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REVIEW

POSSIBLE EFFECTS OF THE ENDOCANNABINOID SYSTEM ON THE PATHOPHYSIOLOGY OF DEPRESSION: MEDICAL TREATMENT APPROACHES BASED ON THIS SYSTEM

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ABSTRACT

World Health Organization sees depression, in other words known as major depressive disorder or clinical depression, as the leading cause of disability worldwide. Interestingly, the mechanism of depression is still not fully clear. Medications used in primary treatment for mood disorders often target the monoaminergic system, however, the low efficacy of these drugs and the increase in the risk of suicide show that other factors might also play a role in the pathophysiology of depression. Therefore, the endocannabinoid system, which has been demonstrated to be strongly associated with depression, has attracted attention. In this review, we aim to discuss the possible role of the endocannabinoid system in the suggested mechanisms of depression and examine the medical treatment approaches that are being developed based on this system to eliminate the adverse effects of current depression medications.

Keywords: Antidepressive agents, depressive disorder, endocannabinoid system

INTRODUCTION

According to the 2021 data from the World Health Organization, approximately 280 million people in the world have depression (1). Nevertheless, it would be wrong to see depression as a psychological disorder that only concerns the person affected. Depression does not only affect the individual psychologically, but people with depression are at a higher risk of cardiovascular diseases, which can be fatal (2). Additionally, suicide, which is perhaps the worst consequence of depression, is the fourth most common cause of death in individuals aged 15-29 (1). Furthermore, if we look at the effects on society, according to a study conducted in the United States in 2021, the national economic burden of depression cases that do not respond to treatment is 43.8 billion dollars (3). Despite treatments such as prescribing antidepressants, electroconvulsive therapy, psychotherapy, and transcranial magnetic therapy, only 30% of patients with major depressive disorder (MDD) experience complete remission or recovery (4). Although the symptoms of depression are attempted to be standardized by the Diagnostic Statistical Manual of Mental Disorders-5 (DSM-5) criteria, they largely vary. MDD is a mental health condition that requires at least five of the nine symptoms defined by DSM-5, including at least one of either anhedonia (loss of interest in pleasurable activities) or depressed mood, lasting for at least two weeks. Other symptoms may include changes in appetite, sleep disturbances, fatigue, difficulty concentrating, and thoughts of death or suicide. The use of *Cannabis sativa*, commonly referred to as marijuana, can be traced back to ancient times. In ancient Chinese cultures, it was used for medicinal purposes, particularly for pain relief. Today, marijuana is used to stimulate appetite in acquired immunodeficiency syndrome-related cachexia, alleviate nausea and vomiting associated with cancer chemotherapy, and for recreational purposes (5). There are over 70 cannabinoids derived from the cannabis plant to

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this day, and they are classified as phytocannabinoids. Three of the most important of these compounds are cannabidiol (CBD), cannabinol, and Δ9-tetrahydrocannabinol (THC), which is the psychoactive component (5). In addition to phytocannabinoids, the cannabinoid group includes naturally produced endocannabinoids [arachidonoyl ethanolamide (AEA) and 2-arachidonoylglycerol (2-AG)] and synthetic cannabinoids (dronabinol, nabilone) (5). Endocannabinoids in the body, unlike other neurotransmitters, are synthesized and stored in vesicles, occurring as "on-demand", and then released retrogradely. Of these endocannabinoids synthesized, AEA is hydrolyzed by the fatty acid amide hydrolase (FAAH), while 2-AG is broken down by monoacylglycerol lipase (MAGL). These three groups of ligands bind to the same G protein-coupled receptors, cannabinoid receptors type 1 (CB1R) and type 2 (CB2R). CB1Rs are generally located in the central nervous system. They are mostly present in brain regions that are mainly responsible for mood, such as the hippocampus, prefrontal cortex, hypothalamus, and basal ganglia (6). This explains why these receptors are targeted in treating depression. On the other hand, the synthesis of CB2Rs takes place in leukocytes, spleen, tonsils, and thymus which are peripheral tissues involved with the immune system, which explains other uses of cannabinoids as anti-inflammatory and immunomodulatory agents, and pain relievers (7). The unmet need for depression treatment encouraged the scientific world to do further research and has raised the question if the endocannabinoid system (ECS) has a promising future in this regard.

