

Role of the endocannabinoid system in depression and suicide

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Depression is one of the most prevalent forms of neuropsychiatric disorder and is a major cause of suicide worldwide. The prefrontal cortex is a crucial brain region that is thought to be involved in the regulation of mood, aggression and/or impulsivity and decision making, which are altered in suicidality. Evidence of the role of the endocannabinoid (EC) system in the neurobiology of neuropsychiatric disorders is beginning to emerge. The behavioral effects of ECs are believed to be mediated through the central cannabinoid CB₁ receptor. Alterations in the levels of ECs, and in the density and coupling efficacy of CB₁ receptors, have been reported in the prefrontal cortex of depressed and alcoholic suicide victims. These findings support our hypothesis that altered EC function contributes to the pathophysiological aspects of suicidal behavior. Here, we provide a brief overview of the role of the EC system in alcoholism, depression and suicide, and discuss possible therapeutic interventions and directions for future research.

Importance of the prefrontal cortex in mood and cognition

The prefrontal cortex is believed to be an important cortical area that participates in a putative brain circuitry involved in the pathophysiology of depression and suicidal behavior. Neuroimaging and post-mortem studies of patients with major depression have identified neurophysiological abnormalities in multiple areas of the prefrontal cortex and its linked brain regions [1,2]. Altered glucose metabolism, and reduced activity and volume of the prefrontal cortex have also been indicated in depression [1,3], and treatment of depression seems to reverse some of these deficits [3,4].

Injuries to the prefrontal cortex are commonly associated with the development of depression or impulsivity and they could be involved in behavioral inhibition, decision making and the expression of emotions [5,6]. These cognitive functions are impaired in patients with depression and suicidal behavior. Among other cortical regions, the dorsolateral prefrontal cortex (DLPFC) is crucial for decision making and in spatial working memory [7,8]. The latter cognitive function is important for maintaining decision goals, considering options and integrating the

two to predict future outcomes and probabilities of meeting goals [7]. Impaired decision-making, possibly due to altered mood and emotion, might be a neuropsychological risk factor for suicidal behavior.

Monoamine hypothesis of depression and suicide

Biological studies of depression and suicidality have focused most frequently on the monoamine neurotransmitter pathways in the prefrontal cortex, particularly 5-hydroxytryptamine (5-HT) and noradrenaline (NA). Moreover, abnormalities in the function of the 5-HT system seem to be independently associated with mood disorders and suicidal behavior [9]. The majority of these studies supports the hypothesis of there being a deficit in 5-HT neurotransmission in depression and suicide.

Among therapeutic agents, antidepressants are the most widely used drugs for the treatment of depression. They exert their therapeutic action through their ability to increase the synaptic content of monoamine neurotransmitters (e.g. 5-HT and NA). However, antidepressants exert their mood-elevating effects only after prolonged administration, indicating that enhanced 5-HT or NA neurotransmission *per se* is not responsible for the clinical actions of these drugs. Whereas currently available treatments are inadequate in many patients, the existence of additional biological substrates could provide potential therapeutic targets. Indeed, there is a growing interest in the notion that the endocannabinoid (EC) system has a crucial role in the regulation of mood, cognition, motivation and emotional behavior.

The EC system in the CNS

The EC system consists of endogenous cannabinoid CB-receptor agonists (ECs), CB receptors and proteins that are involved in the regulation and metabolism of ECs. ECs are a recently discovered class of lipid mediators that includes amides, esters and ethers of long-chain polyunsaturated fatty acids. The first EC was isolated from porcine brain in 1992 and was characterized to be arachidonoyl ethanolamide (AEA) [10]. This compound was later named anandamide, derived from the Sanskrit word *ananda*, which means 'inner bliss'. Several other ECs have been identified recently; their pharmacological properties and physiological functions are currently being studied (Figure 1). They are found abundantly in the cerebral cortex, basal ganglia and limbic structures, and exert their effects mainly through the CB receptors [11].

