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ADVANCES IN DISEASE-MODIFYING THERAPIES FOR PARKINSON'S

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Abstract: Parkinson's Disease (PD) was identified in 1817 by James Parkinson and later named after Jean-Martin Charcot. It is a progressive neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra, resulting in motor symptoms such as rigidity, bradykinesia and resting tremor, as well as neuropsychiatric manifestations [1,2]. Although there are treatments to relieve symptoms, there are no therapies that modify the course of the disease. The challenges to developing such therapies include the multifactorial nature of PD, the heterogeneity of symptoms between patients and the lack of reliable biomarkers [3]. The review of the scientific literature focused on PD-modifying therapies, with an emphasis on an evidence-based approach. Strategies investigated include immunotherapy to reduce α-synuclein, modulation of inflammation, treatments for GBA gene mutations and LRRK2 inhibitors. Agents targeting calcium and iron balance have also been explored, as well as interventions to improve mitochondrial function [4]. The study concludes that it is vital to integrate different areas of health to understand PD, considering its complexity and the need for personalized therapeutic approaches. Advances in the objective quantification of response to treatment and research into biomarkers could revolutionize the management of PD, allowing for more effective and targeted interventions [5].

INTRODUCTION

Parkinson's Disease (PD) was first described in 1817 by James Parkinson, an English physician who called it "agitating paralysis". Years later, the condition was given its current name in honor of Jean-Martin Charcot. PD is a progressive and complex neurodegenerative disease characterized by the gradual loss of dopaminergic neurons in the substantia nigra, a structure located in the midbrain and

responsible for the production of dopamine, a neurotransmitter essential for controlling movement [1,2]. The reduction in dopamine levels results in classic motor symptoms such as rigidity, bradykinesia, rest tremor and postural instability, as well as neuropsychiatric and autonomic symptoms [3].

Although current treatments can relieve motor symptoms such as tremors and muscle rigidity, there are still no therapies capable of modifying the course of the disease, slowing its progression or preventing neuronal loss. The search for these disease-modifying treatments is a major challenge, partly due to the multifactorial nature of PD, which results from a combination of genetic predisposition and environmental influences, making it difficult to identify a single effective therapeutic target [3]. In addition, the heterogeneity of the disease, which manifests itself differently among patients, both in terms of motor and non-motor symptoms and the speed of progression, makes the development of effective treatments for all individuals even more complex [3,4].

Another obstacle is the lack of specific and reliable biomarkers, both for early diagnosis and for monitoring the progression of PD. The lack of objective tools also makes it difficult to assess the effectiveness of new treatments in clinical trials [5]. Finally, the blood-brain barrier, which protects the brain, represents another significant challenge, as it prevents the entry of many substances, making it difficult to develop drugs that can reach the affected neurons [5].

OBJECTIVE

Current scientific literature on advances in disease-modifying therapies for Parkinson's has been thoroughly reviewed and analyzed, emphasizing the importance of an evidence--based approach to the management of this neurodegenerative condition [6]. Despite differences in clinical outcomes and underlying mechanisms, this review provides a comprehensive overview of therapeutic interventions under development and suggests a personalized approach to treatment. In addition to standard care, which remains essential, promising new therapies have been explored, although robust evidence for a universal recommendation is still lacking [6].

METHODS

This integrative review was carried out by searching the virtual databases PUBMED, MEDLINE and the Virtual Health Library (VHL). Articles published between 2019 and 2024 and written in English were included. The search terms used were: "Parkinson's disease", "disease-modifying therapies", "neuroinflammation", "alpha-synuclein aggregation", "mitochondrial dysfunction", and "Parkinson's treatment outcomes" [7].

The article selection process was divided into three phases. Initially, 510 articles were identified. Then, repetitive studies with inconclusive data, preliminary clinical trials, dissertations, theses and conference abstracts were excluded, resulting in 180 articles for detailed review [7]. After full reading, 29 studies were included in the final analysis, excluding publications with redundant data or low clinical relevance. From this selection, the extracted data was organized to compare the different promising therapeutic approaches for modifying Parkinson's disease and their impact on the course of the disease [7].

RESULTS AND DISCUSSION

THERAPEUTIC TARGETS RELATED TO α-SYNUCLEIN, NEUROINFLAMMATION AND GBA GENE CHANGES: IMPACTS ON PARKINSON'S DISEASE (PD)

Misfolded α-synuclein forms so-called Lewy bodies, which are toxic to cells and contribute to the neuronal death characteristic of Parkinson's Disease (PD), being a pathological milestone that promotes neurodegeneration [8]. Therapies are being developed to reduce the aggregation and spread of this toxic protein, including immunotherapy, which induces the immune system to produce antibodies that recognize and eliminate α-synuclein. Another approach involves the use of monoclonal antibodies that bind directly to α-synuclein, preventing it from aggregating and spreading to other cells [8].

