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The Endocannabinoid/Endovanilloid System and Depression

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Abstract: Depression is one of the most frequent causes of disability in the 21st century. Despite the many preclinical and clinical studies that have addressed this brain disorder, the pathophysiology of depression is not well understood and the available antidepressant drugs are therapeutically inadequate in many patients. In recent years, the potential role of lipid-derived molecules, particularly endocannabinoids (eCBs) and endovanilloids, has been highlighted in the pathogenesis of depression and in the action of antidepressants. There are many indications that the eCB/endovanilloid system is involved in the pathogenesis of depression, including the localization of receptors, modulation of monoaminergic transmission, inhibition of the stress axis and promotion of neuroplasticity in the brain. Preclinical pharmacological and genetic studies of eCBs in depression also suggest that facilitating the eCB system exerts antidepressant-like behavioral responses in rodents. In this article, we review the current knowledge of the role of the eCB/endovanilloid system in depression, as well as the effects of its ligands, models of depression and antidepressant drugs in preclinical and clinical settings.

Keywords: Animal model of depression, antidepressant drug, depression, endocannabinoid system, endovanilloid.

INTRODUCTION

Depression is one of the most common mental disorders in the general population and is projected to become the second leading contributor to the global burden of disease by 2020 [1]. This disorder affects all aspects of human life and is characterized by feelings of sadness, loss of interest or pleasure, guilt, loneliness, low self-worth, disturbed sleep or appetite, low energy level, and poor concentration [2].

Multiple potential mechanisms have been indicated in the etiology of depression. The first theory achieved broad popularity in the mid-1960s and associated depression with reduced brain monoamine levels [3]. The monoamine hypothesis of depression was associated with the therapeutic effect of antidepressant drugs and has dominated our understanding of the pathophysiology of depression for the last decades. However, it is now known that etiology of this mental disorder is much more complex. The role of several agents (i.e., stress, infections and genes) in depression have been well examined, but the psychopharmacology of antidepressant drugs is poorly known and the causes of depression have not been completely explained [4].

A few years ago, the first preclinical reports showing antidepressant-like actions of substances that change the activity of lipid-derived molecules, such as endocannabinoids (eCBs) and endovanilloids, generated a new hypothesis concerning the etiology of depression and novel brain targets for new antidepressant drugs [5]. This idea about the engagement of the eCB system in affective disorders derived from observations of marijuana smokers and the drug's effects on mood improvement [6-8]. Δ^9-THC, which is the principle active cannabinoid in cannabis, mediates most of the drug's psychoactive and mood-related effects [9]. Although high-dose cannabis use predicts the escalation of risks for anxiety disorders, depression, psychosis and cognitive impairment, especially among teenagers [10-12], a notably high prevalence of comorbid cannabis use occurs in depressed patients (30–64%) as a form of self-medication [7]. This continued use of cannabis in an attempt to control depressive symptoms suggests possible therapeutic benefits in depression [6, 13].

The present review will summarize the current knowledge of the roles of the eCB system and the endovanilloid system in depression and the mechanism of action of antidepressant drugs and will discuss new directions in studies of depression based on a more comprehensive understanding of the eCB system with its cellular signaling targets that participate in this brain disorder.

THE eCB SYSTEM AND DEPRESSION

The eCB system consists of eCBs, enzymes responsible for the synthesis and degradation of endogenous ligands and G-coupled CB receptors (CB_1 and CB_2). eCBs are the arachidonic acid derivatives formed by the hydrolysis of membrane phospholipids. The most defined eCBs is N-arachidonylethanolamide (anandamide, AEA), which is also classified as N-acylethanolamine [14], endovanilloid [15], and 2-arachidonoylglycerol (2-AG) [16]. Unlike other neurotransmitters, AEA and 2-AG are not stored in secretory vesicles, but are synthesized "on demand" in the postsynaptic neuron through activity-dependent cleavage of membrane

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lipid precursors and then activate CB receptors as retrograde messengers [17]. AEA is formed presynaptically and travels across the synaptic cleft to activate postsynaptic receptors [18]. AEA is removed from the extracellular space through cellular reuptake and enzymatic degradation. Fatty acid amide hydrolase (FAAH) terminates the biological activity of AEA by hydrolyzing it to arachidonic acid and ethanolamine, while 2-AG can be metabolized by either FAAH in the postsynaptic neurons or by monoacylglycerol lipase (MAGL) in pre-synaptic neurons (for review, see [17]). The enzymes involved in eCB catabolism may be important targets for pharmaceutical development. CB_1 and CB_2 are the primary cannabinoid receptors of the eCB system. CB receptors are metabotropic receptors that are made up of an extracellular, ligand-binding, transmembrane part of the heptahelicase and an intracellular part that activates the Gi protein [19]. Following CB receptor stimulation, G protein activation, inhibition of adenylate cyclase and reduction in cAMP concentrations are observed inside the cell. At the same time, the mitogen activated protein kinase (MAPK) pathway is stimulated, causing changes in gene expression, cell division, differentiation and apoptosis in cells Fig. (**1**).

