. 1999). PD is characterized by iron accumulation in the SN, which has not been observed in HD. In HD, increased iron levels have been primarily observed in the basal ganglia (Bartzokis et al. 1999). Iron accumulation in HD is presumably a secondary effect of the disease (Bartzokis and Tishler 2000).

Once iron is accumulated in PD, it could promote neuronal death through oxidative stress. Previous studies indicated that iron participates in the Fenton chemistry to produce deleterious ROS (Koppenol 2001; Lan and Jiang 1997). The formation of ROS, combined with the depletion of endogenous antioxidants, particularly GSH, can lead to oxidative stress in PD (Lan and Jiang 1997; Han et al. 1999; Bharath et al. 2002; Youdim et al. 1990; Aguirre et al. 2007). Indeed, there is a drastic decrease of GSH in SN of PD brains (Riederer et al. 1989; Bharath et al. 2002; Jenner 1991, 1998; Aguirre et al. 2007), which renders dopaminergic neurons more vulnerable to deleterious

ROS. Moreover, iron mediates the decomposition of lipid peroxides to produce highly cytotoxic free radicals, which causes damage to DNA, lipids, or proteins and ultimately leads to neuronal cell death in PD models (Youdim and Riederer 2004). Further, iron-induced oxidative stress increases the vulnerability of PC12 cells to rotenone-induced toxicity, suggesting that oxidative stress is directly involved in iron neurotoxicity (de Groot and Westerink 2014).

In addition, the role of iron in PD is also associated with its ability to link oxidative damage and α-synuclein accumulation. A number of studies indicated that iron accumulates in Lewy bodies (Napolitano et al. 2002) and iron-induced lipid peroxidation promotes α-synuclein aggregation (Götz et al. 2004). In vitro studies also demonstrated that iron induces the intracellular oxidation and further aggregation of α-synuclein, as well as mitochondrial clumping, in dopaminergic neuronal cells (Sangchot et al. 2002; Li et al. 2011, 2010; He et al. 2011). Further molecular mechanistic studies reported that iron might regulate α-synuclein aggregation through the IRE/IRP system in SK-N-SH neuroblastoma cells (Li et al. 2011), and oxidative stress affects α-synuclein aggregation via oxidation of iron to the ferric state (Levin et al. 2011). A recent research reported that synergistic α-synuclein/iron cytotoxicity induces α-synuclein aggregation and neurotoxicity by inhibiting Nrf2/HO-1 in SK-N-SH neuroblastoma cells. Inhibition of Nrf2/HO-1 leads to more α-synuclein aggregation and enhanced toxicity induced by iron, creating a vicious cycle of iron accumulation and α-synuclein aggregation in PD (He et al. 2013). In addition, sodium nitroprusside, a water-soluble iron nitrosyl complex, induces SH-SY5Y apoptosis through ROS-p53 signaling pathway (Cardaci et al. 2008). Chelation of lysosomal iron protects dopaminergic SH-SY5Y cells from H_2O_2 toxicity by inhibiting autophagy and Akt dephosphorylation (Castino et al. 2011). It is known that autosomal dominant PD is partially related to mutations in α-synuclein that enhance the protein aggregation (Gupta et al. 2008). Therefore, those individuals with mutations in α-synuclein could be more susceptible to iron overload. For example, the expression of a mutant form of α-synuclein enhances the susceptibility of neuroblastoma cells to iron exposure (Martin et al. 2003). Perfeito et al. (2014) reported that stimuli ($FeSO_4$ or rotenone) promoting ROS formation and mitochondrial alterations highly correlate with mutant α-synclein phosphorylation at Ser129, which may precede cell degeneration in PD. Under basal conditions, prolonged expression of A53T mutant α-synuclein alters mitochondrial morphology, increases superoxide formation and phosphorylation at Ser129. Exposure to $FeSO_4$ or rotenone increases intracellular ROS levels along with α-synuclein Ser129 phosphorylation and mitochondrial depolarization. Most of these changes were largely evident in A53T mutant α-synuclein expressing cells (Perfeito et al. 2014). Moreover, SH-SY5Y cells stably expressing divalent metal transporter 1 (DMT1) alone or together with mutant α-synuclein enhance iron uptake, which results in oxidative stress and neuronal cell death (Chew et al. 2011; Cardaci et al. 2008; Castino et al. 2011). It has been suggested that human α-synuclein may act as a cellular ferrireductase, responsible for reducing iron(III) to bioavailable iron(II) (Davies et al. 2011). It is currently known that iron interacts with α-synuclein, at least at two biological levels: the first involves the translation of the protein via iron-responsive elements (IREs) that exist in the 5′-UTR of the α-synuclein mRNA (Friedlich et al. 2007). The second consists of a direct binding of iron to the protein itself, leading to its abnormal folding and aggregate formation. Although the binding sites for iron in α-synuclein are not clear yet, previous studies demonstrated a preferential binding of iron(II) in the C-terminal region of α-synuclein (Binolfi et al. 2006) and iron(III)-mediated aggregation of α-synuclein (Kostka et al. 2008). Furthermore, neuronal cell death caused by potent inhibitors (MPTP, 6-OHDA) of complex I of mitochondrial electron transport chain is prevented by the chelation of iron (Youdim et al. 2004; Kaur et al. 2003; Shachar et al. 2004; Youdim and Buccafusco 2005; Zheng et al. 2010). A recent study in mesencephalic neurons showed that low concentrations (0.25–0.5 μM) of MPP^+, an active metabolite of MPTP, induces neuritic tree collapse without significant loss of cell viability (Gomez et al. 2011). This MPP^+-mediated effect can be prevented by decreasing iron supply or by the addition of antioxidants. Therefore, it seems plausible that increased intracellular iron and ROS are involved in the early stage of dopaminergic neuron dysfunction, prior to cell death. At a later stage, a vicious cycle of iron accumulation, complex I dysfunction and increase in ROS levels may result in irreversible oxidative damage and neuronal cell death.