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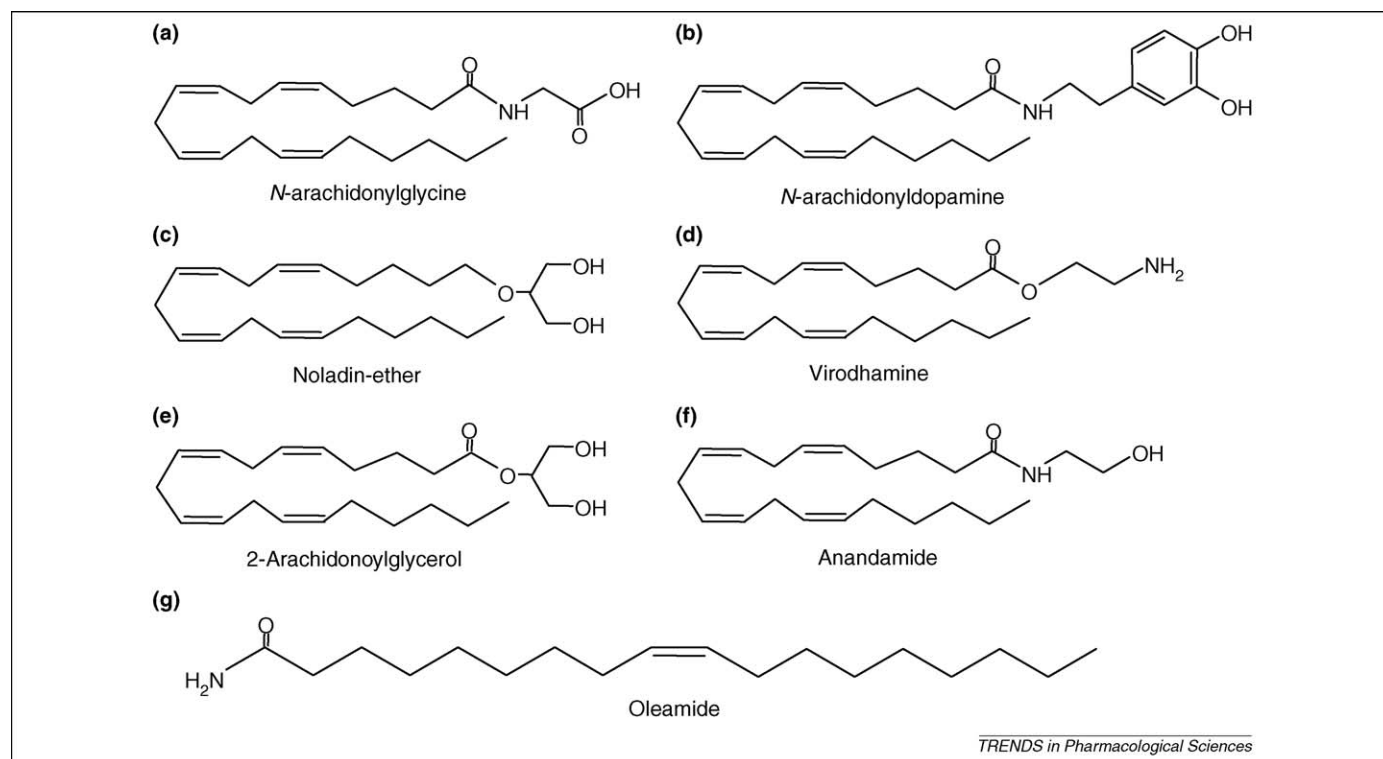


Figure 1. Structure of ECs. The structures of (a) *N*-arachidonylglycine, (b) *N*-arachidonyldopamine, (c) 2-arachidonoylglycerol ether (noladin-ether), (d) *O*-arachidonoyl ethanolamine (virodhamine), (e) 2-arachidonoylglycerol, (f) *N*-arachidonoyl ethanolamide (anandamide) and (g) 9-octadecenoamide (oleamide) are shown. Adapted, with permission, from Ref. [58].

