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Neuroprotective Aspects of Cannabinoid Compounds

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Abstract

The accumulation of reliable data on the effects of cannabinoids is essential for understanding their possible beneficial effects on the central nervous system (CNS). Investigating individual substances along with the action of different combinations may show new possibilities for cannabinoids as neuroprotective agents. The data collected so far reveals the complexity of the mechanism of cannabinoids action on CNS, and even more complex and poorly understood are the effects when combined. Moreover, combining cannabinoids with different drugs and chemicals may lead to a decrease in beneficial effects. These characteristics of their action emphasize the complexity of the molecular mechanisms of neuroprotection and the lack of reliable information that may contribute to the safe and effective use of cannabinoids as medicines with valuable neuroprotective properties. The current brief review summarizes present data related to the protective effects of some cannabinoids on CNS and possible mechanisms involved in cannabinoid-mediated neuroprotection.

Keywords: Cannabinoids; Neuroprotection; Cannabinoid Receptors; THC; CBD; CNS

Abbreviations

CNS - central nervous system
THC - Δ9-tetrahydrocannabinol
CBD - cannabidiol
CB1R - cannabinoid receptor type 1
CB2R - cannabinoid receptor type 2
BHT - dibutyl hydroxytoluene
6-OHDA - 6-hydroxydopamine
PD - Parkinson`s disease
A2AR - adenosine A2A receptor
D2R - dopaminergic D2 receptor
MS - multiple sclerosis

Introduction

Much historical data regarding the medical use of Marijuana throughout the ages is available today, but the Cannabis plant was not introduced to the western world until 1649 when Nicholas Culpeper presented the Latin *Pharmacopoeia Londonensis* in English [1-3]. There Marijuana was described to possess neuroprotective properties as medicine for "inflammation of the head" [4]. Two centuries after, William O'Shaughnessy discovered an effective way to control seizures in forty days old infant, using Cannabis Indica tincture and proclaimed that in the time humankind "possess no remedy at all equal to this in anti-convulsive and anti-neuralgic power" [5].

More than 560 constituents have been identified in Cannabis, among them over 100 phytocannabinoids [6, 7]. The identification and isolation of the two primary components found in Cannabis spp., Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), was finished in the late 1960s [8, 9]. Efforts on the topic made possible to apply the modern pharmacological studies and to observe the effects of cannabinoids in different states, including models of CNS pathology [4, 10, 11]. The implication of new research technics revealed possibilities for modulation of cannabinoids pharmacological effects in different directions [12-15].

Several cannabinoid-based medical products are available for treating conditions involving neuronal alterations, despite the previous strategy using cannabinoids as antiemetic and appetite-stimulating agents [16-19]. Those and more data on the topic have led to a growing interest in understanding cannabinoids activity in case of self- and co-administration, and highlight new perspectives in the field of neuroprotection and drug research.

Endocannabinoid system

The endocannabinoid system plays a key role in excitatory and inhibitory synaptic transmission modulation in the brain [20]. Two G protein-coupled receptors are known in the endocannabinoid system, cannabinoid receptor type 1 (CB1R) and cannabinoid receptor type 2 (CB2R), with endogenous ligands 2-arachidonoylglycerol and N-arachidonoylethanolamide [21]. In CNS more wildly expressed are CB1R, which are abundantly found in the hippocampus, but also present on microglia, astrocytes, and oligodendrocytes [22]. The other receptor subtype, CB2R, is also suggested to be present in CNS [4, 23]. Recent research highlighted its role in mediating neuronal excitability and inflammation in microglia [24, 25]. Nevertheless, endocannabinoids can affect other targets besides CB1R and CB2R. Among them orphan G protein-coupled receptor and the transient receptor potential vanilloid receptor type 1 [4].

THC and CBD activity

The principal psychoactive constituent of Cannabis, THC, which mane pharmacological targets are CB1R and CB2R, can modulate neuronal functions and affect behavior. THC is a partial agonist of CB1R and CB2R and thereby exerts a variety of effects on CNS, including mediating synaptic plasticity [20]. The observed THC-induced dopamine release results from CB1R activation, whereas the potential anti-inflammatory properties are likely CB2R-mediated [26].

CBD is the second most abundant cannabinoid in Cannabis [18]. Within the endocannabinoid system, CBD acts as an inhibitor of the inactivation of endocannabinoids. It blocks the action of fatty acid amide hydrolase and consequently elevates the effects of endocannabinoids. CBD is also reported to cause direct or indirect activation of metabotropic receptors for serotonin or adenosine and can affect ion channels as well as nuclear receptors serving as transcription factors [27].

The main pharmacological difference between THC and CBD is the psychoactive component in their action. Regardless of the adverse events that are present in THC action, CBD does not activate CB1 receptors, and thus did not show psychoactive properties [28]. Data suggest that CBD is well tolerated and has a variety of therapeutic activity, as an anti-inflammatory, antiepileptic, antioxidant, anti-emetic, anxiolytic, and antipsychotic agent [27].

Cannabinoids - CNS benefits

Preclinical study, conducted by Hampson and colleagues, demonstrates the antioxidant properties similar to the antioxidant dibutyl hydroxytoluene (BHT) displayed by CBD and THC. Both cannabinoids reduce the oxidative damage induced by hydroperoxide better than ascorbate and tocopherol, and comparable with BHT, in neuronal cultures. The data also revealed the independence of the neuroprotective effects from the activation of cannabinoid receptors. The neuroprotective properties of CBD against glutamate-induced neurotoxicity were more potent than both ascorbate and alpha-tocopherol. Those results are indicating CBD to be potentially useful in the treatment of oxidative neurological disorders [10].