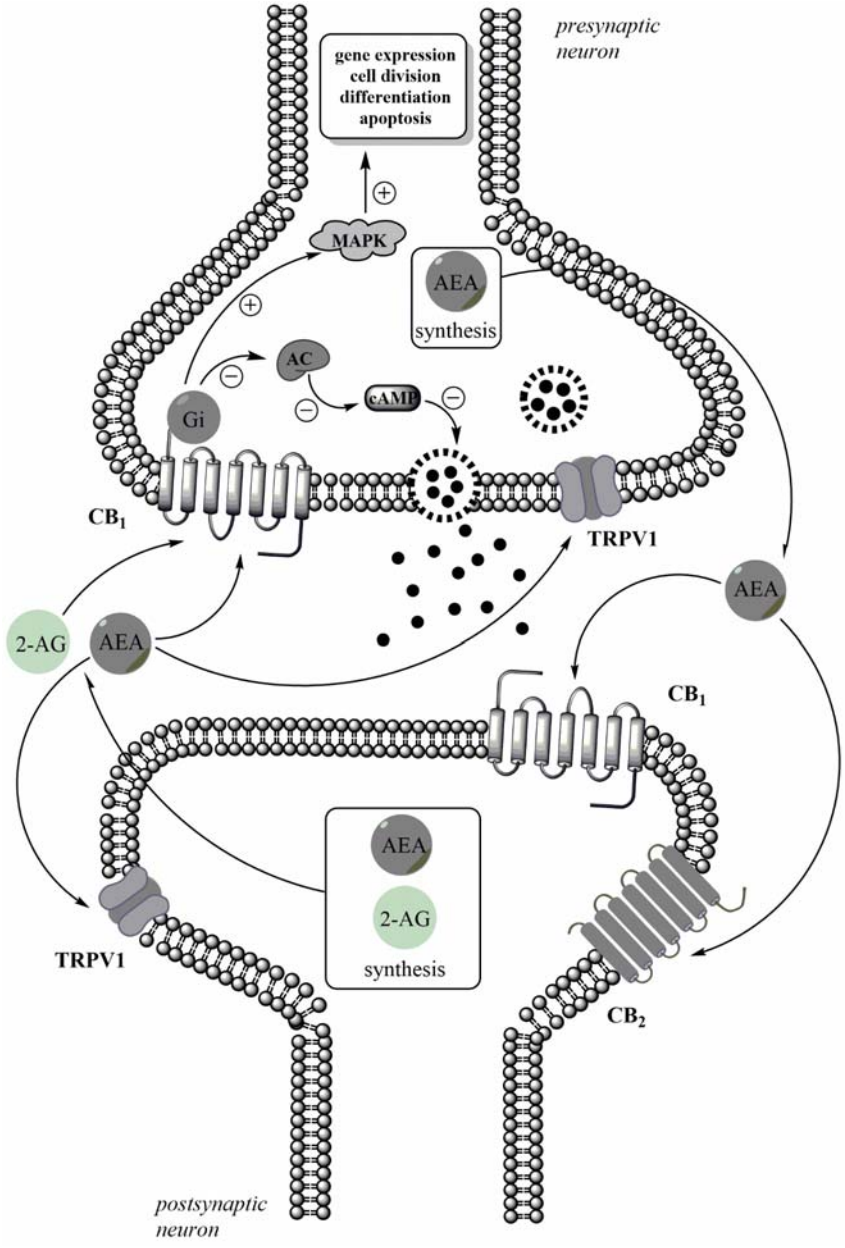

Fig. (1). Schematic illustration of the eCBs action on CB receptors. 2-AG is synthetized in the postsynaptic dendritic compartment, whereas AEA synthesis may occur post- and pre-synaptically. eCBs are released into extracellular and act as retrograde messengers. Activation of CB_1 receptors are associated with Gi-dependent inhibition of adenylyl cyclase (AC) activity, which evoked a decrease of the production of cAMP and resulted in modulation of neurotransmitter release. Via the G-protein, activation of the CB_1 receptor activates MAPK pathway, affecting intracellular gene expression, cell division, differentiation and apoptosis.

eCBs and Depression

Animal Research

At the preclinical level, a deficiency in eCB signaling is linked to a ″depressive-like″ phenotype. In fact, following exposures to several stressors (i.e., chronic unpredictable stress (CUS) and social defeat stress), reduced AEA levels have been noted in the rat hippocampus, hypothalamus, ventral striatum and prefrontal cortex [20], and in the hippocampus and hypothalamus of mice [21]. These data parallel observations in the striatum of olfactory-bulbectomized rats [22] and in the hippocampus of Wistar-Kyoto rats [23], when AEA tissue concentrations were decreased. These findings conflict with recent data in adult rats after a maternal deprivation procedure, in which the levels of AEA increased in some brain areas, such as the nucleus accumbens, caudate-putamen nucleus and mesencephalon [24] (Table **1**). The reasons for these differences are unknown, however, several factors such as the ages of the animals and nervous system development, should be taken into account when comparing the levels of AEA.

