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REVIEW

Iron, cysteine and Parkinson's disease

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Abstract A short review of the role of cysteine and iron in the progression of Parkinson's disease is presented. The complex chemistry of cysteine and iron and its interactions are discussed and put into the context of oxidative stress during neurodegeneration.

Keywords Radicals · Quinones · Metal complexes · Amino acids · Bioinorganic chemistry

Introduction

Parkinson's disease (PD) is the most common neurodegenerative disease and affects approximately 2% of all people over 65 in Europe [1]. It is characterised by loss of dopaminergic neurons in the brain, particularly in the substantia nigra, and, in the vast majority of cases, the formation of Lewy bodies, which are abnormal aggregates of protein comprised mainly of α-synuclein.

Cysteine is a non-essential amino acid and is important for redox balance within the cell, signalling, and glutathione synthesis. Iron is essential and used in many metalloenzymes to carry out an array of chemical transformations. However, concentrations of both species must be regulated or they can have toxic effects. Cysteine/iron interactions are themselves complex and have important roles in the progression of neurodegeneration.

There is substantial evidence that the impairment of Complex I of the mitochondrial respiratory chain has an important role in the pathogenesis of PD [2]. Results from genetic studies [3] have shown that a threonine to alanine polymorphism of dehydrogenase 3 of Complex I significantly reduces risk of PD. Furthermore, administration of Complex I inhibitors [4], i.e. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat, and rotenone, replicate many of the features of PD. This impairment of Complex I suggests that oxidative stress is important in PD [5] and this view is supported by oxidative damage to DNA and protein that occurs in the brain during disease progression.

Oxidative stress describes a large number of different reactions involving many different participants. Oxidative stress can be initiated by catecholamines in the presence of iron and oxygen or peroxide leading to formation of 6-hydroxydopamine [6, 7]. Cysteine can also participate in oxidative stress through its complicated chemistry involving redox, coordination, and nucleophilic reactions, which are exacerbated by its interactions with the redox active transition metal iron. Indeed, combination of cysteine and iron has been reported to potentiate lipid peroxidation through formation of hydroxyl radicals [8].

Concentrations and location of cysteine and iron

In vivo both iron and cysteine levels are strongly controlled because of their potentially toxic effects. Iron is well known to catalyse Fenton-type reactions when suitably coordinated and a significant amount of work has been carried out to investigate these types of reactions [9]. Likewise, the role of elevated levels of cysteine in neurodegeneration has been extensively discussed [10–17]. Cysteine is neuroexcitatory and is believed to interact with the *N*-methyl-D-aspartate (NMDA) receptor [13], allowing Ca^{2+} ions to enter the cell leading to apoptosis. Because

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cysteine's toxicity is attenuated by zinc cations, it has been suggested that ZnCys complexes block the NMDA receptors. Indeed, zinc binding to cysteine is strong ($\log K_1 = 9.04$, $\log K_2 = 8.50$) and the stability constants show zinc can compete successfully with iron (Table 2) for the formation of a cysteine complex. Both these metals are increased during PD [18], however, iron is in higher concentrations and reacts with cysteine to form cystine.

Table 1 collates representative data obtained from patients with PD and controls. One can see that cysteine levels are approximately 250 μM in plasma and this increases after the onset of PD. Interestingly, this increase appears to be higher after levodopa treatment, still the main treatment of PD. Iron levels are also seen to increase dramatically after the onset of PD but only significantly in the substantia nigra [19]. As can be seen from Table 1, although there is an increase, the absolute values depend upon how the samples are treated before measurement.

Chemical reactivity of cysteine and iron

Iron is present mainly as iron(II) and iron(III), although it can reach higher oxidation states in highly oxidising environments during the Fenton reaction [9]. Unless it is complexed, iron(III) tends to form insoluble hydroxides and oxides and iron(II) is prone to oxidation at physiological pHs. Iron's chemistry is therefore dominated by coordination compounds and its accessible redox potential allows it to react with many different compounds. For example, iron(II) tends to bind dioxygen whereas iron(III) can oxidise organic compounds or initiate radical reactions.

Cysteine's reactivity is dominated by the thiol group, which can act as an excellent nucleophile when deprotonated and is easily oxidised. Reactions include the formation of disulfides, thioethers, thioacetals, and thioesters.

Cysteine forms complexes with both iron(II) and iron(III), binding stronger to iron(III). Binding appears to occur through the amine nitrogen and the thiolate sulfur judging by the structure of the non-haeme mono-iron enzyme cysteine dioxygenase with substrate bound [20]. The iron(III) complexes are, however, not stable and undergo internal electron transfer [21, 22] to form the thiyl radical, which unless otherwise trapped, combines with another thiyl radical to form cystine. It is this radical chemistry that explains why the combination of cysteine and iron has been reported to potentiate lipid peroxidation [8].

