Wang *et al. Ageing Neur Dis* 2023;3:16
DOI: 10.20517/and.2023.19

Ageing and Neurodegenerative Diseases

Review

Open Access

Cannabinoid modulations of pain- and stress-related circuits

Ying Wang[1], Qingyu Wang[2], Li Tang[3], Xia Zhang[1]

[1]Institute of Neuropsychiatric Diseases, The Affiliated Hospital of Qingdao University, Qingdao University, Qingdao 266071, Shandong, China.
[2]Department of anesthesiology, The Affiliated Hospital of Qingdao University, Qingdao 266000, Shandong, China.
[3]Qingdao Institute of Measurement Technology, Qingdao 266000, Shandong, China.

Correspondence to: Dr. Ying Wang, Prof. Xia Zhang, Institute of Neuropsychiatric Diseases, Qingdao University, No.308 Ningxia Road, Qingdao 266071, Shandong, China. E-mail: wangying@qdu.edu.cn; Xia.Zhang@qdu.edu.cn

How to cite this article: Wang Y, Wang Q, Tang L, Zhang X. Cannabinoid modulations of pain- and stress-related circuits. *Ageing Neur Dis* 2023;3:16. https://dx.doi.org/10.20517/and.2023.19

Received: 12 Jun 2023 **First Decision:** 31 Jul 2023 **Revised:** 12 Aug 2023 **Accepted:** 23 Aug 2023 **Published:** 25 Aug 2023

Academic Editor: Weidong Le **Copy Editor:** Dong-Li Li **Production Editor:** Dong-Li Li

Abstract

In the past decade, significant advancements have been made in understanding the brain regions and neuronal circuits regulating neurological behaviors. The endocannabinoid (eCB) system, which is ubiquitously distributed in the brain and extensively involved in synaptic modulation, has been believed to play potential roles in neuronal circuit processes and related disorders. Although eCB-based pharmacological studies have made some clinical achievements, they still often encounter conflicting reports or undesired effects due to global manipulation of manifold brain regions and neuronal circuits, which impede the therapeutic application of eCB-based medications. In this review, we are devoted to discussing the versatile forms of eCB-mediated synaptic plasticity and dissecting currently well-studied specific cannabinoid circuits involved in behavioral domains which are closely linked to the organism's survival and life quality, such as pain perception and stress-related emotion disorders. By gaining new insights into selective cannabinoid control in circuits, we can potentially mitigate the drawbacks of traditional pharmacology and facilitate the development of precision medicine with novel therapeutic strategies and drug discoveries.

Keywords: Cannabinoid circuit, endocannabinoids, cannabinoid receptor, pain, mental illness

INTRODUCTION

The Cannabis sativa herb is a famous medicine plant with a long history, indicating the crucial role of cannabinoid signaling in health and disease[1]. In the past decades, variable studies have confirmed that the endocannabinoid (eCB) system is widely involved in neurological behaviors and disorders[2]. Additionally, eCB-based medications, such as cannabinoid type 1 (CB1) receptor antagonists or eCB hydrolase inhibitors, have shown considerable potential for clinical use. However, traditional pharmacological methods always modulate the eCB system in the whole brain without subarea or cell-specificity, which limits their therapeutic purposes. For example, rimonabant, a CB1 receptor antagonist, was clinically used in Europe to treat obesity from 2006, but was suspended from the market in 2008 because of side effects with anxiety and depression[3]. These indicated that the role of eCB system in brain depends on their involved brain regions and cell-type specific neuronal circuits, and global manipulation by eCB-based drugs might induce manifold function. Therefore, it is of great significance to decipher the cannabinoid circuit mechanisms underlying neurological disorders, and target components of the eCB system in specific neuronal circuits to avoid the risk of traditional pharmacological therapies.

The eCB system classically includes eCBs, cannabinoid receptors, and metabolic enzymes for eCB synthesis and degradation [Figure 1]. The CB1 receptor is widely expressed in the brain[4] and modulates the release of multiple neurotransmitters[5-7]. Recent studies have also further focused on the function of subcellular CB1 receptors, including mitochondrial CB1 receptors[8]. It has been reported that mitochondrial and plasma membrane CB1 receptors might drive multimodal behaviors, where striatonigral mitochondrial CB1 drives catalepsy while striatonigral plasma membrane CB1 receptors enable antinociception, which is of great interest[9]. Cannabinoid type 2 (CB2) receptors were traditionally considered as "peripheral cannabinoid receptors"[10]. However, in recent years, brain functional CB2 receptors have been gradually identified both in activated microglia during neuroinflammation[11] and in a small number of neurons[12,13], which deserves further investigation. The well-studied eCBs are 2-arachidonoyl glycerol (2-AG) and N-arachidonoylethanolamine (AEA), which are synthesized on demand in an activity-dependent manner and mediate retrograde signals[14]. The most enzymatic synthesis of 2-AG and AEA occur separately via diacylglycerol lipase α (DAGL-α) and N-acyl-phospholipase D (NAPE-PLD), and the main degradation enzymes for 2-AG and AEA are monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH), respectively[15]. In most brain regions, the eCB system mediates the retrograde depression of both excitatory and inhibitory synaptic transmission, so that bi-directionally modulates neural circuits with either decreasing or increasing effects.