Animal models of depression and stress procedures alter rodent 2-AG brain tissue concentrations. Thus, the 2-AG either decreased in the ventral striatum of olfactory-bulbectomized rats [22] or increased in the thalamus after a chronic mild stress (CMS) procedure [25], in the hypothalamus and midbrain after a CUS procedure [20], in the frontal cortex, hippocampus and hypothalamus after repeated social stress [21], or in the hippocampus and nucleus accumbens after maternal deprivation [24, 26] (Table **1**). On the whole, the evidence from preclinical modelsof dysfunction in the eCB levelsis dependent on brain-region and the research tools (the procedures used to generate *"*depressed" animals*)*.

Reduced AEA levels in rodent models of depression parallel behavioral studies, in which the facilitation of eCB signaling by the AEA uptake inhibitor AM404 [5, 27-29] orAEAalone evoked antidepressant-like activity, which was observed as a reduction of the immobility time in the forced swim test (FST) in animals [28].

Based on the assumption that the eCB system is dampened during depression, antidepressant drugs should alter (reverse) the reduced levels of the eCBs, however, the published evidence is equivocal. A three-week treatment with desipramine, which inhibits the reuptake of noradrenaline (NA) and to a minor extent serotonin (5-HT), did not alter eCB levels [30]. Additionally, the selective 5-HT reuptake inhibitor, fluoxetine, given chronically, does not change the level of eCBs, whereas the monoamine oxidase inhibitor, tranylcypromine, decreases AEA levels in limbic areas and increases 2-AG in the prefrontal cortex [31]. The NA and 5-HT reuptake inhibitor, imipramine, administered chronically (14 days),increases the level of eCBs in the dorsal striatum [32]. Furthermore, unpublished data from our laboratory reveals that 14 days of escitalopram treatment (a selective 5-HT reuptake inhibitor) either increased eCB levels in the hippocampus and dorsal striatum or decreased them in the cortical structures and cerebellum. Finally, chronically administered tianeptine (14 days), a selective 5-HT reuptake enhancer, provoked an increase of the eCB levels in the hippocampus (AEA), dorsal striatum (AEA and 2-AG) and frontal cortex (2-AG) [32] (Table **2**).

These data seem to support the participation of eCBs in the mechanism of action of clinically effective and potential antidepressants, however, in rats subjected to experimental stress, imipramine given acutely [25] or chronically [20] did not reverse the changes in eCB levels in rats exposed to CMS or CUS, respectively, in several brain structures (Table **2**). Because there have been no studies with other antidepressant drugs, further research is urgently needed to validate the relationship between depression-like phenotypes and eCB levels.

Human Research

In humans, there are several lines of evidence that a dysfunction in the eCB system is implicated in the pathogenesis of depression. In *postmortem* studies, elevated levels of eCBs have been observed in the dorsolateral prefrontal cortex of alcoholic suicide victims [33]. The authors proposed that such increases in eCB levels, linked with memories of aversive stimuli, may induce emotional discomfort during depression. In clinical trials of untreated depressed patients, a rise in serum AEA level has been observed [34, 35], while reductions in 2-AG have been observed in human female patients with major depression [34].

eCB Degradative Enzymes

Animal Research

Inpreclinical studies, depression-like behavior seems to be associated with raised brain levels of FAAH (and subsequently reduced local levels of AEA). In animal models of depression, Wistar-Kyoto rats display higher levels of FAAH in the frontal cortex and hippocampus, with unaltered levels of the AEA-synthesizing enzyme N-arachidonyl phosphatidyl ethanolamine specific phospholipase-D (NAPE-PLD) [23], and CMS evokes an up-regulation of FAAH levels in the dorsal hippocampi of both male and female animals [36] (Table **1**). These findings are supported by studies in FAAH knockout mice that revealed anxiolytic-like and antidepressant-like effects linked to altered 5-HT transmission and postsynaptic 5-HT_{1A} and 5-$HT_{2A/2C}$ receptor function [37]. These findings revealed a relationship between abnormalities in FAAH function and the depressive phenotype that were not confirmed by Hill *et al.* [20] and Bortolato *et al.* [25]. In fact, neither CUS nor CMS affected the maximal hydrolytic activity of FAAH or the binding affinity of AEA for FAAH in several rat brain regions [20] or the FAAH activity in the midbrain, striatum and hippocampus of animals [25]. In enzymes related to 2-AG degradation, a decrease of the membrane-associated MAGL expression has been observed in stressed mice [38]. Enhancing eCB signaling by inhibiting degradative enzymes evokes anti-inflammatory effects. In fact, increased AEA levels reduce the levels of pro-inflammatory cytokines and inflammatory mediators [39, 40] and enhance the release of the anti-inflammatory cytokine IL-10 [41]. Notably, one hypothesis of the pathogenesis of depression is that it is

Table 1. Changes within the eCB system in animal models of depression.

