REVIEW

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Role of the endocannabinoid system in the formation and development of depression

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Two types of cannabinoid (CB) receptors have been described in the human body: CB1 and CB2 receptors. CB1 receptor distribution may be related to the cannabinoid functions of memory and cognition regulation as well as motor control. In addition, the endocannabinoid system (ECS) related to CB1 receptors may be involved in human emotion regulation, especially depression occurrence. Indeed, CB1 receptors are all distributed in depression associated neuroanatomical structures and neural circuits. Both animal experiments and clinical studies have demonstrated that impairment of the ECS pathway is present in depression models and patients, and application of both CB1 receptor agonists and anandamide (cannabinoid-like substance) degradation inhibitors produce similar biochemical and behavioral effects as antidepressants. These findings provide a solid basis for understanding the ECS role in the formation and development of depression. Therefore, it can be inferred that the ECS may have an important function in both depression treatment and the effects of antidepressants.

1. Introduction

Depression has become one of the most common mental illnesses that severely afflict humans. However, its etiology remains largely unclear. The latest studies suggest that depression is mainly caused by pathological plastic changes of the brain at the molecular and cellular levels resulting from external stimuli, such as pressure. This eventually alters the neural activities of specific circuits in the brain (Li et al. 2013). Recent studies showed that the endocannabinoid system (ECS) and depression occurrence are closely related. As an essential part of the ECS, cannabinoid type 1 (CB1) receptors are thus inseparable from the formation of depression (Huang et al. 2016). Studies have shown that CB1 receptors promote the neuroprotection and neurogenic function of the hippocampus, and the lack thereof can cause depressive symptoms (Knowles et al. 2016). Therefore, exploring the role of the ECS in the development of depression would provide new targets for its treatment.

2. The endocannabinoid system

Cannabis is an ancient cultivated plant, and has been used by humans for more than a thousand years. In 1964, Mechoulam and Gaoni determined the active compound in cannabis to be Δ9-tetrahydrocannabinol. Cannabis affects the human body mainly by causing changes of perception and the sense of time, short-term memory impairment, mental relaxation, and euphoria. Since the discovery of the ECS in the early 1990s, researchers have carried out extensive and in-depth studies on its composition and functions. It was demonstrated that the ECS has a wide range of physiological effects on the body. Multiple reports (Gorzalka and Hill 2011; Vinod and Hungund 2006) showed that depression formation might be caused by disorders of the central endocannabinoid signaling system.

2.1. Endogenous cannabinoid receptors

Two kinds of CB receptors have been found in the human body: CB1 and CB2 receptors (Svizenska et al. 2008). They are both G protein-coupled receptors, which can activate multiple cell signaling pathways to regulate the neurotransmitter release process. CB1 receptors are mainly distributed in the brain, spinal cord, and peripheral nervous system (Herkenham et al. 1991; Moldrich and Wenger. 1991; Tsou et al. 1998). In the brain, CB1 receptors mainly exist in the basal ganglia (substantia nigra, globus pallidus, and lateral striatum), hippocampal CA1 pyramidal cell layer, cerebellum and cerebral cortex. The distribution of CB1 receptors may be related to the cannabinoid functions of memory and cognition regulation as well as motor control. CB1 receptors show relatively low expression levels in the peripheral nervous system. They are mainly distributed in nerve endings, and mediate neurotransmitter release. On the other hand, CB2 receptors are mostly distributed in peripheral immune cells, e.g. of the splenic marginal zone and tonsil, mainly effecting immune regulation (Munro et al. 1993; Parolaro 1999).

2.2. Endogenous cannabinoids

There are two main endogenous cannabinoid-like (EC-like) substances that have been described (Sugiura and Waku 2002): anandamide (AEA) (Devane et al. 1992) and 2-arachidonic glycerol (2-AG) (Sugiura et al. 1995), which are not typical neurotransmitters. Instead, they may be released from the postsynaptic cell bodies of neurons and dendrites, and reversely transported the presynaptic membrane. AEA and 2-AG exert their biological functions by binding to cannabinoid receptors. 2-AG was shown to be the most abundant endogenous ligand, and CBl and CB2 receptor agonist, while AEA is limited CBl and weak CB2 receptor agonist.

