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Nexus between mitochondrial function, iron, copper and glutathione in Parkinson's disease

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ABSTRACT

Parkinson's disease is neuropathologically characterised by loss of catecholamine neurons in vulnerable brain regions including substantia nigra pars compacta and locus coeruleus. This review discusses how the susceptibility of these regions is defined by their shared biochemical characteristics that differentiate them from other neurons. Parkinson's disease is biochemically characterised by mitochondrial dysfunction, accumulation of iron, diminished copper content and depleted glutathione levels in these regions. This review also discusses this neuropathology, and provides evidence for how these pathological features are mechanistically linked to each other. This leads to the conclusion that disruption of mitochondrial function, or iron, copper or glutathione metabolism in isolation provokes the pathological impairment of them all. This creates a vicious cycle that drives pathology leading to mitochondrial failure and neuronal cell death in vulnerable brain regions.

1. Progression of Parkinson's disease pathology

Parkinson's disease (PD) is neuropathologically characterised by the death of specific neuronal populations and the appearance of α-synuclein-containing Lewy bodies. These two pathological hallmarks exhibit regional differences in their rate of progression. Lewy body pathology occurs before overt neuronal loss, and appears first in olfactory nucleus and dorsal motor nucleus of the vagus, progressing to locus coeruleus and then substantia nigra and many other brain stem nuclei and eventually cortex (Braak and Del Tredici, 2017; Braak et al., 2003). Cell loss is observed most profoundly from the dopaminergic substantia nigra pars compacta, and also neuromelanin-containing locus coeruleus, with cell death also seen in the dorsal motor nucleus of the vagus, and peripheral nervous system noradrenergic neurons innervating the heart and skin, with more moderate neuronal death observed in the ventral tegmental area and other brain stem nuclei at later stages (Alberico et al., 2015; Halliday et al., 2005; Surmeier et al., 2017a; Surmeier and Sulzer, 2013). Hence there is a disconnect between α-synuclein pathology and neuronal loss. These neuropathological features give rise to motor symptoms including bradykinesia, muscular rigidity and resting tremor, and non-motor features including olfactory symptoms, cognitive impairment, psychiatric symptoms and autonomic dysfunction.

Loss of dopaminergic neurons in the substantia nigra pars compacta is the most universal feature of PD, and is responsible for generating the overt motor symptoms associated with parkinsonism. However, substantia nigra pars compacta dopaminergic neuron loss is also evident in other conditions including multiple system atrophy and progressive supranuclear palsy (Dickson, 2012). Neuronal loss from the locus coeruleus generally occurs later and is not quite as profound as degeneration in the substantia nigra pars compacta, and is also observed in Alzheimer's disease and Down syndrome (German et al., 1992; Kelly et al., 2017).

2. Mitochondrial impairment in Parkinson's disease

Mitochondrial impairment occurs early in PD pathogenesis (Lin and Beal, 2006). There is abundant evidence for impaired activity of mitochondrial complex I in PD post-mortem tissue, profoundly from SN, but also other brain regions including frontal cortex and the periphery (Bindoff et al., 1989; Mann et al., 1994; Mizuno et al., 1989; Parker et al., 1989, 2008; Schapira et al., 1990; Schapira et al., 1989). Furthermore, mutations in genes associated with familial PD are involved in mitochondrial dysfunction, including α-synuclein, PINK1, Parkin, DJ-1 and LRRK2 (Ariga et al., 2013; Esteves et al.,

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2014; Nakamura, 2013; Truban et al., 2017).

Further evidence for mitochondrial impairment in the pathogenesis of PD comes from the selective sensitivity of the substantia nigra and locus coeruleus to mitochondrial toxins, including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine, rotenone and paraquat (Giannoccaro et al., 2017; Masilamoni et al., 2017). All are complex I inhibitors and administration causes neuronal death and gives rise to parkinsonism in animal models. In humans, MPTP administration causes parkinsonism (Langston et al., 1983), while environmental exposure to mitochondrial toxins increases the likelihood of developing PD (Tanner et al., 2011).

The sensitivity of the substantia nigra to MPTP may be due in part to the unique metabolism of the toxin in this region. MPTP is metabolised to 1-methyl-4-phenylpyridinium (MPP^+) within astrocytes by monoamine oxidase B, the latter required for dopamine metabolism. MPP^+ is the toxic metabolite that potently inhibits complex I, and traffics from astrocytes into neurons via dopamine transporters. Inhibition of astrocytic dopamine transporters blocks MPP^+ export from astrocytes and prevents MPTP toxicity in mice (Cui et al., 2009). Thus neurons are selectively vulnerable to MPP^+ over glia, and substantia nigra dopaminergic neurons are particularly sensitive to MPTP due to the presence of dopamine transporters, facilitating the uptake of the toxic metabolite MPP^+.

The presence of dopamine concurrent with elevated iron is often postulated to contribute to the sensitivity of substantia nigra neurons. Dopamine is metabolised by monoamine oxidases in a reaction generating hydrogen peroxide. Dopamine can also be oxidised (eventually) to neuromelanin, giving the characteristic black colour to the tissue (substantia nigra is Latin for black substance). In the presence of iron, multiple toxic species can be generated from dopamine and its metabolites, evidence for which has variously been shown in vitro and in vivo (Hare and Double, 2016; Zucca et al., 2015). However, this is unlikely to be the sole reason for neuronal degeneration in PD as other vulnerable regions such as the locus coeruleus do not contain high iron levels, and the frontline treatment for PD, L-DOPA, which is metabolised to dopamine, does not greatly accelerate disease progression, which would be expected if dopamine was the central toxic species.

One salient factor that differentiates degenerating neurons from relatively insensitive neurons relates to basal mitochondrial stress. Many neuronal populations exhibit autonomous pacemaking axonal firing, that is axonal signalling in the absence of synaptic input, including vulnerable regions in PD such as the substantia nigra pars compacta, locus coeruleus and dorsal motor nucleus of the vagus, as well as relatively insensitive ventral tegmental area and Purkinje neurons. However, the vulnerable neurons have an unusual reliance on Cav1 calcium channels (Chan et al., 2007) and have relatively poor calcium buffering (Foehring et al., 2009; Goldberg et al., 2012) as compared to ventral tegmental area or Purkinje neurons (Liang et al., 1996; Schmidt et al., 2007). This pacemaking calcium signalling requires elevated mitochondrial activity, leading to oxidative stress. Indeed neurons in the substantia nigra and dorsal motor nucleus of the vagus, but not ventral tegmental area, exhibit elevated mitochondrial oxidative stress under basal conditions (Goldberg et al., 2012; Guzman et al., 2010; Horowitz et al., 2011). This appears to be a characteristic that differentiates vulnerable neuronal populations in regions including substantia nigra, locus coeruleus and dorsal motor nucleus of the vagus from relatively insensitive regions such as ventral tegmental area neurons (Surmeier et al., 2017b; Surmeier and Sulzer, 2013). Further evidence for a mechanistic involvement of Cav1 channels in pathological mitochondrial stress includes an amplification of this basal oxidative stress in the absence of antioxidant DJ-1, which can be prevented by inhibition of Cav1 channels by isradipine (Goldberg et al., 2012; Guzman et al., 2010). Accordingly, isradipine is currently being investigated in a phase III clinical trial (NCT02168842) following a successful phase II trial which indicated a trend towards efficacy (ParkinsonStudyGroup, 2013).