Animal Model of Depression	Animal	eCB System Change				References
		eCBs Levels		Degradative Enzymes	Receptors Density	
		AEA	2-AG			
Chronic Mild Stress	rat	midbrain- – thalamus- – striatum- – hippocampus- – prefrontal cortex- –	midbrain- – thalamus- ↑ striatum- – hippocampus- – prefrontal cortex- –	FAAH: midbrain- – striatum- – hippocampus- –	midbrain- ↓ hippocampus- – prefrontal cortex- ↑	[25]
	rat	No data.	No data.	FAAH: dorsal hippocampus- ↑ (male and female rats)	dorsal and ventral hippocampus- ↓ CB_1 in male rats dorsal hippocampus- ↑ CB_1 in female rats	[36]
	mice	No data.	No data.	No data.	hippocampus- ↓ CB_2	[102]
Chronic Unpredictable Stress	rat	hippocampus- – limbic forebrain- –	hippocampus- ↓ limbic forebrain- –	No data.	hippocampus- ↓ CB_1 limbic forebrain- –	[65]
	rat	prefrontal cortex- ↓ hippocampus- ↓ hypothalamus- ↓ amygdala- ↓ midbrain- ↓ ventral striatum- ↓	prefrontal cortex- – hippocampus- – hypothalamus- ↑ amygdala- – midbrain- ↑ ventral striatum- –	FAAH: prefrontal cortex- – hippocampus- – hypothalamus- – amygdala- – midbrain- – ventral striatum- –	prefrontal cortex- ↑ CB_1 hippocampus- ↓ CB_1 hypothalamus- ↓ CB_1 amygdala- – midbrain- – ventral striatum- ↓ CB_1	[20]
	rat	No data.	No data.	No data.	ventromedial prefrontal cortex- ↑ CB_1 dorsomedial prefrontal cortex- –	[71]
Social Defeat Stress	mice	frontal cortex- – hippocampus- ↓ hypothalamus- ↓ striatum- – (acute and repeated social stress)	frontal cortex- ↑ hippocampus- ↑ hypothalamus- ↑ striatum- – (repeatedsocialstress)	No data.	No data.	[21]
Maternal Deprivation	rat	hippocampus- –	hippocampus- ↑ (male rats)	No data.	No data.	[26]
	rat	No data.	No data.	No data.	hippocampus- ↓ CB_1- CA1, CA3 ↑ CB_2- dentate gyrus, CA1, CA3	[70]
	rat	No data.	No data.	No data.	frontal cortex- ↓ CB_1 hippocampus- ↓ CB_1	[66]
	rat	No data.	No data.	No data.	CB_1: frontal cortex- ↓ CB_1 ventral striatum- ↑ CB_1 hippocampus- – CB_2: frontal cortex- – ventral striatum- – hippocampus- –	[67]
	rat	No data.	No data.	No data.	hippocampus- ↓ CB_1	[69]

Table 1. contd….

Animal Model of Depression	Animal	eCB System Change				References
		eCBs Levels		Degradative Enzymes	Receptors Density	
		AEA	2-AG			
Maternal Deprivation	rat	nucleus accumbens- ↑ (adolescent and adult) caudate–putamen nucleus- ↑ (adolescent and adult) mesencephalon- ↑ (adolescent)	nucleus accumbens- ↑ (adult) caudate–putamen nucleus- ↑ (adult) mesencephalon- –	No data.	No data.	[24]
	rat	No data.	No data.	No data.	frontal cortex- ↓ CB_1 hippocampus- ↓ CB_1 frontal cortex- ↑ CB_2 hippocampus- – (male and female rats)	[68]
Olfactory Bulbectomy	rat	No data.	No data.	No data.	prefrontal cortex- ↑ CB_1 caudate putamen- – hippocampus- – amygdala- ↑ CB_1 dorsal raphe nucleus- –	[72]
	rat	ventral striatum- ↓ cerebellum- – piriform cortex- – hippocampus- – amygdala- –	ventral striatum- ↓ cerebellum- – piriform cortex- – hippocampus- – amygdala- –	No data.	*basal ganglia*- – *cerebral cortex*- – hippocampus- – amygdala- – *diencephalon*- – *brain stem*- –	[22]
Wistar-Kyoto Rats	rat	frontal cortex- – hippocampus- ↓	No data.	FAAH: frontal cortex- ↑ hippocampus- ↑	frontal cortex- – hippocampus- ↑ CB_1	[23]

highly connected with increased concentrations of pro-inflammatory cytokines [42].

Pharmacological manipulations of FAAH activity alter mood and exert antidepressant-like behavioral responses in rodents. Administration of the FAAH inhibitor (URB597 [5, 23, 27, 28, 43-49]) or the MAGL inhibitor (URB602 [50]) to rodents decreases their immobility time in the FST. Further, a 5-week administration of URB597 resulted in inhibited brain FAAH activity accompanied with a reduction in the body weight and sucrose intake induced by CMS in rats [25]. A very recent study demonstrated a reduction in chronic stress-induced depressive-like behaviors by inhibiting the MAGL with JZL184, followed by an enhancement of eCB signaling in the hippocampus that was linked to the mammalian target of rapamicin (mTOR) pathway [51]. These data point to the potential therapeutic application of eCB-strengthening agents indepression.

Little is known about the effects of antidepressants in FAAH activity assays, however, one study showed that imipramine administration resulted in increased activation of FAAH activity in the ventral striatum and midbrain of rats subjected to CUS and that co-treatment of imipramine and CUS robustly activated FAAH function [20] (Table **2**).