2.3. Synthesis and degradation of endogenous cannabinoids

Endogenous cannabinoid-like substances (2-AG and AEA) have a selective and effective synthesis pathway in the brain. This synthesis pathway is turned on by type I metabotropic glutamate (mGlu) receptor and Ca^{2+} activation (Hillard 2000; Nakane et al. 2002; Okamoto et al. 2004). When the postsynaptic neuron is stimulated, the stimulated mGlu receptor induces membrane depolarization and Ca^{2+} influx, both of which can affect the lipid precursor located in the cell membrane. Then, activation of phospholipase C produces diglycerides, which can be cleaved by diacylglycerol lipase to yield 2-AG. When mGlu receptors and Ca^{2+} effect phospholipids in the cell membrane, N-acyltransferase can be activated, catalyzing the formation of N-arachidonoyl phosphatidylethanolamine (NAPE) from phosphatidylethanolamine (PE). NAPE is further cleaved by phosphodiesterase to generate AEA. Meanwhile, AEA is also directly synthesized by high concentrations of arachidonic acid and ethanolamine in a reaction catalyzed by AEA synthase, a pathway independent of ATP and coenzyme A.

2-AG and AEA transport in neuronal cells is realized by a saturable, temperature-dependent, selective system in the membrane. Indeed, anandamide membrane transporter (AMT) is present in the vast majority of cells. It can be activated by nitric oxide (NO), and inhibited by millimolar concentrations of Δ-THC. AMT internalizes 2-AG, which is rapidly cleaved by fatty acid amino hydrolase (FAAH) or monoacyl-glycerol lipase (MAGL) once inside the neuron. Alternatively, 2-AG may be degraded by monoacyl glycerol kinase (MAGLK) to yield 2-AG-LPA.

AEA inactivation comprises two steps: transport into the cell and hydrolysis by FAAH inside the cell. AEA reuptake by neuronal cells is mediated by AMT. Similarly, AEA is quickly degraded into arachidonic acid (AA) and ethanolamine (EA) by FAAH once inside the neuron. Alternatively, intracellular lipoxygenase (LOXS) and cyclooxygenase-2 (COX-2) can also metabolize AEA, resulting in hydroxy derivative of AEA (HAEAs) and prostate-ethanolamine (PG-EAs).

3. Relationships between the endocannabinoid system and depression

Since the use of cannabinoids produces psychostimulation, the endocannabinoid system may be involved in human emotion regulation, especially depression occurrence (Williamson and Evans 2000). For centuries, people have consumed cannabinoids to enhance mood and euphoria, but cannabis consumption also results in manifestations such as fear and paranoia. The diversity of these manifestations may be determined by the cannabinoid dose used (Rubino and Parolaro 2008). Addiction to cannabis by adolescents can lead to mental disorders and damage to cognitive function. However, an appropriate amount of cannabinoids improves mood. Large-scale epidemiological surveys demonstrated that populations that frequently use cannabinoids less likely suffer from emotional problems compared with non-users (Denson and Earleywine 2006). Case control studies also reported that cannabinoids have an antidepressant effect in depression patients (Gruber et al. 1996). Either endogenous or exogenous cannabinoids function by activating CB1 receptors to exert their effects as psychoactive substances. Therefore, activating the CB1 receptor signaling pathway may help improve mood, and has an antidepressant effect (Pope et al. 2001). In agreement, endogenous cannabinoids and CB1 receptors are all distributed in depression associated neuroanatomical structures and neural circuits, including the prefrontal cortex, limbic system (hippocampus, hypothalamus, and striatum), classic reward area (abdomen striatum and the ventral tegmental area), and brain monoamine nucleus (raphe nuclei and locus coeruleus) (Bisogno et al. 1999).

4. Endocannabinoid signaling pathway impairment and depression formation

Considering the regulatory function of cannabinoids on mood, and the endogenous cannabinoid system distribution in brain regions related to mood and reward, Hill et al. (2005) proposed that the endocannabinoid signaling pathway may be involved in the formation and development of depression. Many existing reports support this notion.

Animal experiments demonstrated that endocannabinoid signaling pathway impairment by genetic modifications or drugs can lead to depression-like behavior (Hill et al. 2010). In addition, blocking the CB1 receptor signaling pathway results in anhedonia (Sanchis-Segura et al. 2004), anxiety, high alertness (Rodgers et al. 2003, Mikics et al. 2009), low appetite (Ravinet et al. 2004), low libido (Gorzalka et al. 2010), weight loss, negative response during stress (Steiner et al. 2008) and other symptoms. Related biological studies also showed that damage to the CB1 receptor signaling pathway increases hypothalamic pituitary adrenal axis (HPA) activity under basal and stress states, leading to suppressed hippocampal neurogenesis and the expression of neurotrophic factors (Hill et al. 2006a). Application of CB1 receptor antagonists significantly reduces 5-HT neuronal activity, thereby causing depression (Zanelati et al. 2010; Di et al. 2008). Therefore, these animal studies indicated that the CB1 receptor signaling pathway may play an important role in the formation and development of depression.

