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Hemochromatosis associated with Parkinson's Disease

Hemocromatose associada à Doença de Parkinson

Hemocromatosis asociada con la Enfermedad de Parkinson

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Abstract
Iron is an essential mineral found in all living organisms and plays a key role in numerous physiological processes, including growth, development, and various cellular functions. This study aims to review the literature on the association between iron metabolism, hemochromatosis, and Parkinson's disease (PD), assessing how iron accumulation may negatively affect health and potentially contribute to the development or progression of PD. This is a qualitative literature review conducted in August 2024. The research was carried out using the Scopus and PubMed databases, resulting in the selection of 25 studies. The objective was to analyze the role of iron accumulation in PD, identifying patterns and gaps in current evidence. In the nervous system, iron plays a critical role in mitochondrial respiration, myelin formation, and neurotransmitter metabolism—functions essential for maintaining neuronal health and cognitive performance. However, excess iron can lead to the production of free radicals, causing oxidative damage that significantly contributes to the onset of various pathological conditions. Since the human body lacks widely efficient mechanisms to eliminate excess iron, the regulation of its absorption, transport, and storage is crucial to prevent toxicity and its harmful effects on the nervous system.
Keywords: Hemochromatosis; Parkinson's disease; Physiology.

Resumo
O ferro é um mineral essencial presente em todos os organismos vivos e é fundamental para inúmeros processos fisiológicos, como crescimento, desenvolvimento e diversas funções celulares. Este estudo tem como objetivo realizar uma revisão da literatura sobre a associação entre metabolismo de ferro, hemocromatose e doença de Parkinson (PD), avaliando como o acúmulo de ferro pode impactar negativamente a saúde, potencialmente contribuindo para o desenvolvimento ou piora da PD. Trata-se de uma revisão qualitativa da literatura realizada em agosto de 2024. A pesquisa foi conduzida nas bases Scopus e PubMed, resultando na seleção de 25 estudos. O objetivo foi analisar o papel do acúmulo de ferro na PD, identificando padrões e lacunas nas evidências atuais. No sistema nervoso, o ferro desempenha papel crítico na respiração mitocondrial, na formação de mielina e no

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metabolismo dos neurotransmissores, com essas funções sendo essenciais para a manutenção da saúde neuronal e do desempenho cognitivo. No entanto, o excesso de ferro pode gerar radicais livres, resultando em danos oxidativos que contribuem significativamente para o desenvolvimento de diversas condições patológicas. Como o corpo humano não possui mecanismos amplamente eficientes para eliminar o excesso de ferro, regular a absorção, transporte e armazenamento é essencial para prevenir toxicidade.
Palavras-chave: Hemocromatose; Doença de Parkinson; Fisiologia.

Resumen
El hierro es un mineral esencial presente en todos los organismos vivos y desempeña un papel clave en numerosos procesos fisiológicos, como el crecimiento, el desarrollo y diversas funciones celulares. Este estudio tiene como objetivo revisar la literatura sobre la asociación entre el metabolismo del hierro, la hemocromatosis y la enfermedad de Parkinson (EP), evaluando cómo la acumulación de hierro puede afectar negativamente la salud y contribuir potencialmente al desarrollo o progresión de la EP. Se trata de una revisión cualitativa de la literatura realizada en agosto de 2024. La investigación se llevó a cabo utilizando las bases de datos Scopus y PubMed, con la selección de 25 estudios. El objetivo fue analizar el papel de la acumulación de hierro en la EP, identificando patrones y lagunas en la evidencia actual. En el sistema nervioso, el hierro es fundamental para la respiración mitocondrial, la formación de mielina y el metabolismo de los neurotransmisores, funciones esenciales para mantener la salud neuronal y el rendimiento cognitivo. Sin embargo, el exceso de hierro puede provocar la producción de radicales libres, causando daño oxidativo que contribuye significativamente a la aparición de diversas condiciones patológicas. Dado que el cuerpo humano carece de mecanismos eficaces para eliminar el exceso de hierro, regular su absorción, transporte y almacenamiento es crucial para prevenir la toxicidad y sus efectos nocivos sobre el sistema nervioso.
Palabras clave: Hemocromatosis; Enfermedad de Parkinson; Fisiología.

1. Introduction

Iron is a vital element present in all living organisms, playing a key role in various physiological functions such as growth and development. The body tightly regulates iron levels through a series of metabolic pathways, ensuring its proper absorption, transport, storage, and utilization. This regulation is critical to maintain iron homeostasis and prevent both deficiencies and toxicities, with specific mechanisms and regulatory proteins involved in managing iron's biological processes effectively (Vogt, 2021).

