Cannabinoid Systems and the Brain

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The use of cannabinoids as therapeutic drugs has increased among aging populations. Age-related changes in the endogenous cannabinoid system could influence the effects of therapies that target the cannabinoid system. At the preclinical level, cannabidiol (CBD) induces anti-amyloidogenic, antioxidative, anti-apoptotic, anti-inflammatory, and neuroprotective effects. These findings suggest a potential therapeutic role of cannabinoids to neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer.

Keywords: cannabis ; cannabinoids ; THC ; CBD ; neurological disorders ; elderly

1. Introduction

A better understanding of age-related changes in CB1 receptor expression and function and the subsequent changes in behavioral effects of cannabinoid agonists may impact the use of cannabinoids in aging populations. There is increasing interest in the therapeutic use of cannabinoids such as cannabidiol (CBD), synthetic tetrahydrocannabinol (THC) and Cannabis extract, among the aged for various indications including pain, inflammation and multiple sclerosis [1][2][3].

Research about cannabis compounds use among older adults is increasing. Health conditions commonly researched concerning cannabis use among older adults include pain management [4], sleep assistance [5], appetite stimulation [6], and managing behaviors of dementia such as agitation [7]. Data from a survey of 568 volunteers (>years) showed that, for the ones who started using cannabis later in life, it was closely connected to medicinal purpose for issues such as pain management, sleep improvement, and to address anxiety and depression symptoms [8]. Interestingly, cannabis has been employed to replace both prescribed or over-the-counter medications [9][10].

Those data corroborate with research that explored beliefs toward cannabis use. Sixty percent of the older adults surveyed, strongly agreed that the use of medical cannabis was acceptable [11], but he favorability of cannabis decreased as age increased. Notwithstanding, most of older adults consider recreational cannabis as risky and a potential gateway drug [11]. In addition, another study showed that older adults who use cannabis medically or recreationally recognize that there is still a stigma attached to cannabis use regardless of its legality [12]. On the other hand, older adults are less worried about the potential perceived risk of using cannabinoids. Between 2015 and 2019, older Americans showed an 18.8% relative decrease in the perceived risk [13].

2. Cannabinoid Systems and the Brain

The endocannabinoid system (ECS) is the most widespread endogenous signaling neurotransmitter system in the brain [14][15][16][17][18][19][20]. This system can regulate feeding behavior, memory, anxiety, and stress response [21][22][23].

The discovery of the ECS is relatively recent. From experiments carried out with molecules isolated from the plant, it was observed that delta-9-tetrahydrocannabinol (Δ9-THC), through its connection with CB1 receptors, is responsible for the neuropsychological and psychopathological effects [15]. These findings triggered countless other studies that allowed the cloning of the cannabinoid receptor 2 (CB2) receptor [16] and the identification of endogenous molecules that compose the system [17]. The ECS consists mainly of cannabinoid receptors CB1 and CB2; endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG); synthesis enzymes such as N-acyl phosphatidylethanolamine (NAPE) and diacylglycerol lipases (DAGL) and degradation or reuptake enzymes as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [24][25][26][27].

AEA and 2-AG are both endocannabinoids synthesized on demand from arachidonic acid [19]. Once released in the extracellular space, endocannabinoids act near the synthesis as retrograde synaptic messengers at presynaptic receptors [14]. AEA acts as a partial agonist at CB1 and CB2 [28], but also works on selective cation channels. Transient receptor potential cation channel subfamily V member (TRPV1), a key element in inflammatory conditions and pain [29]. AEA has a

notable role in several physiological and neurobehavioral processes, such as pain perception [30], emotional behavior [31] and energy metabolism [32]. 2-AG is the most abundant endocannabinoid in the brain and is considered a full agonist of CB1 and CB2 [33]. It has been implicated in numerous physiological processes [34], including several forms of neuroplasticity [35] and its generation and degradation is part of the lipid metabolism [14].

AEA and 2-AG are the most studied and investigated endogenous ligands. These compounds, unlike classical neurotransmitters, are not synthesized at presynaptic terminals or stored in vesicles but are formed based on demand at postsynaptic terminals. AEA and 2-AG act on presynaptic CB1 or CB2 receptors, inhibiting neurotransmitter release. Because the ECS is widely present in the central nervous system, it plays an essential role in the neurobiology of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Several approaches, whether in vitro assays, animal models, and clinical studies, suggest that ECS modulation can reduce proteins involved in AD pathophysiology, such as tau and beta-amyloid [36] and alpha-synuclein form Lewy bodies in PD. The increased reactivity of microglia and astrocytes, as well as the pro-inflammatory [37] markers TNF-α, IL-17, IFN-γ, iNOS, IL-1β, and NF-κB, are factors implicated in these diseases, where ECS modulation can be a critical pharmacological and molecular target. Furthermore, endocannabinoid modulation can prevent mitochondrial damage, facilitate homeostasis, and decrease excitotoxicity, as well as reactive oxygen species (ROS), culminating in restoring memory and cognitive function, prevalent in the diseases mentioned earlier [38][39][40]. As seen in the image (**Figure 1**), adequate functioning of the ECS can be an essential tool in the homeostasis of inflammatory responses, in glial reactivity, in the proper functioning of mitochondrial complexes, and the control of the expression of proteins implicated in the pathophysiology of AD (**Table 1**) and PD. Furthermore, this system and its complex machinery have also participated in synaptic plasticity and neurogenesis events [39]. Both CBD and THC have potential targets for therapeutic effects on neurodegenerative diseases, since they can modulate ECS. CBD acts as an agonist of the receptors TRPV1, PPARγ, and mAChR and as an antagonist of the receptor GPR55 [41][42]. This compound is suggested to act as a negative allosteric modulator of CB1 and CB2 receptors [43]. Finally, CBD inhibits the enzyme FAAH, with a consequent increase in AEA levels. Moreover, AEA can activate CB1, CB2, and TRPV1 receptors (**Table 2**). CBD is relevant for treating neurodegenerative diseases since it can increase the activity of mitochondrial complexes and shows antioxidant and anti-inflammatory effects that are partially mediated by its actions on TRPV1, mitochondria, and PPARγ. On the other hand, THC is a partial agonist of CB1 and CB2 receptors, an agonist of GPR55 and PPARγ, which, just like CBD, can exert anti-inflammatory effects. **Figure 1** summarizes the effects of cannabinoids in dementias.

