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Review Article

Role of Cannabinoid Receptors in Psychological Disorder

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Abstract

Cannabinoid receptors, located throughout the body, are part of the endocannabinoid system. Cannabinoid CB1 and CB2 receptors are G protein-coupled receptors present from the early stages of gestation, which is involved in various physiological processes, including appetite, pain-sensation, mood, and memory. Due to the lipophilic nature of cannabinoids, it was initially thought that these compounds exert several biological effects by disrupting the cell membrane nonspecifically. Recent biochemical and behavioral findings have demonstrated that blockade of CB1 receptors engenders antidepressant-like neurochemical changes (increases in extracellular levels of monoamines in cortical but not subcortical brain regions) and behavioral effects consistent with antidepressant/antistress activity. We aim to define various roles of cannabinoid receptors in modulating signaling pathways and association with several pathophysiological conditions.

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INTRODUCTION

Psychological disorders are responsible for the largest proportion of the global burden of disease worldwide (Whiteford *et al.*, 2015). It has been suggested that by 2030, depression will be the leading cause of disease burden globally (Lépine & Briley, 2011). Uncontrolled excitotoxicity and neuroinflammation contribute to cell death and damage in neurological and neuropsychiatric diseases, including some that are related to stress exposure (neurodegenerative diseases, depression, post-traumatic stress disorder, and schizophrenia) (Tay *et al.*, 2017).

Cannabis is touted to effectively attenuate a wide range of conditions, including asthma, inflammatory bowel disease, glaucoma, multiple sclerosis, menstrual cramps, AIDS, nausea, and cancer (Bruni *et al.*, 2018). Delta-9-tetrahydrocannabinol (THC) is the principal psychoactive constituent of cannabis, and most, if not all, of the effects associated with the use of cannabis, are caused by THC (Kimura *et al.*, 2019). Beyond these effects on physical conditions, cannabis has been reported to improve neurocognitive and psychiatric conditions, such as Alzheimer's disease, anxiety disorders, and bipolar disorder (Abizaid *et al.*, 2019; Sarris *et al.*, 2020; Burggren *et al.*, 2019). The endocannabinoid system (ECS) plays key modulatory roles during synaptic plasticity and homeostatic brain processes (Lu & Mackie, 2016).

This review discusses some relationships between the cannabinoid (CB1 and CB2) receptors and their ligands with the nervous system in health and disease. We will introduce the two major receptors, focusing on the CB1 receptors due to their high expression levels in the CNS. Their endogenous ligands or endocannabinoids (ECB) and some synthetic mimetics that activate and modulate their signaling; the signaling pathways that connect this

receptor to processes inside the cell; and the role of the CB system in the normally functioning CNS and its alteration or therapeutic modulation in a variety of disease states (Tanaka *et al*., 2020).

OVERVIEW OF ENDOCANNABINOID SYSTEM

Before discussing the ECS's functions, it is essential to understand its components. The ECS comprises cannabinoid receptors, endogenous ligands (binding molecules) for those receptors, and enzymes that synthesize and degrade the ligands (Stasiulewicz *et al*., 2020). Exogenous cannabinoids, such as tetrahydrocannabinol, produce their biological effects through their interactions with cannabinoid receptors. 2-arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamide (anandamide) are the best-studied endogenous cannabinoids (Lu & Mackie, 2016).

The most well-known cannabinoid receptors are CB1 and CB2. Studies in the early 1990s provided initial evidence of the existence and purpose of CB1 and CB2 receptors. Both types of cannabinoid receptors are found throughout the entire body but are distributed differently (Zou & Kumar, 2018). The CB1 receptors are concentrated primarily in the Central Nervous System, are most highly expressed by the axons and presynaptic terminal of neurons in the amygdala, hippocampus, cortex, basal ganglia outflow tracts, and cerebellum (Castillo *et al*., 2012). In contrast, CB2 receptors are mainly found in the immune system (Turcotte *et al*., 2016). However, CB1 receptors are also distributed in various peripheral areas like adipose (fat) tissue, and CB2 receptors are expressed to some degree in the brain (Howlett & Abood, 2017).

G protein-coupled receptor (GPCR) domains comprise the extracellular N terminus, seven-transmembrane alpha-helices (TM), loops connecting the TMs, and an intracellular C terminus. Ligand binding generally occurs within a binding site gap formed by the TM bundle, directly to a pocket formed by the extracellular loops, or to a combination of extracellular loop and binding site gap residues (Wheatley *et al*., 2012). Binding induces a conformational change in the receptor, causing activation of a G protein docked to the inner face, which initiates a specific cellular process (Black *et al*., 2016).