In humans, the endocannabinoid system also plays an antidepressant role. The CB1 receptor antagonist rimonabant, a drug for obesity treatment, increases the incidence of anxiety and depression in patients with no family history of mental illness (Christensen et al. 2007; Nissen et al. 2008). In addition, serious rimonabant side effects, including depression, forced the drug out of European and American markets, undermining the use of CB1 receptor antagonists to treat obesity (Hill and Gorzalka 2009). Meanwhile, these studies also provided double-blind, controlled clinical data demonstrating that damage to the endocannabinoid signaling pathway can lead to depression. Further studies reported that the use of rimonabant may inhibit positive emotional memory (Horder et al. 2009) as well as the reward system (Horder et al. 2010). Thus, damage to the CB1 receptor signaling pathway may result in memory for disgust and anhedonia.

Evidence from genetic studies further supports the hypothesis that CB1 receptor signaling pathway impairment increases the risk of depression. Studies have shown that CB1 receptor gene single nucleotide polymorphisms (SNPs) increase mood instability, making the patients more vulnerable to depression after suffering stress (Juhasz et al. 2009), and increasing the risk of resistance to antidepressants (Juhasz et al. 2010). This also leads to slow response of the reward system (Domschke et al. 2008). Another recent study, corroborating previous findings, showed that patients with significantly enhanced CB1 receptor gene SNPs are usually accompanied with affective disorders (Monteleone et al. 2010). Taken together, these findings indicate that the CB1 receptor signaling pathway is involved in the regulatory process of human cognition-emotion, reward system reaction and stress adaptation, and its damage increases the risk of depression.

Similarly, inactivity of the endocannabinoid signaling pathway is observed in both depression patients and depression associated models. Assessments of two separate groups by Hill et al. (2009) revealed relatively low serum levels of endogenous cannabinoids in female patients with refractory depression, suggesting that depression patients may have an impaired endocannabinoid signaling pathway. In addition, animal studies showed that central endocannabinoid signaling is reduced in teeth bite depression models, with CB1 receptor expression levels also significantly reduced in the limbic system (hippocampus, ventral striatum, and hypothalamus) of chronic unpredictable stress model (CUS) rats (Hill et al. 2008a; Reich et al. 2009). Chronic stress can lead to a decreased release of inhibitory neurotransmitters by the striatum and hypothalamus CB1 receptor, suggesting that chronic stress damages the CB1 receptor signaling limbic system (Wamsteeker et al. 2010). Other reports suggested that AEA contents of the cortex limbic system are decreased in the CUS (Hill et al. 2008b etc) and chronic restraint stress (Rademacher et al. 2008) depression models, indicating that chronic stress may cause damage to the AEA signaling pathway.

However, the impact of chronic stress on 2-AG remains unclear. It was reported that hippocampus 2-AG levels tend to be reduced in the chronic unpredictable stress (CUS) model (VanderStelt et al. 2005). Meanwhile, discrepant findings were reported, in which no decrease of hippocampus 2-AG levels were observed in the CUS model. 2-AG expression levels in other brain regions such as the thalamus and hypothalamus tend to increase, and transient increase of 2-AG levels was also described in the CUS model (Hill and Mc Ewen 2010). Therefore, the reduction of AEA levels caused by chronic stress may be stable, while 2-AG is differently affected; this may be associated with the animal species and stress duration. These findings suggest that the ECS located in the cortex limbic system is involved in mood regulation, and endocannabinoid signaling pathway damage can cause depression-like symptoms in experimental animals. Similarly, in humans, blocking the CB1 signaling pathway leads to depression symptoms, such as anhedonia and changes of cognitive activity. Therefore, both animal experiments and clinical studies have confirmed that impairment of the endocannabinoid signaling pathway is related to depression. This provides a solid basis for understanding the role of the ECS in the formation and development of depression.

5. Antidepressant effect of the endogenous cannabinoid system

Since damage to endocannabinoid signaling can cause symptoms of depression, activation of the system may have antidepressant effects. Based on this assumption, it was reported that both direct and indirect activation of CB1 receptors results in similar behavior and biochemical changes caused by antidepressants.

