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The Execution Step in Parkinson's Disease – On the Vicious Cycle of Mitochondrial Complex I Inhibition, Iron Dishomeostasis and Oxidative Stress

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1. Introduction

The evidence for the participation of redox-active iron and reactive oxygen species (ROS) in a number of neurodegenerative diseases, including, Huntington's disease, Alzheimer's disease, Friedreich's ataxia, Amyotrophic lateral sclerosis (ALS) and Parkinson's disease is by now unquestionable.

In particular, in the case of Parkinson's disease (PD) iron accumulation has been demonstrated in the dopaminergic neurons of the substantia nigra pars compacta and neuronal death in this area is prevented by pharmacological agents with iron chelating capacity. Other pathognomonic signs of PD include inhibition of mitochondrial complex I and decreased glutathione (GSH) content. In this chapter we will discuss the effects of complex I inhibition on Fe-S cluster synthesis and iron homeostasis, and the positive feedback loop between iron, glutathione and ROS that ends in cell death. We will also discuss the possible role of hepcidin as a mediator of inflammatory stimuli that trigger iron dishomeostasis.

2. Iron homeostasis and dishomeostasis - the role of iron transporters on iron accumulation

2.1 Iron homeostasis

The components of neuronal iron homeostasis are shown in Figure 1. The scheme includes transferrin and transferrin receptor (TfR), inflow (DMT1; SLC11A2) and efflux (ferroportin 1, FPN1) iron transporters, the iron storage protein ferritin, the ferrireductase Dcytb, responsible for the reduction of extracellular Fe^{3+} to Fe^{2+} prior to transport by DMT1, and the ferroxidase ceruloplasmin, responsible for the oxidation of Fe^{2+} after transport by FPN1 and prior to the binding by apoTf. Transferrin-bound iron uptake starts with the binding of transferrin to surface receptors, followed by internalization into the endosomal system, release of iron mediated by the acidification of the endosome, reduction possibly mediated by Steap3, and transport into the cytosol by endosomal DMT1. Once in the cytoplasm, Fe^{2+}

becomes part of the labile or reactive iron pool where it distributes to mitochondria, neuromelanin and ferritin or engages in electron exchange reactions (Kakhlon & Cabantchik, 2002; Kruszewski, 2003). All the components described in Figure 1 have been detected in the brain (Haeger et al., 2010; Moos et al., 2007; Rouault et al., 2009), with the exception of Steap3, described in erythroid precursor cells (Ohgami et al., 2005).

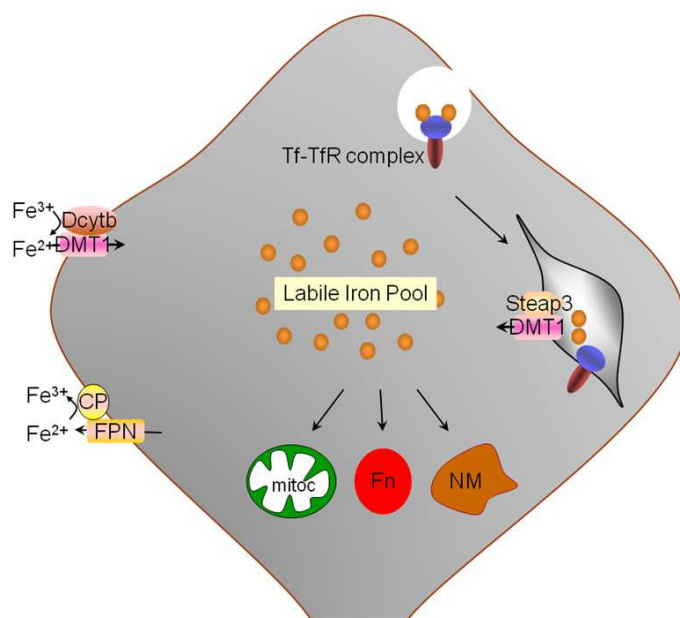


Fig. 1. **Components of neural iron homeostasis.** The molecular components comprise the transferrin-transferrin receptor complex, inflow (DMT1) and efflux (ferroportin, FPN1) iron transporters, the iron storage protein ferritin, the ferrireductase Dcytb, responsible for the reduction of Fe^{3+} prior to transport by DMT1 and the ferroxidase ceruloplasmin, responsible for the oxidation of Fe^{2+} after transport by FPN1 and prior to Fe^{3+} binding to apoTf.

The mammalian DMT1 gene undergoes alternative splicing. The 1A and 1B mRNA DMT1 variants originate from alternative splicing at the 5' end (exons 1A and 1B), while the +IRE or -IRE variants originate from splicing on the 3' end (exons 16/16A and 17) (Hubert & Hentze, 2002). These variants give rise to four DMT1 protein isoforms, all of them active in Fe^{2+} transport (Ludwiczek et al., 2007).