Since iron accumulation in the affected areas in PD is an important event, metal depletion may be a

rational therapeutic method for neurodegenerative diseases. Some iron chelators have been successfully employed in pre-clinical studies of PD. For example, the natural prototype iron chelator/radical scavenger desferrioxamine (Keberle 1964) and the iron-chelating drugs deferiprone and deferasirox were found to be protective against dopaminergic neurodegeneration induced by iron, 6-OHDA, or MPTP (Ben-Shachar et al. 1992, 1991; Molina-Holgado et al. 2008; Dexter et al. 2011). The antibiotic metal chelator clioquinol has been shown to inhibit MPTP-induced neurotoxicity in mice (Kaur et al. 2003). These studies indicate that iron chelation may be an effective therapeutic method for PD. However, the pharmacological manipulation of intracellular iron levels has the potential to cause undesirable side effect, such as the inhibition of iron-containing enzymes, including metalloenzymes, lipoxygenase and ribonucleotide reductase (Hider 1995). It is suggested that other iron chelators must be carefully designed to prevent toxicity and side effects.

Cobalt

Cobalt is an element that exists naturally throughout our environment (Lison et al. 2001). Vitamin B12 contains 4 % cobalt and therefore cobalt is essential to many physiological processes (Kim et al. 2008). Total body content of cobalt is about 1.1–1.5 mg in an adult male. Cobalt chloride ($CoCl_2$) is a well-known hypoxia mimetic agent. These $CoCl_2$-elicited biochemical changes include the production of ROS, a loss of mitochondrial membrane potential, activation of hypoxia inducible factor 1α (HIF-1α) and the expression of a number of genes, such as erythropoietin, vascular endothelial growth factor and endothelin-2/vasoactive intestinal contractor (one of the hypoxia-related factors) (Chandel et al. 1998; Guillemin and Krasnow 1997; Yang et al. 2004; Zou et al. 2002; Kotake-Nara and Saida 2007; Chen et al. 2009, 2010b; Yang et al. 2011b).

Although the role of cobalt in PD pathogenesis has not been well documented, a number of reports suggested that $CoCl_2$, as a hypoxia mimetic, can induce oxidative stress in cultured neuronal cells. It is reported that one of the mechanisms underlying $CoCl_2$-induced neuronal damage is associated with the production of ROS (Zou et al. 2002; Chen et al. 2009; Jung et al. 2008). $CoCl_2$ could function as an oxidative stress-inducing factor since Co(II) can react with H_2O_2 via Fenton-like reaction to produce ROS (Wang et al. 1993). Elevated ROS is capable of attacking nucleic acids, proteins and membrane phospholipids, leading to neuronal cell death (Wang et al. 2000; Chen et al. 2008). In our previous studies, we have showed that $CoCl_2$-induced ROS overproduction and mitogen-activated protein kinase (MAPK) activation are inhibited by a free radical scavenger NAC in PC12 cells, indicating that $CoCl_2$-mediated MAPK activation is dependent on ROS production (Lan et al. 2011). Consistent with our study, Zou et al. (2002) have reported that $CoCl_2$-activated caspase-3 and p38 MAPK are involved in $CoCl_2$-induced apoptosis of PC12 cells. Moreover, we have also demonstrated that the signal pathway of ROS-ERK/12 is involved in the down-regulation of glutamate transporter-1 (GLT-1) protein expression in $CoCl_2$-treated PC12 cells (Xiao et al. 2012). In addition, a significant increase in the DNA-binding activity of activator protein-1 (AP-1) upon $CoCl_2$ treatment has also been observed. This increase is blocked by antioxidants, implying that $CoCl_2$-induced apoptosis is accompanied by ROS-activated AP-1 (Zou et al. 2001).