In general, an agonist-bound receptor activates an appropriate G protein that promotes dissociation of GDP. The GPCR ligands fall into four categories depending on the nature of their interaction: agonists, antagonists, partial agonists, and inverse agonists (Weis & Kobilka, 2018). Agonists bind to the receptor and elicit a cellular response by causing a conformational change. Antagonists bind, prevent agonists from binding, and do not elicit any response. A partial agonist is an intermediate class that, upon binding, does not invoke the complete agonist conformational change but still allows for partial activity. Simultaneously, they "block" the receptor from being available for full agonist binding. When both a full agonist and partial agonist are present, the partial agonist acts as a competitive antagonist, producing a net decrease in the receptor's activation. Inverse agonists bind to a receptor but induce a physiological response opposite to what would be expected from an agonist (Shahbazi *et al*., 2020; Berg & Clarke, 2018). The affinity of a ligand for the receptor is independent of the role: weakly binding full agonists and strongly binding partial agonists are both known (Buchwald, 2019; Patel *et al*., 2019).

Agonists targeting CB2 receptors have been proposed to treat or manage a range of painful conditions, including acute pain, chronic inflammatory pain, and neuropathic pain (Dhopeshwarkar & Mackie, 2014; Vučković *et al*., 2018; Donvito *et al*., 2018). The ECB system is primarily composed of two inhibitory GPCRs, CB1 and CB2, and

two major endogenous ligands, N-arachidonoylethanolamine (anandamide/AEA) and 2-arachidonoylglycerol (2-AG). Besides, ECB signaling is highly regulated by metabolic enzymes, including fatty acid amide hydrolase (FAAH) and monoacylglyceride lipase (MAGL), hydrolyze AEA and 2-AG, respectively (**Figure 1**) (Meyer *et al*., 2018).

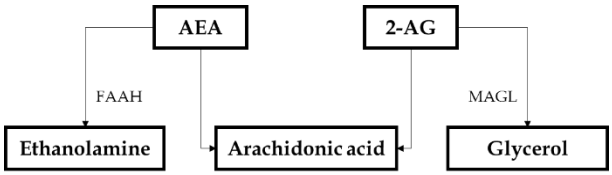

Figure 1. Major pathways of endocannabinoid degradation (Meyer *et al*., 2018)

CANNABINOID RECEPTORS IN ANXIETY

Anxiety disorders, the most prevalent of the psychiatric disorders, cause immeasurable suffering worldwide. Despite impressive advances in pharmacological therapies, improvements in efficacy and side-effect profiles are needed. Anxiety causes chemical changes in the limbic system, including the amygdala, hippocampus, and hypothalamus of the brain (Zou & Kumar, 2018). The present literature review examines the role that the endocannabinoid system may play in these disorders and the potential value of targeting this system to search for novel and improved medications (Patel *et al*., 2017; Kayser *et al*., 2019).

The neural mechanisms by which endocannabinoid signaling affects anxiety are not well understood, yet several mechanisms at the systems, synaptic, and molecular level can be posed based on available data. The majority of available data indicate that ECS has anxiolytic properties in both conditioned and unconditioned anxiety models and that these effects are more active during states of stress or high arousal (Stasiulewicz *et al*., 2020; Patel & Hillard, 2009). Endocannabinoid signaling's anxiolytic effects are mimicked by low doses of direct CB1 receptor agonists (Hill *et al*., 2018). Thus, data exploiting this phenomenon can be used to increase our understanding of the neural mechanisms subserving the endocannabinoid signaling system's anxiolytic actions (Patel & Hillard, 2009).

At the systems level, microinjections of low doses of the direct CB1 agonist THC into the prefrontal cortex (PFC) (Rubino *et al*., 2008), ventral hippocampus, and a dorsal periaqueductal gray area exert anxiolytic effects in the elevated plus-maze (Moreira *et al*., 2007). Stress relief and relaxation are frequently reported as drivers of cannabis use (Turna *et al*., 2017). These effects are blocked by the CB1 receptor antagonist AM251 (Boctor *et al*., 2007). Pharmacological inhibition of FAAH within the PFC produces CB1 receptor-dependent, anxiolytic effects, and over-expression of FAAH (which reduces local N-arachidonoylethanolamine levels) causes the anxiogenic effect in the elevated plus-maze (Navarrete *et al*., 2020; Lutz *et al*., 2015).

