Current options for cannabinoids in the treatment of Parkinson's disease

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Abstract:

The utility of cannabinoids as agents used to treat diseases is a popular topic of discussion these days. The approval of medical marijuana continues to stir up controversy. As far back as ancient times, hemp was used for medicinal purposes. These plants have the ability to produce phytochemicals and other compounds such as flavonoids and terpenes. Respective species of hemp differ in the content of particular chemical compounds and therefore have different possible uses. Among the best-known phytocannabinoids found in hemp are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). They have partially opposing effects and interact with the corresponding receptors of the endocannabinoid system in the body's tissues. We also distinguish between cannabinoids of endogenous origin - endocannabinoids (EC) and synthetic cannabinoids (SC). The effects of THC and CBD on the human body are still being studied. Information about them that appears in the media, is often reported inaccurately or incompletely. There is now a growing body of research into the use of cannabinoids to treat and alleviate the symptoms of many diseases. Due to the neuroprotective effects of THC and CBD, researchers' work has focused on using them to treat neurodegenerative diseases, which include Parkinson's disease (PD).

Introduction

Parkinson's disease (Latin: *morbus Parkinsoni*, PD) - is one of the neurodegenerative diseases of the central nervous system. Its essence is the atrophy of dopaminergic cells located in the dark matter in the brain, resulting in a dopamine deficiency. Lewy bodies are found in the lesioned areas of the brain. [1] In a study on a North American population, the risk of developing PD was shown to increase with age: <1% in the population of men and women aged 45-54 years, up to 4% among men and 2% among women aged >85 years. [2] The causes of this disease are not fully understood. Factors such as exposure to toxic substances, head trauma, lifestyle and genetic factors are believed to increase the risk of the disease. [3] The primary symptoms of PD are bradykinesia, muscle rigidity and resting tremor. Other symptoms include memory impairment, orthostatic hypotension, constipation, depression, pain, weight loss and sleep disorder. [4] Current pharmacological treatments mainly focus on increasing dopamine levels or replacing it altogether. The use of levodopa (LD) is considered the gold standard in PD therapy. It is a precursor to dopamine, which has the ability to cross the blood-brain barrier. In the brain, LD is converted into dopamine. With long-term LD treatment, tolerance to the drug increases, necessitating an increase in dose, thus increasing the risk of side effects in the form of movement disorders such as on-off syndromes and dyskinesias. [5-6] Their risk can be reduced by concurrent use of carbidopa. [7] The potential utility of cannabinoids as agents for the treatment of Parkinson's disease is currently a popular topic of discussion. The legalization of marijuana for medical purposes, has generated a lot of controversy due to the possibility of misuse or abuse. An increasing number of people use cannabis and cannabis derivatives on their own, despite the lack of evidence for the efficacy and safety of the therapy. [8] Studies have shown the usefulness of cannabis/cannabinoids for pain management, seizures, appetite stimulation, muscle spasticity and nausea treatment. The biological effects of cannabinoids may be useful in the treatment of central nervous system diseases such as neurodegenerative diseases, PTSD, addiction therapy, among others. [9] Cannabidiol (CBD), due to its antioxidant, anti-inflammatory properties and good pharmacological tolerance, is being considered for the treatment of Parkinson's disease and Alzheimer's disease (AD). [10] Studies on the neurobiology of Parkinson's disease have shown that the endocannabinoid system can affect structures within the brain responsible for

its pathogenesis. [11] The purpose of this paper is to discuss the potential use of cannabinoids in the treatment of Parkinson's disease. For this purpose, the scientific papers published to date in the PubMed database were reviewed and analyzed. Articles were searched with the use of key words: "cannabinoids", "Parkinson disease", "PD", "cannabidiol", "THC", "CBD." A comparative analysis of the published articles was carried out and the conclusions of this paper were drawn based on them.

Discussion

Endocannabinoid system (ECS)

The endocannabinoid system is involved in maintaining homeostasis. At the level of the nervous system, it shows direct effects on mood, hunger sensation, nerve cell function, neurogenesis, neuroprotection, affects cognitive function, influences learning and memory processes, pain sensation, fertility, pre- and postnatal development. The influence of the endocannabinoid system on cancer, cardiovascular and neurodegenerative diseases is also suspected. [12] ECS is made up of 2 types of receptors: CB1, CB2, their exogenous or endogenous ligands (exo-, endo-cannabinoids), enzymes involved in ligand synthesis and degradation, and the reverse transport system. The best known phytocannabinoids that interact with ECS are delta -9-tetrahydrocannabinol (THC) and cannabidiol (CBD). [12-13] Conduction in the endocannabinoid system is impaired in most neurological diseases. [14] Endogenous ligands of the endocannabinoid system are, for example, anandamide (AEA)-CB1 and 2-arachidonoglycerol (2-AG)-CB2. [15] CBD, unlike psychoactive THC, differs in pharmacology and function. CBD has a lower affinity with CB1 and CB2 receptors and affects the function of many proteins. [16] Slowing the progression of the disease is currently the main goal of Parkinson's disease therapy. In vitro studies have shown that CBD can protect nerve cells from MMP+-induced toxicity. [17] In a study conducted on animal models, it was shown that THC, which is an agonist of the endocannabinoid system, can be effective in treating ascending dyskinesia during levodopa treatment. [18] In studies done in vitro on CBD, it has been shown to have neuroprotective effects inhibiting degeneration in the hippocampus and cerebral cortex, as well as anti-inflammatory and antioxidant properties.[19]

Positive effects of use

Lotan et al. in a non-blind clinical experiment, showed a positive effect of cannabis smoking on motor symptoms in PD such as resting tremors, rigidity and bradykinesia. At the same time, no side effects of its use have been observed. [20]

