PARKINSON'S DISEASE AND ENDOCANNABINOID SYSTEM: A BRIEF UPDATE

ABSTRACT

In Parkinson's disease, dopaminergic neurons located in the substantia nigra of the brain are destroyed, affecting the patients' motor function. The endocannabinoid system is responsible for controlling neuronal homeostasis and its alteration is related to neurodegenerative diseases, such as Parkinson's. A literature review regarding the relationship between the endocannabinoid system and Parkinson's disease was carried out through a search in the Pubmed database. Complete publications from the last year were included, using 15 papers. Treatment with cannabinoid medications for Parkinson's patients should not be the first choice, being restricted to adjuvant therapy as they are elderly and vulnerable. Cannabis extracts have shown in experimental studies neuroprotective and inflammation modulating actions. Pure cannabidiol is safe, with few side effects. Computational analyzes demonstrated that the binding of cannabidiol to the CB1 and CB2 receptors induced structural changes in them. Levels of CB1 receptors were lower in specific areas of the brain of Parkinson's patients and the decline in these receptors was correlated with worse severity of motor symptoms. Selective CB2 receptor agonists have neuroprotective and immunomodulatory actions, reducing inflammation and the formation of defective proteins. Hyperpolarized current-induced inhibition of CB1 receptors improved muscle stiffness but worsened symptoms of depression and anxiety.

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in animals. The use of exogenous cannabinoids in patients with Parkinson's disease is not yet consolidated, and more clinical studies are needed to confirm the safety of the interaction with the endocannabinoid system.

**Keywords:** Parkinson disease; cannabinoids; aged; cannabinoid CB1 receptor; cannabinoid CB2 receptor.

**RESUMO**
Na doença de Parkinson ocorre a destruição dos neurônios dopaminérgicos situados na substância negra do cérebro, afetando a função motora dos pacientes. O sistema endocannabinoide é responsável por controles relacionados à homeostase neuronal, e sua alteração está relacionada a doenças neurodegenerativas, como o Parkinson. Foi realizada uma revisão da literatura referente à relação entre o sistema endocannabinoide e com a doença de Parkinson, por meio de uma busca na base de dados Pubmed. Foram incluídas publicações completas do último ano, com utilização de 15 artigos. O tratamento com medicamentos canabinóides para pacientes com Parkinson não deve ser primeira escolha, sendo restrito à terapia adjuvante, por serem idosos e vulneráveis. Extratos de Cannabis apresentaram, em estudos experimentais, ações neuroprotetoras e moduladoras da inflamação. O cannabidiol puro é seguro, apresentando poucos efeitos colaterais. Análises computacionais demonstraram que a ligação do cannabidiol aos receptores CB1 e CB2 induziu mudanças estruturais nos mesmos. Os níveis de receptores CB1 foram mais baixos em áreas específicas do cérebro de pacientes com Parkinson, e o declínio desses receptores estava correlacionado à pior gravidade dos sintomas motores. Agonistas seletivos de receptores CB2 apresentaram ações neuroprotetora e imunomoduladora, reduzindo inflamação e formação de proteínas defeituosas. A inibição dos receptores CB1 de animais induzida por corrente hiperpolarizada melhorou a rigidez muscular, mas piorou sintomas de depressão e ansiedade. Ainda não está consolidada a utilização de canabinóides exógenos em pacientes com Parkinson, sendo necessários mais estudos clínicos para constatação da segurança da interação com o sistema endocannabinoide.

**Palavras-chave:** Doença de Parkinson; canabinóides; idoso; receptor CB1 de canabinoide; receptor CB2 de canabinoide.

**RESUMEN**
En la enfermedad de Parkinson, las neuronas dopaminérgicas ubicadas en la sustancia negra del cerebro se destruyen, lo que afecta la función motora de los pacientes. El sistema endocannabinoide es responsable de los controles relacionados con la homeostasis neuronal, y su alteración está relacionada con enfermedades neurodegenerativas, como el Parkinson. Se realizó una revisión de la literatura respecto a la relación entre el sistema endocannabinoide y la enfermedad de Parkinson, mediante una búsqueda en la base de datos Pubmed. Se incluyeron publicaciones completas del último año, utilizando 15 artículos. El tratamiento con medicamentos cannabinoïdes para los pacientes de Parkinson no debería ser la primera opción, limitándose a la terapia adyuvante, ya que son personas mayores y vulnerables. Los extractos de cannabis han demostrado, en estudios experimentales, acciones neuroprotectoras y moduladoras de la inflamación. El cannabidiol puro es seguro y tiene pocos efectos secundarios. Los análisis computacionales demostraron que la unión del cannabidiol a los receptores CB1 y CB2 inducía cambios estructurales en ellos. Los niveles de receptores CB1 eran más bajos en áreas específicas del cerebro de los pacientes con Parkinson, y la disminución de estos receptores se correlacionaba con una peor gravedad de los síntomas motores. Los agonistas selectivos del receptor CB2 tienen acciones neuroprotectoras e inmunomoduladoras, reduciendo la inflamación y la formación de proteínas defectuosas.
La inhibición de los receptores CB1 animales inducida por corriente hiperpolarizada mejoró la rigidez muscular pero empeoró los síntomas de depresión y ansiedad. El uso de cannabinoides exógenos en pacientes con enfermedad de Parkinson aún no está consolidado y se necesitan más estudios clínicos para confirmar la seguridad de la interacción con el sistema endocannabinioide.