Hence neurons in vulnerable regions including the substantia nigra, locus coeruleus and dorsal motor nucleus of the vagus are under elevated basal oxidative stress and are highly susceptible to mitochondrial impairment. Other biochemical features of vulnerable regions in PD include accumulation of iron, and depletion of copper and glutathione (Table 1). These will now be discussed in relation to their effect on mitochondrial function.

3. Iron accumulates in vulnerable regions in Parkinson's disease

It is well established from examination of post-mortem tissue that iron is elevated in normal substantia nigra as compared to other brain regions, and is specifically further elevated in PD (Davies et al., 2013; Dexter et al., 1987, 1989, 1990, 1991Griffiths et al., 1999; Riederer et al., 1989; Sofic et al., 1988, 1991). In addition, substantia nigra iron is selectively increased in monogenetic forms of PD as measured by transcranial sonography (Schweitzer et al., 2007) and in autosomal recessive juvenile parkinsonism (Takanashi et al., 2001). Iron is also relatively high in other regions, such as caudate, putamen and globus pallidus (Davies et al., 2013; Zucca et al., 2015), but has been reported to decrease in these regions in PD (Popescu et al., 2009). Although the locus coeruleus degenerates almost as profoundly as substantia nigra pars compacta, it contains very little iron (Zecca et al., 2004). Nevertheless, iron still accumulates in neuromelanin-containing neurons in the locus coeruleus in PD (Davies et al., 2014).

In mice, the relatively insensitive substantia nigra pars reticulata contains approximately 45% more iron than the substantia nigra pars compacta, although pars compacta iron is still elevated over the adjacent ventral tegmental area (Hare et al., 2014). Both the ventral tegmental area and substantia nigra pars compacta contain tyrosine hydroxylase-positive dopaminergic neurons, while the substantia nigra pars reticulata does not. Hence the sensitivity of pars compacta neurons to degeneration may be due to their unique characteristic of both elevated iron and presence of dopamine (Hare et al., 2014), although this would not explain the sensitivity of neurons in the locus coeruleus, where iron levels are approximately 7-fold lower than substantia nigra (Zecca et al., 2004). Toxicity of iron is also determined by the relative abundance of suitable ligands such as ferritin. For example, the locus coeruleus has approximately 10-fold less L-ferritin than the substantia nigra (Zecca et al., 2004). An early histochemical study corroborates the differential distribution of iron between the substantia nigra pars compacta and pars reticulata (Morris and Edwardson, 1994), as does recent magnetic resonance imaging of PD patients: a region of the substantia nigra pars compacta referred to as the dorsolateral nigral hyperintensity (corresponding to lower iron than the adjacent medial pars compacta and pars reticulata regions) is consistently lost in PD (Mahlknecht et al., 2017), corresponding to accumulation of iron in this region.

Histological stains for iron in the substantia nigra find most iron associated with glia and non-pigmented (neuromelanin-free) neurons (Morris and Edwardson, 1994; Zecca et al., 2004). Most increased iron is associated with glial ferritin (Griffiths et al., 1999; Hare et al., 2014; Morris and Edwardson, 1994; Zecca et al., 2001), and ferritin levels have been found to be both elevated and decreased in post-mortem PD substantia nigra (Dexter et al., 1990, 1991; Riederer et al., 1989). Neuronal neuromelanin also robustly binds iron (Double et al., 2003). Although apparently not detectable by histological stains, elevated iron has been detected by X-ray

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Table 1
Regional biochemical characteristics.

	Substantia nigra		Ventral tegmental area	Locus coeruleus
	Pars compacta (SNc)	Pars reticulata		
In normal conditions				
Presence of tyrosine hydroxylase	High	Low	High	High
Presence of neuromelanin	High	Low	High, less than SNc (Liang et al., 2004)	High
Predominant neurotransmitter	Dopamine	GABA	Dopamine	Noradrenaline
Iron content	High	Very high	Low	Low
Copper content	High	Lower than SNc		High
Basal mitochondrial stress	High	Low	Low	High
In Parkinson's disease				
Neuronal loss	Highest	Low	Low, late	High
Iron	Accumulates		Unchanged	Accumulates
Copper	Depleted			Depleted
Ctr1 expression	High	Low		
SOD1 expression	High	Low		
Glutathione	Depleted			
α-synuclein pathology	Late	Late	Little	Early
Sensitivity to mitochondrial toxins	High	Low	Low	High
Degeneration in other diseases	Multiple system atrophy, progressive supranuclear palsy			Alzheimer's, Down syndrome

fluorescence in neuromelanin in substantia nigra dopaminergic neurons and locus coeruleus noradrenergic neurons in PD (Davies et al., 2014; Oakley et al., 2007) and may be the major form of iron storage in neurons (Zecca et al., 2001).

In models of PD, substantia nigra iron is elevated in response to MPTP, rotenone and 6-hydroxydopamine in monkeys, mice and rats (Devos et al., 2014; Hare et al., 2014; Lee et al., 2009b; Lv et al., 2011; Mastroberardino et al., 2009; Mena et al., 2011, 2015; Mochizuki et al., 1994; Oestreicher et al., 1994; Temlett et al., 1994). This elevation in iron is restricted to the substantia nigra, with no change in iron in the neighbouring dopaminergic ventral tegmental area (Lv et al., 2011; Mastroberardino et al., 2009), and the elevated iron has been localised to both neurons and glia (Oestreicher et al., 1994).

The pathological importance of iron is ably demonstrated by experiments in which sequestering iron is neuroprotective. Decreasing labile iron by treatment of mice with chelators including deferoxamine, deferiprone and clioquinol, among others, or overexpressing ferritin invariably prevents the loss of substantia nigra dopaminergic neurons and rescues motor deficits in mouse models of PD (Devos et al., 2014; Kaur et al., 2003; Lee et al., 2009b; Lei et al., 2015; Lei et al., 2012; Mastroberardino et al., 2009; Mena et al., 2011, 2015). Importantly, deferiprone was assessed in a recent phase II clinical trial in PD patients and exhibited efficacy on the unified Parkinson's disease rating scale (Devos et al., 2014). This constitutes the first compelling evidence for efficacy of iron chelation therapy for the treatment of PD.