Endocannabinoid System

The endocannabinoid system is a complex cell-signaling system that plays crucial roles in various physiological processes, including central nervous system development, synaptic plasticity, and the response to endogenous and environmental insults. It consists of endocannabinoids, cannabinoid receptors (CBRs), and the proteins responsible for the synthesis, transport, and degradation of endocannabinoids. Although the two most studied endocannabinoids are 2-AG and AEA, the mechanism of action is generally defined by 2-AG (8). This is because these two molecules have different properties and concentrations. 2-AG, which has a concentration approximately 1000 times higher in the brain, shows a full agonist effect with moderate-to-low affinity to both CBRs; on the other hand, AEA is a partial agonist with high-affinity to CB1R and almost inactive to CB2R (8).

Endocannabinoids are released from postsynaptic neurons in response to the intracellular Ca+2 increase and/or activated Gq/11-coupled receptors, by the mechanisms mentioned above, act as retrograde messengers, and stimulate presynaptic CB1R (9). CB1R and CB2R principally bind to the inhibitory subtype of the G protein; in this way, they may inhibit adenylyl cyclase and voltage-sensitive calcium channels, induce the mitogen-activated protein kinase, and inwardly rectify potassium channels (10). As a result of the various mechanisms mentioned, it inhibits the release of neurotransmitters such as glutamate, GABA, acetylcholine, and serotonin (10). It is mainly CB1 (CB1R) that regulates neurotransmitter release and is primarily located at the presynaptic end of GABAergic interneurons (11). The role of endocannabinoid retrograde signaling in short-term plasticity varies according to the excitation of the presynaptic neuron and the presence of CB1R. The effect of CB1R, stimulated by 2-AG released in response to the postsynaptic Ca+2 increase, is called depolarization-induced suppression of inhibition in the GABAergic afferent and depolarization-induced suppression of excitation in the glutamatergic afferent (9). On the other hand, the effect of 2-AG released by the activation of Gq/11-linked metabotropic glutamate receptors is described as metabotropic-induced suppression of inhibition or metabotropic-induced suppression of excitation according to the cell in which CB1R is located (9). Shortly thereafter, it was shown that retrograde signaling is also responsible for long-term depression (9). Endocannabinoids affect various brain functions such as motor control, cognition, mood, and reward and feeding behaviors by regulating excitatory and inhibitory synaptic release with short-term and long-term effects (12). Therefore, disorders of the ECS are believed to cause many mental disorders, such as depression, schizophrenia, addiction, stress, and anxiety (12).

Prospective role of the endocannabinoid system in depression mechanisms

Despite years of research in the field, the pathophysiology of depression has not been fully elucidated. Our knowledge of the mechanisms of depression and how antidepressants work has been dominated by the monoamine theory of MDD (13). The monoamine hypothesis proposes that depression is caused by the decreased activity of monoamines such as serotonin, dopamine, and norepinephrine in the brain. This hypothesis was developed after the accidental discovery that Iproniazid, a monoamine oxidase inhibitor used against tuberculosis, improved mood by raising monoamine levels at synapses (13, 14). Different antidepressants were later discovered such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors, yet despite these discoveries, the number of patients who did not respond to treatment suggests that there may be different mechanisms for the disease (13, 14). One system that stands out as a non-monoaminergic depression pathway is the hypothalamic-pituitary-adrenal (HPA) axis in mammals. Corticotropin-releasing hormone is released from the hypothalamus in response to stress, stimulates the secretion of adrenocorticotropic hormone from the pituitary gland, which in turn secretes glucocorticoids from the adrenal gland. Many important data, including large cohort studies conducted in 2009, support the theory that depression may result from HPA axis malfunction (15, 16). It is suggested that ECS's major function is to reduce the HPA axis' response to stress, and to promote proper stress recovery (17). These results support rodent data showing that ECS activation has an antidepressant phenotype. In contrast, inhibition often has