**Palabras clave:** Enfermedad de Parkinson; cannabinoides; anciano; receptor cannabinoide CB1; receptor cannabinoide CB2.

1. Introduction

Parkinson's disease (PD) is a degenerative and progressive neurological condition, with a slow course, which affects 1% of the population over 65 years of age. It occurs due to the degeneration of neurons that produce dopamine (dopaminergic), located in a specific region of the brain, called substantia nigra. The absence/decrease of dopamine affects and worsens the patient's motor function. Parkinson's is an incurable disease, but it presents symptomatic multidisciplinary treatment, which can slow its progress, such as physical therapy activities and physical exercises (Brasil, 2019). According to the Associação Brasil Parkinson (ABP), there are prodromal symptoms that indicate the onset of the disease, which appear between five and 15 years before the classic symptoms (slowness of movement - bradykinesia/hypokinesia, tremor and muscle rigidity). The following are prodromal symptoms: intestinal constipation (up to 10 years before); hyposmia (change in smell, from five to 10 years before) and REM sleep behavioral disorder (restless sleep, from 10 to 15 years before). Other symptoms are: muscle pain (usually in the shoulder), orthostatic hypotension, sadness and discouragement and impaired attention and concentration (Associação Brasil Parkinson, 2023a,b). According to the American Parkinson Foundation, other early signs can be observed, such as micrographia (decreased writing), sudden movements during sleep, change in voice (lower, softer or hoarse), masked face (serious expression) and stooping when walking. The symptoms of the disease are apathy, hallucinations and cognitive deficiencies (Parkinson’s Fundation, 2023).

The human endocannabinoid system is composed of cannabinoid
membrane receptors, endogenous agonist ligands or endocannabinoids (anandamide and 2-arachidonoyl-glycerol) and their metabolic synthesis and degradation enzymes. The cannabinoid receptors CB1 and CB2 are coupled to the G protein on the cell membrane. The CB1 receptor is located in the presynaptic nerve terminals (olfactory bulb, hippocampus, lateral striatum, striatal nuclei and cerebellum) of the central nervous system and the CB2 receptor is mainly expressed in cells of the immune system, but can also be expressed in neurons of microglia (Castro, 2018), (Mackie, 2008), (Moreira, 2010). CB1 exists in high density in brain regions important for motor control. The high density of CB1 receptors in the basal ganglia, an area closely involved in the regulation of motor control and its interaction with dopamine, suggests an important relationship between the endocannabinoid system and movement disorders, as occurs in PD. Cannabinoids interact with several neurotransmitters and neuromodulators, such as serotonin, dopamine, glutamate and gamma-aminobutyric acid (GABA). Several of the neuropsychiatric pharmacological effects of Cannabis sativa (marijuana) can be explained by these interactions (Fernandez-Ruiz et al., 2002), (Shier et al., 2012), (Walsh et al., 2013).

The objective of this work was to carry out a brief review of the literature regarding cannabinoids and human endocannabinoid receptors and their relationship with Parkinson's.

2. Theoretical Reference

Ishiguro (2023), through an editorial, addressed the topic of the direction of the endocannabinoid system (endocannabinoidome) in neurodegenerative diseases, emphasizing its role in controlling the function of the nervous system. This system is composed of cannabinoid membrane receptors and signaling molecules, and changes in it are linked to a series of neurodegenerative diseases, such as Alzheimer’s and PD. The editorial discussed therapeutic approaches that aim to modulate the endocannabinoid system as a potentially effective strategy for treating certain diseases. However, there is still a need for additional research to fully understand the role of the endocannabinoid system in
neurodegenerative diseases and to develop effective therapies targeting this system.