The synthesis process of eCBs is in the postsynaptic neurons and the hydrolase process of eCBs is in the presynaptic terminals. Release of eCBs from postsynaptic neurons retrogradely acts on presynaptic terminals to inhibit the release of neurotransmitters from presynaptic terminals via Gi/o-coupled cannabinoid type 1 receptors (CB1Rs). CB1Rs are also expressed in the outer mitochondrial membrane (mtCB1R). CB1R on astrocytes is Gq-coupled. Cannabinoid type 2 receptors (CB2Rs) are recently proved to be expressed on microglial cells in the brain.

It has been well recognized that eCB signaling modulates synaptic activity of those neuronal circuits contributing to pain perception and emotion processing, which has attracted extraordinary attention. Several excellent reviews have discussed these issues in the past few years[16]. Thus, in order to avoid redundancy, this review will provide an update on recent new insights to address the selective cannabinoid circuit mechanisms underlying pain and stress. We discuss the role of the eCB system in both physiological and pathological states. Moreover, we expect to address their potentiation for clinic therapy and to define issues worth further exploration.

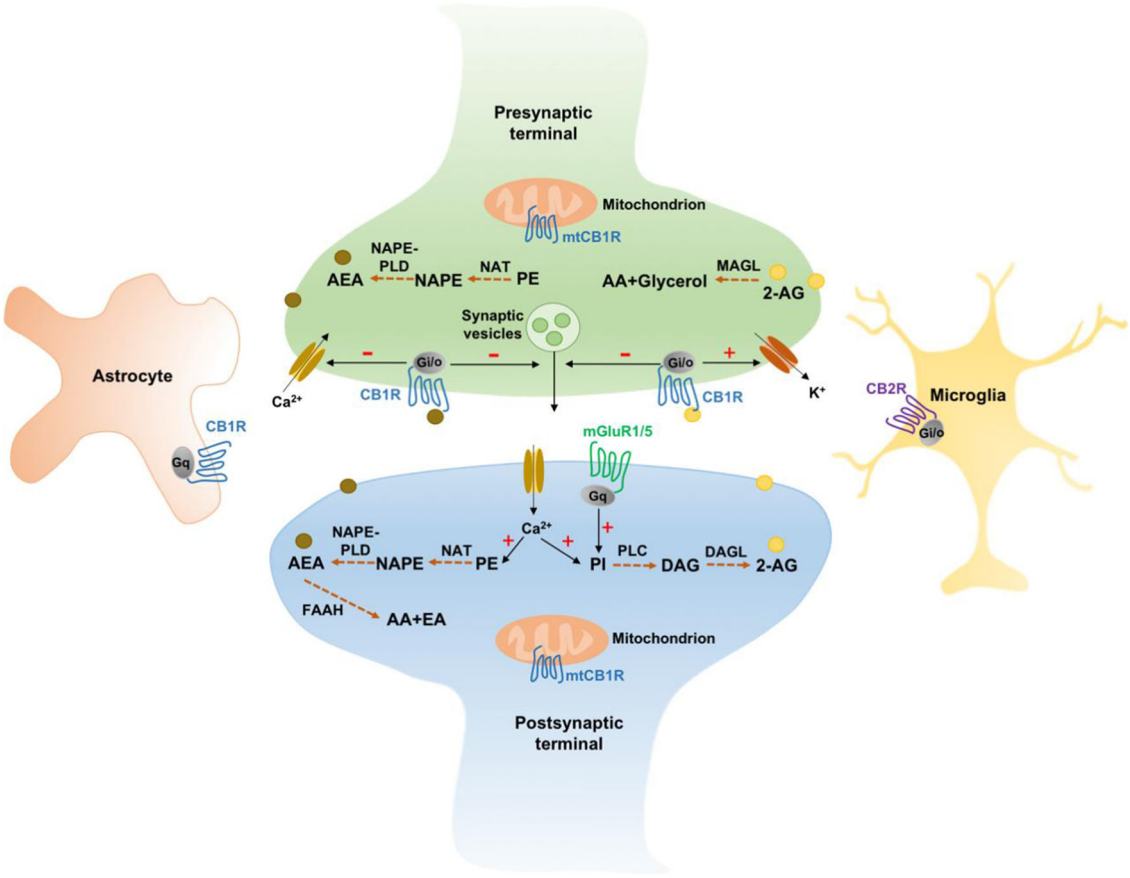

Figure 1. Schematic diagram of the endocannabinoid system. AA: arachidonic acid; AEA: N-arachidonoylethanolamine; CB1R: cannabinoid type 1 receptor; CB2R: cannabinoid type 2 receptor; DAG: diacylglycerol; DAGL: diacylglycerol lipase; EA: ethanolamine; FAAH: fatty acid amide hydrolase; NAPE: N-acyl phosphatidylethanolamine; NAPE-PLD: N-acyl-phospholipase D; NAT: N-acyltransferase; mtCB1R: mitochondrial membrane; MAGL: monoacylglycerol lipase; PE: phosphatidyl ethanolamine; PI: phosphatidyl; PLC: phospholipase C; 2-AG: 2-arachidonoyl glycerol.

CANNABINOID MODULATION OF SUPRASPINAL PAIN-RELATED CIRCUITS

Chronic pain, which afflicts more than 20% of the global population, is one of the most common complaints people go to the doctor with and remains challenging to treat[17]. Although opioid-based therapy is already widely used in pain control, its adverse effects and withdrawal reactions are intractable. Recently, cannabinoids have emerged as attractive alternatives for pain therapy, with a number of clinical and preclinical studies proving their analgesic effects over the past few decades[18,19]. CB1 receptors are 10-fold more prevalent as compared to μ-opioid receptors in the central nervous system, and they are widely distributed in pain-related circuits[20]. Although cannabinoids are not as efficacious as opioids in reducing acute pain[21], they appear to be more effective in chronic pain states[22]. For example, delta-9-tetrahydrocannabinol (Δ9-THC), a partial CB1 receptor agonist, can relieve chronic pain that is often refractory to conventional analgesics[18]. The synthetic cannabinoid