There are currently two known CB-receptor subtypes, CB₁ and CB₂. CB₁ receptors are localized primarily in the CNS, whereas CB₂ receptors are expressed peripherally and are associated mainly with the immune system [12]. Recent studies have also revealed the existence of CB₂ receptors in the CNS [13]. The human CB₁ receptor contains 472 amino acids and is a G-protein-coupled receptor (GPCR). CB₁ receptors are the most abundant neuromodulatory GPCR and are highly expressed in the cortex, hippocampus, cerebellum and basal ganglia [12]. These receptors are coupled negatively to adenylyl cyclase (AC), and N- and P/Q-type Ca²⁺ channels, and positively to A-type and inwardly rectifying K⁺ channels and mitogen-activated protein kinases (MAPKs) by G_{i/o} proteins [12].

The regulatory mechanisms that govern the EC system are not clearly understood at present. Nevertheless, neuroanatomical and electrophysiological studies of the mammalian CNS have revealed that CB₁ receptors are located in the presynaptic terminals of neurons [12,14]. It has been proposed that ECs are synthesized in postsynaptic neurons following the stimulus-dependent cleavage of membrane phospholipids and are released into the synaptic cleft, where they function as retrograde messengers [14]. Several studies have indicated a role for the cellular uptake mechanism – the AEA membrane transporter (AMT) – in limiting the activity of ECs. An intracellular membrane-bound serine hydrolase, fatty acid amide hydrolase (FAAH), which is preferentially located in the somatodendritic compartments of neurons, is involved in the inactivation of AEA and related lipids [15].

In the CNS, ECs activate the CB₁ receptor and regulate the synaptic transmission of excitatory and inhibitory

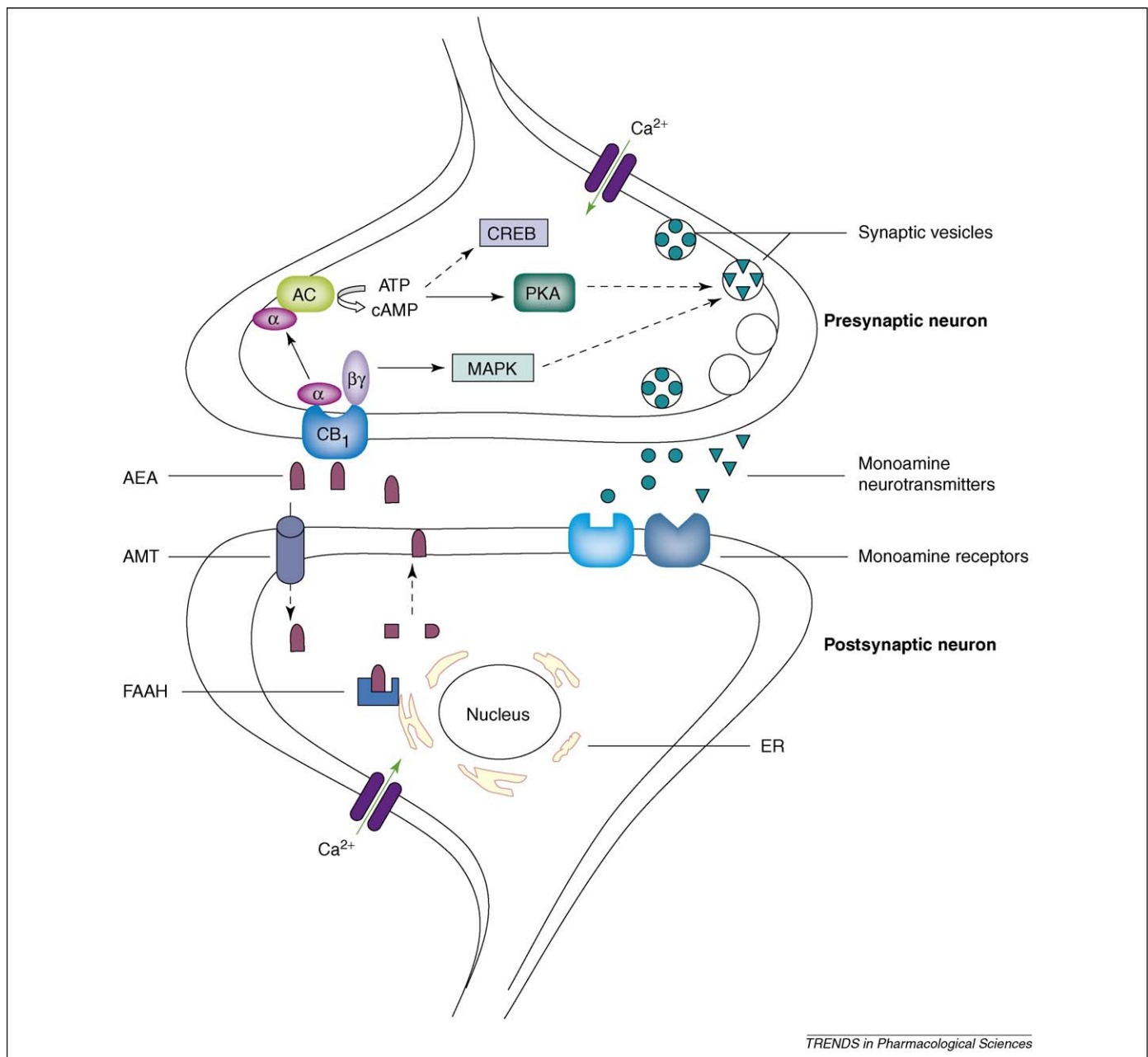
circuits by modulating the release of several monoamine neurotransmitters [12,14]. The effects of ECs seem to depend on the localization of CB₁ receptors within the excitatory or inhibitory neural circuits (Figure 2).

