Chapter 9
Pros and Cons of Cannabinoids as a Potential Therapeutic Target for Treating Parkinson's Disease:
Cannabinoid Receptor–Mediated Mechanism of Action

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ABSTRACT

Medical marijuana or cannabis is a psychedelic drug composed of highly lipophilic tetrahydrocannabinol (THC) and cannabidiol (CBD) components derived from the plant C. sativa and C. indica. Parkinson's disease (PD), in which interactivity of biochemical and cellular signaling pathways induces endogenous cannabinoid system, a neuromodulatory system, transmits specific physiological effects when coupled with G-protein-coupled receptor (GPCR) via type 1 cannabinoid receptor (CB1) and type 2 cannabinoid receptor (CB2). Much recent research indicates that interactions between the cannabis system and dopamine in the basal ganglia area diminish levodopa-induced dyskinesia (LID) and other symptoms. Due to the limited number of pharmacological treatment options presently available for PD, in-depth research with clinical trials are crucial in the search for molecules with therapeutic potential studies in a wide range of epidemiological work for PD to increase neural transmission. This chapter reviews the mode of action of cannabinoids in PD.

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INTRODUCTION

Parkinson's disease is an adult-onset movement disorder characterized by loss of dopaminergic neurons in the midbrain. Many therapeutic approaches offer some symptomatic relief including dopamine replacement, deep brain stimulation and stem cell therapy. Recent studies have demonstrated that cannabinoids may further alleviate neurological symptoms in patients with movement disorders. This chapter aims to highlight cannabinoid characteristics pertinent to parkinsonism, and weighs the benefits and drawbacks of medicinal cannabis for patients with Parkinson's disease (PD).

PARKINSON'S DISEASE

Parkinson's Disease is a long-lasting, advanced neurological disorder, that distresses the nerve cells in the brain, causing muscular stiffness, tremors, and, over time, a deterioration in speech, walking, and motor abilities. More than 1 million Americans suffer from PD, which has a societal cost of more than 50 billion dollars and is the second most prevalent neurodegenerative ailment (Dorsey et al., 2007; Marras et al.,2018). One to two people out of every 1000 are affected with PD, and as people become older, their frequency rises. It affects 1% of those over 60 years of age (Babayeva et al., 2016). In the world's most populous nations, it is predicted that there will be nine million people affected by PD by the year 2030 (Suryadevara et al., 2017). Although four cardinal motor symptoms of bradykinesia, resting tremor, stiffness, and postural instability are frequently used to clinically identify PD, the symptoms of PD are more widespread. Non-motor manifestations of PD are numerous and comprise conditions like insomnia, sleep fragmentation, Rapid eye movement (REM), sleep behavior disorder (RBD), depression, anxiety, cognitive changes, hallucinations, hyposmia, pain, and autonomic dysfunction (constipation, orthostatic hypotension, and urinary incontinence) (Lees et al., 2009; Postuma et al., 2015; Schapira et al., 2017). PD is linked with a substantial social and economic impact because the disease progression necessitates extensive use of pain management, which has a significant impact on patients and their caretaker's daily routines; furthermore, these maladies do not have effective long-term therapies due to the substantial side impacts of current therapies and their progressive loss of efficacy (Gauthier et al., 2021).

The majority of the motor deficits seen in PD patients are caused by the loss of projections to the striatum, which results from the dopaminergic neurons in the substantia nigra pars compacta diminishing off progressively (Dauer and Przedborski, 2003; Olanow et al., 2009). Dopamine is depleted as a consequence of this neurodegenerative process, which encourages the failure of vital pathways involved in the regulation of voluntary movements, including those in the basal ganglia, cerebral cortex, thalamus, and brainstem (Alexander and Crutcher, 1990; Dauer and Przedborski, 2003; Olanow et al., 2009). Several interconnected dysfunctions that promote an imbalance in cellular homeostasis and the synthesis of trophic factors lead to the degeneration of dopaminergic neurons. Alterations in proteostasis, oxidative stress, mitochondrial damage, and other mechanisms are among those in action (Olanow et al., 2009; Winklhofer and Haass, 2010; Stojkovska et al., 2015; Guo et al., 2018).

PD is categorized by the necrosis of dopaminergic neurons in the substantia nigra, the brain area involved in the biosynthesis of the neurotransmitter dopamine (DA), causing a reduction in the synaptic cleft. Dopamine degradation by the monoamine oxidase B (MAO-B) promotes glutamate buildup and oxidative stress with the generation of free radicals, which results in excitotoxicity. The signs of PD are progressive physical limits such as stiffness, bradykinesia, tremor, postural instability, and difficulty