α-synuclein represents a clear and specific target for therapeutic interventions, and immunotherapy, by reducing the levels of this toxic protein, has the potential to modify the course of the disease, slowing or halting its progression [9]. Pre-clinical studies in animal models have shown promising results, suggesting that this strategy may be effective in combating the disease [9].

Inflammation in Parkinson's disease is closely linked to the aggregation of α-synuclein. When this protein accumulates in the form of clusters, it triggers an inflammatory response that contributes to neurodegeneration [9]. Immune cells, such as microglia and macrophages, are activated by the presence of α-synuclein, releasing inflammatory substances that can cause damage to neurons. Genetic variations in HLA genes, which encode proteins essential for the immune system, are also associated with an increased risk of developing PD, suggesting the relevance of immunological factors in the pathogenesis of the disease [9,10].

In view of this, various therapeutic strategies are being explored to address the role of inflammation in PD. Currently, therapies such as sargramostim, which stimulates the production of regulatory T cells, and inhibitors of myeloperoxidase and the NLRP3 inflammasome, are being investigated for their potential to reduce inflammation and neurodegeneration in the context of PD [9,10]. Other agents, such as statins and immunosuppressants, are being evaluated for their neuroprotective and anti-inflammatory effects [9,10].

Modulating the immune system, however, presents challenges, as Parkinson's is a multifactorial and complex disease. Excessive suppression of the immune system can increase the risk of infections, and the identification of specific therapeutic targets is complicated by the multifaceted nature of inflammation [11]. Although promising, this approach requires further research to fully understand immune interactions and develop effective and safe treatments [11].

The GBA gene, in turn, contains the instructions for the production of the β-glucocerebrosidase enzyme, which is essential for the breakdown of glucocerebrosides inside cells [12]. Mutations in the GBA gene result in defective or reduced production of this enzyme, leading to the accumulation of glucocerebrosides, which affects cell cleansing mechanisms such as autophagy. Failure to eliminate damaged proteins, such as α-synuclein, contributes to the formation of Lewy bodies and, consequently, to the neurodegeneration observed in PD [12].

Therapies under development to combat the effects of mutations in the GBA gene include pharmacological chaperones, which help stabilize the mutant β-glucocerebrosidase, allowing it to function more effectively and reduce the accumulation of glucocerebrosides

[12]. One example is ambroxol, which also promotes autophagy. In addition, therapies based on increasing the ability to eliminate aggregated proteins, such as rapamycin and modulators of the mTOR pathway, are being investigated. Inhibitors of α-synuclein, such as NPT200-11, are also being studied to prevent the formation of Lewy bodies and reduce cell damage [12,13].

These therapeutic approaches aim to improve cellular function and minimize the neurodegeneration characteristic of Parkinson's Disease, offering new hope for more effective treatments [12,13].

NEW THERAPEUTIC APPROACHES IN DEVELOPMENT FOR LRRK2

The LRRK2 gene is like an instruction manual for the production of the LRRK2 kinase. This protein performs several important functions within our cells, such as maintaining cell structure and autophagy [14]. The Gly2019Ser mutation is like a typo in this instruction manual. This error causes the LRRK2 protein to function abnormally, making it more active. This hyperactivity interferes with the cell cleaning process, causing dysfunctional proteins, such as the alpha-synuclein protein, to accumulate inside the cells [14,15].

To combat the effects of the Gly2019Ser mutation, scientists have developed drugs called LRRK2 inhibitors [14,15]. These drugs act as brakes, decreasing the excessive activity of the mutant protein. By reducing the activity of LRRK2, it is hoped to restore the cell cleansing process and prevent the accumulation of toxic proteins. Although the results in the laboratory are promising, a significant challenge is the pulmonary toxicity observed with some of these drugs [14,15].

A promising strategy for treating Parkinson's disease associated with mutations in the LRRK2 gene is the use of antisense oligonucleotides. These small RNA fragments bind to the messenger RNA of the LRRK2 gene, blocking the production of the mutant protein [16]. By "silencing" the LRRK2 gene and preventing the synthesis of this protein, it is hoped to reduce its harmful effects. This approach, which aims to minimize the impact of mutations in the gene, is currently being investigated in clinical trials as a possible therapeutic strategy for the disease [16,17].

AGENTS THAT TARGET SPECIFIC NEURAL RESCUE PATHWAYS

CALCIUM TREATMENT

The substantia nigra pars compacta plays a vital role in controlling movement and is made up of neurons that function as "pacemakers". These neurons depend on a strict balance of ions, especially calcium, to maintain their normal functions [17]. Calcium is crucial for the release of neurotransmitters, such as dopamine, which is essential for motor coordination, as well as acting as an intracellular messenger in synaptic plasticity, regulating the strength of connections between neurons [17]. However, an excess of calcium can be harmful, leading to consequences such as oxidative stress, which results in the production of free radicals that damage cells, and mitochondrial dysfunction, where excess calcium damages mitochondria, compromising energy production and leading to cell death [17,18].