The EC system in depression and suicidality

Human studies

There is limited information available about the role of the EC system in depression and/or suicide. A possible role for the CB₁ receptor in the pathophysiology of depression has been revealed by post-mortem study [16], which demonstrated higher levels of CB₁ receptor and CB₁-receptor-mediated G-protein activation in the DLPFC of depressed suicide victims compared with normal controls. Furthermore, a genetic risk factor for depression in Parkinson's disease (PD) was recently found to be associated with polymorphisms of the *CNR1* gene [17]. According to this study, PD patients with long alleles in the *CNR1* gene are less susceptible to depression. Although the relationship between genotype and phenotypic behavior is yet to be established, alteration in the expression of *CNR1* might have a greater role in the depressive disorder.

Recent studies, however, also indicate an association among cannabis abuse, mood alteration and the involvement of the EC system in the etiology of schizophrenia. For example, long-term cannabis abuse alters cognition and attention, and might include symptoms of anhedonia, which resemble negative symptoms of schizophrenia [18]. Post-mortem studies have also shown a higher density of the CB₁ receptor in the prefrontal cortex, striatum and anterior cingulate cortex of schizophrenics [19,20]. These brain regions have a crucial role in normal cognition,



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Figure 2. The synaptic EC system. AEA, which is synthesized in the postsynaptic membrane, is a retrograde signaling molecule that binds to the presynaptic CB₁ receptor. This, in turn, acts upon various effectors – including AC, MAPK, and K⁺ and Ca²⁺ channels – via G_{αi/o} proteins. The inhibition of AC activity and the subsequent decrease in cAMP content leads to reduced activity of protein kinases, primarily PKA, leading to the modulation of ion channels and neurotransmitter release. The activity of AEA is limited by AMT following hydrolysis by the endoplasmic reticulum (ER)-bound FAAH.

particularly in relation to motivation and attention. Because CBs impair these processes, hyperactivity of the CB₁ receptor in these regions might be associated with negative symptoms of schizophrenia. In addition to the CB₁ receptor, ECs are also elevated in the cerebrospinal fluid of schizophrenics [21]. From post-mortem studies of depressed suicide victims, enhanced CB₁-receptor signaling in specific brain regions seems to be associated with symptoms of psychotic and affective disorders.

With regard to post-mortem studies, changes in the prefrontal cortex of depressed suicide victims cannot prove whether biochemical alterations are related to the presence of depression or to suicide *per se*. In this regard, a recent post-mortem study revealed elevated levels of the CB₁ receptor and CB₁-receptor-mediated

G-protein signaling in the DLPFC of alcoholic suicide victims compared with alcoholic non-suicide subjects [22]. Consistent with previous findings in depressed suicide victims [16], this study provided further evidence linking sensitization of cortical CB₁-receptor-mediated G-protein activation to suicide. Higher EC levels (AEA and 2-AG) were also observed in the DLPFC of alcoholic suicide victims in this study. Further studies are warranted to compare the findings from non-suicide depressed subjects with those from depressed suicide victims to substantiate these findings.