4. The iron-mitochondria nexus

Mitochondria play a key role in regulating iron metabolism. They are the site of Fe-S cluster assembly and heme synthesis. Fe-S clusters are integral for the function of many proteins including complex I of the electron transport chain and other iron metabolism proteins (Liddell, 2015). Of these, the bifunctional cytosolic protein aconitase/iron regulatory protein 1 is central to the regulation of iron metabolism. In iron-replete cells when Fe-S cluster assembly is sufficient, aconitase/iron regulatory protein 1 binds an Fe-S cluster, promoting aconitase activity. However, under low iron conditions, Fe-S cluster assembly is impaired, resulting in insufficient Fe-S cluster binding. Under these conditions, iron regulatory protein 1 lacks aconitase activity and exhibits an iron regulatory role, binding to iron-responsive elements on the mRNA of iron trafficking genes, increasing translation of iron import proteins such as transferrin receptor and divalent metal transporter 1, and downregulating iron storage (ferritin) and export (ferroportin). Together, this coordinates iron trafficking proteins to facilitate cellular iron accumulation (Muhlenhoff et al., 2015). Pathological disruption of Fe-S cluster assembly leads to aberrant iron regulatory protein signalling and a false iron starvation phenotype due to lack of Fe-S cluster binding by iron regulatory protein 1. In diseases such as Friedreich's ataxia (Rotig et al., 1997) and several other conditions involving disrupted Fe-S assembly (Stehling et al., 2014), this leads to mitochondrial iron accumulation in a futile attempt to fuel Fe-S cluster assembly.

Analysis of iron regulatory proteins in post-mortem tissue implies that iron regulatory protein signalling is disrupted in PD. Firstly, there is no clear change in ferritin levels in PD substantia nigra, with levels variously reported as increased (Riederer et al., 1989), decreased (Dexter et al., 1990, 1991) or unchanged (Mann et al., 1994). This discrepancy may be due to methodological differences (Dexter et al., 1991; Mann et al., 1994). The elevated iron in PD substantia nigra without a clear concomitant increase in ferritin is consistent with a dysregulation of iron regulatory protein signalling and likely increase in free or labile iron (Hirsch, 2006). The iron import protein divalent metal transporter 1 (containing an iron-responsive element) is also increased in PD substantia nigra, indicative of dysregulated iron regulatory protein signalling (Ayton et al., 2015). In mice treated with MPTP, the increased iron content is accompanied by decreased ferroportin, also indicative of dysregulated iron regulatory protein signalling (Lee et al., 2009b). On the other hand, transferrin receptor expression is reportedly low in normal SN (Faucheux et al., 1993), and although there is no loss of transferrin receptor from the SN in PD (Ayton et al., 2015; Faucheux et al., 1993), a specific loss of transferrin receptor from neuromelanin-containing neurons in SN has been reported (Faucheux et al., 1997), and there is a loss of transferrin receptor in 6-hydroxydopamine and MPTP-treated rats and mice (Gal et al., 2010; He et al., 1999; You et al., 2016). This decreased transferrin receptor expression concomitant with elevated cellular iron levels suggest normal iron regulatory protein signalling in PD, in contrast to other iron trafficking proteins. However, it is important to note that iron regulatory protein-independent modulation of transferrin receptor levels has been observed (Kaur et al., 2009).

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Mitochondrial inhibition impairs Fe-S cluster synthesis, which leads to mitochondrial iron accumulation (Stehling et al., 2014). For example, the PD-related mitochondrial toxin rotenone impairs Fe-S cluster assembly and causes iron regulatory protein-mediated mitochondrial iron accumulation in vitro (Mena et al., 2011) and in rodents (Mastroberardino et al., 2009; Mena et al., 2015). Hence it is likely that the iron accumulation evident in response to complex I inhibition by other mitochondrial toxins is also driven by impaired Fe-S cluster assembly and aberrant iron regulatory protein signalling.

Elevated mitochondrial iron causes oxidative stress, impairs mitochondrial function and leads to neuronal death (Munoz et al., 2016). Sequestering mitochondrial iron by overexpression of mitochondrial ferritin protects neuronal cells from multiple mitochondrial toxins in vitro (Shi et al., 2010; Wang et al., 2016; You et al., 2016). Furthermore, iron chelators that can access mitochondrial iron, including deferiprone, show efficacy in the MPTP mouse model (Devos et al., 2014; Mena et al., 2015). As discussed above, deferiprone recently exhibited efficacy in a phase II clinical trial in PD patients (Devos et al., 2014). Hence a pathologically relevant pool of elevated iron appears to be localised to mitochondria in PD. This elevation may be driven by aberrant iron regulatory protein signalling as a result of mitochondrial dysfunction.

In addition to disrupting Fe-S cluster assembly, mitochondrial dysfunction increases oxidative stress. Iron binding by aconitase/iron regulatory protein 1 is exquisitely sensitive to radicals such as superoxide (Gardner and Fridovich, 1991) and nitric oxide (Jaffrey et al., 1994). Hence iron regulatory protein signalling may be additionally dysregulated by the elevated mitochondrial stress abundantly evident in PD, disrupting the binding of Fe-S clusters to iron regulatory protein 1.

Together these studies show that normal iron metabolism requires adequate mitochondrial activity. The impaired mitochondrial activity evident in PD can disrupt iron regulation, causing accumulation of mitochondrial iron. Conversely, iron accumulation causes oxidative stress, disrupting mitochondrial function. Hence both aberrant iron metabolism and mitochondrial dysfunction impair each other, and both are evident in PD.

5. Copper is depleted from vulnerable regions in Parkinson's disease

In normal brain, the substantia nigra and locus coeruleus are highly enriched for copper as compared to other brain regions, with approximately 2–3-fold more copper in these regions compared to cortex (Davies et al., 2013, 2014; Dexter et al., 1991; Rios et al., 1995). Accordingly, a major cuproprotein superoxide dismutase 1 is highly expressed in the substantia nigra and striatum of mice (Pardo et al., 1995), and seems to be specific to the substantia nigra pars compacta and not pars reticulata (Hare et al., 2014). Furthermore, the copper importer Ctr1 is abundant in the pars compacta but not pars reticulata (Davies et al., 2013). Hence it is likely that the elevated copper is restricted to the substantia nigra pars compacta, and indicates that copper content is another factor that distinguishes the vulnerable pars compacta from the adjacent insensitive pars reticulata in normal brain (Table 1).

In PD, the copper contents of the substantia nigra and locus coeruleus are selectively decreased by approximately 50% compared to control, with no significant change in other regions (Ayton et al., 2013; Davies et al., 2014; Dexter et al., 1991, 1987, 1989; Popescu et al., 2009). This decrease has been detected specifically within neuromelanin-containing neurons in both the substantia nigra pars compacta and locus coeruleus (Davies et al., 2014). Furthermore, Ctr1 is decreased in these neurons, but not from neuromelanin-containing neurons in the ventral tegmental area (Davies et al., 2014). That copper and Ctr1 are lost from both substantia nigra pars compacta and locus coeruleus, but not ventral tegmental area neurons in PD indicates that copper loss in PD is specific to the vulnerable areas (Davies et al., 2014), consistent with impaired capacity to uptake copper in PD.