Human Research

In the latest study by [52], greater FAAH activity was identified in the ventral striatum of alcohol-dependent suicides, compared to alcohol-dependent nonsuicides. This *postmortem* study seems to indicate increased FAAH activity as a crucial factor for depression and suicide in depressed human patients.

CB Receptors

CB_1 Receptors

CB_1 receptors contributed to the depressive-like phenotypes in both animal and human studies. These receptors are widely localized in brain structures implicated in the pathogenesis of depression (the prefrontal cortex, frontal cortex, hippocampus, cerebellum) and are linked to anhedonia (the dorsal striatum and nucleus accumbens) [53, 54]. At the functional level, CB_1 receptors modulate brain neurotransmission, including the NA, 5-HT, dopamine (DA),

Table 2. Modulation of the eCB system by antidepressants.

Drug (Dose, Treatment, Route)	Animal/ Animal Model of Depression	eCB CHANGE				References
		eCBs Levels		Degradative Enzymes	Receptors Density	
		AEA	2-AG			
Desipramine (10 mg/kg); chronic (21 days), i.p.	rat	prefrontal cortex- – hippocampus- – hypothalamus- – amygdala- –	prefrontal cortex- – hippocampus- – hypothalamus- – amygdala- –	No data.	prefrontal cortex- – hippocampus- ↑ CB_1 hypothalamus- ↑ CB_1 amygdala- –	[30]
Imipramine (20 mg/kg), chronic (35 days), i.p.	rat; chronic mild stress	midbrain- – thalamus- – striatum- – hippocampus- – prefrontal cortex- –	No data.	No data.	No data.	[25]
Imipramine (10 mg/kg); chronic (21 days); i.p.	rat; chronic unpredictable stress	Reduction not reversed.	Rise not reversed.	prefrontal cortex- – hippocampus- – hypothalamus- – amygdala- – midbrain- ↑ FAAH ventral striatum- ↑ FAAH	Reduction in the hippocampus fully reversed.	[20]
Imipramine (15 mg/kg); single; i.p.	rat	prefrontal cortex- – frontal cortex- – hippocampus- ↑ dorsal striatum- – nucleus accumbens- – cerebellum- –	prefrontal cortex- – frontal cortex- ↑ hippocampus- – dorsal striatum- – nucleus accumbens- – cerebellum- ↓	No data.	No data.	[32]
Imipramine (15 mg/kg); chronic (14 days); i.p.	rat	prefrontal cortex- – frontal cortex- – hippocampus- ↑ dorsal striatum- ↑ nucleus accumbens- – cerebellum- –	prefrontal cortex- – frontal cortex- ↑ hippocampus- – dorsal striatum- ↑ nucleus accumbens- – cerebellum- ↓	No data.	No data.	[32]
Tranylcypromine (10 mg/kg); chronic (21 days), i.p.	rat	prefrontal cortex- ↓ hippocampus- ↓ hypothalamus- ↓	prefrontal cortex- ↑ hippocampus- – hypothalamus- –	No data.	prefrontal cortex- ↑ CB_1 hippocampus- ↑ CB_1 hypothalamus- –	[31]
Fluoxetine (5 mg/kg); chronic (21 days), i.p.	rat	prefrontal cortex- – hippocampus- – hypothalamus- –	prefrontal cortex- – hippocampus- – hypothalamus- –	No data.	prefrontal cortex- ↑ CB_1 hippocampus- – hypothalamus- –	[31]
Fluoxetine (10 mg/kg); chronic (14 days), s.c.	rat; olfactory bulbectomy	No data.	No data.	No data.	Rise in the prefrontal cortex fully reversed.	[72]
Fluoxetine (10 mg/kg); chronic (14 days), s.c.	rat	No data.	No data.	No data.	prefrontal cortex- – cerebellum- – (- ↑ CB_1 receptor inhibition of adenylyl cyclase- prefrontal cortex; - ↓ CB_1 receptor inhibition of adenylyl cyclase- cerebellum) without altering receptor density	[86]

Table 2. contd….

Drug (Dose, Treatment, Route)	Animal/ Animal Model of Depression	eCB CHANGE				References
		eCBs Levels		Degradative Enzymes	Receptors Density	
		AEA	2-AG			
Citalopram (10 mg/kg); chronic (14 days), s.c.	rat	No data.	No data.	No data.	hypothalamus- ↓ CB_1 hippocampus- ↓ CB_1 medial geniculate nucleus- ↓ CB_1	[87]
Escitalopram (10 mg/kg); single, i.p.	rat	prefrontal cortex- – frontal cortex- – hippocampus- – dorsal striatum- – nucleus accumbens- – cerebellum- –	prefrontal cortex- – frontal cortex- ↓ hippocampus- – dorsal striatum- – nucleus accumbens- – cerebellum- –	No data.	No data.	[32]
Escitalopram (10 mg/kg); chronic (14 days), i.p.	rat	prefrontal cortex- – frontal cortex- – hippocampus- ↑ dorsal striatum- ↑ nucleus accumbens- – cerebellum- –	prefrontal cortex- ↓ frontal cortex- ↓ hippocampus- ↑ dorsal striatum- ↑ nucleus accumbens- – cerebellum- ↓	No data.	No data.	[32]
Tianeptine (10 mg/kg); single, i.p.	rat	prefrontal cortex- – frontal cortex- – hippocampus- – dorsal striatum- – nucleus accumbens- – cerebellum- –	prefrontal cortex- – frontal cortex- – hippocampus- – dorsal striatum- – nucleus accumbens- – cerebellum- –	No data.	No data.	[32]
Tianeptine (10 mg/kg); chronic (14 days), i.p.	rat	prefrontal cortex- – frontal cortex- – hippocampus- ↑ dorsal striatum- ↑ nucleus accumbens- – cerebellum- –	prefrontal cortex- – frontal cortex- ↑ hippocampus- – dorsal striatum- ↑ nucleus accumbens- – cerebellum- –	No data.	No data.	[32]