More recently, it has been reported that $CoCl_2$-mediated repression of mechanistic target of rapamycin (mTOR) signaling could be significantly alleviated by an antioxidant in PC12 cells, which suggests that $CoCl_2$ suppresses mTOR signaling via ROS (Zhong et al. 2014). Aside from mTOR signaling, endothelin system which is important for vascular homeostasis could also be modulated by $CoCl_2$. The expression of endothelin-2 is increased by $CoCl_2$ and conversely $CoCl_2$ decreases the expression of the endothelin-1 in PC12 cells, which could be inhibited by the antioxidant NAC (Kotake-Nara and Saida 2006; Kotake-Nara et al. 2005). Meanwhile, the expression interleukin-6 (IL-6), which has both pro- and anti-inflammatory properties, is up-regulated upon the differentiation of PC12 cells by $CoCl_2$ (Kotake-Nara and Saida 2006). These results indicate that $CoCl_2$ modulates the expression of endothelin-2 and endothelin-1 through ROS and $CoCl_2$-mediated oxidative stress may be associated with inflammation. $CoCl_2$-induced inflammatory response in PC12 cells, including an increase in nitric oxide (NO) production and IL-6 secretion, was also observed in our previous study (Lan et al. 2013).

The inflammatory response in PC12 cells upon $CoCl_2$ treatment could be blocked by NAC, suggesting that $CoCl_2$-induced inflammatory response correlates with oxidative stress in PC12 cells (Zhong et al. 2014; Kotake-Nara et al. 2005; Kotake-Nara and Saida 2006; Lan et al. 2013). It is well known that astrocytes, as the major glial population, play an important role in the central nervous system (CNS). It has been reported that $CoCl_2$ treatment induces intracellular ROS generation and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene expression, but inhibites TSP-1 (Thrombospondin-1) mRNA expression in astrocytes (Chen et al. 2011). $CoCl_2$-induced down-regulation of TSP-1 mRNA was blocked by the addition of the potent antioxidant NAC, suggesting that ROS is involved in $CoCl_2$-mediated effects in astrocytes. Taken together, these studies suggest that $CoCl_2$ modulates several vital signaling pathways mainly through ROS and more precise molecular mechanism of $CoCl_2$-induced oxidative stress needs to be further investigated. In view of the role of cobalt in the neuronal cells, as well as cobalt-mediated formation of α-synuclein fibril (Uversky et al. 2001), we speculate that cobalt may be potentially implicated in PD.

Conclusions

Although molecular mechanism underlying the etiology and pathogenesis of PD are not fully understood, transition metals and oxidative stress have been well documented to be implicated in PD-related neuronal lesions. In this review, we briefly discuss the association of oxidative stress with PD and elaborate on the mechanisms underlying the neurotoxicity of transition metals. Transition metal-mediated neuronal cell death generally involves ROS production and protein aggregation. However, ROS may also facilitate metal accumulation when neurons are under oxidative stress. Which one, metals or ROS, comes first to initiate neurodegeneration has not been answered yet. It is plausible that either transition metal overload or an imbalance in ROS metabolism alone can trigger neuronal cell death and mutually reinforce the neurotoxic effects. On the other hand, although the antioxidants coping with oxidative stress have been successfully used to inhibit the cytotoxicity of ROS in cellular or animal models of PD, no antioxidants have been shown to be effective in clinic. As ROS per se is important for cellular functions, a delicate control of ROS homeostasis is critical to combat cytotoxic ROS. Considering the complexity of physiological conditions, we envisage that targeted delivery of antioxidants to the cells with metal overload or under oxidative stress can provide spatial and temporal control of intracellular ROS levels. The development of dopaminergic neuron-specific targeted drug delivery is urgently needed for the translational research of PD.

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Compliance with ethical standard

Conflict of interest The authors declare that they have no competing interests.

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