Animal studies related to stress and depression

Pharmacological studies have revealed the importance of the EC system in depressive-like responses in rodents. For

example, the CB₁-receptor antagonists and/or inverse agonists rimonabant (SR141716; see Chemical names) and AM251 exert antidepressant-like effects in animal models [23–25]. In addition, rimonabant produces antidepressant activity similar to that of fluoxetine in various animal models of depression [26]. Moreover, such an effect was absent from CB₁^{-/-} mice treated with AM251 [23], indicating a role for the CB₁ receptor in depression.

The mechanism underlying the antidepressant-like effects of rimonabant remains to be determined. However, the monoamine systems of the midbrain serve important adaptive functions in response to acute stress, and long-term alterations in their activity might contribute to the development of depression [1,9]. A key component in the action of clinically effective antidepressants is their ability to increase the levels of central monoamine neurotransmitters. Nevertheless, the CB₁ receptor regulates the release of neurotransmitters. For instance, rimonabant increases 5-HT, NA and dopamine (DA) levels in the prefrontal cortex [24,27]. Furthermore, fluoxetine decreases the expression of CB₁ receptors in rodents [28]. Elevated synaptic 5-HT content elicited by fluoxetine seems to have a direct and/or indirect influence on the expression of CB₁ receptors, indicating a potential role of interaction between the 5-HT and EC systems in mood regulation.

By contrast, the CB₁-receptor agonist WIN552122 increases NA levels in the rat frontal cortex [29]. In addition, the CB₁-receptor partial agonist tetrahydrocannabinol (Δ^9 -THC) elevates prefrontal cortical DA and glutamate levels [30]. These cannabinoids and URB597 (an inhibitor of FAAH) also increase the firing activity of 5-HT- and NA-containing neurons [31,32]. Moreover, pharmacological manipulation with AM404 (an AMT inhibitor) and HU210 (a CB₁-receptor agonist) elicit an antidepressant-like response in the rat forced-swim test [33]. A similar effect also occurs in rats through the inhibition of AEA hydrolysis [32]. These findings indicate an antidepressant-like effect that occurs by enhancement of the AEA–CB₁-receptor signaling pathway. The contrasting results pertaining to CB₁-receptor-mediated neurotransmitter release have yet to be explained; however, dose and duration of treatment, and brain region of interest (e.g. prefrontal compared with frontal cortex) are important contributing factors to this discrepancy.

Alterations in the central EC system due to stress might also be associated with mood changes that occur in depression. Indeed, recent studies have highlighted the modulation of the EC system in the stress paradigm. For instance, Hill *et al.* [34] demonstrated downregulation of the EC system in the rat hippocampus by chronic unpredictable stress. Acute stress, however, induces elevated levels of prefrontal cortical AEA [35], and midbrain AEA and 2-AG in rodents [36]. Although the occurrence of major depression has been linked to an increased vulnerability to stress, the impact of stress on the EC system with regard to how the neurochemical alterations modulate other brain regions, particularly the prefrontal cortex, and how it might affect mood are of particular interest.

Immobility tests in rodents have been used extensively as measures of depressive-like symptoms. Behavioral studies using mice that lack CB₁ receptors, however, yielded

mixed results. For instance, both decreased [37,38] and increased [39] spontaneous locomotor activity has been reported in CB₁^{-/-} mice. The reasons for these discrepancies are unclear; however, the use of different genetic backgrounds and environment might be among other contributing factors. Although the effect of *CNR1* deletion might not be behavior specific, neuroadaptive changes associated with receptor deletion seem to have an important role. Clearly, there is currently an inadequate understanding of the mechanisms of CBs in mood regulation. It must be investigated whether ECs exert their mood-altering effects via CB₁-like or non-CB (vanilloid) receptors.

