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Review Article

Endocannabinoid signaling and epigenetics modifications in the neurobiology of stress-related disorders

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Stress exposure is associated with psychiatric conditions, such as depression, anxiety, and post-traumatic stress disorder (PTSD). It is also a vulnerability factor to developing or reinstating substance use disorder. Stress causes several changes in the neuro-immune-endocrine axis, potentially resulting in prolonged dysfunction and diseases. Changes in several transmitters, including serotonin, dopamine, glutamate, gamma-aminobutyric acid (GABA), glucocorticoids, and cytokines, are associated with psychiatric disorders or behavioral alterations in preclinical studies. Complex and interacting mechanisms make it very difficult to understand the physiopathology of psychiatry conditions; therefore, studying regulatory mechanisms that impact these alterations is a good approach. In the last decades, the impact of stress on biology through epigenetic markers, which directly impact gene expression, is under intense investigation; these mechanisms are associated with behavioral alterations in animal models after stress or drug exposure, for example. The endocannabinoid (eCB) system modulates stress response, reward circuits, and other physiological functions, including hypothalamus–pituitary–adrenal axis activation and immune response. eCBs, for example, act retrogradely at presynaptic neurons, limiting the release of neurotransmitters, a mechanism implicated in the antidepressant and anxiolytic effects after stress. Epigenetic mechanisms can impact the expression of eCB system molecules, which in turn can regulate epigenetic mechanisms. This review will present evidence of how the eCB system and epigenetic mechanisms interact and the consequences of this interaction in modulating behavioral changes after stress exposure in preclinical studies or psychiatric conditions. Moreover, evidence that correlates the involvement of the eCB system and epigenetic mechanisms in drug abuse contexts will be discussed.

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Overview of stress response and circuitry

Stress is an important and evolutionarily conserved response that modulates several central nervous system (CNS) regions and the endocrine system to prepare the organism to face a challenging experience. The stressors, stimuli that trigger the stress response, can be chemical, physical, psychological, or combinations of these; and they can recruit different brain regions, which could overlap depending on the circumstances [1]. In general, stress exposure activates the hypothalamus–pituitary–adrenal (HPA) axis, leading to release of glucocorticoids (GCs) by the adrenal gland. GCs promote their stress effects mostly by activating glucocorticoid receptors (GR) in the periphery and in the brain, altering the expression of several genes to promote adaptation [2,3]. A simplified view of key brain regions involved in stress response is depicted in Figure 1. However, as reviewing this topic is beyond the scope of this study, the reader can find

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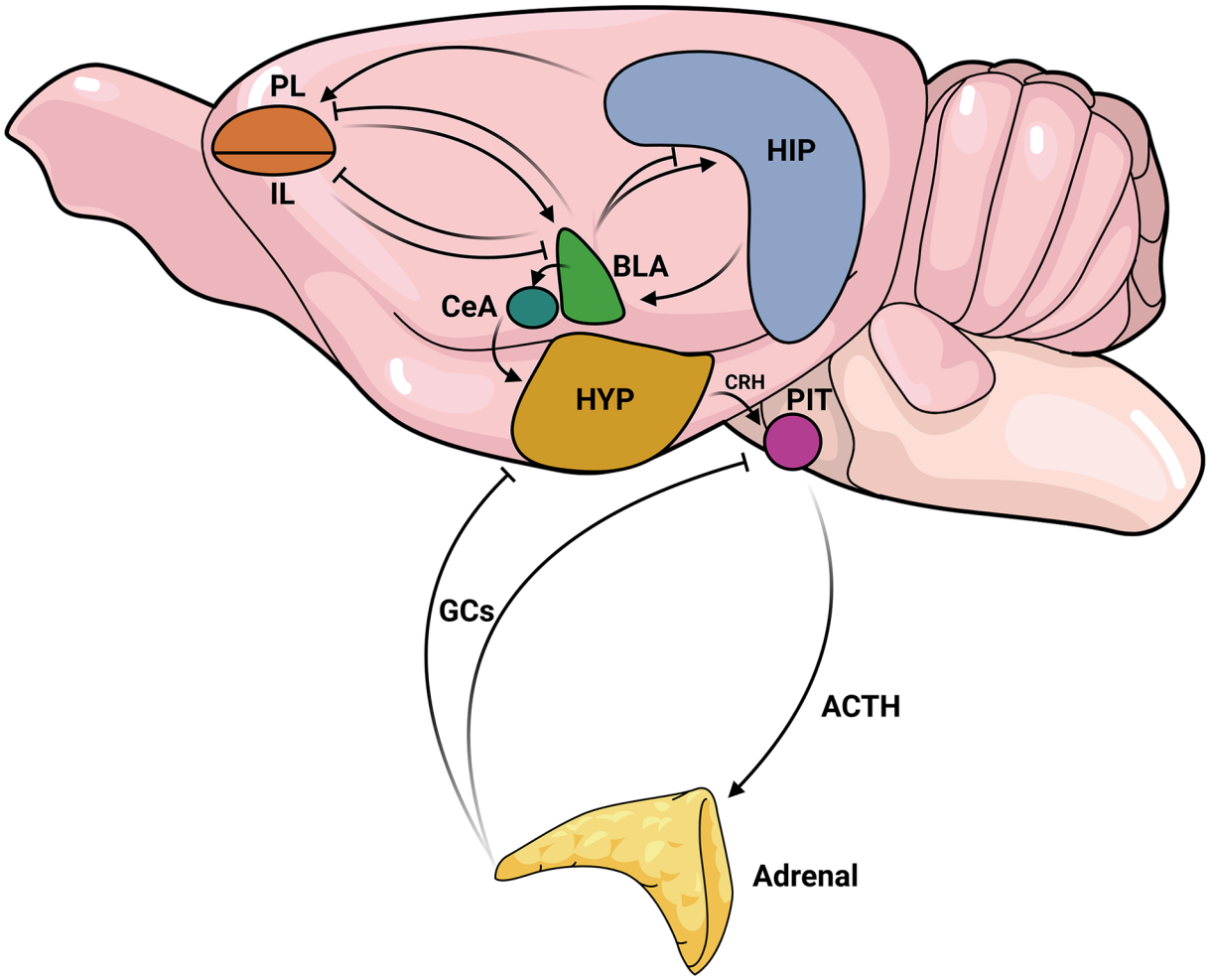

Figure 1. A simplified view of the key brain regions involved in the stress response

The amygdala (basolateral-BLA and central-CeA nuclei) is a key region in initiating the stress response. It is an input region for projections sent by other regions, particularly by different subdivisions of the medial prefrontal cortex (mPFC). Specifically, the prelimbic region (PL) of the mPFC exerts excitatory influence on amygdala. In contrast, the infralimbic region (IL) inhibits the basolateral amygdala (BLA). The hippocampus (HIP) contributes to stress response by providing contextual information, with excitatory projections to the PL-mPFC and BLA. The BLA, in turn, inhibits the PL, IL, and has both inhibitory and excitatory projections to the HIP. The balance of these two projections controls the parallel HIP outputs. Integrating this information, the BLA activates the amygdala's output region, the CeA, which sends excitatory projections to the hypothalamus (HYP), stimulating the production and release of corticotropin-releasing hormone (CRH). CRH acts on the pituitary gland triggering the synthesis and release of adrenocorticotropic hormone (ACTH). ACTH, in turn, is released in the blood and stimulates the synthesis of glucocorticoids (GCs) in the adrenal gland. Finally, released GCs establish a negative feedback loop within the hypothalamus and pituitary, modulating the peripheral and central nervous system areas to facilitate adaptive responses to stress. Depending on the duration and type of stressors, increased amygdala activity, cortical dysfunction and hippocampal atrophy can occur, impairing the ability of this adaptive response to occur, contributing to psychiatric disorders.

more comprehensive reviews about this topic, with figures summarizing the current knowledge, in several recent review studies [1,4–7]. Here, we will present some critical information about the central regions affected by stress, that influence behavioral response: the prefrontal cortex, amygdala, and hippocampus.