Neuro-biochemical changes induced by antidepressants mainly include increased monoamine neurotransmitter levels (especially 5-HT), reduced HPA axis activity, and increased neurotrophic factor levels and hippocampal neurogenesis. Both exogenous and endogenous cannabinoids can adjust the 5-HT and noradrenergic neuronal systems, with effects similar to conventional antidepressant drugs. Studies have shown that both the plant-derived cannabinoids THC and endogenous cannabinoids AEA inhibit monoamine oxidase (MAO) activity (Fisar 2010; Mazor et al. 1982), and serum MAO activity is also lower in individuals consuming cannabis (Stillman et al. 1978). These findings indicate that such a change is also present in humans. In addition, cannabinoids can produce effects similar effect as tricyclic and selective serotonin reuptake inhibitor (SSRI) type antidepressants, regulating the reuptake of monoamine neurotransmitters (Banerjee et al. 1975; Steffens and Feuerstein 2004; Velenovska and Fisar 2007), especially inhibiting 5-HT, noradrenaline and dopamine reuptake. CB1 receptor agonists activate 5-HT neurons in the dorsal raphe nucleus and noradrenergic neurons in the locus coeruleus (Bambico et al. 2007; Mendiguren and Pineda 2007). Inhibition of FAAH-mediated AEA degradation also activates CB1 receptor-dependent 5-HT and noradrenergic neurons (Bambico et al. 2010). Therefore, similar to traditional antidepressant drugs, activating the CB1 receptor signaling pathway (by applying CB1 receptor agonists or inhibiting endocannabinoid degradation) can also promote monoamine neurotransmitter transfer.

Studies assessing the HPA axis demonstrated that the ECS has an effect similar to that of antidepressants. Promoting the neurotransmission of endogenous cannabinoids can inhibit stress induced HPA axis activity (Patel et al. 2004). Suppressing the FAAH-mediated degradation of AEA prevents glucocorticoid hypersecretion under stress. Therefore, enhancement of central endocannabinoid signaling may reduce HPA axis activity.

CB1 receptor signaling induction will also promote hippocampal synaptic plasticity, and produce an effect similar to that of antidepressants. In animal experiments, chronic application of CB1 receptor agonists increases nerve growth in adult and juvenile rats (Bambico et al. 2005). Elevated AEA levels caused by FAAH knockout promote cell proliferation in the mouse hippocampus (Cravatt et al. 2001), while drugs that suppress AEA reuptake and promote AEA degradation block stress, reducing cell proliferation in the hippocampus (Hill et al. 2006b). In addition, cannabinoids also increase the hippocampal expression of brain derived neurotrophic factor (BDNF) (Derkinderen et al. 2003). Therefore, like conventional antidepressants, the ECS can also enhance hippocampal synaptic plasticity.

Behavioral studies showed that activation of the CB1 receptor signaling pathway can produce similar behavioral effects as conventional antidepressants. Applying CB1 receptor agonists (Adamczyk et al. 2008) and endocannabinoid reuptake inhibitors (Bambicoand Gobbi 2008; Bambico et al. 2009) in stress animal models both produce antidepressant-like effects. For example, immobility time is shortened in forced swimming and tail suspension experiments.

In summary, application of both CB1 receptor agonists and AEA degradation inhibitors can produce similar biochemical and behavioral effects as antidepressants. These studies demonstrated that increased activity of CB1 receptors results in antidepressant effects (Fig. 1).