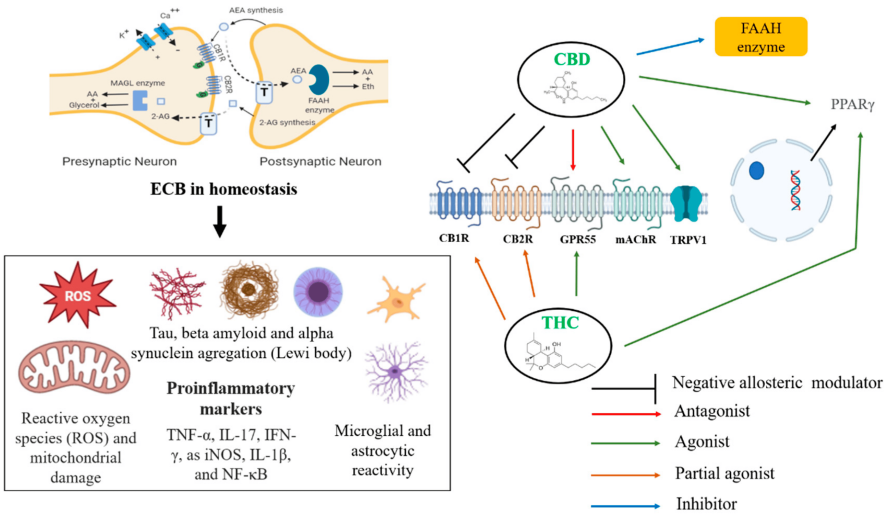

Figure 1. Potential targets and therapeutic effect of CBD in dementias. Legend: TRPV1, transient receptor potential vanilloid type 1; PPARγ, peroxisome proliferator-activated receptor gamma; GPR55, G-protein-coupled receptor 55; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; FAAH, fatty acid amide hydrolase; mAChR, muscarinic acetylcholine receptor; 2-AG, 2-arachidonoylglycerol; AEA, anandamide; T, transporter.

Table 1. Potential targets and therapeutic effect of CBD in dementias.

Receptors	Action	Pharmacology Propriety
CB1	**Direct antagonist and negative allosteric modulation antagonist**	**Attenuation of learning deficit, memory, and psychotic effects of THC**
CB2	**Antagonist & reverse agonist**	**Anti-inflammatory**
GPR55	**Antagonist**	**Antitumor**

Receptors	Action	Pharmacology Propriety
5HT1A	Agonist	Analgesia and anxiolytic
mAChR	Agonist	Cognition improvement
TRPV1	Agonist	Anti-inflammatory and analgesia
PPARγ	Agonist	Antioxidant and anti-inflammatory

Legend: CB1 Cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; GPR55, G-protein-coupled receptor 55; 5HT1A Serotonin 1A receptor; mAChR, muscarinic acetylcholine receptor; TRPV1, transient receptor potential vanilloid type 1; PPARγ, peroxisome proliferator-activated receptor gamma.

Table 2. Practical management with cannabinoids in Parkinson's and Alzheimer's disease.

Neuropsychiatric Disorder	Potential (Off Label) Indication	Suggested Dose Regimen
Parkinson's disease	Resistant tremor or dyskinesia	Starting dose: CBD (<0.3% THC) 5 mg once daily. Increase 5 mg every 3 days. Maximum dose: 20 mg twice a week.
	Resistant anxiety	Starting dose: CBD (<0.3% THC) 5 mg once daily. Increase 5 mg every 3 days. May split the dose in two or three intakes. Maximum dose: 90 mg twice a week (CBD monotherapy).
	Agitation due psychosis partially treated with quetiapine or clozapine	1 mg of THC can be initiated with CBD or after 20 mg of CBD without a positive effect. Increase THC to a maximum of 20 mg combined to a maximum of 40 mg of CBD.
	Persisted sleeping disturbance albeit treated with two first-line treatment	Starting dose: CBD (<0.3% THC) 5 mg at night. Increase 5 mg every 3 days. Maximum dose: 20 mg
Alzheimer's disease	Persisting agitation or aggression besides non-pharmacologic and first-line drug treatment implemented	Starting dose: CBD (<0.3% THC) 5 mg once daily. Increase 5 mg every 3 days. May split the dose in two or three intakes. Maximum dose: 20 mg twice a week.
	Major adverse event with first-line drug treatment for agitation, anxiety, or aggression	1 mg of THC can be initiated with CBD or after 20 mg of CBD without a positive effect. Increase THC to a maximum of 20 mg
	Persisting anorexia albeit traditional treatment for dementia and exclusion of secondary causes	Starting dose: CBD (<0.3% THC) 5 mg once daily. Increase 5 mg every 3 days. Maximum dose: 10 mg twice daily

Note: CBD = cannabidiol; THC = delta-9-tetrahydrocannabinol.

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