Iron as a therapeutic target for Parkinson's disease

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Résumé

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ABSTRACT
Iron enrichment in the substantia nigra pars compacta (SNc) reflects an involvement in dopamine metabolism and fuelling neuronal activity. In Parkinson's disease (PD), a progressive damage of the SNc is associated with the appearance of siderotic foci, largely caused by increased labile iron levels resulting from an imbalance between cell iron import, storage and export. At the molecular cell level, mutations in a-synuclein cause alterations in dopamine and iron transport. Those alterations might trigger an iron-dependent cell death pathway, ferroptosis, offering new prospects for treatment. The application of iron-sensitive sequences in magnetic resonance imaging has become a useful tool to identify early stages of nigral pathology. In mammalian models, chelators that strongly scavenge intracellular iron protect against oxidative neuronal damage. Moderate iron chelation, with deferiprone, that conserves systemic iron offers a novel therapeutic strategy for neuroprotection. Iron can be scavenged from labile iron complexes in the brain and transferred either to higher-affinity acceptors in cells or extracellular transferrin. Promising preclinical and clinical proof of principle trials have led to a current large randomized clinical trial that aims to demonstrate the efficacy of conservative iron chelation. Outcomes could provide a first-in-class treatment strategy to slow disease progression.

Mots-Clés: Parkinson's disease, iron

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