The prefrontal cortex (PFC) is responsible for complex functions such as integrating and processing different stimuli for decision-making, goal-directed behaviors, and working memory [8,9], in addition to emotional processing. The medial portion of the PFC (mPFC), the most studied in studies related to aversion and stress [10], is mainly divided into the prelimbic (PL) and the infralimbic (IL) portions, which can have distinct or opposite functions [11,12] due

to their partially distinct connections and projections [13,14]. In general terms, the PFC is greatly activated during acute stress, and the excess of glutamate release and its impaired reuptake mediated by GCs may result in neurotoxicity [15], proinflammatory factors release, and neuronal death [16,17]. These changes can be related to the neuronal atrophy observed in the PFC of depressed and PTSD patients and animal models involving stress exposure [18,19] which could result in weakened PFC projections to the amygdala and hippocampus, impairing modulatory function exerted by PFC on these brain regions [20,21].

The amygdala is also an essential structure for emotional processing [5] and is divided into different nuclei. The basolateral nucleus (BLA) integrates and processes aversive/stressful stimuli received by several brain regions, being greatly activated during stressful events [5] and fear memory conditioning acquisition and consolidation [22,23]. BLA sends several outputs to the central nucleus (CeA) and the medial nucleus (MeA), which in turn project to other brain areas that will be responsible for triggering adaptative behaviors to facing stress [5]. As mentioned before, the amygdala receives inhibitory projections from the IL mPFC, which can be weakened after stressful situations, resulting in a lack of inhibition of BLA by the PFC and hyperactivation of the amygdala [24,25]. For instance, depressed and PTSD patients have bigger and more active amygdala than healthy volunteers [26–28].

Finally, the hippocampus, which is connected to the amygdala and PFC [29], comprises the dentate gyrus (DG) and Ammon's horn/Cornus Ammonics (CA) subfields 1, 2, and 3. The CA1 region has outputs to several regions, including the PL and IL mPFC and BLA [30–32]. The hippocampus plays an important role in memory acquisition and discrimination of aversive contexts [33,34]. It also inhibits excessive activation of the HPA axis during stress response [35]. However, stress exposure can cause hippocampus atrophy and decreases neuronal plasticity, impairing its function and resulting, for example, in fear extinction learning deficits and fear generalization [33,36], anxiety-like and depressive-like behaviors [37]. Moreover, decreased hippocampal volume is reported in anxiety disorders, PTSD, and depression in humans [38–41]. Interestingly, based on a monozygotic twins study, it was suggested that a smaller hippocampal volume could be a risk factor for developing PTSD after traumatic events rather than a consequence of PTSD [42].

Although many other brain areas can be involved, it is well-known that a proper synchronization between the amygdala, mPFC, and hippocampus is necessary for adequate stress response and fear processing mechanisms. Therefore, impairment in this circuitry is frequently observed in psychiatric disorders. This poor connectivity can be associated with impaired molecular mechanisms in those brain regions, including dysfunctional neurotransmitter systems, such as endocannabinoids, and epigenetic modifications, which could control neuroplastic changes resulting in long-lasting consequences, such as impaired behavior.

The (endo)cannabinoid signaling in stress response

The endocannabinoid (eCB) system, activated by stress exposure, is considered a stress-buffer system and essential for several physiological conditions. The main eCBs are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which are produced on demand post-synaptically in response to an increase in neuronal activity, by actions of N-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL) on membrane phospholipids, respectively. These eCBs are released in the synaptic cleft and act retrogradely in cannabinoid receptors ($CB_{1/2}$) or post-synaptically in CB_2, or in glial cells. $CB_{1/2}$ are G_i-coupled receptors, then their activation result in the inhibition of adenylyl cyclase, the protein kinase A (PKA), and cellular Ca^{2+} influx, culminating in a blockade in neurotransmitter release that was increased before. Finally, AEA will be degraded by the fatty acid amide hydrolase (FAAH) enzyme mostly in the postsynaptic neuron, whereas 2-AG will be metabolized by the monoacylglycerol lipase (MAGL) enzyme in the presynaptic neuron [43].

Contrasting to $CB_{1/2}$ receptors, the vanilloid receptor 1 ($TRPV_1$) is expressed both pre- and post-synaptically. TRPV1 can be activated by AEA, increasing the Ca^{2+} influx and neurotransmitter release. Pieces of evidence suggest that AEA has its actions preferentially via CB_1 receptors, whereas, at higher concentrations, the predominant effect could reflect its effects on $TRPV_1$. This is one of the possible explanations for the bell-shaped dose-response curve often seen with AEA in behavioral responses [44]. It has been shown, for example, that by inhibiting CB_1 receptors with an antagonist, the extinction learning process is impaired [45,46], and the treatment with a $TRPV_1$ receptor agonist has a similar effect [47]. Moreover, the administration of a FAAH inhibitor facilitated the extinction learning process in wild-type mice [46]. Finally, the facilitation of CB_1 signaling by a drug that blocks FAAH and antagonizes $TRPV_1$ receptors is more potent in blocking the expression of fear conditioning than inhibiting these two targets individually, supporting the opposite role for CB_1 and $TRPV_1$ receptors in triggering fear behavior [48].

Overall, a very reductionist description of the eCB system is described here. In the past few years, several other targets of the eCB system were described, such as the G-protein-coupled receptor 55 (GPR55) and the peroxisome

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proliferator-activated receptor γ (PPARγ), which interact with eCBs and other substrates, promoting different effects. A more recent detailed review of this topic can be found in [43].

The eCB system is altered in several pathological conditions, such as cancer, gastrointestinal and cardiovascular diseases, eating disorders [49], and stress-related psychiatric conditions [39,40,50,51]. For instance, studies have shown that depressed women have decreased serum levels of AEA and 2-AG [52]. Moreover, depressed suicide victims have increased expression of CB_1 receptors in the dorsolateral PFC [53]. Finally, genetic studies have shown that polymorphisms of the CB_1 receptor have greater prevalence in depressed and anxious patients [54,55] and are correlated with treatment-resistant depression [56]. Interestingly, pharmacological studies indicate that the administration of rimonabant, a CB_1 antagonist, increases symptoms of depression and anxiety in healthy individuals [57] and that the effects of conventional antidepressant drugs depend on the eCB signaling [58].

In PTSD patients, reduced peripheral AEA levels and higher expression of CB_1 receptors in the brain are also reported [59]. Interestingly, non-PTSD individuals carrying the C385A allele of the rs324420 polymorphism, a mutation of the FAAH gene, had increased AEA levels, enhanced fear extinction [60], and lower amygdala reactivity during fear extinction recall [61]. Also, polymorphisms of the CB_2 receptor and FAAH enzyme have been associated with greater susceptibility to childhood trauma and the development of psychiatry disorders later in life [62,63]. Other polymorphisms in the eCB system, including in the CB1 receptor, are associated with fear extinction and/or PTSD [64–66].

Altogether these data suggest a strong relationship between the eCB system and psychiatry conditions. Based on the existing evidence, impaired eCB signaling in the brain, induced by stress or as consequences of polymorphisms, could be involved in the neurobiology of stress-related disorders, including depression and PTSD. Therefore, targeting these changes in the eCB system is a potential tool to improve the outcome of those disorders, potentially achieving remission in treatment-resistant patients. However, this still need further investigation. More about these discussions can be found in excellent recently published reviews [64,67,68].