Speciation

Iron is present mainly as iron(III) at pH 7 and with suitable coordination, it is stabilised against precipitation as hydroxo species. Iron(II) is also present and in this case is stabilised in vivo usually by strong-field nitrogen donors.

At physiological pH the carboxyl group of cysteine is deprotonated and the amine group is protonated. The value of pK_{SH} can largely be associated with $\log K_2$ (8.13) due to the large separation of the $\log K$ values although microconstants are available [23]. This value of pK_{SH} means that at physiological pHs the thiol is present in both protonated and deprotonated forms and this fact dominates reactivity.

Table 1 Concentrations of cysteine and iron in both controls and patients with Parkinson's disease

	Location	Control	Patients with Parkinson's disease
Cysteine [48]	Plasma	220 μM	260 μM levodopa treated
Cysteine [49]	Plasma	280 μM	490 μM levodopa treated
			340 μM before levodopa treatment
Total iron [18]	Substantia nigra	10,000 nmol/g dry weight	13,000 nmol/g dry weight
Total iron [50]	Substantia nigra	860 nmol/g fresh weight	1,522 nmol/g fresh weight

Table 2 Physical data for cysteine and its interactions with iron

Protonation consts.	$\log K_1$	10.11[a]	$\log K_2$	8.13[a]	$\log K_3$	~2[b]
Stability consts.	Iron(II) $\log K_1$	6.66[c]	Iron(III) $\log K_1$	13.70[d]		

To aid comparison, constants measured under similar temperatures and the same ionic strength have been chosen

[a] 25 °C, 0.1 M KNO_3 [51]

[b] Published values vary greatly; glass electrodes do not function properly at very low pHs

[c] 20 °C, 0.1 M $NaClO_4$ [23]

[d] 25 °C, 0.1 M KNO_3, determined through kinetic experiments as iron(III) oxidises cysteine anaerobically [52]

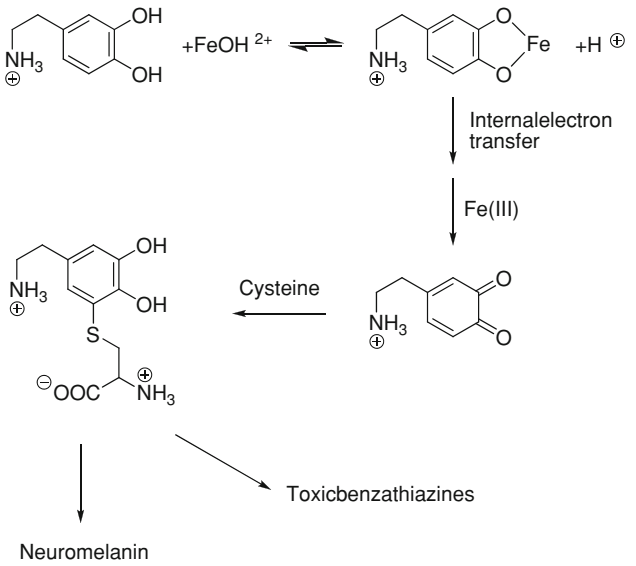

Fig. 1 Reaction pathway by which 5-cysteinyldopamine can be formed from iron(III), dopamine, and cysteine. In healthy cells, 5-cysteinyldopamine is used to form neuromelanin but during neurodegeneration it may also further react to form toxic benzathiazines

Cysteine as a nucleophile

The thiolate group acts as an extremely effective nucleophile, able to attack quinones and other electrophiles. In dopaminergic neurons (Fig. 1), cysteine is able to attack the 5-position of dopaminoquinone to form 5-cysteinyldopamine [24], which is an important component of neuromelanin [25–28]. Neuromelanin is formed in dopaminergic neurons and is a polymer formed from oxidation products of catecholamines. It forms spherical particles, granules, of approximately 30 nm in diameter with a pheomelanin core suggesting a kinetic model in which cysteine is initially used up to form 5-cysteinyldopamine before eumelanin is formed [27]. However, although cysteine reacts rapidly with quinones it seems to attenuate melanin formation in vitro [24].

It is not known, however, whether cysteine addition to dopaminoquinone is the source of 5-cysteinyldopamine in vivo or whether initially glutathione attacks to form 5-glutathionyldopamine followed by cleavage by gamma-glutamyl transpeptidase and peptidase [11]. Dopaminoquinone itself is formed by oxidation of dopamine by iron(III) [29] or oxygen [30] or both [7] and, indeed, all catecholamines undergo similar chemistry [11]. Iron concentrations increase during the onset of Parkinson's disease (see Table 1) and this could be caused by 6-hydroxydopamine, formed from dopamine, releasing iron from the iron storage protein ferritin [31]. The iron that is released could then be bound to melanin [28, 32] where it could also promote oxidative stress.