In contrast to the PFC and hippocampus, very low THC doses produce only anxiogenic effects when administered into the basolateral amygdala (BLA); this was also dependent upon CB1 receptor activation. These data suggest that the PFC and hippocampus are likely anatomical sites of action that subserve ECS's anxiolytic effects. More specifically, the balance of ECS in favor of an increase in the PFC plus hippocampus and reduced signaling in the amygdala could be required for maximal anxiolytic effects (Patel & Hillard, 2009). Endocannabinoid signaling differs from that of classical neurotransmitters. They are synthesized on demand in post-synaptic neurons in response to neuronal activation and act on their targets located presynaptically or in the post-synaptic neuron itself to mediate retrograde or non-retrograde signaling, respectively (Kano, 2014). Endocannabinoids act on presynaptic CB1 receptors during retrograde signaling to suppress in response to

stimuli, which normally provoke anxiety. Both the anxiogenic and psychotropic effects of THC would appear to preclude its use for treating anxiety-related disorders, at least when administered on its own (Lee *et al*., 2017; Papagianni *et al*., 2019).

NEURAL MECHANISMS OF ENDOCANNABINOID MODULATION IN DEPRESSION

The neurobiology of depression is complex; however, a large body of evidence supports the hypothesis that dysregulation of the Hypothalamic-Pituitary-Adrenal axis (HPA axis) plays a critical role (Hasler, 2010). In particular, HPA axis hyperactivation and reduced feedback inhibition are seen in humans with depression and in animal models of depression. Anti-depressants' ability to suppress HPA axis hyperactivity is coupled with their clinical efficacy (Herman *et al*., 2016).

Recent studies strongly suggest that the ECS's primary role is to dampen HPA axis activation by stress and allow for appropriate stress recovery (Stephens & Wand, 2012). These findings are consistent with the data obtained in rodents described above that ECS inhibition is generally pro-depressive. Simultaneously, its activation results in an anti-depressant phenotype and leads to the hypothesis that the HPA axis's dampening is the mechanism by which ECS interacts with depression. However, HPA axis inhibition does not entirely explain ECS's effects to alter coping behaviors in the forced swim assay (Barden, 2004). Poleszak *et al*. (2020) evaluated the potential interaction between the CB2 receptor ligands (i.e., JWH133 – CB2 receptor agonist and AM630 – CB2 receptor inverse agonist) and several common anti-depressant drugs that influence the monoaminergic system (i.e., imipramine, escitalopram, reboxetine) (Ibarra-Lecue *et al*., 2018). Cannabis amotivational syndrome is based on apparent apathy and abolished the ability to concentrate and follow routine life observed in those who consume marijuana frequently (Volkow *et al*., 2016). There is both preclinical and clinical evidence supporting the view that cannabis use is associated with an amotivational state (Lawn *et al*., 2016). Considerable research has failed to identify a cannabis-specific motivational syndrome, and its existence remains controversial. A study by Lac and Luk (2018) sought to elucidate amotivational syndrome by examining connections between marijuana use and self-efficacy constructs of initiative, effort, and persistence. Results showed that marijuana intake was significantly longitudinally related to lower initiative and persistence in their college student sample. Due to this, higher dose THC should be avoided in people with major depressive disorder (MDD) or low mood. However, a cross-sectional survey on patterns of use and perceived efficacy suggested that over 1429 participants identified as medical cannabis users, over 50% reported using medicinal cannabis specifically for depression (Sarris *et al*., 2020). Various medicinal cannabis trials in mental disorders are listed in **Table I**, while various EC system changes in neurodegenerative disorders are listed in **Table II**.

Table I. Medicinal cannabis trials in mental disorders

Mental disorder	Cannabinoid studied	Method	Results
Social anxiety (Bergamaschi *et al*., 2011)	CBD (600 mg)	24 treatment-naïve patients with social anxiety were blindly allocated to receive CBD or placebo 1.5 hours before a simulated public speaking test. 12 unmedicated healthy controls also completed the test. Self-reports on the visual analogue mood scale, negative self-	Pre-test CBD administration in social anxiety patients versus placebo, resulted in significantly reduced anxiety, cognitive impairment and discomfort in speech performance, and significantly decreased hyperalertness in anticipatory speech. CBD and control groups however did not differ, reflecting

		statement scale, and physiological measures were taken at six time points during the test	similar response profiles during the public speaking test
Insomnia (Shannon & Opila-Lehman, 2016)	CBD capsules (25 mg) + liquid (6-25 mg)	Patient (10 y.o. girl with prior early childhood trauma) was prescribed fish oil (750 mg daily) + 1 CBD oil capsule daily for 5 months. CBD liquid (12–24 mg) was added to the regime for 1 month and reduced to 6–12 mg p.r.n (or 'when needed'). Sleep assessed monthly via SDSC	SDSC scores decreased over the 5-month period, indicating an increase in sleep quality and quantity
Schizophrenia (Leweke *et al*, 2012)	CBD (600-800 mg)	42 individuals with schizophrenia were randomly assigned to receive 600–800 mg of CBD or amisulpride over 4 weeks. The PANSS and BPRS were administered every 14 days. Blood was also collected	Both treatments were effective in reducing PANSS and BPRS scores at each time point. CBD was tolerated better, with fewer side effects reported. Anandamide levels were higher in the CBD group post-treatment