It is generally accepted that the two +IRE isoforms are post-transcriptionally regulated by the IRE/IRP system, which regulates translation of iron homeostasis proteins, which include the TfR, DMT1 and ferritin, in response to the concentration of reactive iron in the cytoplasm (Garrick & Garrick, 2009). Knowledge of differential transcriptional regulation of DMT1 expression is emerging. Both the inflammatory cytokine nuclear factor kappa B (NFkB) and the nuclear factor Y regulate DMT1(1B) expression in embryonic carcinoma cells (Paradkar & Roth, 2006). In contrast, hypoxia up regulates expression of the DMT1(1A) isoform, presumably through activation of hypoxia inducible factor 1b (HIF1b) (Lis et al., 2005; Wang et al., 2010a).

2.2 Iron essentiality in the brain

Iron is an essential element for the development of early cognitive functions. Late fetal and early postnatal iron deficiency causes learning and memory disabilities in humans that

persist following iron repletion (Lozoff et al., 1996; Grantham-McGregor & Ani, 2001; Beard & Connor, 2003; Felt et al., 2006). In animal models, nutritional iron deficiency interferes with hippocampus-depending learning (McEchron & Paronish, 2005; Ranade et al., 2008) and synaptic plasticity (Jorgenson et al., 2005). These functional failings have been ascribed to the iron requirements of metabolic pathways involved in neurotransmitter synthesis and myelin formation. Enzymes involved in neurotransmitter synthesis that contain iron as a prosthetic group are recognized targets of iron deficiency (Kwik-Urbe et al., 2000; Taneja et al., 1986; Youdim et al., 1980). Tryptophan hydroxylase, required for serotonin synthesis, tyrosine hydroxylase, required for dopamine and norepinephrine synthesis, monoamine oxidases A and B involved in dopamine catabolism, glutamate decarboxylase, involved in gamma-aminobutyric acid synthesis and glutamate transaminase, involved in L-glutamate synthesis, belong to this group.

Current understanding of the molecular mechanisms underlying the essential role of iron in neuronal function is in large part unknown. Just of late, a role for iron in synaptic plasticity and the associated postsynaptic Ca^{2+} signals has begun to emerge (Hidalgo et al., 2007; Hidalgo & Núñez, 2007). Recent work has shown that in hippocampal neurons, iron chelation with desferrioxamine blocks NMDA-induced calcium signals and the ensuing ERK1/2 activation (Muñoz et al., 2011). Moreover, iron chelation decreases basal synaptic transmission and inhibits iron-induced synaptic stimulation in hippocampal slices, and also impairs sustained long-term potentiation (LTP) induced by strong stimulation. Together, these results suggest that upon NMDA receptor stimulation, iron is required for the generation of calcium signals which in turn promote ERK1/2 activation, an essential step of sustained LTP.

Iron concentration in cerebrospinal fluid (CSF) ranges between 0.2 and 1.1 μM whereas transferrin concentration is around 0.24 μM (Symons & Gutteridge, 1998; Moos & Morgan, 1998). Thus, CSF iron often exceeds the binding capacity of transferrin, and non transferrin bound iron (NTBI) uptake is expected to occur in neurons that express DMT1.

In the brain, DMT1 is expressed in hippocampal pyramidal and granule cells, cerebellar granule cells, pyramidal cells of the piriform cortex, substantia nigra and the ventral portion of the anterior olfactory nucleus, striatum, cerebellum, hippocampus and thalamus, as well as in vascular cells throughout the brain and ependymal cells in the third ventricle (Gunshin et al., 1997; Williams et al., 2000; Burdo et al., 2001).

The pervasive presence of DMT1 in neurons suggests that this transporter is necessary for their regular function (Hidalgo & Núñez, 2007; Wright & Baccarelli, 2007; Pelizzoni et al., 2011; Muñoz et al., 2011). Hippocampal neurons express the 1B, but not the 1A, isoform (Haeger et al., 2010). Since expression of the 1B isoform responds to NF κ B, regulation of neuronal DMT1 levels by inflammatory stimuli is possible.

2.3 Iron toxicity

Iron is an intrinsic ROS producer. When one or more of its six ligand binding sites is not tightly bound iron becomes redox-active and capable to engage in one-electron exchange reactions producing free radicals (Graf et al., 1984). This is due to the occurrence of the Haber-Weiss and Fenton reactions. The thermodynamic balance of these reactions indicates that in the reductive environment of the cell, iron, in the presence of oxygen, catalyzes the consumption of GSH and the production of the hydroxyl radical (Halliwell, 2006b; Bórquez et al., 2008). In dopaminergic cells, another source of free radicals derives from the non-enzymatic oxidation of dopamine mediated by redox-active iron, resulting in semiquinones

and H_2O_2 production (Zoccarato et al., 2005). Thus, iron, both through the Fenton reaction or by dopamine oxidation, is a dangerous pro-oxidant agent.