Animal model studies also corroborate the involvement of eCB signaling in the development of behavioral changes related to psychiatric symptoms. For instance, CB_1 KO mice have elevated levels of depression- and anxiety-like behaviors after stress [69–72]. Moreover, these mice also have impaired fear extinction, a key feature of PTSD animal models [73]. Pharmacologically, these behavioral alterations are reproduced after chronic administration of CB_1 antagonists [74,75]. CB_1 agonists have also been shown to have antidepressant and anxiolytic effects after stress [76–78]. Furthermore, several papers reported the participation of the eCB system, particularly CB_1 receptors, promoting fear extinction facilitation in different animal models [45,46,79,80]. CB_2 participation in promoting behavioral responses seems to be more complex. The overexpression of this receptor promoted reduced levels of anxiety-like behaviors in the light-dark box and elevated plus maze in mice [81]. However, evidence shows that chronic administration of a CB_2 antagonist produces an anxiolytic effect [82]. Another study from the same group observed that the overexpression of CB_2 receptors reduced depressive-like behaviors in mice, whereas the administration of AM630, a CB_2 antagonist, induced an antidepressant effect in wild-type mice. The drug had no effect in the transgenic line [83]. Moreover, CB_2 KO mice have impaired contextual, but not cued, fear conditioning and enhanced spatial memory [84]. More studies using genetic and molecular techniques with specific cell types, such as microglia and astrocytes, are needed to investigate the interaction of CB_2 expression and activity with other signaling systems involved in mood regulation and behavior.

Multiple mechanisms involved in the physiopathology of psychiatric conditions, like major depression, anxiety, and PTSD, can be regulated by the eCB system. Therefore, the resultant effects from eCB system manipulation have been related to several molecular alterations. For example, eCBs can counteract dysregulation in neurotransmitter systems [85–87], promote neuroplasticity [88,89], and attenuate inflammatory effects [90–93] induced by stress. In mice, both genetic deletion and the antagonism of CB_1 receptors in the mPFC prolonged CORT release after stress. It has been proposed that the activation of CB_1 in mPFC GABAergic interneurons disinhibits excitatory neuronal projections that are responsible for terminating stress response [94].

A more recent proposal regarding stress consequences implies the modulation of epigenetic mechanisms in the brain to promote behavioral changes. This review will focus on the crosstalk between the eCB system and epigenetics mechanisms to modulate the stress response. Considering a general knowledge about epigenetic mechanisms are necessary to understand how they can impact the eCB system, in the next section we will give an overview about this knowledge.

Key epigenetic mechanisms in stress response

Epigenetics focuses on the interaction between the environment and genome, whereby gene expression is modulated in response to new stimuli. In the short or long term after stress experiences, several epigenetic marks can be modified to adapt the organism to the environment; these marks can even be transmitted between generations. Because of a maladaptive response, these epigenetic changes can predispose the organism to diseases. There are three major epigenetic mechanisms for the regulation of gene expression: DNA modifications, histone modifications, and interference RNAs. Below, we will briefly describe each one of them, associating them with modifications in important stress-related systems.

DNA methylation

The DNA is passive to chemical modifications that do not change the nucleotide sequence but regulate gene transcription. Among many modifications described in the literature, cytosine methylation at the 5′ position (5mC) is the most investigated. The DNA-methyltransferases (DNMTs) family of enzymes in mammals, comprising DNMT1, DNMT3a, and DNMT3b, catalyzes the reaction of a methyl group addition to a cytosine [95]. The reaction occurs mainly in CpG dinucleotides, distributed throughout the genome but more concentrated in CpG islands in promoter regions of the genes. 5mC is recognized by methyl-CpG binding proteins (MBPs), such as methyl-CpG binding protein 2 (MeCP2), commonly related to psychiatry diseases [96,97]. 5mC is usually associated with the repression of gene expression, but it also can promote gene expression activation depending on the location of the CpG island in the gene body [98]. Despite some stability, DNA methylation is a dynamic process constantly subject to reversal (demethylation) by active and passive forms. The passive form occurs through DNA damage or replication, while the active form is a process based on methyl-cytosine modifications through the ten–eleven translocation (TET) enzyme family and the activation-induced cytidine deaminase/apolipoprotein B mRNA-editing enzyme complex (AID/APOBEC) [98].

Both DNA hyper- and hypomethylation of stress-related genes are found in various neuropsychiatric and neurological diseases [99–102]. Most clinical studies focus on genes related to glucocorticoid response and serotonin neurotransmission [100,103]. The promoter region of the glucocorticoid receptor gene (NR3C1) appears to be extremely sensitive to DNA methylation. Various stressor events, including child abuse, war and genocide-related trauma, maternal depression, or violence during pregnancy, correlate with increased [104–110] and decreased [105,111,112] methylation levels in NR3C1. Methylation of NR3C1 is also altered in the post-mortem brains of suicide victims and is associated with childhood traumatic experiences [113,114]. In these works, methylation levels frequently are inversely proportional to NR3C1 expression, and low levels of GR can directly impact the feedback of glucocorticoid release and HPA activity, contributing to altered responses to stress. Regarding the serotoninergic system, the serotonin transporter gene (SLC6A4) methylation levels are related to traumatic events, child abuse, work stress, and depression [115–121], and although it does not correlate with mRNA expression in the blood of patients, the hypomethylation of SLC6A4 is proposed to be a biomarker of diagnosis and drug response to major depression [118,122].

Histones modifications

Histones are proteins that, together with DNA, make the chromatin and organize its packaging state. There are four types of histones: H2A, H2B, H3, and H4. The addition of chemical groups to amino acid residues of the histones alters their binding to DNA modulating the access of transcription factors. The addition of group acetyl, or acetylation, is a modification primarily associated with gene expression. It occurs due to the action of histone acetyltransferases (HATs) and is erased by histone deacetylases (HDACs). Histone methylation is another modification related to gene expression or repression depending on the location of the methyl group. It is catalyzed by histone methyltransferases and reversed by histone demethylases, also occurring on lysine residues [123,124].

In humans, there are only a few works exploring histone mark changes in the context of stressful experiences and neuropsychiatric diseases. In these studies, they found differences in tri-methylation of H3 at lysine 27 (H3K27me3) and at lysine 4 (H3K4me3) levels in the brains of suicide victims when it was compared between control and depressive groups [125–127]. On the other hand, in animal models, several types of stressors, such as maternal separation, social stress, restraint stress, and chronic mild stress, induce alterations in HDACs and histone acetylation/methylation levels in a global or gene-specific manner [128–130]. Interestingly, antidepressant drugs with different mechanisms of action, such as ketamine, imipramine and fluoxetine, not only ameliorate behavior alterations after the stress but also alters HDACs activity and expression, or impact levels of acetylation at specific histone residues associated with important genes related to synaptic plasticity, such as *Nr2b* and *Bdnf* genes [131–138].

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Non-coding RNAs

Micro RNAs (miRNAs), small interfering RNAs (siRNAs), long non-coding RNAs (lncRNAs), and piwi RNAs (piRNAs), along with others, are regulatory non-coding RNAs, which regulate transcription and translation processes most often through binding to mRNA [139]. Among these, miRNAs are the most characterized regarding their biogenesis and role in diseases. The binding of miRNA to complementary sequences of mRNAs induces their cleavage or, in the case of partial complementarity, induces the inhibition of translation in ribosomes [139].

miRNAs can either be regulated by stress signaling or act as a regulator of the stress response [140]. The capacity of a single miRNA to bind several mRNAs allows it to modulate entire cellular pathways, which in part explains altered levels of the same miRNA in different diseases. On stress-related diseases, it is possible to highlight some stress-regulated genes such as *Nr3c1, Bdnf, Ntrk2, Slc6a4*, and *Crhr1* [141–144], which are also found to be regulated by histone modifications and DNA methylation [145–147]. Moreover, the miRNA network regulates and is regulated by proteins related to other epigenetic processes, such as HDACs, DNMTs, and MeCP2 [148]. Due to the stability and the facility to detect changes in easily accessible tissues, such as blood and saliva, miRNAs are indicated as excellent biomarker candidates for disease and treatment responsiveness [149].