Table II. Changes in EC system in neurodegenerative disorders

Study model	Changes in EC system
Changes in the EC system components in Alzheimer diseases, Preclinical studies, AbPPswe/PS1DE9 model of AD (Maroof *et al*., 2014)	< Striatal AG level > CBR/effector coupling
Changes in the EC system components in Parkinson's diseases, Pre-clinical studies, Reserpine treated rats (Di Marzo *et al*., 2000)	> 2-AG in globus pallidus Impaired locomotion > AEA in globus pallidus & substantia nigra
EC system targeted pharmacological compounds treating Alzheimer diseases, Pre-clinical studies, Ab injected rats (Ramirez *et al*., 2005)	< Ab induced microglial activation < Cognitive impairment

CANNABINOID RECEPTOR IN EPILEPSY

Cannabidiol good affinity at the plausible concentration for 5-HT1A and 5-HT2A receptors, and 5-HT2A receptors act as a target for fenfluramine, a drug for which some evidence supports efficacy drug-resistant epilepsies such as Dravet syndrome (Ceulemans *et al*., 2012). A minimal number of studies have reported changes in 5-hydroxytryptamine (5-HT) receptor expression and function in people with epilepsy, although it remains unclear whether this is a consequence of the disease or a component of pathogenesis. Thus, while 5-HT involvement in pathogenesis remains uncertain, some 5-HT receptor subtypes may represent a valid therapeutic target in epilepsy through which CBD could be acting (Theodore *et al*., 2007; Theodore *et al*., 2012). Glycine receptor (GlyR) is predominantly expressed in the CNS, neuronal cells, brainstem, and spinal cord, and there is much less evidence of their role in disorders of the cerebrum, such as epilepsy. However, recent research in rodent species has shown significant, functional GlyR expression in cortex and hippocampus at least up to postnatal day 14, where they serve to modulate neuronal network function (Avila *et al*., 2013), and emerging evidence suggests a role in hyperexcitability disorders (Harvey *et al*., 2008). These findings suggest that investigation of GlyR function in healthy and epileptic, mature human cortex is warranted in order to lend further credence to GlyR-mediated antiepileptic effects of CBD.

CANNABINOID RECEPTORS IN ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common neurodegenerative disease in Western Europe, and a significant public health problem as the number of cases increases with the aging of the population. It manifests with a progressive decline in memory and intellectual abilities, impoverishment of language, disorientation, and behavioral skills (Mayeux & Stern, 2012). The AD is also characterized by enhanced beta-amyloid peptide (Aβ) deposition and glial activation in senile plaques,

selective neuronal loss, and cognitive deficits (Licastro & Chiappelli, 2003). The role of cannabinoid receptors in AD and their possible protective effects after Aβ treatment showed that senile plaques in AD patients express CB1 and CB2 cannabinoid receptors and markers of microglial activation (Pizza *et al*., 2011). Furthermore, while high levels of CB1-positive neurons are present in control cases, they are significantly reduced in microglial activation areas. Also, G-protein coupling and CB1 receptor protein expression are markedly decreased in AD brains where protein nitration is increased (Ramirez *et al*., 2005). Cannabinoids prevent both Aβ-induced microglial activation, cognitive impairment, and loss of neuronal markers and abrogate microglia-mediated neurotoxicity after Aβ addition to rat cortical cocultures. These results indicate that cannabinoid receptors are involved in the pathology of AD and that they may control the neurodegenerative process occurring in the disease (Cassano *et al*., 2017).

CONCLUSION

Stress-related mood and anxiety disorders affect millions of people in the United States. Endocannabinoids are lipids that act as a kind of a neurotransmitter. Mainly, they activate the CB1 and CB2 brain receptors. CB1 can be found in several brain areas, including the neocortex, the hippocampus, the amygdala, the cerebellum, and the hypothalamus. These brain areas are involved in emotional and behavioral reactions, homeostasis, learning, memory, and decision-making. The effects on emotion mediated by cannabinoid compounds are believed to be due to regulating activity at the cannabinoid CB1 receptors. However, some limited evidence implicates the cannabinoid CB2 and a putative novel cannabinoid receptor (GPR55) in some observed emotional responses. Effects on emotion are likely the result of a net effect of the summated neurochemical responses. Compounds that indirectly regulate activity at the cannabinoid receptors more consistently reduce anxiety both in preclinical and clinical models.

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