Overwhelming evidence indicates that iron accumulation is a common feature of a number of neurodegenerative disorders of the central nervous system that include Huntington's disease, Alzheimer's disease, Friedreich's ataxia, Amyotrophic lateral sclerosis (ALS) and Parkinson's disease (Jellinger, 1999; Sayre et al., 2000; Bartzokis et al., 2000; Perry et al., 2003; Zecca et al., 2004; Berg & Youdim, 2006; Wilson, 2006; Weinreb et al., 2011).

Iron accumulation has been demonstrated in the dopaminergic neurons of the substantia nigra pars compacta (Youdim et al., 1989; Hirsch et al., 1991; Gorell et al., 1995; Vymazal et al., 1999). Interestingly, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a drug that causes experimental Parkinson's disease up regulates DMT1(+IRE) protein expression in mice ventral mesencephalon, where it increases neuronal death presumably through abnormal increases in cellular iron content (Salazar et al., 2008; Jiang et al., 2010). Additionally, DMT1(-IRE) mediates L-DOPA neurotoxicity in primary cortical neurons (Du et al., 2009).

The position of iron dishomeostasis in the progression of events leading to neuronal death is unknown, since iron accumulation has been detected in tissue from patients who have died after the final steps of the pathology. Nevertheless, since neuronal death caused by MPTP or 6-hydroxydopamine intoxication is blocked by pharmacologic or genetic chelation of iron (Kaur et al., 2003; Shachar et al., 2004; Youdim et al., 2004; Youdim & Buccafusco, 2005; Zheng et al., 2010) or by dysfunction of the iron transporter DMT1 (Salazar et al., 2008), it is possible that iron dishomeostasis takes place in the late stages of the disease as part of a vicious cycle resulting in uncontrolled oxidative damage and cell death. A recent study in mesencephalic dopaminergic neurons shows that low (0.25-0.5 μ M) concentrations of MPP+, the active metabolite of MPTP and a potent mitochondrial complex I inhibitor, induces neuritic tree collapse without loss of cell viability (Gómez et al., 2010). This collapse was effectively prevented by decreasing iron supply or by the addition of antioxidants. Thus, it seems plausible that increased intracellular iron is involved in the early steps of dopaminergic neuron dysfunction.

Iron toxicity is not restricted to dopaminergic neurons. Neurotoxic concentrations of NMDA induces iron-induced the NO-Dexas1-PAP7 signaling cascade in glutamatergic PC12 cells. Upon activation, PAP7 binds to intracellular DMT1 and relocates it to the plasma membrane. Increased intracellular iron, the physiological function of DMT1, increases the production of hydroxyl radicals. Thus, the DMT1-iron uptake-hydroxyl radical signaling pathway appears to mediate NMDA neurotoxicity (Cheah et al., 2006).

3. Decreased mitochondrial Fe-S cluster synthesis as a consequence of complex I dysfunction

3.1 Mitochondrial complex I inhibition in PD

Decreased activity of mitochondrial complex I, found in post-mortem tissue of PD patients (Schapira et al., 1990; Tretter et al., 2004; Banerjee et al., 2009; Hattingen et al., 2009), is probably a founding event in neuronal death. Interestingly, this phenotype is replicated in experimental PD induced by MPTP intoxication, which induces parkinsonian symptoms in mice, primates and humans. Inhibition of complex I leads to impaired mitochondrial ATP production and an accelerated production ROS (Langston et al., 1983; Singer & Ramsay, 1990; Scotcher et al., 1990; Noll et al., 1992).

The association between complex I inhibition and PD is further supported by the observation that rats intoxicated with the selective inhibitor of complex I rotenone, develop a syndrome similar to PD, characterized by neuronal degeneration and the formation of inclusion bodies rich in alpha-synuclein (Betarbet et al., 2000). Likewise, inhibition of glutaredoxin 2, an enzyme involved in Fe-S synthesis, produced an alteration in iron metabolism in a model of Parkinson's disease (Lee et al., 2009). Additionally, mutations in mitochondrial proteins PINK-1 and DJ-1 result in a genetic form of PD, leading further support for an important role of mitochondria in PD neurodegeneration (Bonifati et al., 2003; Valente et al., 2004; Blackinton et al., 2005).

ROS seem to have a negative effect on complex I activity. Experiments with isolated synaptosomal mitochondria revealed that low concentrations of H_2O_2 decrease complex I activity by 10%. This relatively minor effect of H_2O_2 was additive to partial inhibition of complex I induced by low (5 nM-1 μ M) concentrations of rotenone (Chinopoulos & Adam-Vizi, 2001). Similarly, sub-mitochondrial particles exposed to O_2^- , H_2O_2 , or $\cdot OH$ presented decreased activity of NADH dehydrogenase, a marker of complex I activity (Zhang et al., 1990). Thus, an initial inhibition of complex I could generate a positive loop between ROS generation and further complex I inhibition.