Copper deficiency impairs mitochondrial function via insufficient supply of copper to complex IV. Indeed, complex IV activity is impaired in LRRK2 mutant PD patients (Mortiboys et al., 2015) and in mutated PINK1 and DJ-1 patient fibroblasts and animal models (Lopez-Fabuel et al., 2017). Hence disrupted copper entry into the substantia nigra in PD can directly impair mitochondrial activity.

Copper deficiency also impacts the activity of other cuproproteins. There is a profound loss of the copper-dependent activity of ceruloplasmin, despite no change in ceruloplasmin protein level in PD substantia nigra (Ayton et al., 2013) and cerebrospinal fluid (Olivieri et al., 2011). Ceruloplasmin is a major cuproenzyme considered the major systemic copper carrier, and is found glycosylphosphatidylinositol-anchored to the extracellular surface of astrocytes in the brain (Jeong and David, 2003). Enzymatic activity of ceruloplasmin requires occupancy of all six copper sites, formation of which is dependent on copper supply to the secretory pathway (Hellman et al., 2002).

In mice, MPTP alters copper levels in an apparently dose-dependent manner. MPTP at a total dose of 150 mg/kg causes approximately 50% decrease in striatum and midbrain copper levels, whereas 90 mg/kg causes only small decrease (Rios et al., 1995), and 40 mg/kg actually increases substantia nigra copper by 19% (Ayton et al., 2013). Regardless, ceruloplasmin activity is severely decreased in MPTP-treated mice (Ayton et al., 2013), indicating substantial disruption of copper metabolism in response to this toxin.

6. Copper-dependent iron trafficking

Ceruloplasmin activity coordinates cellular copper and iron levels via its key role in iron export. Ceruloplasmin is a ferroxidase responsible for oxidising Fe^{2+} exported by ferroportin to Fe^{3+}, to promote iron binding to transferrin and prevent Fe^{2+}-mediated oxidation reactions. Deletion of ceruloplasmin in mice causes glial iron accumulation (Jeong and David, 2003, 2006), elevated substantia nigra iron and the development of parkinsonism (Ayton et al., 2013; Patel et al., 2002). This can be rescued by iron chelation via deferiprone (Ayton et al., 2013). Lack of ceruloplasmin also exacerbates MPTP toxicity in mice, presumably due to elevated iron, a hypothesis supported by similar exacerbation of MPTP toxicity in conjunction with iron loading (You et al., 2015). Conversely, peripheral administration of ceruloplasmin protects against MPTP toxicity, indicating improved iron trafficking provides protection against MPTP (Ayton et al., 2013). In PD patients, the effectiveness of deferiprone iron chelation therapy correlates with the extent of ceruloplasmin loss (Grolez et al., 2015), suggesting loss of ceruloplasmin correlates with pathological iron accumulation.

Aceruloplasminemia patients harbouring loss-of-function mutations in ceruloplasmin also have disrupted iron metabolism, with glial iron accumulation (Gonzalez-Cuyar et al., 2008; Oide et al., 2006) and certain mutations are associated with elevated nigral iron and parkinsonism (Hochstrasser et al., 2004, 2005; McNeill et al., 2008). If iron accumulation is central to PD pathogenesis, it could be expected that loss of ceruloplasmin should be more strongly associated with parkinsonism. That the relationship is relatively mild can be explained by two aspects. Firstly, ceruloplasmin is mainly expressed in astrocytes and lack of ceruloplasmin function causes glial iron accumulation (Jeong and David, 2003),

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possibly eliciting only minimal disruption to neuronal iron metabolism. Secondly, amyloid precursor protein provides complementary iron trafficking activity. Amyloid precursor protein is also a cuproprotein, and has been shown to be involved in iron export in association with ferroportin (Duce et al., 2010; Wong et al., 2014). Deletion of amyloid precursor protein from mice causes nigral iron accumulation, neuron loss and parkinsonism (Ayton et al., 2015). Iron chelation partially prevents nigral neuron loss in amyloid precursor protein knockout mice and overexpression of amyloid precursor protein protects against MPTP toxicity in wild type mice (Ayton et al., 2015). Correlating with iron accumulation, amyloid precursor protein expression is diminished in the substantia nigra of PD patients and by MPP^+ treatment in cultured neuronal cells (Ayton et al., 2015). While amyloid precursor protein appears to colocalise with tyrosine hydroxylase-positive neurons in human substantia nigra (Ayton et al., 2015), astrocytes also express amyloid precursor protein in vivo (Banati et al., 1995; Clarner et al., 2011; Gehrmann et al., 1995), although its role in glial iron trafficking is yet to be specifically determined.

Both ceruloplasmin (Mazumder et al., 2006) and amyloid precursor protein expression in astrocytes are strongly upregulated by inflammation (Banati et al., 1995; Clarner et al., 2011; Gehrmann et al., 1995). That the clear inflammation evident in PD (Rocha et al., 2015) is not accompanied by increased ceruloplasmin or amyloid precursor protein activity further indicates that there is an insufficient supply of copper to meet the requirements of these cuproproteins in PD.

Disrupted copper uptake in PD substantia nigra not only prevents adequate supply of copper for the enzymatic activity of amyloid precursor protein, but also disturbs its subcellular localisation. Copper regulates amyloid precursor protein trafficking from the perinuclear region to the cell surface (Acevedo et al., 2011) in a phosphorylation-dependent manner, and copper depletion prevents this trafficking (Acevedo et al., 2014). Disrupted amyloid precursor protein trafficking to cell surface is evident in tau knockout mice, which exhibit iron accumulation and parkinsonism (Lei et al., 2012). Hence impaired amyloid precursor protein trafficking due to copper depletion contributes to iron accumulation.

In addition to diminished copper availability via decreased Ctr1 expression, ceruloplasmin and amyloid precursor protein activity can be further decreased by oxidative stress. In PD patients, ceruloplasmin is oxidised in cerebrospinal fluid, causing release of copper and loss of ferroxidase activity, and the extent of ceruloplasmin oxidation correlates with PD clinical progression (Olivieri et al., 2011). In mice, MPTP treatment causes loss of both ceruloplasmin activity (Ayton et al., 2013) and amyloid precursor protein expression (Ayton et al., 2015).

In addition to inflammation, amyloid precursor protein expression is also regulated by iron regulatory protein signalling. Amyloid precursor protein contains an iron-responsive element promoting its translation under iron-replete conditions (Rogers et al., 2002). Amyloid precursor protein expression is inhibited in a manner dependent on aberrant iron regulatory protein signalling, possibly involving nitric oxide (Ayton et al., 2015). Hence disrupted iron regulatory protein signalling evident in PD as a result of mitochondrial and oxidative stress (as discussed above) contributes to iron accumulation via impaired amyloid precursor protein expression. In this way, amyloid precursor protein regulation differs from ceruloplasmin, and explains why amyloid precursor protein expression is decreased (Ayton et al., 2015) while ceruloplasmin expression is maintained in PD, the latter losing copper-dependent activity (Ayton et al., 2013) due to diminished copper availability.