Furthermore, iron is critical for proper brain function. It significantly contributes to various cellular processes in the nervous system, including mitochondrial respiration, myelin formation, and neurotransmitter metabolism. These processes are fundamental for maintaining neuronal health and optimal cognitive performance. However, excessive iron accumulation can lead to severe oxidative damage, as excess iron promotes the generation of free radicals. These free radicals have the potential to damage cells and tissues, contributing to various pathological conditions. Given the lack of a widespread export system for excess iron in the body, maintaining strict control over iron absorption, transport, and storage is of utmost importance. Such regulation ensures that iron fulfills its cellular functions correctly and prevents its levels from becoming toxic (Hinarejos, 2020; Kulaszyńska, 2024; Afzal, 2023).

This study aims to conduct a comprehensive analysis of the available literature on the association between hemochromatosis and Parkinson's Disease. The objective is to investigate how hemochromatosis may negatively impact the health of affected individuals by evaluating evidence on the relationship between excessive iron accumulation and the development or progression of Parkinson's Disease.

2. Methodology

A systematic literature review research of a quantitative nature in relation to quantity of articles and qualitative in relation to discussions (Pereira et al., 2018) was carried out regarding the number of selected articles and qualitative regarding the discussion about the articles.

This study is a qualitative literature review conducted in August 2024, aiming to investigate the relationship between iron accumulation in the central nervous system and Parkinson's Disease (PD). The search was performed in the Scopus and PubMed databases using combinations of controlled descriptors such as "Hemochromatosis," "Parkinson's Disease," and "Iron Overload". These combinations facilitated the identification of relevant articles addressing both iron accumulation and its pathophysiological implications in PD.

Initially, the search yielded 129 articles, which underwent screening based on their titles and abstracts. Following this step, 21 articles were selected for full-text review. Four articles were subsequently excluded for failing to meet the inclusion criteria, resulting in 17 articles forming the primary body of the review. Additionally, targeted searches without predefined strategies were conducted to supplement the review with pertinent information as needed during the study's development.

The inclusion criteria comprised review articles and clinical trials published within the last 10 years, available in open access, and written in English or Portuguese. Both in vitro and in vivo studies conducted on humans or animal models of Parkinson's Disease were considered, with a focus on analyzing the role of iron and the pathological mechanisms involved. Exclusion criteria included articles with limited relevance to the proposed topic, studies addressing other pathologies unrelated to PD, and articles employing methodologies outside the scope, such as case reports or observational studies lacking relevant experimental data.

The selection and analysis process followed the principles of integrative review, allowing for a comprehensive and contextual understanding of the available evidence on the impact of iron in Parkinson's Disease. The qualitative analysis of the studies aimed to identify patterns, inconsistencies, and gaps in the current literature, contributing to a critical synthesis of iron's role and its potential influence on the neurodegenerative mechanisms of PD.

3. Results

A study involving 39,533 participants identified alterations in ferric levels and gray matter atrophy in eight distinct brain regions through magnetic resonance imaging. However, only three regions (the caudate nucleus, substantia nigra, and putamen) demonstrated a direct relationship with Parkinson's Disease (PD). Additionally, genes associated with this iron accumulation were identified, indicating a genetic basis for this condition. Nevertheless, there is no clear evidence to determine whether this accumulation is a cause or consequence of the disease (Casanova et al., 2024; Camona et al., 2024; Negida et al., 2024; Ci et al., 2020).

The pathophysiology and role of metals in the progression of PD remain under investigation and are often controversial. In an animal model of PD, an edematous process in the striatum suggested a vasogenic cause linked to blood-brain barrier damage as a potential mechanism for iron accumulation. Moreover, microglial activation in the affected region implies a pathological effect of iron aggregates, as microglia can degrade neuromelanin, a protein that stores iron in neurons (Ward, 2022; Ruan 2022).

The role of astrocytes in iron storage and regulation in the central nervous system was also identified. Astrocytes can secrete ferritin, safely and non-reactively storing iron. However, alterations in enzymes such as ceruloplasmin, which control ferritin storage in astrocytes, may disrupt iron homeostasis, leading to accumulation. Transferrin, capable of removing iron from neurons, also plays a role and changes in the expression of its receptors may be associated with PD; its concentration is reduced in PD models (Jiménez, 2021).