Rivas-Santisteban et al. (2023) carried out a study in rats, to verify the interaction between the CB1 receptor and the AT2 angiotensin receptor, since the renin-angiotensin system is important for regulating the correct functioning of some brain circuits. They examined the expression of AT2-CB1 heteromers in the primary striatal neuron of rats that had been hemilesionated with 6-hydroxydopamine (6-OHDA), a neurotoxin that induces damage in dopamine-producing cells. It was found that the interaction between CB1 and AT2 receptors was capable of forming heteromers, which are complex compounds and this interaction was observed mainly in the striatum, a region of the brain involved in motor and reward functions. This suggested the existence of a cross-talk between the endocannabinoid and angiotensin systems. Increased expression of heteromers may have implications for the function and pathology of the striatum, which is involved in motor and reward processes. These findings have provided a new perspective on the interaction between the endocannabinoid and angiotensin systems and their possible relevance to neurological disorders such as PD. However, according to the authors, more research is needed to understand the functional and therapeutic implications of these interactions.

Ajalin et al. (2022) carried out a study with positron emission tomography to investigate the role of the CB1 receptor in PD, with the aim of understanding its role in the progression of the disease and its therapeutic implications. In the study, FMPEP-d2, a CB1 receptor agonist radioligand, was used, with a sample of 16 individuals with PD and 10 healthy individuals. It was observed that CB1 levels were lower in specific areas (substantia nigra) of the brain of PD patients when compared to healthy individuals, suggesting malfunction of the endocannabinoid system in this situation. There was also a correlation between the severity of motor symptoms and the decline in CB1 levels, highlighting the potential of CB1 as a therapeutic target for the development of new therapies.

Basile and Mazzon (2022) performed a simple review to determine the role of CB2 receptors in PD. The authors found that despite some positive effects of these receptors, such as neuroprotective action, more in-depth studies are
necessary to confirm their action potential, so that new therapeutic possibilities for the treatment of PD can emerge.

Colizzi et al. (2022) carried out a systematic review and meta-analysis evaluating 33 articles, to investigate palmitoylethanolamide (PEA), an endogenous lipid that modulate CB1 and CB2 receptors, administered orally, and its effects on neurocognitive disorders in animals and humans. It was observed that PEA demonstrated neuroprotective and anti-inflammatory properties, through the indirect activation of cannabinoid receptors. Furthermore, it can improve cognitive function, reduce oxidative stress and promote neuronal regeneration, showing positive effects on the expression of proteins related to neuronal growth and the modulation of immune system cells. These findings suggested that PEA may play an important role in protecting and regulating the nervous system, offering new therapeutic options in neurocognitive disorders. As it does not present relevant side effects, PEA has become a good treatment option, as it does not present imminent health risks. However, more research is needed to better understand the mechanisms and clinical efficacy of PEA supplementation.

Costa et al. (2022) carried out a literature review on the clinical and biological changes caused by the cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD) in Parkinson’s disease and dementia. The authors noted that, although the treatment of these diseases with cannabinoids is promising, more in-depth studies are still needed to prove the long-term effectiveness of this treatment, as the patients treated, most of whom are elderly, are more vulnerable. Due to this, its use is restricted to adjuvant therapy and is contraindicated as a first-choice treatment.

Dávila et al. (2022) carried out a computational study to examine the binding interaction between CBD and the CB1 and G-protein-coupled receptor 55 (GPR55) receptors. Through computational analyzes and molecular modeling they demonstrated that CBD binds differently to the two receptors, resulting in distinct functional responses. At CB1 receptors, CBD acts as an antagonist and the mode of interaction between CBD and GPR55 is debatable. Molecular modeling analyzes showed that the interaction of CBD with receptors induced conformational changes in the structure of these receptors, which could explain...
the differences in their activity, highlighting the complexity of the interactions between CBD and cannabinoid receptors. This suggested that the pharmacological properties of CBD may be influenced by the specific conformation of target receptors. However, as the study was based on computational analyzes and molecular modeling, more experimental research is needed to validate and corroborate these findings.

Hasumi and Maeda (2022) carried out a study to investigate the effects of CBD on motor dysfunction induced by the antipsychotic haloperidol (which induces motor side effects) in zebrafish larvae. They compared the effects of CBD with the drug ropinirole (ROP), a dopamine activator. Haloperidol induces PD-like motor effects. After administration of haloperidol (10mg/L), to induce motor impairment in zebrafish larvae, they were treated with CBD (concentrations of 1, 5 and 10mg/L, with 16 larvae/group) or ropinirole hydrochloride-ROP (concentrations of 1, 5 and 10mg/L, with 16 larvae/group). It was observed that CBD improved the motor dysfunction caused by haloperidol and its effects were comparable to those of ropinirole, suggesting that CBD may have therapeutic potential to alleviate motor symptoms associated with haloperidol or possibly other dopamine-related disorders. These findings provided a positive outlook on the use of CBD as a therapeutic agent for motor dysfunction. However, more research is needed to better understand the underlying mechanisms and determine the applicability of these findings in humans.