3.2 Mitochondrial iron-sulfur cluster synthesis

By being the locus of heme and iron-sulfur (Fe-S) clusters synthesis, the mitochondria is an essential organelle for cell iron homeostasis (Rouault & Tong, 2005). Fe-S clusters, formed by the tetrahedral coordination of sulfur groups with Fe atoms, are small inorganic cofactors believed to be the first catalysts in the evolution of macromolecules. In eukaryotes the most common species of Fe-S clusters are the 2Fe-2S and 4Fe-4S forms (Rouault & Tong, 2005; Lill & Muhlenhoff, 2008; Ye & Rouault, 2010). Today, Fe-S clusters are found as prosthetic groups of a wide range of proteins. In mitochondria, proteins such as NADH dehydrogenase (complex I), succinate dehydrogenase (complex II), cytochrome c reductase (complex III) and aconitase contain Fe-S clusters. Fe-S clusters are also exported to cytosol for incorporation into cytoplasmic proteins that require them, such as aconitase, xanthine oxidase, glutamine phosphoribosyl pyrophosphate amidotransferase and nuclear proteins involved in DNA repair (Martelli et al., 2007). For a compendium of Fe-S clusters see The Prosthetic Groups and Metal Ions in Protein Active Sites (PROMISE) <http://metallo.scripps.edu/promise/MAIN.html>.

The biogenesis of Fe-S clusters in mitochondria has been proposed as a sensor of the cellular Fe status, being high Fe-S cluster levels indicative of high intracellular iron concentrations and vice versa (Rouault & Tong, 2005). Additionally, the loss of function of proteins involved in mitochondrial biogenesis of the clusters or in cluster export to the cytoplasm, has been associated with deregulation of cytoplasmic Fe metabolism, mitochondrial accumulation of Fe and clinical manifestations such as sideroblastic microcytic anemia, myopathy and ataxia (Rouault & Tong, 2008). Recent data from our laboratory indicate that inhibition of complex I by rotenone results in decreased synthesis of Fe-S clusters, as shown by the decreased activity of the Fe-S cluster-containing enzymes cytosolic aconitase, mitochondrial aconitase, xanthine oxidase and glutamyl phosphoribosyltransferase as well as the activation of cytosolic Iron Regulatory Protein 1 (IRP1) (Mena et al., 2011). We think that as a consequence of decrease synthesis of Fe-S complexes, and the consequent activation of IRP1, a decreased activity of complex I results in a false "low iron" signal that activates the iron uptake system.

In consequence, diminished Fe-S cluster synthesis could play a fundamental role in promoting the accumulation of iron observed in PD. Future research is needed to evaluate its participation in neurodegenerative diseases in which iron accumulation is observed.

4. Cell death in PD: necrosis, apoptosis or necroptosis?

The two main pathways of cell death in neurodegenerative and other ROS-related disorders are apoptosis and necrosis. Apoptosis, also termed “programmed cell death” is understood as a regulated process consisting in the activation of caspases by endogenous or external stress signals. Necrosis, morphologically characterized by a gain in cell volume, plasma membrane rupture and subsequent loss of intracellular contents, is considered as an uncontrolled form of cell death. Lately, evidence is accumulating indicating that necrotic death may be also regulated by a set of signal transduction pathways (Kroemer et al., 2009). A third cell death pathway is “necroptosis” or programmed necrosis. Necroptosis death begins by activation of death receptors and its execution involves the active disintegration of mitochondrial, lysosome and plasma membranes. Necroptosis participates in the pathogenesis of several diseases, including ischemic injury, neurodegeneration and viral infection (Vandenabeele et al., 2010). The execution step of necroptosis includes mitochondrial dysfunction, decreased ATP levels, increased oxidative stress and increased labile iron pool mediated by increased ferritin degradation (Vandenabeele et al., 2010).

While the evidence that iron overload in the brain causes necrotic death is scanty (Lobner & Ali, 2002; Maharaj et al., 2006), overwhelming evidence points to apoptosis as the most common pathway of death (Wang et al., 1998; Zaman et al., 1999; Barzilai et al., 2000; Kuperstein & Yavin, 2003; Liu et al., 2003; Zheng et al., 2005; Kooncumchoo et al., 2006; Xu et al., 2008; Kupersmidt et al., 2009; Shi et al., 2010; Ziv et al., 1997). The possible participation of necroptosis in neurodegenerative processes has not been explored but the common characteristics of redox-active iron, oxidative stress and mitochondrial dysfunction, all of which contribute to the execution of necroptosis, make possible that necroptosis may be involved in iron-associated neuronal death.

5. Inflammation and hepcidin – a nexus to iron dishomeostasis

In addition to iron accumulation, other event strongly associated with neuronal death in PD and other neurodegenerative disorders is the presence of inflammatory processes characterized by the occurrence of reactive microglia and the massive production of proinflammatory cytokines. Although both phenomena have been studied as independent events leading to the progression of disease, the recent identification in central nervous system of hepcidin, a hormone that mediates the relationship between systemic iron homeostasis and inflammation, might change our views.