γ-aminobutyric acid (GABA) and glutamate systems, inhibit the stress axis and restore brain neuroplasticity Fig. (**2**) [55]. The GABAergic interneurons (inhibitory) and glutaminergic (excitatory) neurons represent opposing players regulating the excitation state of the brain. Interestingly, these cell types both highly express CB_1 receptors [56], thus, CB receptor-mediated signaling is responsible for maintaining the homeostasis of excitatory and inhibitory neurotransmitters. Additionally, they are many findings which suggest a functional correlation among eCBs and dopaminergic systems during striatal signaling. In fact, *in vivo* striatal administration of the D_2 dopamine receptor agonist quinpirole induces a local increase in the level of AEA [57] and quinpirole perfusion into striatal slices *in vitro* evokes the same increase [58]. Additionally, CB_1 receptor agonists stimulate DA release in the nucleus accumbens [59].

Animal Research

In preclinical studies, genetic deletion of CB_1 receptors in mice results in a phenotype that strikingly resembles the profile of severe, typical depression; a similar depression-like behavioral phenotype was found after CB_1 receptor blockade [60-64]. These findings correlate well with the lower density of CB_1 receptors in animal models of depression induced by stress in rats [20, 25, 36, 65], and such down-regulation of CB_1 receptors has been observed in the midbrain, hippocampus, hypothalamus and ventral striatum. In maternal deprivation models, a reduction of the CB_1 receptors occurs in the frontal cortex [66-68] and hippocampus [66, 68-70]. Interestingly, thischange in CB_1 receptor density was also apparent in the rat prefrontal cortex, where a rise was observed in animal models of depression evoked by stress factors [20, 25, 71] or by lesion of the olfactory bulbs [72] (Table **1**).

Facilitation of CB_1 receptor signaling exerts antidepressant-like behavioral responses in rodents, but it is worth noting that many side effects, particularly related to psychosomatic activation, will limit the therapeutic use of direct agonists. Nonselective (CB_1/CB_2) agonists such Δ^9-THC [13, 73, 74], CP55,940 [27], WIN55,212-2 [46] and

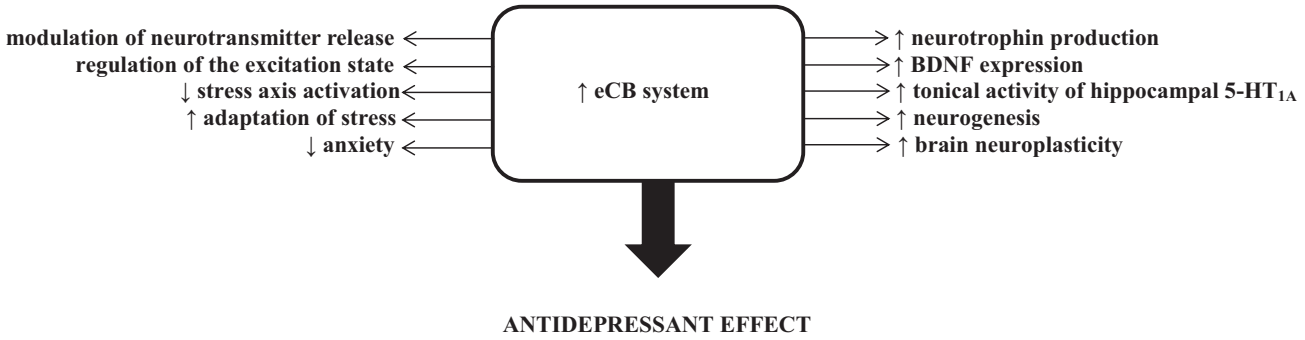

Fig. (2). Increased eCB stimulation produced several biochemical changes (modulation of neurotransmitter release, regulation of the excitation state, inhibition of the stress axis, rise of neurotrophin production and promotion of the neurogenesis process), which are implicated in antidepressant effects.

HU-210 [5, 45, 75] given acutely or subchronically decrease immobility time in the FST in rodents, indicating their antidepressant activity. In contrast, long-term exposure to Δ^9-THC [76] and WIN55,212-2 [77] during adolescence (but not during adulthood) induces depression-like and anxiety-like behaviors in adulthood in rats, and the extended immobility time after Δ^9-THC exposure was also observed in mice [78]. However, based on the bimodal action of eCB ligands on mood, a case could be made for the opposite. The antagonism of CB_1 receptors with rimonabant (SR141716) or AM251 produces antidepressant effects in rodents [63, 74, 79-85], but these findings are not useful for translational research as they have not been replicated in human studies (see below).