Luo et al. (2022) carried out a study on therapeutic potential of *Sceletium tortuosum* (a South African herb used by Khoisan natives that inhibits serotonin reuptake) in the treatment of neurodegenerative disorders. The authors investigated by using computational analysis the interaction between active compounds of *Sceletium tortuosum* and target proteins associated with neurodegenerative diseases, such as Alzheimer's disease and PD, as they also act on the CB2 cannabinoid receptor. Compounds from *S. tortuosum* modulated multiple biological targets involved in the pathological processes of these diseases, including inflammation, oxidative stress and mitochondrial dysfunction. Furthermore, there were interconnections between the target proteins, suggesting synergistic action of the plant compounds. According to the authors,
S. tortuosum can be considered a promising candidate for the development of new treatments for neurodegenerative disorders. However, more research is needed, including clinical studies, to validate and explore the therapeutic potential of this plant more comprehensively.

Morash et al. (2022) carried out a study to identify minimal therapeutic mixtures essential for the treatment of PD, investigating the therapeutic properties of extracts from the Cannabis plant. The researchers used cellular and animal models and this approach allowed them to observe the effects of the extracts more comprehensively. Parkinson’s disease (PD) models induced by the neurotoxin 6-hydroxydopamine were used. The results suggested that certain combinations (minimum essential mixtures containing CBD + CBDV (Cannabidivarin) or CBD + CBC (Cannabichromene) of compounds present in the Cannabis plant demonstrated greater therapeutic effects, and may present statistically significant beneficial effects, showing neuroprotective and inflammation modulating activities. Furthermore, symptomatic treatment of PD with levodopa proved harmful as some cases demonstrated dyskinesia (involuntary movements) after 24 months of treatment with this medication. These findings provided a promising basis for future research and further development in the field of treatment in Parkinson’s disease.

Peball et al. (2022) carried out research to evaluate the effects of nabilone (a synthetic cannabinoid derived from THC on the sleep of 31 patients with PD. Nabilone use has been noted to be linked to improvements in sleep disturbances in Parkinson’s patients, as participants reported longer overall sleep duration, fewer awakenings during the night, and better overall sleep quality. Furthermore, no significant adverse effects were observed associated with the use of nabilone, which may be a promising therapeutic option to improve sleep quality in patients with PD. Nabilone showed affinity for both CB1 and CB2 receptors, however, more research is needed to corroborate these findings.

Soti et al. (2022) carried out a study to investigate the activated hyperpolarization current (Ih), which plays an important role in controlling the rhythmic activity of neuronal circuits, in CB1 receptors, in the behavior of mice with PD induced by the neurotoxin 6-hydroxydopamine (6-OHDA). The authors also investigated the effects (motor and non-motor) of the WIN55,212-2 agonist
and the selective CB1 antagonist AM251. AM251 has improved motor and memory effects. The 6-OHDA+CB1 agonist WIN55,212-2 increased neuronal excitability due to the increase in Ih current mediated by channels controlled by cyclic nucleotide-gated-channels (HCN) present in dopaminergic neurons located in the ventral tegmental area of the mice. The results suggested that the Ih current played an important role in the behavioral response to CB1 receptor antagonism in an animal model, and this may have implications for understanding the mechanisms underlying PD and developing targeted therapies.

Souza et al. (2022) carried out a systematic review on the adverse effects of CBD administered orally. The most common side effects were mild and moderate, while serious effects were rarer and observed mainly in the combination of CBD with antiepileptic drugs in the treatment of epilepsy. Because of this, constant monitoring of the patient is important, especially at the beginning of treatment with CBD. Due to the growing global demand for CBD in various systemic conditions, more safety data from clinical studies with larger samples, different dosages and different types of products is still needed.

Urbi et al. (2022), through a systematic review and meta-analysis of 41 articles, verified the effects of cannabinoid receptor agonists (nabilone, CBD, THC and others) and endocannabinoid enzyme inhibitors (as FAAH and MAGL), in animal models with PD. They found that cannabinoids use was statistically positive, especially in motor behavioral assessment tests on rodents in controlled environments, such as the rotarod test (time spent on a rotating rod, with a gradual increase in speed) and the pole test (time taken from the top of a stick to the base), but did not show favorable results in the open field test (locomotor activity in a horizontal plane). Despite good results, there were many variables that could have affected them, such as the use of different agonists, different methodologies and study biases, making it necessary to carry out clinical trials for further investigation.