5.1 Hepcidin, the master regulator of iron homeostasis

Hepcidin is a cationic peptide of 25 amino acids secreted into blood circulation by the liver. The mature peptide derives from a precursor of 84 amino acids that after two successive proteolytic cleavages generates the mature peptide. Hepcidin was initially described as a peptide with antimicrobial activity (Krause et al., 2000), however further studies revealed that it also acts as a major regulator of circulating iron levels (Nicolas et al., 2001; Pigeon et al., 2001).

Two processes contribute to the levels of circulating iron, the recycling of senescent red blood cells (RBC) and intestinal iron absorption. The recycling by spleen macrophages of heme iron from senescent RBC is the main contributor of iron to the circulation, providing about 95% of daily turnover. The recycling of RBC iron comprise the phagocytosis of senescent RBC, the release of the iron in the heme moiety of hemoglobin by heme oxygenase-1 and the subsequent release of this iron into the plasma mediated by FPN1 (De Domenico et al., 2008; Kovtunovych et al., 2010).

The physiological function of hepcidin is to down-regulate the levels of circulating iron. It does so by down-regulation of the iron exotransporter FPN1 in macrophages. The binding of hepcidin to FPN1 present in the plasma membrane of splenic macrophages induces the endocytosis of the complex and the subsequent degradation of FPN1 in the lysosome (Nemeth et al., 2004). The decreased levels of FPN1 lead to the accumulation of iron in macrophages and the decrease of circulating iron (Ganz, 2006).

Hepcidin synthesis is regulated by multiple stimuli that have an effect in the regulation of circulating iron levels: (i) increased iron levels induce an increase in hepcidin synthesis in the liver through a mechanism that depends on transferrin receptor 1 and 2, the hemochromatosis protein (HFE) and hemojuvelin/BMP (De Domenico et al., 2007; Gao et al., 2010); (ii) erythropoietin, a hormone that stimulates red blood cell production. Erythropoietin blocks hepcidin synthesis in order to increase circulating levels of iron necessary for hemoglobin synthesis (Wrighting & Andrew, 2006; Pinto et al., 2008); (iii) inflammatory stimuli, mainly the cytokine IL-6, that through stimulation of hepcidin synthesis reduces circulating levels of iron, preventing its use for the proliferation of pathogens (Wrighting & Andrews, 2006) and (iv) hypoxia, that through activation of the hypoxia inducible factor I down-regulates the synthesis of hepcidin in order to increase blood iron levels required for the synthesis of heme in new red blood cells, to counteract oxygen deprivation (Peyssonnaud et al., 2007).

The interaction of hepcidin with FPN1 generates an antiinflammatory response. Binding of hepcidin to FPN1 induces the recruitment and activation of the tyrosine kinase Janus kinase 2 (JAK-2) (De Domenico et al., 2009), which phosphorylates FPN1 in 2 adjacent tyrosines present in a cytosolic loop. Activation of JAK-2 allows for the phosphorylation and translocation to the nucleus of signal transducer and activator of transcription 3 (STAT-3), which induces the expression of genes that encode for proteins whose role is to suppress the inflammatory response (De Domenico et al., 2010a). Within them are the receptor for interleukin 17, a cytokine with antiinflammatory properties and the suppressor of cytokine signaling 3 (SOCS-3) (De Domenico et al., 2010b), a modulator that inhibits the transduction pathways associated with receptors for proinflammatory cytokines IL-6 and tumor necrosis factor-alpha (Crocker et al., 2008).

5.2 Hepcidin expression in the CNS

Hepcidin shows a wide distribution in the CNS, most notably in the midbrain, with a clear presence in the superior colliculus, the geniculate nucleus, some fiber bundles of the substantia nigra pars reticulata and the substantia nigra pars compacta (Zechel et al., 2006) and the striatum (Wang et al., 2010b). Hepcidin is expressed mainly in glial cells, as well as in neurons and endothelial cells of choroid plexus (Zechel et al., 2006; Marques et al., 2009). Hepcidin expression changes with age: increased mRNA levels of hepcidin in cortex, striatum and hippocampus have been observed with aging (Wang et al., 2010b).

As stated above, hepcidin synthesis is induced by inflammatory stimuli. Bacterial lipopolysaccharide (LPS), a potent inflammatory agent, induces liver hepcidin expression. LPS also increases hepcidin expression in the brain. After an intraperitoneal injection of LPS, a transient transcription of the gene for hepcidin ensues in the choroid plexus, which correlates with increased levels of pro-hepcidin in the cerebrospinal fluid (Marques et al., 2009). The highest hepcidin expression was observed at 3 hours returning to baseline levels 24 hours after the injection. Interestingly, LPS treatment induces a 10-fold increase in hepcidin expression in the substantia nigra (Wang et al., 2008), which correlates with a marked increase in iron levels observed in this region in PD.