Interaction of the EC system and the hypothalamic–pituitary–adrenal axis

The hypothalamic–pituitary–adrenal (HPA) axis, the neuroendocrine system, has a crucial role in mood regulation [1]. It is a major regulator of circulating levels of glucocorticoid hormones – cortisol in humans and corticosterone in rodents – which are elevated in depression and in response to stress. Activation of the HPA axis by CB₁ receptors has been observed in recent studies [40–42] (central amygdala and the paraventricular nucleus) following stimulation of the neurons containing corticotrophin-releasing factor [43]. Furthermore, the CB₁-receptor-stimulated increase in corticotrophin and corticosterone levels was attenuated by rimonabant [44,45]. The level of adrenocorticotrophin was also lower in CB₁^{-/-} mice [46]. EC signaling also inhibits the HPA axis through the CB₁ receptor [47,48]. Basal and stress-induced plasma levels of adrenocorticotrophin and corticosterone are higher in CB₁^{-/-} mice, indicating a context-dependent alteration in the function of the HPA axis [49]. Although the discrepancy among these findings is yet to be determined, they indicate an interaction between the EC system and the neuroendocrine system. Given the importance of the HPA axis in the pathophysiology of depression and suicidality [50], the EC system might have an important role in the regulation of mood and emotional response, which are impaired in patients with suicidal behavior (Figure 3).

Co-morbidity of drug abuse with depression and suicide

Although psychosocial problems might contribute to suicide, most suicides occur in context with psychiatric illness. In particular, mood and substance-abuse disorders are major risk factors for suicide. Although clinical studies of cannabis abuse in mood disorders have provided contrasting results, many studies have reported a negative impact of chronic cannabis abuse. For instance, cannabis dependence has been found to be associated with increased rates of psychotic and depressive symptoms, in addition to suicide attempts [51–53]. Besides cannabis, an association among alcohol abuse, depression and suicidality has also been suggested [53,54].

Psychological and psychosocial studies indicate that some factors in suicide are associated primarily with impulsivity, and this behavior might be part of a diathesis for suicidal behavior [6]. Although Δ^9 THC is beneficial in some disease conditions [42], this psychoactive ingredient, in addition to abuse of cannabis and alcohol, induces certain forms of impulsive behavior in humans [55–57]. Moreover,

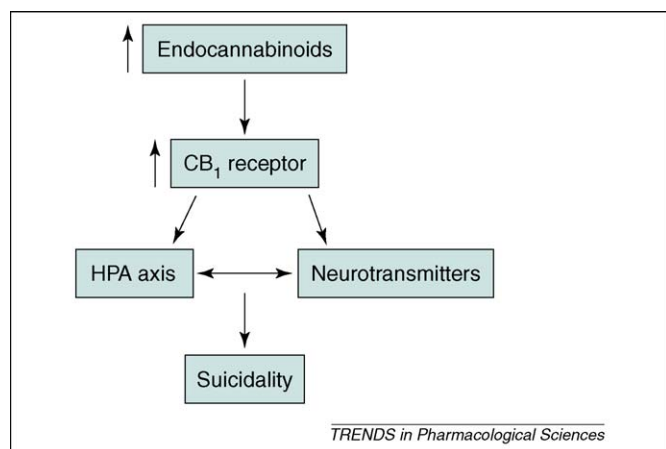


Figure 3. CB₁ receptors modulate the function of the HPA axis and monoamine neurotransmitter systems. These systems are impaired in patients with suicidal behavior. Hyperactivity of EC–CB₁–receptor-mediated signaling and its influence on the HPA axis and monoamine systems might be one of the neurochemical abnormalities associated with suicidality.

reduction in impulsive and/or motivational behavior (e.g. place preference and drug reward) for alcohol could be achieved by genetic deletion and pharmacological blockade of the CB₁ receptor in rodents [58,59]. Consistent with these findings, pharmacological activation of the CB₁ receptor in rodents results in motivation to drink more alcohol [58]. Biochemical studies also indicate that a difference in CB₁-receptor function could be a contributing factor to varied preference for alcohol-seeking behavior [58]. Furthermore, genetic deletion of the FAAH enzyme [60] and an injection of URB597 to the prefrontal cortex enhance rodent motivation to drink alcohol [61]. These studies clearly indicate the role of the EC system in alcohol addiction.