The antioxidant and anti-inflammatory activity of CBD and THC were suggested to be the reason for their neuroprotective effect, demonstrated in conditions of 6-hydroxydopamine (6-OHDA)-induced neurodegeneration. In this model of Parkinson's disease (PD), both cannabinoids have shown to alleviate the oxidative damage produced by 6-OHDA *in vivo* and *in vitro* [11].

In combination, CBD ameliorates the side effects of THC, like intoxication, sedation, and tachycardia, permitting the administration of higher doses of THC [14]. Moreover, CBD achieves synergy with THC, potentiating the beneficial effects, and thus increasing the clinical efficacy of both cannabinoids [13, 14]. In their study in 2011, García and colleagues observed preservation of tyrosine hydroxylase-positive neurons by another cannabinoid, a homolog of THC, tetrahydrocannabivarin (THCV), which attenuated the 6-OHDA-induced motor inhibition. The authors suggest THCV treatment as a promising approach for delaying the progression in PD and for mitigating the parkinsonian symptoms due to its ability to activate CB2 but to block CB1 receptors [29].

Within a randomized, placebo-controlled, double blind, crossover trial conducted in the UK is reported that the stimulation of the cannabinoid receptors in globus pallidus by cannabinoid receptor agonist (nabilone) significantly decreases levodopa-induced dyskinesia in PD patients [30]. In a study published in 2014, Cerri and colleagues demonstrate interesting aspects of the neuroprotective properties of combined and single treatment with CB1R antagonist and adenosine A2A receptor (A2AR) antagonist. In a 6-OHDA-induced model of PD in rats, they observe promoted dopaminergic neuron survival in *substantia nigra* pars compacta for both types receptor antagonists when given alone, but a weakening of this effect when combined [12]. A2AR is a suggested target for neuroprotection as well as CB1R, but combining those two therapeutic approaches did not promoted further neuroprotection [12, 31-36].

Some authors suggest that A2AR and CB1R might functionally interact, doe to their high expression and colocalization in the striatum, and their involvement in the modulation of motor activity in PD [12]. Such interplay may involve dopaminergic D2 receptors (D2Rs) as well, within striatal A2AR-D2R and CB1R-D2R heterodimers [37]. Moreover, *ex vivo* evidence suggested the presence of receptor heterotrimers of type A2AR-CB1R-D2R in neuronal tissues from parkinsonian rats and primates [38, 39]. In an animal model of PD, Di Marzo and colleagues observed full movement recovery in reserpine-treated rats by co-administration of selective D2R agonist and selective CB1R antagonist. Their observations suggest that modulation of the endocannabinoid system signaling might be used in the treatment of basal ganglia-related movement disorders, as PD [15].

Cannabinoid-based medications

Nabilon and Dronabinol are designed as synthetic THC and synthetic THC analog respectively and approved by FDA for treatment of nausea and emesis in patients with acquired immunodeficiency syndrome-related weight loss or undergoing cancer chemotherapy [19]. The pharmacological effect of these products is based on the modulation of the nervous activity in the medulla oblongata [19]. Still, cannabinoid related adverse events are frequent, with over 70 % of patients experienced side effects like sedation, psychiatric disturbances, speech disorders, memory impairment et ctr [18, 19].

Sativex (nabiximols) is oromucosal spray based on Cannabis sativa extract, in which the active substances are THC and CBD in approximately 1:1 ratio [40]. Sativex is indicated for the symptomatic treatment of neuropathic pain in multiple sclerosis (MS). The product is approved for medical use in many countries worldwide and become the first commercially available cannabinoid-based medication used as an add-on therapy for the treatment of drug-resistant spasticity in MS patients [16]. Research on Sativex action demonstrates that Sativex is well tolerated and reduces spasticity and recognizes the clinical effectiveness of Sativex in spasticity management [16, 41].

Epidyolex is the first pharmaceutical formulation of highly-purified, plant-derived CBD [17]. The active substance in the product is 100 mg/ml CBD. Epidyolex is assessed by EMA with Procedure No. EMEA/H/C/004675/0000 of the Committee for Medicinal Products for Human Use in July 2019, for treatment of seizures associated with rare epileptic encephalopathies with childhood-onset. Previously it became the first FDA-approved prescription CBD.

Only in the first half of 2019, approximately 2.7 million people in Canada reported using Cannabis for medical purposes [18]. Gathering more data on the topic is essential for understanding the mechanisms of neuroprotection demonstrated by different cannabinoid compounds and their possible favorable effects, especially in the context of their widespread use.

Discussion

Due to their apparent biological activity and influence on CNS, cannabinoids have been widely used unregulated through Cannabis use for centuries. Still, the reliable data on their pharmacological action is not sufficient to determine the potential benefits of cannabinoids as medicines. The data collected so far reveals the complexity of the mechanism of cannabinoids action on CNS, and even more complex and poorly understood are the effects when combined. Moreover, combining cannabinoids with different xenobiotics may lead to a decrease in their beneficial effects. The use of standardized extracts of Cannabis spp. in experimental research may reveal the perspective cannabinoid combinations. More efforts are needed to understand the range of health benefits that cannabinoids can offer and uncover all the neuroprotective aspects of cannabinoid compounds.

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