Possible crosstalk between the eCB system and epigenetic mechanisms in stress response and psychiatric disorders

(Endo)cannabinoid control of epigenetic mechanisms

Cannabis use induces epigenetic alterations, supporting a relationship between the eCB system and epigenetic mechanisms. For instance, *Cannabis*-dependent patients have reduced methylation of the CB_1 receptor gene promoter (*Cnr1*) and increased CB_1 expression in the blood [150]. The same profile of methylation and CB_1 expression was observed in peripheral blood lymphocytes of patients with schizophrenia reporting the use of *Cannabis* [151]. Moreover, prenatal *Cannabis* exposure decreased D_2 receptors mRNA in Nucleus Accumbens (NAc) and amygdala of aborted fetuses, which was replicated in an animal model. In this model, there was increased di-methylation at lysine 9 of H3 (H3K9me2), a repressive mark, and decreased H3K4me3, mentioned earlier, an enhancer mark, and RNA polymerase II at the *Drd2* gene locus [152,153], supporting the role of an epigenetic mechanism induced by *Cannabis* in decreasing D_2 expression. These changes have implications for drug addiction, which will be discussed later, and other psychiatric conditions. For instance, the chronic administration of a CB_1 agonist to adolescent male rats has been implicated in greater susceptibility to stress and anxiety-like behavior, in addition to increase DNMT and global methylation levels in the PFC of their adolescent offspring [154]. Also, paternal activation of CB_2 receptors was implicated in impaired offspring growth via reduced expression of TET enzymes and altered DNA methylation in several genes [155].

Regarding treatment with CBD, it was demonstrated that acute CBD treatment decreased immobility in mice in the forced swimming test, similar to what was observed with DNMT inhibitors (5-AzaD and RG108). Interestingly, the combination of ineffective doses of CBD and DNMT inhibitors induced similar antidepressant effects, suggesting CBD effects could be directly modulating DNMTs. In fact, all drugs prevented the swimming stress-induced reduction of the DNA methylation in the PFC and the increase in the hippocampus. However, whereas the DNMT activity was decreased by swimming stress in the PFC and increased in the hippocampus, CBD could only counteract the first in this work [156]. In contrast, the hippocampal neurodegeneration induced by iron administration in neonatal rats, which induces mitochondrial DNA methylation alterations, was reverted by treatment with chronic CBD during adulthood [157]. Finally, subacute treatment with CBD induced hypomethylation of DNMT3a in the mouse hippocampus [158], a mechanism already shown to induce gene expression related to neurogenesis [159,160]. These pieces of evidence suggest a role for DNA methylation in CBD effects in animal stress models. As described before, many of these makers are also involved in stress-related disorders, and CBD has anxiolytic/antidepressant effects in psychiatric patients [161]. Therefore, it is possible to suggest that these CBD effects may involve DNA methylation; however, there are no studies in humans with this analysis, which would be very useful for better conclusions.

Histone modifications may also be involved in effects mediated by cannabinoids. Repeated co-administration of THC and CBD increased the acetylation in lysine 9 (H3K9ac) and 14 (H3K14ac) of H3 in the ventral tegmental area of adult mice [162]. In another study, acute CBD treatment increased levels of methylation and acetylation markers H3K4me3, H3K27me3, and H3K9ac in the cerebral cortex. In contrast, it decreased H3K9ac levels in the hypothalamus and H3K4me3 in the pons in rats, demonstrating that its effects are brain area-specific [163].

Chronic unpredictable stress (CUS) increased the nuclear expression and activity of HDAC2 and decreased the expression of CB1 levels, mainly in glutamatergic neurons, in the mouse cingulated cortex. Moreover, CUS reduced the expression of H3K9ac associated with CB_1 and Neuropeptide Y (NpY) genes. They also showed that URB597, a

FAAH inhibitor, which is expected to increase anandamide levels, reverted stress effects in the *Npy* gene, but not in *Cnr1*, and anxious behavior [164]. Like stress, a $TRPV_1$ agonist (capsaicin), which increased immobility in the forced swimming test, increased HDAC2 expression in the mouse DG of the hippocampus [165] and enriched HDAC2 expression at *Dlg4*, *Syp*, *Gria1*, and *Gria2* gene promoters, all related to neuroplasticity [166]. In contrast, genetic deletion of $TRPV_1$ receptors, which induced an antidepressant-like phenotype, reduced HDAC2 levels in the same brain region and consequently increased levels of H3 and H4 global acetylation. In addition, $TRPV_1$ knockout mice, contrary to what was observed with capsaicin injection, showed increased levels of plasticity and neurogenesis-related genes in the hippocampus, in addition to being resilient to stress [166]. Therefore, considering anandamide activates CB_1 and $TRPV_1$ receptors, we suggest that the bell-shaped profile of anandamide effect on behavior may be mediated by differential effects on CB_1 and $TRPV_1$ receptors, among other mechanisms, regulating the expression and activity of HDAC2, histone acetylation levels, gene expression, and neuroplasticity.

As described before, miRNAs play an essential role in gene expression regulation, being implied in several diseases. eCB system activity, in turn, seems to regulate miRNA expression and, therefore, could impact the pathogenesis and treatment of stress-related diseases. In mice, chronic mild stress (CMS) increased expression of some miRNAs in the PFC (miR-9-5p, miR-128-1-5p, and miR-382-5p) [167] that target *Drd2*, *Clock*, *Map2k*, *Mapk1*, and *Bdnf* genes [168–170], all related to the physiopathology of depression. Moreover, CMS induced decreased expression of others miRNAs (miR-16-5p, miR-129-5p, and miR-219a-5p) [167], which target *Slc6a4*, *Htr2a*, *Bdnf*, *Grm7*, *Camk2a,* and *Camk2g* genes, which are also related to depression physiopathology and antidepressant response [168,171–174]. In the same study, stressed animals treated with anandamide showed increased expression of all these miRNAs compared with the vehicle group; the depressive-like effect of stress in the forced swimming test was reverted [167]. Moreover, early life stress-induced depressive-like behavior in rats and downregulated miR-16 in males and miR-135a in females in the mPFC. These changes were reversed when rats received a FAAH inhibitor [175].

Additionally, lower expression levels of *let-7d* miRNA were observed in the cortex and hippocampus of CB_1 knockout mice or after CB_1 knockdown in zebrafish embryos. Conversely, the knockdown of *let-7d* in zebrafish embryos increased the expression of CB_1 receptors, suggesting negative feedback in this regulation [176,177]. Moreover, *let-7d* overexpression in adult mouse hippocampus induced anxiolytic- and antidepressant-like effects [178]. Thus, it is arguable that anxiolytic and antidepressant effects induced by CB_1 activation are promoted by *let-7d* expression and that this mechanism may be impaired in psychiatric conditions, such as depression. Furthermore, the anxiolytic and antidepressant effects induced by *let-7d* increased expression may occur, between other mechanisms, by the negative regulation of dopamine D3 receptors, mu-opioid receptors, TLX, an orphan nuclear receptor, and upregulation of miR-9, regulating neuroplasticity, cellular proliferation, neuronal differentiation, and migration [178–180].

In summary, the eCB system activity regulates the expression and activity of epigenetic enzymes, such as TETs, DNMTs, and HDACs, which result in differential global and specific-site levels of DNA and histone modifications. Moreover, the eCB system is also involved in miRNA expression regulation. All these alterations change gene expression related to neurotransmission, neurogenesis, and neuroplasticity. These mechanisms, also altered by stress, may be involved in the development of psychiatric conditions; therefore, more studies are needed to better understand how they work in physiological and pathological conditions to determine if they could be targets for treating these conditions.

