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Dopamine mediated iron release from ferritin is enhanced at higher temperatures: Possible implications for fever-induced Parkinson's disease

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Abstract

A new molecular mechanism is proposed to explain the pathogenesis of fever-induced Parkinson's disease. This proposal is based on dopamine and 6-hydroxydopamine-mediated free iron release from ferritin magnetic nanoparticles, which is enhanced at higher temperatures, and which may lead to substantial peroxidation and injury of lipid biomembranes of the substantia nigra in the brain.
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1. Introduction

Iron represents a paradox for living systems by being essential for a wide variety of metabolic processes, but also having the potential to cause harmful effects [1]. Most brain iron is stored in an inactive form encapsulated as magnetic nanoparticles in the protein, ferritin. This ubiquitous protein consists of an iron core and a shell of 24 subunits, which are assembled into two different molecules: L-ferritin (19 kDa) and H-ferritin (21 kDa), the ratios of which vary between tissues. The increased amounts of iron in the substantia nigra (SN) might be a sign of a free, redox active iron which is able to induce oxidative stress [2,3].

Parkinson's disease (PD) is a neurologically based disorder first described by Parkinson in 1817 that affects approximately 1% of the world's population over 55 years in age. It is characterized by hypokinesia, rigidity, and tremor, and can be related to an extreme deficiency of the neurotransmitter dopamine in the striatum [4].

A central role of iron in the pathogenesis of PD, due to its increase in substantia nigra pars compacta dopaminergic neurons and reactive microglia and its capacity to enhance production of toxic reactive oxygen radicals, has been discussed for many years. Recent transcranial ultrasound findings [5] and the observation of the ability of iron to induce aggregation and toxicity of synuclein have

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reinforced the critical role of iron in the pathogenesis of nigrostriatal injury. Because many neurodegenerative diseases show increased accumulation of iron at the site of neurodegeneration, it is believed that maintenance of cellular iron homeostasis is crucial for the viability of neurons. Oligodendrocytes, microglia and astrocytes contain high levels of ferritin and the number of ferritin-positive astrocytes increases with advancing age. In PD, the number of ferritin-immunoreactive microglial cells in the SN increases dramatically with many reactive microglial cells located in close proximity to melanin-containing or degenerating neurons [6]. This might be of importance for the pathogenesis of PD because iron release from ferritin induced by activated microglia has been demonstrated and a contribution of iron released from ferritin to free radical-induced cell damage has been shown [7].

Recently a plausible mechanism for the propagation of cytotoxins involved in Parkinsonism has been proposed [8] based on the following steps: Iron (II) interacts with peroxide via Fenton's reaction producing OH-radicals of Fe(IV) ferryl species. They can readily oxidize the neurotransmitter dopamine to the neurotoxic 6-hydroxydopamine (6-OHDA) which is a strong reducing agent. The produced 6-OHDA, in turn, is able to reduce and possibly release iron, as iron(II), from the iron storage protein ferritin. This cycle of events may explain the development of Parkinson's disease due to the continuous production of cell-damaging species.

It has been reported that Parkinson's disease might occur as a result of a long periods of high temperature (fever), and this has been associated with acidosis [9].

As an alternative hypothesis, we are suggesting that the key molecular factor in fever-induced Parkinsonism may be dopamine and/or 6-OHDA-mediated enhanced free iron release from ferritin at higher temperatures.

2. Materials and methods

2.1. Chemicals

Horse spleen ferritin, ferrozine (3-(2-pyridyl)-5,6-bis(4-phenylsulfonic acid)-1,2,4-triazine), dopamine, 6-OHDA, TBA (2-thiobarbituric acid), and trichloric acid were obtained from Sigma (St. Louis, USA). Other chemicals were from commercial sources and were of the highest analytical grade.

2.2. Iron release assay

Iron reduction and release was determined by the spectrophotometric measurement of the iron-ferrozine complexes [10,11]. Reaction mixture containing ferritin (200 μg/ml), ferrozine (200 μM), and 6-hydroxydopamine (100 μM) or dopamine (100 μM) was incubated at various physiological temperatures (36–42 °C) in 10 mM phosphate buffered saline. The absorbance at 562 nm (the absorption coefficient of iron–ferrozine complex is $27\,900\ M^{-1}\,cm^{-1}$) was measured against a blank containing the same reaction mixture except 6-OHDA (or dopamine) using a spectrophotometer Specol 210 (Carl Zeiss, Jena, Germany).

2.3. Lipid peroxidation measurement

Extent of lipid proxidation at various temperatures was determined by measuring thiobarbituric acid reactive substances (TBARS) [12,13]. The reaction mixture described above was combined with phosphatidylcholine liposomes (5 μmol/ml) and 45 min after dopamine or 6-OHDA addition, TBA reagent consisting of 15% trichloric acid, 0.375% TBA and 0.5% HCl was added and heated at 100 °C for 15 min. After cooling in ice-cold water, the mixture was centrifuged at $1250 \times g$ for 10 min. The absorbance of the supernatant at 535 nm was read against a blank containing 2 ml TBA and 1 ml distilled water. The concentration of TBARS was calculated using the molar absorption coefficient of $156\,000\ M^{-1}\,cm^{-1}$.

3. Results and discussion

Figs. 1 and 2 show that both dopamine and 6-OHDA lead to release of iron from horse spleen ferritin and that the release at 42 °C is almost four times higher than at 36 °C for dopamine and five

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