Based on these observations, in which the eCB system is damped during depression (above), antidepressant drugs should increase brain CB_1 receptor levels and/orreverse the reduced levels of the CB_1 receptor density associated with depressive phenotypes. In fact, a rise in CB_1 receptor expression has been demonstrated following chronic treatment with desipramine in the hypothalamus and hippocampus [30], following tranylcypromine in the the prefrontal cortex and hippocampus and after fluoxetine in the prefrontal cortex [31]. Furthermore, fluoxetine-induced enhancement of the CB_1 receptor-dependent inhibition of adenylyl cyclase in the prefrontal cortex did not correlate with receptor density [86], and chronically administered citalopram caused a reduction in the CB_1 receptor density in the hypothalamus, hippocampus and medial geniculate nucleus [87] (Table **2**).

With animal models of depression, chronic fluoxetine administration reversed the increased CB_1-receptor signaling in the prefrontal cortex of bulbectomized rats [72], while imipramine reversed the reduced CB_1 receptor density only in the rat hippocampus during exposure to CUS [20] (Table **2**).

The eCB system alters the activity of the serotonergic system through CB_1 receptors, including transmission and receptor expression [37]. In the CB_1 knockout mice, the activity of serotonergic neurons was facilitated in the dorsal raphe nucleus along with altered 5-HT feedback and with increased 5-HT extracellular levels in the prefrontal cortex. In this mouse genotype, fluoxetine failed to facilitate serotonergic neurotransmission in the prefrontal cortex [88], while the antidepressant effect of desipramine was blocked [63]. Recently, microdialysis in the rat prefrontal cortex revealed that CB_1 receptors control extracellular 5-HT levels; selective CB_1 receptor stimulation reduced the effect of citalopram on local 5-HT levels, while CB_1 receptor blockade increased it [89].

These data not only link CB_1 receptor functionality with serotonergic antidepressants [63, 86, 90] but strongly support the engagement of CB_1 receptors in depression.

Human Research

In human *postmortem* studies, the CB_1 density in cortical areas either decreased in mood disorders [34, 91] or increased in depressed suicide victims [92, 93]. Elevated level of the CB_1 receptors have been observed in the dorsolateral prefrontal cortex [33] and in the ventral striatum [52] of alcoholic suicide victims; the latter changes were not associated with alcohol dependence, as in alcohol-dependent non-suicides a downregulation of CB_1 receptors was noted [52]. To support the involvement of tonic CB_1 receptor activation in the pathophysiology of depression, the body of clinical evidence indicates that the dysfunction of the CB_1 receptors is a critical factor for the development of depressive symptoms. In clinical trials administration of the CB_1 receptor antagonist rimonabant (SR141716A) to humans for the treatment of obesity evoked adverse psychiatric effects [94]. 20 mg/kg/day of the drug caused depressed mood disorders and an increased risk of developing anxiety in the obese people, leading to their exclusion from the rimonabant therapy [94]. Treatment with rimonabant also resulted in suppression of positive affective memories, a decrease of neural responses to rewarding stimuli and the development of anhedonia [95]. In other clinical trials, acute and multiple doses of taranabant, a CB_1 receptor inverse agonist,used for the treatment of obesity, caused anxiety and mood changes in healthy male volunteers [96, 97].

CB_2 Receptors

Some investigators indicate that CB_2 receptors can play a role in depression [98-100]. These receptors are localized in

glial cells and neurons in the hippocampus, hypothalamus, amygdala, cerebellum and cerebral cortex [101], which suggests that they may be involved in the regulation of mood disorders [102].

Animal Research

The first study of CB_2 receptors in depression uncovered a decreased density of these receptors in the midbrain, striatum and hippocampus in stressed mice [103]. In the CMS model, a reduced CB_2 receptor density was reported in the mouse hippocampus [102]. These findings were not confirmed in a maternal deprivation model where the density of CB_2 receptors either increased in the rat frontal cortex [68] and hippocampus [70], or did not change in the hippocampus [67, 68] (Table **1**). These conflicting changes in CB_2 receptor density may be a result of the sensitivity of the different methods used (immunohistochemistry [70] vs. Western blot [67, 68]). Are duction in brain CB_2 receptors noted in some models of depression correlates with genetic studies in which CB_2 receptor overexpression creates a behavioral endophenotype resistant to depressogenic stimuli [102]. Additionally, CMS evokes a drop in the expression of the BDNF and CB_2 receptor genes in the hippocampus of stressed mice, which was reversed by chronic administration of a CB_2 antagonist (AM630) [102]. Further, chronic administration of the CB_2 receptor agonist JWH015 increased sucrose consumption in control mice in CMS [103], while another agonist,GW405833, decreased the immobility time in FST in rats with neuropathic pain [99]. In contrast to CB_2 receptor stimulation, the chronic administration of a CB_2 receptor antagonist did not change the sucrose consumption in mice in CMS, but it also reduced the immobility time during FST [102, 103].

Presently, there is no data showing the changes in CB_2 receptor density elicited by antidepressant drugs.