So far, only a few studies combine stress protocols, modulation of the eCB system, and evaluation of epigenetic output, highlighting the need for more studies addressing that combination. These studies are summarized in Table 1. How eCB system molecules modulate epigenetic factors in stress-related contexts are outlined in Figure 1A.

Epigenetic control of the endocannabinoid system

Although the relevance of the epigenetic mechanisms to the activity of the endocannabinoid system is well known [181–184], this regulation in the context of stress is less explored. The investigation of epigenetic control of the eCB system relies mainly on the regulation of *Cnr1* and *Faah* genes. This specificity can be explained by the attention these two genes receive due to their pharmacological importance in physiology and disease and their susceptibility to being regulated by epigenetic marks.

DNA methylation levels of *Cnr1*, for example, is reported to be inversely proportional to mRNA and protein expression of the gene [185–191]. *Cnr1* methylation pattern is recurrently found altered in a variety of situations, such as diet [190,192,193], patients with schizophrenia [189], and THC consumption [150]; *Cnr1* is also susceptible to demethylation by the agent 5-aza-2-deoxycytidine [194]. On the other hand, *Faah* hypermethylation is associated with alcohol consumption [195], while hypomethylation, along with an increase in mRNA and protein expression, is related to Alzheimer's disease patients [196]. Nonetheless, the methylation of *Cnr1* and *Faah* in stressful conditions

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Table 1 Studies combining stress protocol, eCB system modulation and epigenetic output in animal models

Pharmacological intervention	Sex, strain, age	Stress	Behavioral outputs	Molecular outputs	Reference
Prenatal CB1 agonist (WIN55212-2; 1.2 mg/Kg/day); from PND30 to PND49	♂ Rats, adolescent and adult	Offspring (PND60) exposed to Unpredictable stress during one week	Anxiogenic effect in the OFT induced by WIN in stressed offspring (PND68)	WIN ↑ global methylation and DNMT3a levels in the PFC of stressed offspring WIN ↑ DNMT1 levels in the PFC only in non-stressed offspring	[154]
FAAH inhibitor (URB-597; 1.0 mg/Kg/day); from the 5th to the 11th week of stress protocol	♂ mouse, 6 weeks old	CUS for eleven weeks	Not evaluated	CUS ↑ expression and activity of HDAC2 in the cingulate cortex CUS ↓ expression of H3K9ac associated with npy and cnr1 genes in the cingulate cortex URB reverted the effect of stress in the npy gene	[164]
TRPV1 KO TRPV1 KD in DG	♂ mouse, 4-5 weeks old	CUS for 14 days	CUS induced learned helplessness (LHT) in WT, but not in TRPV1 KO. Antidepressant- and anxiolytic effect of TRPV1 KO in the FST and NSFT, independent of stress exposure. TRPV1 KD in the DG mimics the TRPV1 KO phenotype in the FST	↓ HDAC2 levels in the hippocampus of TRPV1 KO ↑ H3 and H4 global acetylation levels in TRPV1 KO hippocampus ↑ expression of neuroplasticity and neurogenesis genes in TRPV1 KO hippocampus TRPV1 KD in the DG mimics the TRPV1 KO phenotype	[166]
AEA; 5 mg/Kg/day; After forced swimming pretest, 5 hours before and 1 hour after FST	♂ mouse, 3 months old	CMS for 7 weeks	CMS induced depressive-like behavior in the FST and SPT AEA ↓ the stress effect in the FST	CMS ↑ miR-9-5p, miR-128-1-5p, and miR-382-5p, and ↓ miR-16-5p, miR-129-5p, and miR-219a-5p expression in the PFC AEA ↑ expression of miR-9-5p, miR-128-1-5p, miR-382-5p, miR-16-5p, miR-129-5p, miR-219a-5p in the PFC of stressed mice	[167]
FAAH inhibitor (URB-597; 0.4 mg/Kg/day); From PND45 to PND60)	♂ and ♀ rats	ELS (from PND7 to PND 14)	ELS: ♂: ↓ distance traveled and ↑ freezing time in the OFT; ♀: ↑ freezing time in the OFT; URB treatment: ↑ SP in stressed ♂ and ♀; ↓SP in non-stressed ♀; ↑ the SR discrimination index in stressed ♂ and ♀; ↓ SR in non-stressed ♂; ↓ immobility in the FST in stressed ♂ and ♀; ↑ immobility in FST in non-stressed ♂;	URB treatment: ↑ expression of miR-135a in the mPFC and ↓ it in the LHa and DR of non-stressed ♂ and ♀; Normalized the expression of miR-135a in the mPFC of stressed ♀; ↓ expression of miR-135a in the CA1 region of non-stressed ♂; ↑ the expression of miR-135a in the CA1 region of non-stressed ♀; ↓ miR-135a expression in the DR of stressed ♀; Normalized the expression of miR-16 in the mPFC of stressed ♂; ↑ expression of miR-16 in the mPFC of non-stressed ♂ ↑ expression of miR-16 in CA1 region of non-stressed ♀ ↑ expression of miR-16 in the LHa of stressed ♂ ↓ expression of miR-16 in the LHa of non-stressed ♀; ↑ expression of miR-16 in the DR of stressed ♀;	[175]

Continued over

Table 1 Studies combining stress protocol, eCB system modulation and epigenetic output in animal models (Continued)

Pharmacological intervention	Sex, strain, age	Stress	Behavioral outputs	Molecular outputs	Reference

↑: increased; ↓: decreased; ♀: female animals; ♂: male animals; AEA, anandamide; CA1, Cornus Ammonics subfield 1 of hippocampus; CB_1 and CB_2, cannabinoid type 1 and 2 receptors; CMS, chronic mild stress; CUS, chronic unpredictable stress; DG, dentate gyrus; DNMT, DNA-methyltransferase; DR, dorsal raphe; ELS, early life stress; FAAH, fatty acid amide hydrolase; FST, forced swimming test; HDAC, histone deacetylase; KD, knockdown; KO, knockout; LHa, lateral habenula; LHT, learned helplessness test; mPFC, medial prefrontal cortex; NSFT, novelty suppressed feeding test; OFT, open field test; PFC, prefrontal cortex; PND, postnatal day; SP, sucrose preference; SPT, sucrose preference test; SR, social recognition; $TRPV_1$, transient receptor potential vanilloid type 1.

are less explored. Chronic stress induces depressive-like behavior and results in hypermethylation in *Cnr1* [188], including in several CpG islands of *Cnr1* gene in sperm of the stressed rats and in their offspring's brains [197]. In PTSD patients, the *Cnr1* gene was one of several uniquely methylated genes found in patient's PBMC [198], suggesting variations in CB_1 expression could be involved in the pathology of this disease, as well as other psychiatric diseases, as discussed in previous reviews [67,199].

Histone modifications are also found in *Cnr1* and *Faah* genes. Ethanol treatment in mice is correlated with an increase in histone acetylation marker H4K8a and *Cnr1* expression and a decrease in histone methylation marker H3K9me2 in the neocortex and hippocampus [200,201]. On the other hand, histone methylation marker H3K9me2 and mRNA expression of the *Cnr1* gene are induced at dorsal root ganglion in a model of nerve injury in mice [202]. Although no change in DNA methylation was observed in a model of binge-eating behavior, histone acetylation H3K9ac associated with the *Faah* gene and its mRNA expression decreased after frustration stress [203]. Moreover, after exposure to CUMS, histone acetylation H3K9ac decreased in the *Cnr1* gene, although its mRNA expression remained unchanged [164].