The therapeutic efficacy of modulating copper levels in the substantia nigra has been assessed. The copper drug diacetylbis(N(4)-methylthiosemicarbazonato)copper^{II} (Cu^{II}(atsm)) exerts potent neuroprotective effects in multiple animal models of PD, preventing dopaminergic neuron loss and rescuing motor impairments (Hung et al., 2012). A positron emission tomography imaging study demonstrates that Cu^{II}(atsm) selectively localises to the striatum in PD patients (Ikawa et al., 2011). However, the mechanism/s by which Cu^{II}(atsm) elicits its neuroprotective effects are unclear. Cu^{II}(atsm) has been demonstrated to deliver bioavailable copper to endogenous proteins (Roberts et al., 2014), hence the protection afforded by Cu^{II}(atsm) in PD models may involve copper delivery, enhancing the activity of cuproproteins including complex IV, ceruloplasmin and amyloid precursor protein, correcting mitochondrial impairment and iron trafficking, respectively. In addition, Cu^{II}(atsm) effectively detoxifies nitric oxide (Hung et al., 2012). As discussed above, amyloid precursor protein expression is hypothesised to be suppressed by nitric oxide-induced disruption of iron regulatory protein signalling (Ayton et al., 2015). Therefore, Cu^{II}(atsm) could correct aberrant iron regulatory protein signalling by degrading nitric oxide, correcting expression of amyloid precursor protein and other iron metabolism proteins, and thereby limit toxic iron accumulation.

These studies demonstrate that the substantia nigra in PD is characterised by disruption of copper trafficking and insufficiency of ceruloplasmin and amyloid precursor protein, two key cuproproteins directly involved in iron trafficking. Further, these studies demonstrate that aberrant iron trafficking is sufficient to instigate neuronal death in the substantia nigra, implicating iron accumulation per se in the pathogenesis of PD.

7. Glutathione is depleted from substantia nigra in Parkinson's disease

A robust feature of PD is the selective loss of glutathione from the substantia nigra. Many studies have reported substantial glutathione depletion (30–50%), coupled with elevated proportion of oxidised glutathione in post-mortem PD substantia nigra tissue (Fitzmaurice et al., 2003; Pearce et al., 1997; Perry and Yong, 1986; Sian et al., 1994a, 1994b; Sofic et al., 1992). Although this has yet to be verified in PD patients in the clinic, recent advances in magnetic resonance spectroscopy technology have shown decreased substantia nigra glutathione in MPTP-treated marmosets (Heo et al., 2017). A clinical trial (NCT01470027) investigating magnetic resonance spectroscopy detection of glutathione in PD patients has recently been completed but yet to report. A histochemical study showed a profound loss of glutathione from surviving dopaminergic neurons in PD substantia nigra, while glutathione was maintained in glia (Pearce et al., 1997), hence it may be an early feature in PD. Depletion of glutathione from rat brain substantia nigra is sufficient to induce dopaminergic neuron death and motor impairment (Garrido et al., 2011). Three small phase I/II clinical trials assessing glutathione delivery to PD patients have produced mild yet positive results (Hauser et al., 2009; Mischley et al., 2015; Sechi et al., 1996). Hence loss of glutathione per se is sufficient to kill substantia nigra neurons, and therapeutic rescue of glutathione levels may provide clinical benefit.

8. Relationship between glutathione and mitochondria

Glutathione plays several important roles in mitochondria, and lack of glutathione causes mitochondrial dysfunction (Jha et al., 2000; Lee et al., 2009a). Conversely, mitochondrial and oxidative stress are well known to deplete cellular glutathione levels, e.g. MPTP causes loss of glutathione in mice (Kaur et al., 2003; Yong et al., 1986). In addition to its well-known functions as an antioxidant and substrate for glutathione peroxidases, glutathione is also

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critical for maintaining the redox status of proteins via glutaredoxins. Glutaredoxins catalyse the reduction of glutathione-protein mixed thiols. Glutaredoxin 2 is a mitochondrial isoform in mammalian cells (Gladyshev et al., 2001). Deletion of glutaredoxin 2 causes mitochondrial defects including glutathionylation of complex I and IV and uncoupling protein-3, disrupting their activity (Mailloux et al., 2013; Wu et al., 2011, 2014). Furthermore, glutaredoxin 2 activity is dependent on glutathione levels (Lee et al., 2009a). Hence loss of glutathione can disrupt mitochondrial function, and aberrant mitochondrial function can deplete glutathione levels.

9. Glutathione is required for copper uptake

Glutathione plays a key role in copper metabolism. Early studies showed more than 60% of cellular copper is associated with glutathione in hepatoma cell lines (Freedman et al., 1989). Furthermore, glutathione is required for copper accumulation by HEK293 cells (Maryon et al., 2013). Depletion of cellular glutathione by buthionine sulfoximine treatment robustly decreases copper uptake, an effect which is not altered by knockdown or overexpression of copper chaperone for superoxide dismutase or Atox1, suggesting glutathione binds copper imported by the plasma membrane transporter Ctr1 as an intermediate before being bound by higher affinity chaperones (Maryon et al., 2013). Indeed, Banci et al. (2010) proposed copper is trafficked along affinity gradients, likely trafficked from glutathione to higher affinity chaperones such as Atox1, copper chaperone for superoxide dismutase and Cox17, then to their very high affinity final cuproproteins. In addition to copper uptake, a high level of reduced glutathione is also required to maintain Atox1 in a reduced state, facilitating copper trafficking to the secretory pathway (Hatori et al., 2012, 2016). In vivo, depletion of glutathione in drosophila gives rise to a neuronal copper deficiency phenotype that can be partially rescued by copper (Mercer et al., 2016). Hence glutathione is required for copper uptake and must be maintained in reduced form for appropriate copper trafficking. In PD, depleted glutathione in the SN may impair copper trafficking, leading to the observed decreased copper levels.

10. Glutathione modulates iron metabolism via interaction with Fe-S clusters

Glutathione is involved in the regulation of iron. In yeast, severe depletion of glutathione impairs mitochondrial Fe-S cluster assembly and evokes a profound iron starvation phenotype (Kumar et al., 2011). In various neuronal cell lines and drosophila, while glutathione depletion invariably causes iron accumulation, the reported involvement of iron regulatory protein signalling is unclear, variously reported as increased, decreased or unchanged (Kaur et al., 2009; Lee et al., 2009a; Wang et al., 2016). Of note, when glutathione is depleted, mitochondria are reported as the predominant site of iron accumulation (Lee et al., 2009a), and overexpression of mitochondrial ferritin normalises iron content and expression of iron-related proteins (Wang et al., 2016), suggesting mitochondria are the key organelle affected by glutathione depletion. Conversely, elevated iron decreases glutathione, in brains of amyloid precursor protein knockout mice fed a high iron diet (Duce et al., 2010), and frataxin-null yeast (Auchere et al., 2008). Hence depleted glutathione can drive iron accumulation, and elevated iron can deplete glutathione levels.