The study by Shohet et al. focused on the properties of cannabis components in modulating pain sensation in patients with Parkinson's disease. It showed a decrease in pain during treatment. [21] Both studies were conducted 30 minutes after smoking a cannabis cigarette, and in order to objectify their results, they used the UPDRS III scales (assessment of motor function), visual pain scale, (VAS), McGill pain assessment questionnaire (assessment of pain symptoms), among others. [20-21] In an experiment conducted on Parkinson's disease patients, the effect of CBD on parasomnia-like REM sleep behavior disorder (RBD) has been studied. It demonstrated a significant reduction in the frequency of episodes without adverse effects. [22] Dos-Santos-Pereira et al. in a study conducted on mice, proved the efficacy of cannabinodiol in combination with capsazepine in alleviating the symptoms of dyskinesia occurring during PD treatment with levodopa. (LID). [23] In a randomized double-blind, placebo-controlled experiment, the effect of CBD on anxiety symptoms in PD patients was examined. The authors of the experiment, during a test based on public speaking, examined the intensity of symptoms in the form of tremors and anxiety experienced by patients. During the study, patients were monitored for the following parameters: heart rate, blood pressure, frequency and amplitude of muscular tremors. The Visual Analog Mood Scales (VAMS) and patients' self-assessment were also used in the analysis. Patients using CBD have been shown to have lower levels of anxiety and less severe tremors when speaking. [24] In a pilot study conducted on patients with Parkinson's disease, positive effects were shown in treating dystonia with oral use of capsules containing CBD (100-600 mg/day) [25], as well as psychotic symptoms, which were treated for more than 4 weeks with oral CBD capsules starting at a dose of 150 mg/day. [26] In a study conducted at the Medical University of Innsbruck, an experiment was conducted to evaluate the effectiveness of Nabilon, a synthetic THC analog, in treating the non-motor associated symptoms of Parkinson's disease. In a randomized double-blind study, the positive effects of Nabilon treatment were confirmed, primarily in reducing anxiety and sleep disorders. The most commonly observed adverse effects were feelings of fatigue, dizziness, drowsiness and dry mouth; one patient had a transient panic attack. [27] A study conducted at Jena University Hospital on a group of patients diagnosed with PD has been aimed to determine the risk of malnutrition. One in two patients surveyed was found to be undernourished or at risk of malnutrition. [28] Cannabis

has appetite-stimulating properties, which may be another indication for its use in the treatment of underweight in PD. [9]

Negative effects of use

In practice, cannabinoids are most often used for non-therapeutic purposes. In a survey conducted among college students and young adults, it was found that the largest proportion of respondents used marijuana for social adjustment. The next largest group were people who tried marijuana out of curiosity or for fun. The fewest were those using marijuana because of feelings of anxiety, depression and wanting to relax. [29-32] Among the early effects of marijuana use, we can include specific behavioral changes: impaired motor coordination, impaired judgment, slower reaction time, anxiety, social withdrawal. Within 2 hours of marijuana use, the following physiological changes can be detected: an increase in appetite, dry mouth, tachycardia. In social functioning, chronic cannabis use can affect interpersonal relationships, finances, work issues, and cause housing problems. Mental problems in the form of anxiety, depressive states, suicidal thoughts may occur. Among the physical effects of cannabis use, we can include cognitive impairment, memory impairment, self-injury, and accidental injury. [8] Numerous studies have shown the negative effects of long-term cannabinoid (marijuana) use in young people. More short-term memory problems and decision-making problems were observed in this group. [33] Adverse symptoms of synthetic cannabinoid (SC) use include anxiety attacks, ruminations, as well as sleep disorders, hyperactivity, paranoid episodes, and suicidal thoughts. [34-35] Koob and Volkov defined drug dependence as "a chronic recurrent disorder" involving seeking and using, loss of control over the amount consumed, and the appearance of negative emotions when access to the drug is limited. [36] In recent years, more and more research has focused on determining the pathomechanism of marijuana addiction. Compounds such as delta-9-tetrahydrocannabinol (THC) and synthetic cannabinoids (CS) have been shown to directly affect the reward system by contributing to addiction. Cannabinoids affect dopamine secretion level, which explains the incidence of withdrawal symptoms that occur after discontinuing their use. The endocannabinoid system has also been shown to be involved in the development of addiction. [37] Arianna Marconi et al. conducted a meta-analysis on the level of cannabis use vs. propensity for psychosis. The purpose of the study was to benchmark 10 published scientific papers. Each showed that the risk of schizophrenia and psychotic symptoms is higher in

marijuana users relative to people who do not use it. A dose-effect relationship has also been confirmed between marijuana abuse and an increased risk of developing psychosis. [38]

Conclusions

Due to regulatory restrictions, we have a small number of studies on the effects of cannabinoids on the course and treatment of Parkinson's disease. Available literature suggests the potential involvement of cannabinoids and the endocannabinoid system in the pathogenesis of neurodegenerative diseases such as Parkinson's disease. The effect of cannabinoids on dopaminergic conduction has also been demonstrated. Uniform regulations regarding the legalization of cannabis-based remedies would enable more research. The presence on the market of cannabis preparations of unclear origin, in the absence of clearly defined standards of use, especially as a substitute for nicotine and alcohol, can lead to their abuse, and thus the occurrence of serious adverse effects that threaten life and health. A clear need for more clinical trials to determine the validity of using cannabinoids to treat the symptoms of Parkinson's disease, as well as other conditions linked to the endocannabinoid system, has been noted.

Disclosure

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Conflict of interest

The authors deny any conflict of interest

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