In animal models of Parkinson's Disease, disruptions in lipid metabolism homeostasis (cholesterol, lipolysis, and deacylation) associated with iron accumulation have been linked to oxidative stress and damage. The reaction of iron with hydrogen peroxide can result in hydroxyl radicals (OH-), leading to cell death. While such alterations occur throughout the

brain, they are particularly significant in the midbrain for PD progression. A reduction in dopaminergic neurons and substancia nigra in the midbrain coincided with biomarkers associated with ferroptosis, suggesting a direct role in neurodegeneration and cell death (Maniscalchi, 2024, Sanchez Campos et al., 2015; Li et al. 2021; Jiménez-Jimenéz et al., 2021).

Mitochondrial dysfunction has also been identified in animal models of PD. Free iron accumulation induces mitochondrial oxidative damage by altering membrane potential. Overexpression of specific genes increases the storage of iron in an unsafe, reactive form, while the absence of genes protecting dopaminergic neurons from oxidative stress also plays a critical role in the pathology. This highlights the complex, multifaceted nature of the mechanism, involving both the activation and deletion of various genes. Henrich (2023); Cheng (2022)

A recent study (Xiao, 2024) explored the convergence of ferroptosis pathways, iron accumulation, and mitochondrial alterations, resulting in substantia nigra deterioration in PD due to iron-induced mitochondrial changes and subsequent ferroptosis. Bouchaoui (2023) similarly linked reduced mitochondrial membrane potential to the production of reactive oxygen species (ROS), supporting Asano's findings (Asano et al., 2015; Bouchaoui et al., Xiao et al., 2024).

Other oxidative stress pathways were also studied. Wang (2019) associated iron-induced ROS with alpha-synuclein deposition, another key pathological factor in PD. In vitro and in vivo analyses demonstrated that iron, through ROS generation, increases the expression of two kinases, PLK2 and CK2, which phosphorylate alpha-synuclein, converting it into its toxic form (Wang et al., 2019).

4. Final Considerations

This study advances the understanding of the relationship between brain iron accumulation and Parkinson's Disease (PD), demonstrating that alterations in ferric levels and gray matter atrophy occur across various brain regions. Among the eight regions identified, the caudate nucleus, substantia nigra, and putamen stood out due to their direct association with PD, suggesting that iron accumulation in these areas is closely tied to disease progression. The identification of genes linked to iron accumulation supports the hypothesis of a genetic predisposition to neurodegeneration, though it remains unclear whether the accumulation is a cause or consequence of PD.

The pathophysiology involving iron is complex and multifactorial. Animal studies indicate that iron accumulation promotes oxidative stress, mitochondrial dysfunction, and microglial activation, contributing to neuromelanin degradation and neuronal damage. Evidence pointing to astrocytes as central regulators of ferric levels suggests that dysfunctions in these mechanisms, such as ceruloplasmin alterations and impaired ferritin secretion, may disrupt iron homeostasis and lead to pathological deposition in neurons.

The relationship between iron and ferroptosis, a form of iron-induced cell death, is particularly noteworthy, especially in the substantia nigra, where neuronal degeneration is most pronounced in PD. Iron's interaction with lipid metabolism and its ability to generate reactive oxygen species (ROS) exacerbate oxidative stress, promoting alpha-synuclein phosphorylation and the formation of toxic aggregates that intensify neurodegeneration. This pathological cycle suggests that iron not only contributes to disease progression but also interconnects with other PD-related pathways.

Despite robust evidence linking iron to PD, the exact nature of this relationship remains to be clarified. Findings indicate that brain iron accumulation is a significant phenomenon in PD, but whether it serves as a causal factor or consequence requires further investigation. Mitochondrial dysfunction, induced by iron and culminating in ferroptosis, underscores the need for future studies exploring these pathways as potential therapeutic targets. Moreover, pharmacological

approaches aimed at reducing iron concentrations in the affected regions have also been attempted; however, no evidence of their efficacy and safety has been found (Negida, 2024; Liu, 2019).

In conclusion, our results suggest that iron plays a central and multifaceted role in PD pathogenesis, influenced by genetic factors and disruptions in metal homeostasis. Determining whether iron acts as an initial trigger or exacerbates a pre-existing neurodegenerative state is critical for developing more effective therapeutic interventions. Deepening the study of iron accumulation mechanisms and their interactions with specific cellular processes may open new avenues for the treatment and management of Parkinson's Disease.

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