A relationship in alcoholics between the *CNR1* gene and attention deficit hyperactivity disorder (ADHD) has recently been reported [62]. Some of these patients also exhibit suicidal behavior [63] that seems to be associated with impaired decision-making and impulsivity [64]. Although further investigations are required to examine the underlying mechanism of the EC system in ADHD, a recent study indicated the use of CB₁-receptor antagonists as potential therapeutic agents for the treatment of ADHD [65]. Taken together, the association of the EC system with alcohol addiction and a high incidence rate of suicide in abusers of cannabis and alcohol indicates that an abnormal EC system could be one of the contributing factors for suicidal behavior. Although existing data support a strong association among various neuropsychiatric disorders, substance-abuse disorders and suicide, the nature of such a relationship is complex and might vary depending on the disorder in question and the substance abused. The existence of a causative relationship among cannabis and alcohol abuse, alcoholism, depression and suicidality remains to be established.

Possible mechanism of the dysfunctional EC system in depression and suicide

The consequence of elevated levels of CB₁ receptors in the DLPFC of depressed suicide victims is currently unknown [16]. The upregulation of CB₁ receptors due to the feedback response to low levels of ECs in depression *per se* could be a

mechanism. However, the observed sensitization of the CB₁ receptor and its mediated G-protein activation despite higher EC levels in the DLPFC of alcoholic suicide victims [22] are of particular interest. Such a trend in the brain of depressed suicide victims cannot be ruled out. Although the underlying mechanism remains to be established, changes in the metabolism and uptake of ECs seem to be responsible for altered EC levels. Elevated levels of ECs and CB₁ receptors in the DLPFC of suicide victims raise the following questions: what is the mechanism that causes these changes and what are the functional consequences? It remains to be elucidated whether alterations in CB₁ receptors in the prefrontal cortex of individuals with these disorders reflect a primary pathology or a compensatory homeostatic adaptation.

Abnormalities in the cAMP–PKA–CREB pathway have also been reported in the post-mortem prefrontal cortex of depressed suicide victims [66]. Because the CB₁ receptor is the most abundant neuromodulatory GPCR, alterations in its levels seem to have a greater impact on the cAMP pathway. Upregulation of the CB₁ receptor might enhance the ability of the G_i protein to inhibit AC activity. This seems to account for the decreased activity of the cAMP–PKA–CREB pathway, which might have an important role in the pathophysiology of depression and suicide.

Concluding remarks

One of the most demanding tasks in psychiatry is to protect patients from suicide attempts. Preventive strategies could be improved by increasing knowledge of the pathophysiological disturbances that underlie these attempts. In this review, we have presented evidence for a role of the EC system in alcoholism and depression, which are believed to be high-risk factors for suicide. We hypothesize that the sensitization of CB₁-receptor-mediated G-protein signaling in the prefrontal cortex is one of the etiological or neuroadaptive factors in the pathophysiology of suicide.

Although the focus of this article has been on the EC system in depression and suicide, it is important to note that the role of this system might constitute just one facet of a complex mental illness. Further exploration of overlapping neural circuitry and functional relationships between the EC system and other monoamine neurotransmitter systems will be essential for understanding the pathophysiology of mental disorders. A major issue to consider is how a single CB₁-receptor subtype accounts for several of these behavioral manifestations. It is possible that the activation of multiple signaling pathways by the CB₁ receptor and the existence of subtypes of CB or CB₁ receptors contribute to this heterogeneity. Although pharmacological agents that target the CB₁ receptor and proteins that participate in the regulation and metabolism of ECs (e.g. FAAH and AMT) are potential therapeutic drugs for several disorders, further preclinical and clinical studies are needed to evaluate the role of the EC system in various pathophysiological conditions.

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Chemical names

AM251: 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl-1H-pyrazole-3-carboxamide.

AM404: N-(4-hydroxyphenyl) arachidonoylamide.

HU210: 3-(1,1-dimethylheptyl)-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzopyran-9-methanol.

SR141716: N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide.

URB597: 3'-carbamoyl-biphenyl-3-yl-cyclohexylcarbamate.

WIN552122: 2-(3-dihydro-5-methyl-3-(4-morpholinyl-methyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6yl)-1-naphthalenylmethanone mesylate.

Δ^9 THC: 11-nor- δ -9-tetrahydrocannabinol.

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