Vuic et al. (2022) carried out a review on CB2 receptors in neurodegenerative proteinopathies. This receptor plays an important therapeutic role in neurodegenerative diseases, being involved in physiological and pathological processes, in addition to having been studied for the treatment of
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diseases such as Alzheimer's, PD and multiple sclerosis. It was observed that selective CB2 receptor agonists (as JWH-133, HU 308, JWH–015) presented immunomodulatory and neuroprotective properties, modulating inflammation and the formation of defective proteins. There are challenges to be overcome, such as prolonged administration, determining effective and safe doses, drug interactions and possible peripheral side effects. Furthermore, CB2 receptor is a safer therapeutic target than CB1, which is associated with unwanted psychoactive effects. According to the authors more studies are needed to fully understand the therapeutic potential of the CB2 receptor and identify new treatment opportunities for neurodegenerative diseases.

3. Methodology

A bibliographic search was carried out in the Pubmed database, using the keywords 'Cannabinoids AND Parkinson disease', including articles published in the last year, available in full, and articles unrelated to the topic and those not in the English language excluded.

4. Results and Discussions

From 21 articles found in the last year, 15 were used which met the established criteria.

The usual history of a patient with PD consists of a gradual increase in tremors, increased slowness of movement, a shuffling gait, and a forward-leaning posture. Tremors occur at rest, becoming more intense when nervous and disappearing during sleep. The slowness of movements also evolves quickly, with loss of automation (Associação Brasil Parkinson, 2023a). Motor symptoms are evident later in the course of the disease, when 60-80% of the substantia nigra neurons have already been lost or compromised (Parkinson’s Fundation, 2023), compromising the quality of life of elderly people with PD.

Combinations of compounds from the Cannabis plant can have significant beneficial effects, showing neuroprotective and inflammation-modulating activities (Morash et al., 2022). For Costa et al. (2022) due to the elderly being
more vulnerable, the use of exogenous cannabinoids is restricted to adjuvant therapy and is not a first-choice treatment for PD. For Ishiguro (2023), additional research is still needed to fully understand the role of the endocannabinoid system in neurodegenerative diseases, and to develop effective therapies targeting this system.

CB2 cannabinoid receptors showed neuroprotective action (Basile; Mazzon, 2022). Also CB1 receptor levels are lower in specific areas of the brain of PD patients when compared to healthy individuals, suggesting malfunction of the endocannabinoid system, with a correlation between the severity of motor symptoms and the decline in levels of CB1 (Ajalin et al., 2022). Selective CB2 receptor agonists presented immunomodulatory and neuroprotective properties reducing inflammation and the formation of defective proteins, with CB2 receptors being safer than CB1, which are associated with unwanted psychoactive effects (Vuic et al., 2022). Furthermore inhibition of CB1 receptors, through activated hyperpolarization current, improved motor symptoms, such as muscle stiffness, but worsened non-motor symptoms, such as depression and anxiety in mice with Parkinson's (Soti et al., 2022).

Nabilone is a medication that binds to cannabinoid receptors, improving sleep disorders in PD patients increasing sleep duration, improving sleep quality and causing fewer sleep interruptions during the night (Peball et al., 2022). PEA, an endogenous lipid, demonstrated neuroprotective and anti-inflammatory properties, through indirect activation of cannabinoid receptors, in addition to improving cognitive function, reducing oxidative stress and promoting neuronal regeneration. This medication can be a therapeutic option for neurocognitive disorders, without relevant side effects (Colizzi et al., 2022). The use of pure CBD orally, a derivative of Cannabis presented mild and moderate side effects, with serious effects occurring when combining CBD with antiepileptics. Because of this, patients must be monitored by their doctor when starting CBD treatment (Souza et al., 2022). CBD can act as a therapeutic agent for motor dysfunction (Hasumi; Maeda, 2022). However, the study was carried out on zebrafish larvae, requiring further studies to determine the applicability of these findings to humans.
5. Conclusion

PD is incurable, but its signs and symptoms are treatable in a multidisciplinary way, so that the patient has a better quality of life. Treatment does not prevent the progression of the disease, and mainly includes physiotherapy and physical exercises. Among drug treatments, cannabinoid agonists and other medications that bind to human endocannabinoid receptors (CB1 and CB2) can be used. Among these, the combination of Cannabis extracts, nabilone (synthetic cannabinoid derived from THC and palmitoylethanolamide (PEA). However, studies are still very recent and experimental, presenting little robust scientific evidence that allows the safe use of effective therapies that act on the endocannabinoid system, for the treatment of neurodegenerative diseases, such as Parkinson's.

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