In Parkinson's disease, L-type calcium channels, such as Cav1.3, are considered to be hyperactive, allowing excessive calcium to enter nerve cells, which contributes to neuronal death. Isradipine, a blocker of these channels, has emerged as a possible solution to mitigate these harmful effects [17,18]. This drug can reduce oxidative stress by decreasing calcium entry, which results in a decrease in the production of free radicals and the protection of cells against oxidative

damage. In addition, Isradipine can preserve mitochondrial function, ensuring an adequate supply of cellular energy and preventing neuronal death [17,18]. Although studies in animal models have shown that Isradipine protects dopaminergic neurons and improves symptoms of parkinsonism, clinical trials have shown mixed results, reflecting the complexity of Parkinson's disease and the multiple factors involved in its pathogenesis [19,20].

TREATMENT WITH IRON CHELATORS

Deferiprone is a drug that acts as a "magnet" for iron in the body, binding to excess iron and forming a complex that facilitates its elimination from the body. This process is known as chelation, which becomes particularly relevant in the context of Parkinson's disease, where iron overload can be an aggravating factor [20]. Excessive accumulation of iron in the substantia nigra, an area of the brain fundamental for movement, can lead to damage to nerve cells through a mechanism called oxidative stress. The free radicals generated by this reaction have the potential to cause significant cell damage, accelerating neuronal degeneration [20].

In Parkinson's disease, excess iron not only causes direct damage to nerve cells, but also contributes to the accumulation of the protein alpha-synuclein. The relationship between iron overload and the formation of Lewy bodies suggests that removing excess iron with deferiprone could not only reduce oxidative damage, but also decrease the formation of these pathological structures [21]. In short, by eliminating excess iron, deferiprone aims to slow down the progression of Parkinson's disease and improve neuronal health [22].

MITOCHONDRIAL AGENTS

Mitochondria, often described as the "power plants" of cells, play an essential role in Parkinson's Disease (PD). Mitochondrial dysfunction is one of the main factors in the pathogenesis of PD, contributing to neuronal death by reducing ATP production and increasing reactive oxygen species (free radicals) [23]. This oxidative stress, caused by the overproduction of free radicals, is one of the main factors responsible for the neurodegeneration characteristic of the disease. In addition to compromising cellular energy production, mitochondrial dysfunction can trigger cascades of events that culminate in programmed cell death, accelerating the progression of PD [24].

To address these dysfunctions, various therapeutic approaches are being investigated with the aim of improving mitochondrial function in PD patients. Substances such as pioglitazone and inosine, which have shown promising results in animal models, have not demonstrated significant benefits in large clinical trials [25,26]. Coenzyme Q10, an antioxidant important for cellular energy production, has shown inconsistent results in clinical trials, although it continues to be evaluated in patients with genetic mutations linked to mitochondrial dysfunction. In addition, ursodeoxycholic acid (UDCA) has shown potential for improving mitochondrial function and reducing cellular stress caused by the accumulation of lipids in cells [27,28].

CONCLUSION

It is essential that there is a convergence between all areas of health to understand and boost the study of PD, since many mechanisms of its formation have not yet been discovered, but science has found that there is a wide range of mechanisms capable of modifying the course of Parkinson's disease [28,29]. The pathogenesis is multifaceted, including gene

mutation, α-synuclein aggregation, neuroinflammation, mitochondrial dysfunction, selective neuronal susceptibility and inadequate compensatory processes. The complexity of these interconnected pathways and the resulting heterogeneity of clinical phenotypes will require a targeted therapeutic approach for some individuals [28,29].

Advances in methodologies to objectively quantify individual response potential to disease-modifying approaches have the potential to revolutionize the ability to influence the progression of Parkinson's Disease (PD). These methodologies, based on specific measures of deficiencies in biological pathways, make it possible to assess the impact of therapeutic interventions with greater precision. In addition, the study of biomarkers plays a key role in providing tools to monitor more precisely whether a medical intervention is generating satisfactory results, enabling more effective adjustments to treatment [28,29].

These techniques go beyond simple genotyping, highlighting the need for a more in-depth study of the LRRK2 and GBA genes. This detailed analysis can help to understand exactly which alterations at cellular level the next studies for new treatments should address. Furthermore, research into pluripotent cells offers a promising avenue, since their ability to differentiate into neurons and self-renew could become a useful therapeutic strategy in the near future [28,29].

The application of techniques to measure the pathological species of α-synuclein, neuroinflammation, mitochondrial and lysosomal dysfunction, as well as an individual's gut microbiome, will enable a more accurate prediction of who will or will not respond to treatments. Agents that act at advanced stages of these processes are particularly relevant for most patients with Parkinson's disease, thus reducing dependence on the individual characteristics of the disease and increasing the chances of therapeutic success [28,29].

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