a pro-depressive phenotype, and they support the theory that ECS interacts with depression via suppressing the HPA axis (17). Genetics are known to play a role in MDD, but it has been a common hypothesis that variations in certain genes may have greater contributions. Genetic research on the *CB1* gene (CNR1) in humans has looked at single nucleotide polymorphisms connected to depressive symptoms and responsiveness to antidepressants. For instance, the clinical response to SSRIs appears to be indirectly influenced by CNR1 (18). Studies have shown that CNR1 variants are associated with resistance to antidepressant treatments and the occurrence of MDD (19, 20). However, there are also studies that claim the opposite: Juhasz et al. (21) found that the *CNR1* gene is associated with high neuroticism and low agreeableness and interacts with recent negative life events to predict current depressive symptoms. On the other hand, Hillard and Liu (22) argued that endocannabinoid signaling plays a role in the etiology and treatment of major depressive illness and that the *CNR1* gene may be a potential target for new antidepressant therapies. Despite conflicting evidence, research of the role of the *CNR1* gene in MDD is ongoing. Another mechanism that is thought to be related to depression is neurogenesis. Many preclinical and human studies have revealed that MDD is linked to decreased brain-derived neurotrophic factor (BDNF) activity, induced apoptosis, and decreased neurogenesis in certain parts of the brain (23-25). Besides that, clinical investigations show that MDD patients receiving long-term antidepressant maintenance therapy, do not display the hippocampus atrophy seen in those not taking medication, and successful antidepressant treatments have been shown to induce hippocampal neurogenesis and increased BDNF (26, 27). Considering how the ECS affects the proliferation and differentiation of hippocampal cells, we can conclude that CB1 signaling plays a significant role in promoting neurogenesis. When adult rats were used as model organisms, long-term administration of the CB1 agonist HU210 increased neurogenesis in the hippocampus, and induced behavior resembling that of an antidepressant during the forced swimming test (28). This finding suggests that the enhancement of hippocampus neurogenesis is responsible for the antidepressant-like effects produced by the CB1R agonist (29). As for the relationship between MDD and neuroinflammation, many studies have revealed that cytokines, hormones, and oxidative stress markers are involved in the pathophysiology of depression (30). For instance, cortisol, a hormone produced by the adrenal gland in response to stress, has been linked to the development of depression (30). Another study supporting this theory showed that patients with major depression had higher average levels of interleukin-6 and C-reactive protein compared to the control group without depression (31). The immunomodulatory properties attributed to CB2R in particular suggest that ECS may affect the neuroinflammatory process in MDD (32). CB2 agonists exert their neuroprotective effects by inhibiting neurotoxic factors and suppressing microglial activation (33). Also, many genetic and pharmacological studies in rodents have supported the effect of CB2R on emotional behavior, including depressive-like behaviors (34). García-Gutiérrez et al. (35) revealed that overexpression of CB2 receptors in mice, reduced depressive-like behaviors in the tail suspension test. In parallel, CB2-Knockout mice that lack CB2 receptors, exacerbates stress-induced neuroinflammatory responses (36).