Glutathione can regulate iron metabolism by interacting with Fe-S clusters and modulating their trafficking and assembly in mitochondria. As described above, Fe-S cluster assembly and trafficking are essential for coordination of iron metabolism via iron regulatory proteins (Muhlenhoff et al., 2015). Glutathione has recently been shown to directly coordinate with Fe-S clusters, potentially playing a role in trafficking Fe-S clusters (Fidai et al., 2016). Furthermore, glutathione interacts with Fe-S clusters via glutaredoxins. In addition to its role in thiol redox control, glutaredoxin 2 interacts with Fe-S clusters in mitochondria (Hoff et al., 2009). In-solution studies show that this coordination is dependent on the presence of reduced glutathione: when reduced glutathione becomes limiting or under oxidising conditions, the Fe-S cluster dissociates from glutaredoxin 2 (Berndt et al., 2007; Mitra and Elliott, 2009). Knockdown of glutaredoxin 2 in neuronal cells produces the same mitochondrial iron accumulation phenotype as glutathione depletion (Lee et al., 2009a). These results suggest that the depletion of glutathione described above induces the iron accumulation phenotype via impaired glutaredoxin 2 activity.

In addition to glutaredoxin 2, a second mitochondrial glutaredoxin, glutaredoxin 5 is required for mitochondrial Fe-S cluster assembly, a role conserved from yeast to humans (Rodriguez-Manzaneque et al., 2002; Ye et al., 2010). Glutaredoxin 5-mediated Fe-S cluster assembly is also required for mitochondrial heme synthesis (Wingert et al., 2005; Ye et al., 2010). Knockdown of glutaredoxin 5 in erythroblasts results in an iron starvation phenotype and mitochondrial iron accumulation (Ye et al., 2010). Mutation in glutaredoxin 5 gives rise to sideroblastic anemia, with erythrocytes exhibiting impaired heme synthesis and mitochondrial iron accumulation (Ye et al., 2010). This effect appears to be restricted to erythrocytes, most likely due to their high requirement for heme synthesis and expression of erythrocyte-specific isoform of the heme synthesis protein 5'aminolevulinate synthase 2, which is repressed by iron regulatory protein signalling, unlike ubiquitous 5'aminolevulinate synthase 1 (Ye et al., 2010). Nevertheless, while fibroblasts from these patients do not exhibit iron accumulation, they do have altered expression of iron trafficking proteins (Ye et al., 2010). Given the apparent higher demand for iron in the substantia nigra, altered supply of glutathione to glutaredoxin 5 may be sufficient to impair Fe-S cluster and heme biogenesis in the substantia nigra, contributing to iron dysregulation.

As mitochondrial dysfunction can deplete glutathione levels, and given the elevated mitochondrial stress evident in normal substantia nigra, glutathione loss may be an early event instigating the observed deficits in iron and copper. Depleted glutathione will decrease copper trafficking and copper levels, leading to decreased activity of cuproproteins such as complex IV, ceruloplasmin and amyloid precursor protein, causing mitochondrial impairment and leading to aberrant iron metabolism, respectively, hence glutathione is required for mitochondrial function, copper uptake and trafficking, and coordinating appropriate iron metabolism. Conversely, iron and/or mitochondrial dysfunction both deplete glutathione levels.

11. Glutathione is regulated by the transcription factor Nrf2

Nrf2 is a transcription factor that regulates a battery of phase II antioxidant genes. These include NAD(P)H quinone dehydrogenase 1, heme oxygenase 1, ferritin and many enzymes of glutathione metabolism, including glutamate-cysteine ligase, the rate-limiting enzyme of glutathione synthesis. Under normal conditions, Nrf2 is constitutively targeted for proteasomal degradation in the cytosol by its negative regulator, Keap1. Hence under normal conditions, Nrf2 signalling is very low. However, under conditions of oxidative stress, Nrf2 dissociates from Keap1 and translocates and accumulates in the nucleus where it binds to antioxidant response elements, promoting the transcription of hundreds of genes (Liddell, 2017). Expression of Nrf2 is not required for the maintenance of basal glutathione content (Liddell et al., 2016), but is required for upregulation of glutathione in response to stimulation

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(McMahon et al., 2001).

Nrf2 signalling in the substantia nigra is complex. In normal human post-mortem substantia nigra, Nrf2 is mainly cytosolic, whereas nuclear Nrf2 is strongly elevated in PD patients (Ramsey et al., 2007). However, this does not appear to translate into a functional increase in antioxidant proteins, as there is no difference in glutamate-cysteine ligase activity in the substantia nigra of post-mortem PD brain compared to age-matched controls (Sian et al., 1994b), and glutathione content is decreased (see above). Interestingly, γ-glutamyl transferase is selectively increased in the substantia nigra of PD brain (Sian et al., 1994b). That γ-glutamyl transferase is the only one of several Nrf2-regulated enzymes of glutathione metabolism to be changed in PD (Sian et al., 1994b) suggests that it may also be regulated by factors other than Nrf2. γ-Glutamyl transferase is involved in trafficking glutathione from astrocytes to neurons (Hirrlinger and Dringen, 2009), and increased activity could indicate increased export of glutathione from astrocytes as a response to oxidative stress.

In mice, Nrf2 signalling is elevated in normal substantia nigra compared to other brain regions (Chen et al., 2009; Jakel et al., 2005; Lv et al., 2015), providing further evidence that the substantia nigra is experiencing elevated oxidative stress under normal conditions (as discussed above). However, as in human PD substantia nigra, translation of Nrf2 signalling to functional antioxidant proteins in mouse substantia nigra appears to be impaired, with lower specific NAD(P)H quinone dehydrogenase 1 activity in substantia nigra than striatum (Chen et al., 2009).

In mouse models of PD, Nrf2 signalling in substantia nigra is also further elevated in response to MPTP (Chen et al., 2009; Ozkan et al., 2016; Swanson et al., 2013), 6-hydroxydopamine (Jakel et al., 2005), and in the A53T α-synuclein model (Gan et al., 2012). However, all these models exhibit severe pathology. Together these studies indicate that endogenous Nrf2 signalling is insufficient to counter localised elevated oxidative stress in both normal and PD substantia nigra.