5.3 FPN1 expression in the CNS

As described above, the iron transporter FPN1 is the receptor for hepcidin. The expression of this transporter-receptor in mouse brain is quite ubiquitous; it is present in oligodendrocytes, microglia, astrocytes and neurons (Song et al., 2010). Space-temporal expression of FPN1 in neurons is variable (Moos & Rosengren Nielsen, 2006). In young brain a high immunoreactivity is found in the neurons of the hippocampus and striatum (cell bodies and in projection fibers), a mild expression in the substantia nigra pars compacta and the superior colliculus and low expression in the substantia nigra pars reticulata (Boserup et al., 2011). In the adult brain, FPN1 immunoreactivity is lower in the projections of the striatum, but no differences have been found in neuronal cell bodies (Moos & Rosengren Nielsen, 2006).

An interesting fact is that the spatial distribution of FPN1 and hepcidin are similar. Although the effects of hepcidin on FPN1 levels can differ according to cell type (Chaston et al., 2008), the injection of hepcidin in mice lateral cerebral ventricle, causes a decrease in the levels of FPN1 in the cerebral cortex, hippocampus and striatum (Wang et al., 2010b), suggesting that their cellular targets in the brain generate the same response than that observed in macrophages, that is, iron retention inside the cells. This conclusion is strengthened by the fact that high doses of hepcidin produce an increase in the iron storage protein ferritin, thus indicating increased cellular iron concentration in these brain areas.

Unexpected for a high cell iron situation, in the hippocampus and cortex of rats treatment with hepcidin induces the decrease of both FPN1 protein and mRNA and an increase in total DMT1 (Li et al., 2011), a situation that should drive further iron accumulation.

Hippocampal neurons in culture treated with hepcidin also show a decrease in the expression of FPN1, which is reflected in a reduction of the iron released from these cells (Wang et al., 2010b). There are no studies in other cell types, however, and it is possible that the response in glial cells should be similar to neurons and macrophages, particularly since microglia cells derive from the same precursor cells that give rise to macrophages (Ginhoux et al., 2010).

5.4 Hepcidin - a nexus between inflammation and iron accumulation in PD

Reports of some cases of PD associated with head trauma (Lees, 1997) and encephalitis (Jang et al., 2009) strongly suggest that inflammation can promote this neurodegenerative disease. Currently, there is a growing array of evidences describing inflammatory properties in the parkinsonian brain. Indeed, many cases of PD are accompanied by general inflammation of the brain, with a dramatic proliferation of reactive amoeboid macrophages and microglia HLA-DR⁺ in the substantia nigra (McGeer et al., 1988). In the striatum, macrophage

proliferation is accompanied by high expression of pro-inflammatory cytokines such as TNF- α , IL-1 β , IFN- γ and IL-6 (Mogi et al., 1994; Muller et al., 1998), which are expressed by glial cells (Hirsch et al., 1998). Particularly, the presence of IL-1 β , IL-6 and TNF- α has been observed in cerebrospinal fluid and the basal ganglia of patients with PD (Nagatsu, 2002). In addition to increased expression of inflammatory cytokines by activated microglia, factors released by dead dopaminergic cells appear to increase the neuroinflammatory and immune response, leading to irreversible destruction of these cells (Orr et al., 2002).

In general, pro-inflammatory cytokines such as TNF- α and IL-1 have neurotoxic effects, while anti-inflammatory molecules are neuroprotective (Allan & Rothwell, 2001). Intriguingly, IL-6, a classical proinflammatory cytokine, has a dual effect, at low concentrations it protects for neuronal death while at larger concentrations it is highly toxic (Li et al., 2009).

It is not completely understood how the inflammatory response is generated in PD. It has been proposed that the inflammatory response is a product of the oxidative load induced by the metabolism of dopamine (DA). Deamination of DA by monoamine oxidase generates hydrogen peroxide (Gotz et al., 1994), whereas the not enzymatic auto-oxidation produces additionally DA quinones and semiquinones (Stokes et al., 1999). These metabolites, in conjunction with the highly toxic hydroxyl radical generated through the Fenton reaction, are likely to alter protein structure and decrease glutathione levels by generating increased oxidative stress (Halliwell, 2006a), which could lead to activation of an inflammatory response (Park et al., 1999; Di Loreto et al., 2004). In fact, antioxidants such as green tea polyphenols are strong inhibitors of the inflammatory response (Conner and Grisham, 1996; Singh et al., 2010), and may reduce the incidence of dementia, AD, and PD (Mandel et al., 2011).