Work by Dryhurst [33–36] has shown that 5-cysteinyldopamine is not the final product and the reduced redox potential of subsequent species leads to a cascade of toxic benzathiazines that have been shown to produce Parkinson-type symptoms in rats [35, 36].

Cysteine oxidation

Cysteine can be oxidised in a number of different ways. One-electron oxidation can occur anaerobically after complexation with iron(III) resulting in the thiyl radical [21, 22]. This radical, in most cases, combines with another thiyl radical to form cystine but can also combine with dioxygen to form the thiol peroxyl radical [37]. Dioxygen is well known to oxidise cysteine to form the disulfide. This reaction is catalysed by ions of many transition metals including copper and iron [38]. The kinetics are complicated because the peroxide formed can also react. The main product is disulfide except at low cysteine concentrations when sulfenate, sulfinate, and sulfanate are also formed [39, 40].

Cysteine can also be oxidised by hypohalous acids [41] and at high pH the sulfenate can be observed transiently (although ultimately the main product is the disulfide with small amounts of oxygenated products including the sulfinate). Because hypohalous acids are produced during inflammatory response by myeloperoxidase a redox cascade may start with the oxidation of cysteine [42] and therefore these reactions may well be important in the progression of oxidative stress. Indeed, myeloperoxidase levels increase in patients suffering from PD [43].

Enzymatic breakdown of cysteine

The main enzymatic route for cysteine breakdown is given in Fig. 2. The initial step involves the oxidation of the thiol group to the sulfinate [44]. This reaction is catalysed by the non-haeme mono-iron enzyme cysteine dioxygenase [45] [CDO, (EC 1.13.11.20)]. In rats it has been shown that CDO is degraded by the 26-S proteasome system [46]. The ubiquitin–proteasome system is used to degrade misfolded and damaged proteins. The 26-S proteasomes are multi-subunit proteases found in the cytosol. A characteristic feature of PD is the presence of Lewy bodies containing normal and damaged proteins including ubiquitin, neurofilaments, parkin, α-synuclein, and others. It is not yet fully understood how Lewy bodies are formed but this may be linked to the ubiquitin–proteasome system failing [47] leading to subsequent failing of the initial step of cysteine oxidation by CDO.

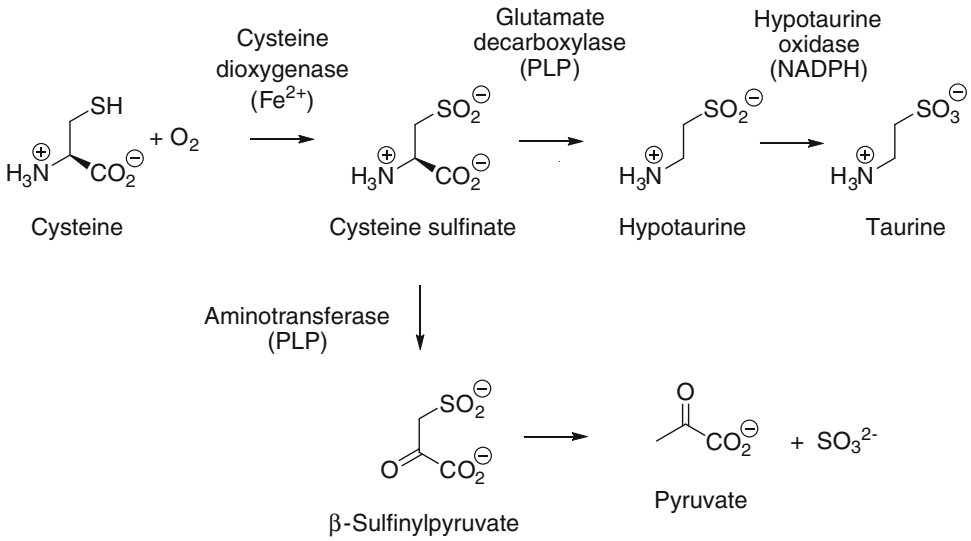

Fig. 2 The enzymatic pathway by which cysteine is broken down via cysteine sulfinate in the brain. The cofactor for each enzyme is given in *brackets*. Fe^{2+} high-spin iron(II), *PLP* pyridoxal-5′-phosphate, *NADPH* reduced nicotinamide adenine dinucleotide phosphate. The last step from *β*-sulfinylpyruvate to pyruvate is believed to be spontaneous

Conclusions

During the progression of PD the concentrations of cysteine and iron are allowed to significantly increase leading to oxidative stress through a number of different mechanisms. These processes include complex formation, redox reactions, and enzymatic reactions. Although a large amount of the basic chemistry of cysteine and iron is well characterised there is still a lot that is not yet fully understood about their role in vivo. For example the underlying reasons for the lack of control of the concentrations of cysteine and iron remain a serious unresolved problem. This area is proving to be a very fertile ground for further research.

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