Promising antidepressant drugs: an approach to the endocannabinoid system

Cannabidiol and THC both affect the ECS, but in clinically different ways. While THC is responsible for users' "high" feelings, early studies have shown that CBD exhibits potential therapeutic effects (37). In connection with this, in this section, we will talk more about CBD, which is a natural negative allosteric modulator of CB1Rs and CB2Rs. It has been noted that CBD possesses neuroprotective and anti-inflammatory properties, though the exact mechanism is unknown (18). An ongoing, unpublished, double-blind, randomized, and placebo-controlled clinical study (NCT03310593) examines CBD's potential to alleviate anxiety and depression in bipolar disorder patients (38). The findings of this will be important in ascertaining whether CBD is a viable option for enhancing the pharmacological therapy of these types of psychiatric patients. Primarily through the activation of 5-HT1A serotonergic receptors, CBD showed antidepressant efficacy in animal models of depression, producing an antidepressant-like effect whether administered alone or in conjunction with sub-effective dosages of the antidepressants fluoxetine or desipramine (39, 40). Studies have shown that these effects of CBD in the animal model vary depending on the strain, gender, age, and the pattern of CBD administration, meaning whether it is acute or chronic (40-44). The chronic unpredictable stress paradigm that mimics depression in laboratory rodents evokes passive coping attitudes such as learned helplessness and anhedonia that meet MDD diagnostic criteria. 26 studies were included in a review and meta-analysis that was published in 2022 and showed that cannabinoid treatment lessened the effects of chronic unpredictable stress on anhedonia, learned helplessness, novelty-suppressed feeding, time in the anxiogenic setting, and entry into the anxiogenic context. However, more research is required to decide whether CBs are an effective long-term treatment for stress-related psychopathologies like depression due to the fact that mice received substantially more benefit from cannabinoid protective effects than rats (45). Numerous synthetic cannabinoids have been created to focus on distinct ECS mechanisms. Enzyme inhibitors for the enzymes FAAH and MAGL are URB597 and JZL184, respectively. To test the role of URB597 on depression the following study was conducted using a common set up of the sucrose preference test. This experiment involves measuring rats' preference of drinking sweetened water or plain water to gauge reward sensitivity over differing levels of URB597. The condition of anhedonia is thought to be reflected in decreased ingestion of pleasant solutions (46). Chronic administration of URB597 exerts antidepressant-like effects such as normalizing body weight gain and sucrose intake in rats

exposed to chronic mild stress. As a result of the drug regimen, AEA levels in the midbrain, striatum, and thalamus increased (47). These findings support earlier studies demonstrating that URB597 improves acute stress-coping in the mouse tail-suspension test and the rat forced swim test (FST) (48, 49). URB597 is thought to be a possible treatment for anxiety and depressive disorders based on *in vitro* and *in vivo* investigations, but clinical trials of URB597 have been put on hold because of severe side effects (18, 50). Rimonabant (SR141716) and AM251 are CB1R antagonists and have inverse agonist effects when administered chronically. These drugs have also been studied as potential targets for depression treatment. A meta-analysis of the randomized trial data revealed that those who received 20 mg of rimonabant for obesity treatment, were 2.5 times more likely to stop taking the medication because of depressive mood disorder than those who received a placebo (51). This medication had to be taken off the market after three years due to the high risk of serious psychiatric disorders, including anxiety and suicidal thoughts (18). Likewise, in other studies, 21 days of intraperitoneal rimonabant (10 mg/kg) treatment raised immobility time in FST and declined sucrose preference (52).

CONCLUSION

Although the monoamine hypothesis is the most emphasized theory in the pathophysiology of MDD, genetic factors, hyperactivation of the HPA-axis, neuroinflammation, and loss of neurogenesis also play a role. This review summarizes the effects of ECS on these theoretical etiologies of MDD. The roles of ECS in etiology suggest that antidepressant effects can be produced through this system, and in most rodent studies, activating the ECS appears to produce antidepressant-like responses in various behavioral tests. Depending on the dosage, mode of administration, and other variables, effects can vary, but in general, direct and indirect activation of ECS components has the potential to be antidepressants. Unfortunately, results in human studies are not compatible with animal models. This is because most studies in humans have examined depression as a secondary condition while addressing a medical disorder other than depression (pain, multiple sclerosis) (46). For instance, a recent meta-analysis yielding 924 records from clinical trials found that there were no studies investigating the efficacy of CBD by assessing depressive symptoms as the primary outcome (53). In conclusion, ECS is thought to play a role in both the development and treatment of MDD, although further research is required to prove this hypothesis.

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