Human Research

A high incidence of Q63R polymorphism in the CB_2 gene was found in depressed and alcoholic Japanese subjects [103]. In *postmortem* studies, the CB_2 mRNA levels in the prefrontal cortex, in contrast to CB_1 levels, did not decrease during postnatal development in humans ranging in age from birth to 50 years, and the CB_2 levels in the prefrontal cortex of either major depression or bipolar disorder patients were not significantly different when compared to age-matched controls [92]. Based on this human research, CB_2 receptors seem to display secondary/additional targeting during depression, in contrast to the CB_1 receptors' dominant role in depression.

THE ENDOVANILLOID SYSTEM AND DEPRESSION

The endovanilloid system is composed of endogenous vanilloids, synthesizing and catabolic enzymes and receptors (TRPV1). Three different classes of endovanilloids have been recognized, including AEA and its congeners (i.e., the *N*-acylethanolamines (NAEs)), the *N*-acyldopamines (*N*-oleoyl-dopamine and *N*-arachidonoyl-dopamine (NADA)) and some lipoxygenase derivatives of arachidonic acid (i.e., 12-hydroperoxyeicosatetraenoic acid (12-HPETE)) [104]. These endovanilloids are synthesized and released in an activity-dependent manner *via* enzymatic conversion. AEA and NAEs biosynthesis depends on NAPE-PLD activity while 12-lipoxygenase (12-LOX) is required for 12-HPETE formation. The endovanilloids are inactivated rapidly by FAAH (the main degrading enzyme for AEA and NAEs) and cathechol-*O*-methyl-transferase (COMT) (required for NADA degradation). The endovanilloids activate TRPV1 receptors, nonselective cation channels that may be activated by physical and chemical agents. TRPV1 receptors are widely expressed in various areas of the brain, including the hippocampus (pyramidal neurons of the CA3 region) and cerebellum (Purkinje's neurons). In line with this information, the co-expression of TRPV1 and CB_1 receptors in brain neurons allows for cross-talk between endovanilloids and eCBs [104].

The physiological and pathological roles of the endovanilloid system still have not been fully elucidated, however, pharmacological manipulation of the activity of TRPV1 receptors might be useful to treatpain, anxiety, emesis and locomotor disorders. Despite the demonstrated the roles of TPRV1 receptors in locomotion, emotion and cognitive behaviors, their role in depression is still not established. The localization of the TRPV1 receptors in the brain suggests their role in emotional responses [105]. Stimulation of TPRV1 receptors causes the depolarization of neurons and the release of glutamate, which is implicated in the release of others neurotransmitters (GABA, DA, NA or 5-HT) [15]. Additionally, the endovanilloid ligands with the eCB ligands bi-directionally modulate presynaptic Ca^{2+} levels and neurotransmitter release [106]. The endovanilloids seem to play a role as autocrine neuromodulators and/or second messengers in the brain.

Animal Research

From the preclinical point of view, the loss of TRPV1 induces "antidepressant, anxiolytic, abnormal social and reduced memorial behaviors" [107]. TRPV1 knockout mice exhibit reduced immobility time the FST and reduced latency times in the novelty-suppressed feeding paradigm, demonstrating a decreased depressive response [107]. An acute, desensitizing dose of selective agonists of TRPV1 (olvanil and capsaicin) reduce the immobility time in mice [108-110] but raises this parameter in rats (olvanil) [111], while selective antagonists of TRPV1 (capsazepine) reduce the immobility in mice [109]. In addition, capsazepine also increases the antidepressant activity of a sub-threshold dose of fluoxetine in the FST in mice [109]. Moreover, a synthetic agonist of CB_1 and TRPV1 receptors, arvanil, elicits significant antidepressant-like effects in mice [108]. TRPV1 receptors modulate input to the locus coeruleus, which is implicated in major depression, stress and memory [112].

Human Research

No data.

CONCLUSIONS

In conclusion, the eCB and endovanilloid system, through different effects on cellular processes (levels of neurotransmitters, neurogenesis, the HPA axis) may function as a central player to connect previously known theories of depression and may play a significant role in the pathogenesis of the disease and the mechanism of action of

antidepressants, and it may serve as a target for drug design and discovery. It should be emphasized that, according to recent theories of depression, one of the causes of this disease is impaired neurogenesis, and endogenous ligands of the eCB system can reinforce hippocampal neurogenesis by increasing brain-derived neurotrophic factor (BDNF) expression, raising the possibility of a role for the eCB system in antidepressant drug action, and underscoring the role of these fascinating lipid mediators in depression. The endovanilloid ligands as potential brain modifiers could also be novel therapeutic targets for the treatment of depression. However, their role in depression is still poorly understood and future studies are needed to clarify the exact contribution of endovanilloids to the pathogenesis of depression and to the mechanism of action of antidepressant drugs.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

AEA	=	anandamide
2-AG	=	2-arachidonoylglycerol
eCBs	=	endocannabinoids
12-HPETE	=	12-hydroperoxyeicosatetraenoic acid
LC-MS/MS	=	liquid chromatography tandem mass spectrometry
NAEs	=	N-acylethanolamines
NADA	=	N-arachidonoyl-dopamine

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