Several miRNAS are reported as modulators of genes of the eCB system, including genes of *Cnr1*, *Cnr2*, and *Faah* (Table 2). Except for the miR-let-7d, which inhibits but does not have *Cnr1* as a direct target [176], all described miRNAs have predicted pairing to their targets so far [176,192,204,205,206,207,208,209,210,211]. All these miRNAs directly bind to the transcript, inhibiting eCB-related gene expression.

Similar to what is seen in studies evaluating DNA methylation and histone modifications related to the eCB system, most works describe miRNAs regulating *Cnr1* expression in the context of stressful or psychiatric conditions. For instance, miR-128 is down-regulated in the blood of PTSD patients [224] but is up-regulated in the brain of depressed subjects [225]; however, it is also reported to increase in blood after 12 weeks of antidepressant treatment [146]. Overall, these data could suggest that miR-128 participates in disease and treatment response, but this pattern can be different depending on the psychiatric condition and the evaluated tissue. In animal models, miR-128 up-regulation is found in the amygdala, PFC, and hippocampus of stressed mice [220,225,226], which indicates it can participate in brain functions. Another miRNA, miR-301a, is also up-regulated in the brain of depressed suicide victims [227] and chronically stressed rats [228]. miR-494 findings in the blood and brain are contrasting: it was upregulated in blood of major depression patients [235] and after antidepressant treatment [146], in depression episodes [232], in a PTSD rat model [233]; however, it was downregulated in the brain of depressed suicide victims [227] or in the brain of acutely stressed rats [219]. miR-494 also had an anxiolytic effect in ethanol-exposed rats [231]. Moreover, miR-29a is up-regulated in the blood of stressed students but down-regulated in treatment-resistant depression patients [214,215]. After restraint stress, rats subjected or not to maternal separation have up-regulation of miR-29a in the amygdala and PFC [216], which is increased in the cerebral spinal fluid of MDD patients [217]; it is also increased in the frontal cortex of mice exposed to acute restraint stress [219] but decreased in the frontal cortex after chronic stress [218] and in the hippocampus 1 h after footshock stress in a fear conditioning paradigm [220]. Similarly, 1 h after fear conditioning, there was also a reduction in the miR-30b expression in the hippocampus [220], as seen after acute restraint stress [219], whereas chronic stress increases the same miR-30b in the hippocampus [223]. Another miRNA, miR-let-7d, appears to be important in various stress processes. It was reduced in the blood of MDD patients, and increased after antidepressant treatment [146,235]; its levels changed in the PFC, hypothalamus, hippocampus, and amygdala of animal models after different types of stressors [220,223,234,236]. Meanwhile, overexpression of miR-let-7d in the hippocampus has anxiolytic and antidepressant effects in mice, corroborating its function in behavior and potential impact in neuropsychiatry diseases [178]. Although there is no evidence of alterations in humans, miR-338-5p and miR-23a are altered after protocols of social stress and chronic unpredictable stress [212,223,229].

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Table 2 miRNAs related to the eCB system in animal models involving stress exposure or in psychiatric patients

Gene	miRNA	Population/Model	Sample	Results	Reference
Cnr1	MiR23a [192]	CSD susceptible mice	Hippocampus	↑	[212]
	miR-29a [204]	MS-ARS rats	mPFC	↑	[213]
		Treatment-resistant depression	Serum	↓	[214]
		Chronic academic stress students	Total blood	↑	[215]
		ARS mice	Basolateral amygdala	↑	[216]
	miR-29b [205]	MDD patients	Cerebral spinal fluid	↑	[217]
		CUMS mice	PFC	↓	[218]
		ARS mice	FC	↑	[219]
		Fear conditioning mice	Hippocampus	↓	[220]
	miR-30b [206]	MDD suicide subjects	PFC	↑	[221]
		ARS mice	FC	↑	[219]
		CSD rats	Ventral hippocampus	↑	[222]
		CUMS resilient mice	Amygdala	↓	[223]
		Fear conditioning mice	Hippocampus	↓	[220]
	miR-128 [207]	PTSD patients	Total blood	↓	[224]
		Tail shocks rats	Amygdala	↑	[225]
		Fear conditioning mice	PFC	↑	[226]
		Fear conditioning mice	Hippocampus	↑	[220]
		MDD patients after escitalopram treatment	Total blood	↑	[146]
		Depressed suicide subjects	Amygdala	↑	[225]
	miR-301[a] [192]	Depressed suicide subjects	PFC	↓	[227]
		CUMS mice	Ventral tegmental area	↓	[228]
	miR-338-5p [208]	Psychological stress susceptible mice	PFC	↑	[229]
		CUMS resilient mice	Amygdala	↓	[223]
	miR-494 [209]	Depressed suicide subjects	PFC	↓	[227]
		MDD patients	Plasma	↑	[230]
		Ethanol exposed rat overexpressing antagomiR-494	Amygdala	Anxiolytic	[231]
		MDD patients after escitalopram treatment	Total blood	↑	[146]
		MDE patients	Peripheral blood mononuclear cells	↑	[232]
		PTSD Rat model	Serum	↑	[233]
		ARS mice	FC	↓	[219]
	miRNA let-7d [176]	ARS mice	PFC	↓	[234]
		MDD patients	Total blood	↓	[235]
		MDD patients after escitalopram treatment	Total blood	↓	[146]
		PTSD mice model	PFC	↓	[236]
			Hypothalamus	↑	[236]
		Mice overexpressing miRNA let-7d	Hippocampus	Anxiolytic	[178]
				Antidepressant	[178]
		CUMS resilient mice	Amygdala	↑	[223]
		Fear conditioning mice	Hippocampus	↓	[220]
Cnr2	miR-187-3p [210]	ARS mice	Basolateral amygdala	↓	[216]
		Contextual fear conditioning mice	Dorsal hippocampus	↓	[237]
		Extinction of contextual fear conditioning mice	Basolateral amygdala	↑	[238]
		Psychological stress susceptible mice	mPFC	↓	[229]

Continued over

Table 2 miRNAs related to the eCB system in animal models involving stress exposure or in psychiatric patients (Continued)

Gene	miRNA	Population/Model	Sample	Results	Reference
		CUMS susceptible mice	Amygdala	↓	[223]
	miR-665 [209]	CUMS resilient mice	Amygdala	↑	[223]
Faah	mir-411 [211]	MS rats	Hypothalamus	↑	[239]
		MS rats	PFC	Inversely proportional to sucrose preference	[240]
		CUMS rats	Hippocampal Dentate Gyrus	↑	[241]

↑: miRNA up-regulation; ↓: miRNA down-regulation; ARS, acute restraint stress; CRS, chronic restraint stress; CSD, chronic social defeat; CUMS, chronic unpredictable mild stress; MDD, major depressive disease; mPFC, medial prefrontal cortex; MS, maternal separation; PFC, prefrontal cortex, PTSD, post-traumatic stress disorder.

These works evidence a complex control by different miRNAs, including similarities or differences among patients with different psychiatric conditions and differences in animal models involving stress exposure.

There are two miRNAs reported to modulate *Cnr2* in animal models of stress: miR-187-3p and miR-665. miR-187-3p is regulated in several stress protocols, including chronic mild stress, acute restraint stress, psychological stress, and after fear conditioning, indicating that miRNA as having an important role in stress responses in general [216,223,229,237,238]. Both acute and chronic stressors can decrease miR-187-3p expression in the amygdala, while it was up-regulated after the evaluation of extinction of conditioned fear memory [238]. Additionally, miR-665 is altered in the amygdala, being up-regulated after chronic mild stress [223]. miR-411, for the best of our knowledge, is the only FAAH miRNA regulated by stress, and it is only found regulated in animal models; it was increased in the hypothalamus, PFC, and hippocampus after maternal separation or chronic unpredictable mild stress [239–241].

eCB system genes are considerably sensitive to epigenetic control, particularly under stressful experiences, although the mechanisms are not completely elucidated. The discussed evidence highlights the importance of epigenetic mechanisms in the eCB system response to stress and in its dysfunction. For instance, histone modifications are fundamental to memory consolidation and extinction [242,243], and intervention in these processes could be key to treating trauma-related disorders. In fact, some stressors can induce histone modifications in the *Faah* and *Cnr1* genes, which can reverberate or not in mRNA expression; moreover, the histone modifications, as acetylation, is one of the proposed mechanisms for the action of antidepressant drugs [244]. Even when the gene or the protein expression is not altered, epigenetic markers can influence the gene expression pattern in response to the environment. DNA methylation and miRNA expression are already suggested as biomarkers of disorders, prognosis, treatment prediction, and response. Considering the findings with the CB_1 receptor in human and animal models, epigenetic modifications in the *Cnr1* gene are promising biomarkers in neuropsychiatry conditions [67].