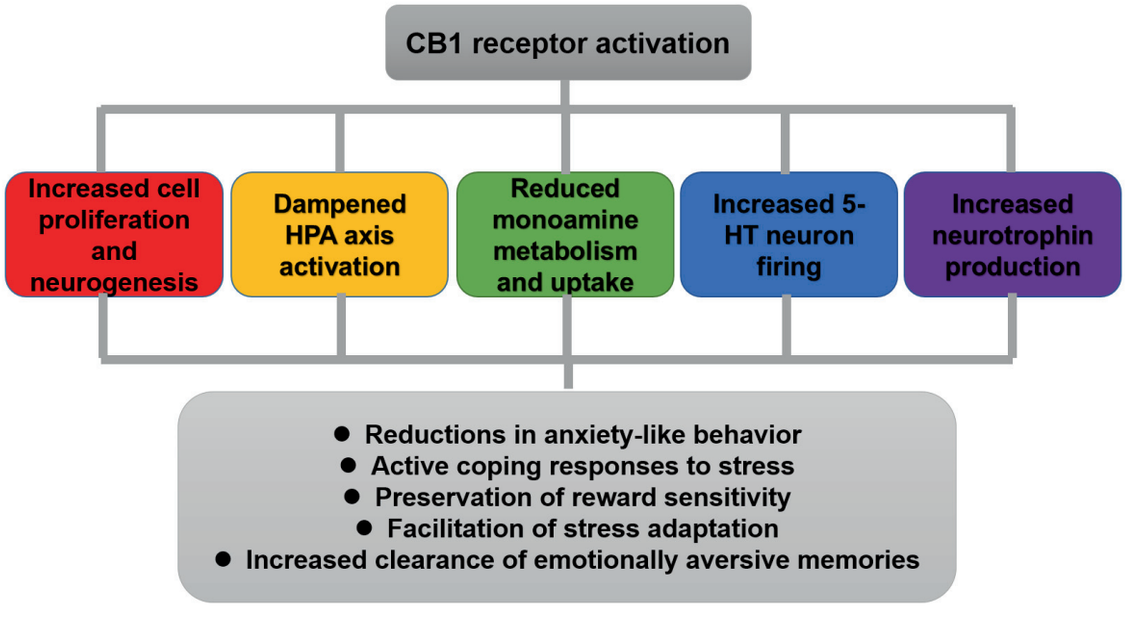

Fig.1: Anti-depressive effect of CB1 receptor activation

6. Antidepressant treatment and the endogenous cannabinoid system

Although the ECS plays such an important role in the occurrence of depression, it remains unclear whether it is targeted by antidepressants. It was reported that SSRI type antidepressants, such as fluoxetine, enhance CB1 receptor activity in the prefrontal cortex (Mato et al. 2010). Monoamine oxidase inhibitors enhance CB1 receptor activity in both the prefrontal cortex and hippocampus. Finally, application of tricyclic antidepressants also enhances CB1 receptor activity in the hippocampus and hypothalamus.

In depressive patients after ECT treatment, the amygdala CB1 receptor signaling is induced, while CB1 receptor activity and AEA levels in the prefrontal cortex decrease (Hill et al. 2007). Sleep deprivation therapy can improve hippocampal 2-AG levels and serum AEA content, and locomotor activities with antidepressant effects increase hippocampal CB1 receptor mRNA levels as well as hippocampal AEA content (Chen and Bazan 2005). Thus, the ECS plays an important role in both depression treatment and the effect of antidepressants. Animal experiments and clinical studies showed that damage to the endogenous cannabinoid signaling pathway may result in depression-like symptoms. However, how the ECS participates in the anti-depressant treatment needs further studies.

7. Conclusion

A number of recent studies have demonstrated that depression formation can result from central ECS disorders. There are two kinds of CB receptors in human body: CB1 and CB2 receptors. The distribution of CB1 receptors may be related to the cannabinoid functions of memory and cognition regulation as well as motor control. Both endogenous and exogenous cannabinoids function by activating CB1 receptors to exert their effects as psychoactive substances. Therefore, activating the CB1 receptor signaling pathway may help improve mood, and has an antidepressant effect. Indeed, endogenous cannabinoids and CB1 receptors are all distributed in depression associated neuroanatomical structures and neural circuits. Both animal experiments and clinical studies have confirmed that impairment of the endocannabinoid signaling pathway is present in depression models and patients. This provides a solid basis for understanding the role of the ECS in the formation and development of depression. Studies have also demonstrated that CB1 receptor gene single nucleotide polymorphisms (SNPs) increase mood instability, making the patients more vulnerable to depression after suffering from stress and increasing the risk of resistance to antidepressants; this also results in slow response of the reward system. Since damage to endocannabinoid signaling can cause depressive symptoms, activation of the system may also have antidepressant effects. Indeed, both direct and indirect activation of CB1 receptors lead to similar behavioral and biochemical changes as antidepressants. Application of both CB1 receptor agonists and AEA degradation inhibitors produces similar biochemical and behavioral effects as antidepressants. These findings demonstrate that increased activity of CB1 receptors has antidepressant effects. Overall, the ECS plays an important role in both depression treatment and the effect of antidepressants. However, how it participates in the anti-depressant treatment requires further studies.

Conflicts of interest: The authors declare that there are no conflicts of interest.

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