An inflammatory component has also been observed in several animal models of PD: the injection of 6-hydroxydopamine, MPTP and rotenone generates microglial activation, astrogliogenesis and secretion of inflammatory cytokines (Barnum & Tansey, 2010). The injection of LPS, a potent inducer of inflammation, has also been used as a model of PD. Stereotaxic injection of LPS in the nigro-striatal pathway induced a strong macrophage/microglial reaction in substantia nigra, being the substantia nigra more responsive than the striatum to the inflammatory stimulus (Herrera et al., 2000). Furthermore, no detectable damage to either the GABAergic or the serotonergic neurons was observed, a demonstration of the particular sensitivity substantia nigra pars compacta neurons to inflammatory stimuli.

The abundant evidence for the existence of inflammatory processes in PD, and the induction of hepcidin synthesis by cytokines such as IL-6, suggest that brain hepcidin levels should be higher in inflammatory processes. Hepcidin should induce differential iron accumulation in the diverse cell types present in the brain, based in the different levels of expression of its receptor, FPN1. In the adult brain, the expression of FPN1 is lower in neurons than in glia, thus hepcidin would induce a redistribution of iron, accumulating it mainly in the glial cells, which would act as an "iron sponge". Additionally, the activation of the signal transduction pathway associated with the binding of hepcidin to FPN1, could reduce the inflammatory response generated during neurodegeneration. Alternatively, the decrease in FPN1 induced by hepcidin binding in neurons could result in increased iron accumulation and oxidative stress, which could accelerate the death of these cells.

Future studies on the participation of hepcidin on the dysregulation of iron homeostasis in glia and neurons as a response to inflammation, will provide valuable information about its protective or deleterious role in the progress of neurodegenerative diseases.

6. Glutathione metabolism in PD – a cause or a consequence of increased ROS and increased iron content?

The tripeptide glutathione (γ -L-glutamyl-L-cysteinylglycine) is the most abundant and the main antioxidant agent in the central nervous system, where it reaches mM concentrations (Meister & Anderson, 1983; Dringen et al., 2000). In its redox cycling, glutathione is present either in its reduced (GSH) form or its oxidized disulfide (GSSG) form, the ratio GSH/GSSG being faithful reflection of the redox state of the cell (Schafer & Buettner, 2001).

Early post-mortem studies revealed decreased levels of GSH in degenerating substantia nigra of PD patients (Perry et al., 1982; Sofic et al., 1988; Sian et al., 1994), the observation implicating that GSH depletion may play a major role in the neurodegenerative process. The question arises whether GSH depletion is an early event during the progression of the disease or a reflection of increased oxidative stress resulting, for example, from mitochondrial complex I inhibition or from iron accumulation.

Chronic sub-maximal inhibition of GSH synthesis in N27 dopaminergic cells results in about 50% inhibition of mitochondrial electron transport chain complex I without ensuing cell death, inhibition that was reversed upon removal of the inhibitor (Chinta & Andersen, 2006). Thus, increased oxidative stress generated by complex I inhibition should result in decreased GSH levels and further inhibition of complex I. Conversely, a decrease in GSH levels, provoked by unknown causes, could result in inhibition of complex I activity.

Iron induces the consumption of GSH. After exposure to increasing concentrations of iron, SH-SY5Y dopaminergic cells undergo sustained iron accumulation and a biphasic change in intracellular GSH levels, increasing at low (1-5 μ M) Fe and decreasing thereafter. Indeed, cell exposure to high iron concentrations (20-80 μ M) markedly decreases the GSH / GSSG molar ratio and the GSH half-cell reduction potential, which associated with loss of cell viability (Núñez et al., 2004).

It is therefore possible that a decrease in GSH levels is a consequence of the increased oxidative load produced by the increase in intracellular Fe. Nevertheless, increased iron and decreased GSH may be intertwined in a positive feedback loop, since in dopaminergic neurons the pharmacological reduction of GSH levels results in increased levels of TfR and an increased labile iron pool (Kaur et al., 2009). Thus, the question remains as to which of the three processes initiates the oxidative spiral, but a reasonable assumption is that if one of them ensues the others will follow.

7. A positive feedback loop in the death of neurons

We propose that inhibition of mitochondrial complex I by endogenous and/or exogenous toxins, and inflammatory processes produced by trauma or other causes, result in a vicious cycle of increased oxidative stress, increased iron accumulation and decreased GSH content (Figure 2). In this scheme, neuronal death linked to complex I dysfunction is brought about by a positive feedback loop in which complex I inhibition results in decreased Fe-S cluster synthesis, IRP1 activation, increased DMT1 and TfR expression and iron accumulation. Complex I dysfunction and increased cellular iron result in decreased GSH levels. Both increased oxidative stress and low GSH levels further inhibit complex I activity. Central to this scheme is the deregulation of iron homeostasis since iron chelators effectively block cell death and prevent early events in neurodegeneration such as neuritic tree shortening. Another input to this cycle is brought about by inflammatory cytokines that induce hepcidin synthesis which, by inducing FPN1 degradation, results in increased cellular iron.