Although endogenous Nrf2 appears to be insufficient to counter oxidative stress in PD, it remains a critical determinant of dopaminergic neuron survival and PD pathology. Ablation of Nrf2 in mouse models of PD worsens survival, while overexpression of Nrf2 is protective (Chen et al., 2009; Gan et al., 2012; Jakel et al., 2007). Furthermore, a genetic association has been determined between NFE2L2 (Nrf2 gene) variants and PD risk (Todorovic et al., 2015; von Otter et al., 2014). Hence increasing Nrf2 activity enhances resistance to PD symptoms.

Many Nrf2-inducing agents are being investigated for the treatment of PD, including dimethyl fumarate (Ahuja et al., 2016; Campolo et al., 2017; Lastres-Becker et al., 2016), triterpenoids (Kaidery et al., 2013), curcumin (Cui et al., 2016; Khatri and Juvekar, 2016), and resveratrol (Gaballah et al., 2016). Meanwhile, PD drugs deprenyl and apomorphine have been shown to activate Nrf2 in vitro (Hara et al., 2006; Nakaso et al., 2006; Xiao et al., 2011).

12. Copper regulates Nrf2 activation

Nrf2 activation is influenced by copper. Experimental exposure to harmful doses of copper induces Nrf2 signalling (Jiang et al., 2014; Song et al., 2014), which is blocked in Nrf2-deficient cells (Song et al., 2014). Nrf2 is also induced by subtoxic levels of copper. The neuroprotective compound pyrrolidine dithiocarbamate increases brain copper levels, induces Nrf2 signalling (Liddell et al., 2016) and improves cognitive deficits in Alzheimer's disease model mice (Cheng et al., 2006; Malm et al., 2007). As discussed above, Cu^{II}(atsm) exhibits robust efficacy in multiple animal models of PD (Hung et al., 2012), and has been demonstrated to deliver bioavailable copper to endogenous proteins (Roberts et al., 2014), hence the protection afforded by Cu^{II}(atsm) in PD models may involve copper delivery. Cu^{II}(atsm) has recently been shown to activate Nrf2 in heart (Srivastava et al., 2016), therefore Cu^{II}(atsm) may be protective in PD models by activating Nrf2 in a copper-dependent mechanism. These studies demonstrate that therapeutically increasing copper activates protective Nrf2 signalling. This suggests that endogenous copper modulates Nrf2. The copper depletion evident in PD substantia nigra may contribute to the impaired Nrf2 signalling evident in PD. As Nrf2 is a master regulator of glutathione and cellular antioxidant mechanisms, copper depletion may disrupt glutathione levels, which can drive aberrant iron metabolism, and mitochondrial and oxidative stress via impaired Nrf2 signalling.

While stimulating Nrf2 signalling prevents neuronal death in models of PD, it remains to be determined whether restoring glutathione levels is central to this protective effect, and whether this occurs via correcting iron and/or copper metabolism, preventing mitochondrial impairment or generalised restoration of redox balance, all of which are functions implicated for glutathione.

13. Ferroptosis, a glutathione-dependent cell death pathway, in Parkinson's disease

Ferroptosis is a recently described distinct form of non-apoptotic programmed cell death involving disruption of glutathione resulting in iron-mediated lipid peroxidation and cell death (Dixon et al., 2012; Yang et al., 2014). An essential regulator of ferroptosis is glutathione peroxidase 4 (Yang et al., 2014), which unlike other glutathione peroxidases, can detoxify membranous lipid hydroperoxides (Brigelius-Flohe and Maiorino, 2013). Ferroptosis can be experimentally induced by depletion of glutathione by buthionine sulfoximine or erastin, thus limiting glutathione availability as a substrate for glutathione peroxidase 4, or by direct inhibition or deletion of glutathione peroxidase 4 (Friedmann Angeli et al., 2014; Yang et al., 2014). Ferroptosis causes mitochondrial abnormalities including presence of shrunken and ruptured mitochondria (Dixon et al., 2012; Friedmann Angeli et al., 2014). Mitochondrial iron is also implicated, with sequestration of mitochondrial iron by overexpression of mitochondrial ferritin preventing erastin toxicity in a neuronal cell line and drosophila (Wang et al., 2016). Autophagic degradation of ferritin increases labile iron, decreases glutathione and increases sensitivity to erastin in fibroblasts and cancer cells, indicating elevated iron exacerbates ferroptosis (Hou et al., 2016). On the other hand, chelation of iron, for example by deferoxamine or deferiprone, blocks ferroptosis (Dixon et al., 2012; Do Van et al., 2016; Friedmann Angeli et al., 2014). Hence ferroptosis is modulated by iron availability. The exact mechanisms of ferroptosis are still being elucidated, but the presence of acyl-CoA synthetase long-chain family member 4 is required for ferroptosis to occur (Doll et al., 2017). This protein esterifies two fatty acyls (arachidonoyl and adrenoyl) into the phospholipids phosphatidylethanolamines (Kagan et al., 2017) and its inhibition is sufficient to block ferroptosis (Doll et al., 2017; Kagan et al., 2017). These long unsaturated fatty acids are more prone to lipid peroxidation, which can be inhibited by lipid radical scavengers ferrostatin-1, liproxstatin-1 and vitamin E analogues, preventing cell death (Dixon et al., 2012; Friedmann Angeli et al., 2014).

Originally described for cancer cells (Dixon et al., 2012; Yang et al., 2014), ferroptosis has been studied in the context of neurodegeneration. Induction of ferroptosis via conditional ablation of glutathione peroxidase 4 from neurons in adult mice induces a rapid paralysis phenotype coupled with muscle atrophy and death (Chen et al., 2015). These mice display features of ferroptosis, and phenotype progression is slightly delayed by vitamin E

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administration (Chen et al., 2015). Conditional ablation of glutathione peroxidase 4 from forebrain neurons in adult mice induces cognitive deficits accompanied by hippocampal degeneration and markers of ferroptosis including elevated lipid peroxidation (Hambright et al., 2017). When fed a vitamin E deficient diet, hippocampal degeneration in these mice was greatly accelerated, along with the appearance of a prominent locomotor impairment (Hambright et al., 2017). Neurodegeneration was abrogated by treatment with liproxstatin-1 (Hambright et al., 2017).