Possible cross-talk between eCB system and epigenetics in drug abuse and stress

The eCB system is critical to the reward-related effects of dopamine, which is involved in the neurobiological mechanism underlying drug addiction [245]. Indeed, the modulation of the eCB system regulates molecular and behavioral responses promoted by distinct addictive drugs, including psychostimulants and alcohol [246,247]. Stress is an important risk factor in the neurobiology of drug addiction [248,249]. Previous stress exposure is correlated to the vulnerability to developing the disorder and the reinstatement of drug seeking. Interestingly, behavioral and molecular evidence indicates that the eCB system is a required element in the ability of stress to modulate drug responses [250,251]. This convergence is consistent with the fact that exposure to addiction drugs promotes changes in important brain structures also involved in stress biology, such as the PFC, nucleus accumbens, hippocampus, and amygdala, which are also important targets for cannabinoids [252]. In this way, similarly to what was described for stress events, exposure to addiction drugs also modulated the eCB system, which involves epigenetic mechanisms.

For instance, cocaine self-administration (SA) promotes histone modifications and chromatin looping in the eCB system-associated genes [253]. Animals exposed to cocaine demonstrated increased H3K4me3 enrichment on the hippocampus's promotor regions of FAAH and DAGLα coding genes. Moreover, using a 4C-seq approach targeting the *Cnr1* promoter, authors also demonstrated that cocaine SA induces remodeling of chromatin loops in the hippocampus and the NAc, suggesting that 3D chromatin architecture at the *Cnr1* locus was substantially changed

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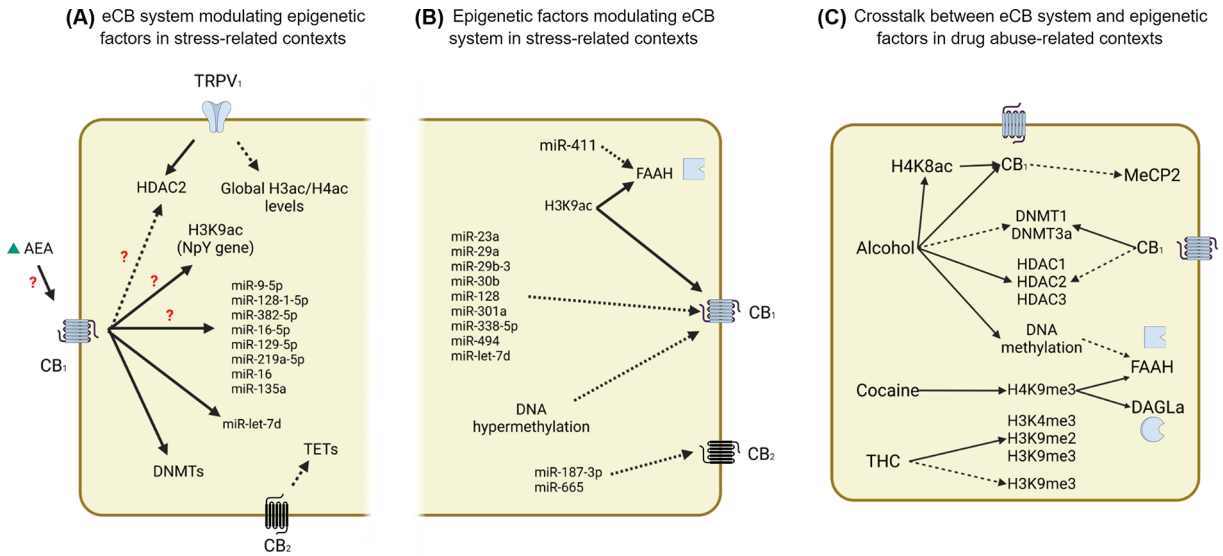

Figure 2. Mechanisms involved in the cross-talk between the eCB system and epigenetic mechanisms in stress- and drug abuse-related contexts

(**A**) In stressful contexts, interference with the eCB system can modulate a wide range of epigenetic factors. CB_1 receptors, for example, modulate the expression of DNMTs and the microRNA let-7d. Moreover, the inhibition of FAAH and consequent increase in AEA levels, which may act at CB_1 receptors, increases the expression of several miRNAs (miR-9-5p, miR-128-1-5p, miR-382-5p, miR-16-5p, miR-129-5p, miR-219a-5p, miR-16, and miR-135a) and H3K9ac levels at npy gene, and decreases the expression and activity of HDAC2. Moreover, $TRPV_1$ receptors activation increases the expression of HDAC2 and reduces global H3/H4 acetylation levels. Finally, CB_2 receptors have been shown to reduce TET enzyme levels. (**B**) Stress can regulate eCB genes through epigenetics tools. CB1 expression is reported to be sensitive to hypermethylation and increased levels of H3K9ac of the gene and affected by miRNAs (miR-23a, miR-29a, miR-29b-3, miR-30b, miR-128, miR-301a, miR-338-5p, miR-494, and miR-let-7d). FAAH expression may also be altered by H3K9ac and the miR-411. Furthermore, CB2 is one target of miR-187-3p and miR-665 expression. (**C**) The cross-talk between the systems in the context of drug abuse is very diversified since drugs with different mechanisms of action promote different alterations. For example, alcohol increases H4K8ac in the CB1 gene, and its protein expression is related to the down-regulation of MeCP2. Alcohol also down-regulates DNMT1 and DNMT3a and upregulates HDAC1, HDAC2, and HDAC3, and all these effects are blocked by CB1 antagonism. Moreover, DNA methylation of the FAAH gene is affected by alcohol exposure. Cocaine consumption is reported to increase H4K9me3 in FAAH and DAGLα genes. Regarding exposure to cannabinoids, THC induces global levels of H3K4me3 and H3K9me2 and can increase or decrease H3K9me3 depending on the exposure. More details about these mechanisms can be found in the main text. Dashed arrows indicate inhibition or reduction. Continuous arrow indicate induction or increase. Question mark indicates that the CB1 involvement after FAAH inhibition was not directed tested.

following cocaine exposure [253]. Pieces of evidence also have demonstrated that the eCB system undergoes epigenetic modulation by alcohol, as briefly mentioned before. A blind epigenome-wide analysis of datasets that explored hazardous drinkers and binge drinkers versus controls evidenced that *Faah* hypermethylation is associated with alcohol consumption [195]. Accordingly, an elevation in the expression of CB_1 associated with increased H4K8ac at the *Cnr1* promoter was observed in adult mice exposed to alcohol on postnatal day 7 (PD7) [254]. These results provide evidence that epigenetic mechanisms contribute to altered regulation of the eCB system in response to specific abuse drugs.