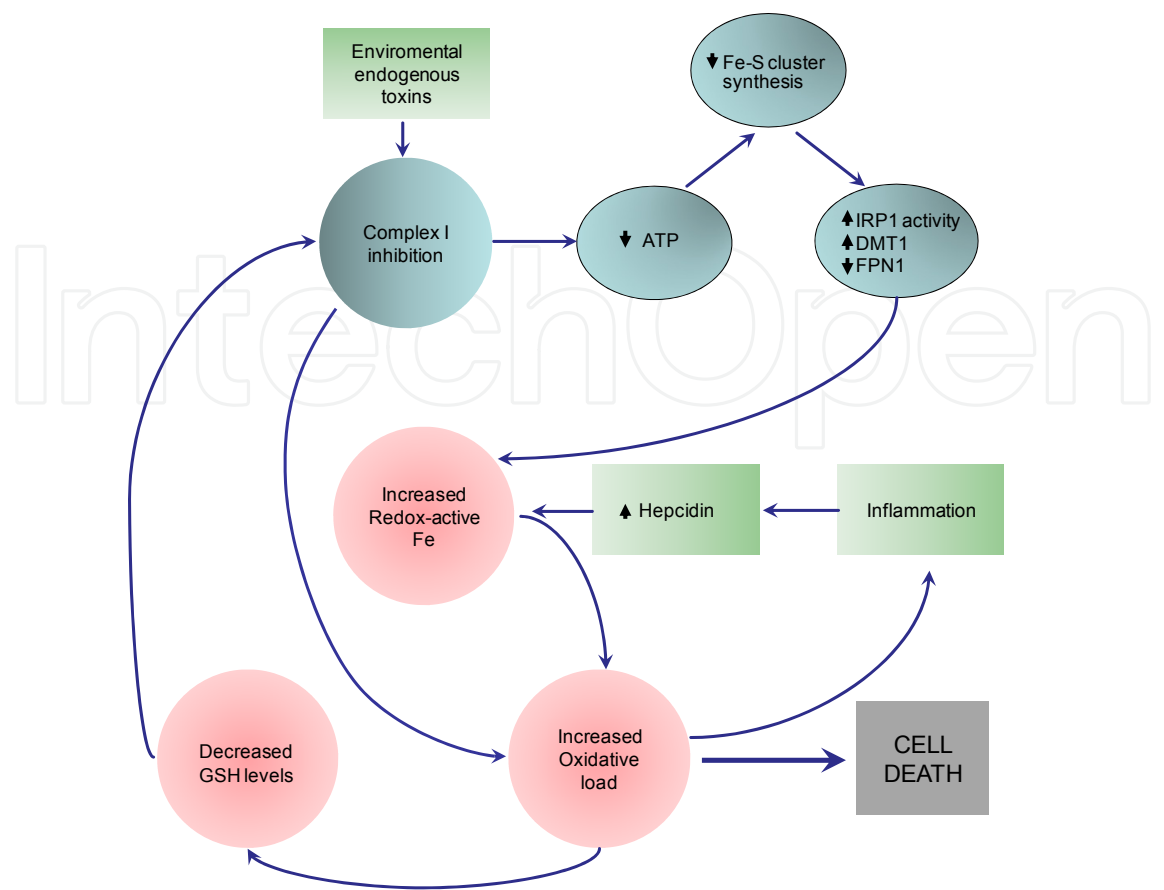


Fig. 2. **A positive feedback loop resulting in uncontrolled oxidative load.** Complex I inhibition results in decreased levels of ATP and decreased Fe-S synthesis (see text). Decreased Fe-S cluster synthesis results in activation of IRP1 that needs a 4Fe-4S cluster to acquire its inactive state. Increased IRP1 activity results in increased DMT1 and transferrin receptor and decreased FPN1 synthesis, which results in increased iron accumulation. Increased iron induces increased oxidative stress and GSH consumption. Both increased oxidative stress and decreased GSH produce further complex I inhibition.

8. Conclusion

Diminished activity of mitochondrial complex I, iron accumulation, oxidative stress and inflammation are common pathognomonic signs of sporadic PD. It is possible that the initiation of any one of these processes will initiate or enhance the others, through the generation of positive feedback loops that will produce apoptotic neuronal death. Intervention of these positive loops should result in prolonged life of the affected neurons. Still unanswered is the question of why substantia nigra pars compacta neurons are so particular prone to this dysregulation.

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Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. The main obstacle to developing neuroprotective therapies is a limited understanding of the key molecular mechanisms that provoke neurodegeneration. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Previously implicated culprits in PD neurodegeneration, mitochondrial dysfunction, and oxidative stress may also act in part by causing the accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons. Neurotoxin-based models have been important in elucidating the molecular cascade of cell death in dopaminergic neurons. PD models based on the manipulation of PD genes should prove valuable in elucidating important aspects of the disease, such as selective vulnerability of substantia nigra dopaminergic neurons to the degenerative process.

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