Given that ferroptosis involves mitochondrial impairment, elevated iron and diminished glutathione, all cardinal features of PD, ferroptosis has also been studied in relation to PD (Guiney et al., 2017). In vitro, the ferroptosis inhibitor ferrostatin-1 prevents rotenone and MPP^+ toxicity in a neuronal cell line (Ito et al., 2017; Kabiraj et al., 2015). In a melanoma cell line, inhibition of complex I causes ferroptosis, which can be prevented by ferrostatin-1 or overexpression of glutathione peroxidase 4, and exacerbated by knockdown of glutathione peroxidase 4 (Basit et al., 2017). Perhaps the best evidence for the involvement of ferroptosis in PD comes from a study which found LUHMES cells, a human dopaminergic neuron precursor cell line, were highly sensitive to erastin as compared to other neuronal cell lines (Do Van et al., 2016). In this study, ferrostatin-1 prevented the toxicity of glutathione depletion by erastin, buthionine sulfoximine and N-ethylmaleimide, the PD-related toxins MPP^+, dopamine, rotenone and paraquat, and glutamate in LUHMES cells. Iron chelation by deferiprone also protected against many of these toxins (Do Van et al., 2016). Examination of post-mortem PD brain found a substantial loss of mRNA for proteins inhibited by erastin and a 6-fold increase in glutathione peroxidase 4 mRNA in substantia nigra but not other regions including striatum and cortex (Do Van et al., 2016). Whether the latter translates to increased glutathione peroxidase 4 activity is unclear. Glutathione peroxidase 4 protein is decreased in the substantia nigra of post-mortem PD brains compared to controls, but increased relative to surviving cell density (Bellinger et al., 2011). Erastin inhibits components of system X_c^- (Dixon et al., 2012) but their mRNA are elevated in erastin-treated LUHMES cells in a presumably compensatory mechanism (Do Van et al., 2016). Glutathione peroxidase 4 mRNA in PD substantia nigra could be similarly upregulated to compensate for loss of activity, or could be upregulated in surviving neurons. Regardless, it appears that key components regulating ferroptosis are altered in PD. Finally, MPTP toxicity in mice can be prevented by pre-treatment with ferrostatin-1 (Do Van et al., 2016). This suggests that the vulnerable neurons in PD may be dying via ferroptosis, and that inhibition of ferroptosis may be neuroprotective in PD.

14. Conclusions

Parkinson's disease is biochemically characterised by the disruption of mitochondrial function and the metabolism of iron, copper and glutathione. These changes are specific to the degenerating brain regions in PD and together determine regional vulnerability. Emerging evidence indicates that the recently described cell death pathway ferroptosis may be critical in PD (Guiney et al., 2017). While ferroptosis is initiated primarily by

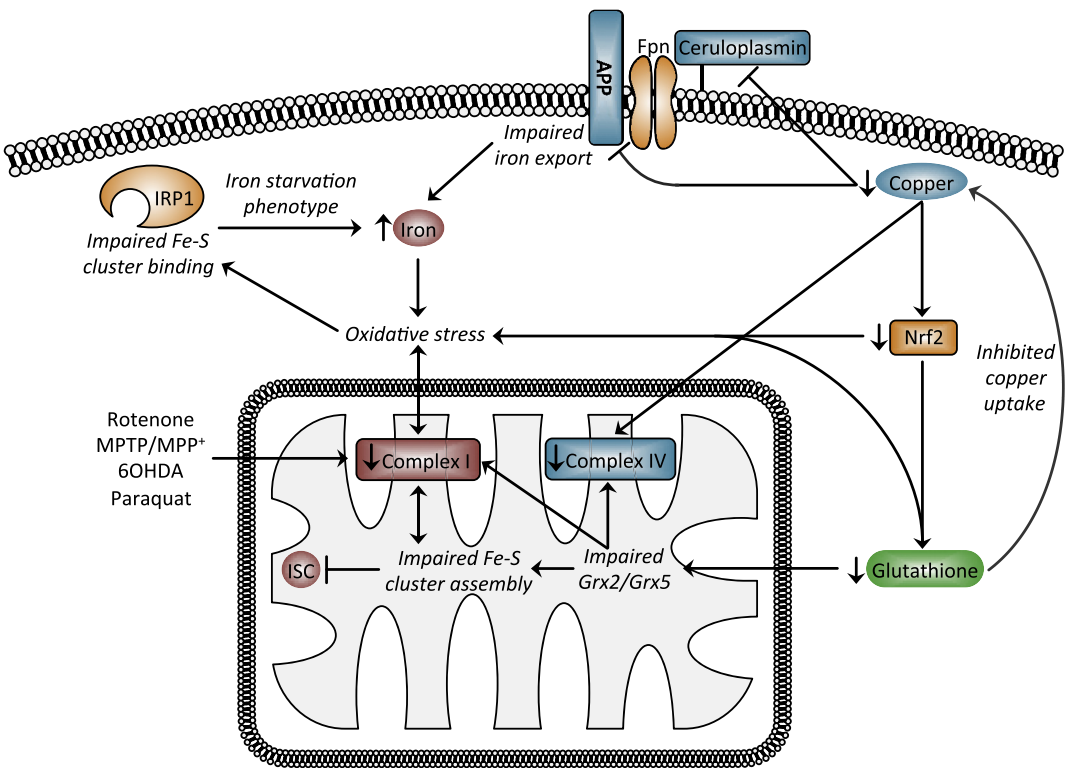

Fig. 1. Interplay between mitochondrial dysfunction, iron accumulation, diminished copper content and depleted glutathione levels in Parkinson's disease. The loss of complex I activity evident in PD and in response to toxins including rotenone, MPTP/MPP^+, 6-hydroxydopamine and paraquat induces oxidative stress. This depletes glutathione levels, which are required to maintain copper uptake, and Fe-S cluster assembly and binding to iron regulatory protein 1 directly and via mitochondrial glutaredoxins. Impaired Fe-S cluster assembly impairs complex I activity and results in aberrant iron regulatory protein 1 signalling and a false iron starvation phenotype, resulting in iron accumulation. This exacerbates oxidative stress and loss of mitochondrial function, depleting glutathione and diminishing copper uptake. Lack of copper decreases Nrf2 signalling and thereby glutathione, and inhibits activity of cuproproteins including complex IV in mitochondria and amyloid precursor protein and ceruloplasmin, the latter diminishing iron export and exacerbating iron accumulation. 6OHDA, 6-hydroxydopamine; APP, amyloid precursor protein; Fpn, ferroportin; Grx2, glutaredoxin 2; Grx5, glutaredoxin 5; IRP1, iron regulatory protein 1; ISC, Fe-S cluster; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

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disruption of glutathione and exacerbated by elevated iron, this review discusses how disruption of mitochondrial function, iron, copper or glutathione metabolism alone is sufficient to impair all other factors (Fig. 1). Therefore disruption of any one of these features can instigate a self-perpetuating cycle of increasing pathology, leading to neuronal cell death and PD. Therapeutically targeting each of these factors provides protection in animal models of PD, and are being pursued in the clinic. This includes directly abrogating iron accumulation via iron chelators such as deferiprone, mitochondrial stress via calcium channel blockers such as isradipine, glutathione depletion via glutathione administration or Nrf2 activation, and copper depletion via copper drugs such as Cu^{II}(atsm). Given the interdependent nature of these pathological features, although treatments target a specific pathology, they are likely to abrogate pathology and restore function of all these factors. Therefore, in regards to treatment, perhaps it is not relevant which impairment/s occur first. However, in order to elucidate the natural course of the disease at a biochemical level and provide biomarkers for early intervention, longitudinal studies are required to determine the sequence of events, utilising for example advances in clinical imaging techniques for mitochondrial function, iron and glutathione content.

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