Interestingly, epigenetic changes promoted by exposure to alcohol also appear to be modulated by the eCB system. Nagre and colleagues observed that treatment with ethanol in PD7 mice impaired DNA methylation through reduced DNA methyltransferases (DNMT1 and DNMT3A) levels; these effects were reversed by the blockade of CB_1 before ethanol treatment [255]. Similarly, alcohol exposure at the PD7 was associated with enhanced HDAC1, HDAC2, and HDAC3 expression, which was also prevented by administering a CB_1 receptor antagonist before alcohol exposure [256]. Moreover, using a similar protocol, another study demonstrated that exposure to ethanol activates the apoptotic caspase-3 enzyme via CB_1 in neonatal mice and causes a reduction in MeCP2 levels [257]. Regarding miRNA processes, a reduction in the expression of brain CB_1 was coupled with an increased complementary miR-26b in a mouse model of fetal alcohol spectrum disorders [258].

Corroborating the role of the eCB system in the regulation of drug response during development, converging pieces of evidence support that treatment with THC in early phases of development promotes epigenetic changes [259]. For instance, prenatal THC exposure significantly modifies the histone methylation profile in the NAc. Subjects exposed to THC during prenatal stage showed a decreased level of the H3K4me3 [152]. Similarly, persistent changes in H3K9, increased dimethylation and reduced trimethylation, were observed in the NAc of adult rats following adolescent THC exposure [260]. Another study observed a significant increase of H3K9me2 in the hippocampus and the amygdala of female rats exposed to THC during adolescence [261]. Moreover, using the same adolescent THC exposure, there was an enhancement in H3K9me3 in the nucleus accumbens, hippocampus, and PFC [261,262]. Preconception THC exposure also disrupts DNA methylation in the NAc, with cross-generational effects. In a study comparing rats with or without parental THC exposure, 1027 differentially methylated regions (406 hypermethylated and 621 hypomethylated) associated with parental THC exposure were found in the subsequent generation, even though they were not directly exposed to the drug [263].

Confirming the correlation between the inheritance of paternal epigenetic changes and cannabinoid exposure, developmental changes in the offspring were associated with premating paternal THC exposure [264]. Exposure to cannabinoids has also been associated with changes in sperm DNA methylation. The analysis of sperm DNA from adult rats exposed to 2 mg/kg of THC for 12 days identified 627 genes whose methylation status was altered [265]. Similarly, significant differential methylation of genes related to neurodevelopment was observed in the sperm of rats exposed to THC via oral gavage [266]. Similarly to the preclinical reports, substantial changes in both hypo- and hyper-DNA methylation, with the latter predominating, were determined in the sperm methylome of marijuana smokers [265]. The impact of cannabis exposure on DNA methylation status also was investigated directly in human spermatogenesis *in vitro*. The results revealed alterations in DNA methylation levels of genes related to autism, HCN1, and NR4A2 [267]. These studies provide compelling evidence that preconception exposure to cannabinoids can impact reproduction and paternal epigenetic inheritance, potentially leading to altered DNA methylation patterns that have an impact on gene expression and developmental outcomes in offspring.

Altogether these findings support the idea that the eCB system is involved in regulating epigenetic mechanisms and has an essential role in the effects of addictive drugs. Since this response profile also was observed with stress exposure and considering the role of stress in the neurobiology of the substance use disorder, future studies might evaluate the involvement of the eCB system in the modulation of drug addiction by stress.

Final remarks

In the last two decades, much attention was directed toward understanding how exposure to different stressors could result in long-term changes in the organism that could result in psychiatric disorders. In this context, a boom of studies evaluating epigenetic changes in animal models and a run to find epigenetic markers related to psychiatric conditions arose, bringing many new understandings in the neurobiology of psychiatric conditions.

Among several physiological systems affected by epigenetic modulation, one has, in particular, been in the spotlight of scientists for more than 20 years: the endocannabinoid system. As overviewed in this review, the eCB system has a fundamental role in controlling many functions, including the fine control of stress response and circuits involved in drug abuse. Although not fully explored, eCB system genes are sensitive to epigenetic control [183,184,268,269]. The discussed evidence highlights the importance of epigenetic mechanisms in the eCB system response to stress, drugs of abuse, and the dysfunctions caused by them. As epigenetic marks can persist, the long-term alteration in the expression of cannabinoid-related proteins may be part of triggering diseases, particularly after stressors or substance use disorder. More recently, as discussed, many studies have investigated if the behavioral consequences of exposure to stressors in animals' models could result in epigenetic regulation of the eCB system. Changes in miRNAs that regulate eCB system molecules, for example, are observed after acute protocols of stress in animal models but also in postmortem brains of depressive subjects. Epigenetic changes can persist through generations, indicating how stress and drug exposure, for example, can modify the neurobiology along the generations.

As also discussed, in animal models, cannabinoids, including THC and CBD, promote several behavioral changes related to psychiatric disorders and induce epigenetic modifications, mainly related to DNA methylation and histone modifications. Besides, *Cannabis* use in humans appears to induce epigenetic changes not only in the eCB system but also in the dopaminergic system and others, indicating a potential mechanism by which it could lead to psychiatric disorders, including substance use disorder. Finally, exposure to cannabinoids during critical periods of brain development can induce persistent brain and behavioral changes in adulthood.

As summarized in this review, therefore, there appears to have a close relationship between modulation of the eCB system and evaluation of epigenetic changes (DNA methylation, histones modifications, and miRNAs) under

stress conditions (Figure 2A) and how epigenetic markers under stress conditions, mainly miRNAs, influence the expression of eCB-related molecules (Figure 2B). Furthermore, common drugs of abuse, including alcohol, cocaine, and cannabis (THC), could promote their long-term effects by promoting epigenetic changes that impact the eCB system (Figure 2C). The elucidation of epigenetic mechanisms controlling, or being controlled by, the eCB system in stress-related disorders is essential to better understand the neurobiology of those disorders and to provide new treatment approaches. Finally, understanding the cross-talk between those systems can potentially lead to the identification of biomarkers, such as miRNAs, which could help to predict the course of the disease and treatment response.

Data Availability

Data sharing is not applicable.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

AID-APOBEC, activation-induced cytidine deaminase/apolipoprotein B mRNA-editing enzyme complex; ARS, acute restraint stress; AEA, anandamide; BLA, basolateral amygdala; CA, Ammon's horn/Cornus Ammonics subfield; CB, cannabinoid receptor; CeA, central amygdala; CNS, central nervous system; CRS, chronic restraint stress; CSD, chronic social defeat; CUMS, chronic unpredictable mild stress; D2, dopamine receptor D2; DG, dentate gyrus; DAGL, diacylglycerol lipase; DNMT, DNA methyltransferase; eCB, endocannabinoid; FAAH, fatty acid amide hydrolase; GABA, gamma-aminobutyric acid; GC, glucocorticoid; GPR55, G protein-coupled receptor 55; GR, glucocorticoid receptor; HAT, histone acetyltransferase; HDAC, histone deacetylase; HPA, hypothalamus-pituitary-adrenal; IL, infralimbic; MAGL, monoacylglycerol lipase; MBP, methyl-CpG binding protein; MDD, major depressive disease; MeCP2, methyl CpG binding protein 2; MeA, medial amygdala; miRNA, micro RNA; mPFC, medial prefrontal cortex; MS, maternal separation; NAc, nucleus accumbens; NAPE-PLD, N-acyl phosphatidylethanolamine phospholipase D; NpY, neuropeptide Y; NR3C1, glucocorticoid receptor gene; PBMC, peripheral blood mononuclear cell; PD7, postnatal day 7; PFC, prefrontal cortex; PKA, protein kinase A; PL, prelimbic; PPARγ, peroxisome proliferator-activated receptor gamma; PTSD, post-traumatic stress disorder; SA, self-administration; SLC6A4, solute carrier family 6 member 4; TET, ten-eleven translocation enzyme; TRPV1, vanilloid receptor 1; 2-AG, 2-arachidonoylglycerol; 5mC, cytosine methylated at the 5′ position.

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