ajulemic acid, a synthetic derivative of Δ9-THC-11-oic acid, which is a main metabolite of Δ9-THC, could also alleviate neuropathic pain[23]. Moreover, other compounds in cannabis, such as terpenes, also showed promising therapeutic effects in modern pain management[24]. However, cannabinoid drugs are therapeutically limited with side effects because of cross roles[25]. Therefore, selective cannabinoid circuit control is crucial for precise pain modulation. With the development of technologies for circuit dissection, the eCB-based pain modulatory circuits are beginning to be deciphered. For example, it has been verified that the CB1 receptors in principle

neurons, but not GABAergic neurons, cortical glutamatergic neurons or D1-expressing neurons, contribute to the analgesic effect of THC[26]. Notably, cannabinoid analgesia involves multiple pain-modulating pathways, including peripheral nociceptors and their ascending pathway, descending pathway, and central circuits. Although studies using conditional CB1-KO and CB2-KO mice indicate that the peripheral nociceptors and their ascending spinal mechanisms may play a more important role than supraspinal mechanism in mediating cannabinoid analgesic effects[27], and peripheral neuronal and lymphoid CB2 receptors could protect neuropathic pain without psychotropic effects[28], we cannot ignore the recent development in eCB-based supraspinal modulation of pain. Therefore, to avoid repeating reviews about peripheral mechanisms of cannabinoid analgesia, we expect to focus on the eCB-based supraspinal pain-related circuits [Figure 2].

The cannabinoid-based antinociception in the descending PAG-RVM-spinal system is via GABA disinhibition, which suppresses GABAergic afferent inputs in the PAG or RVM and activates the descending circuit. Similarly, in the mPFC, BLA and Po, activation of CB1 receptors could also inhibit pain via GABA disinhibition. Moreover, in the ACC, AEA-induced activation on CB1 receptors could reduce inflammatory pain-related behaviors, but the underlying cell-type specific circuit needs further investigation.

Descending pain modulatory pathway

The anatomical loci and eCB mechanisms have been well studied in the descending pain modulatory circuit, which includes periaqueductal grey (PAG), rostral ventromedial medulla (RVM), and projections to the spinal cord[29]. Activation of the descending PAG-RVM-spinal system, either from within the PAG, RVM or higher central nucleus, could elicit analgesia by inhibiting ascending nociceptive transmission at the spinal cord level. Particularly, the PAG and RVM are rich in CB1 receptors, and they have been regarded as major sites mediating the analgesic action of eCB-based drugs. It was reported that microinjection of cannabinoid agonists directly into the PAG or RVM elicited analgesia, which could be blocked in the presence of a CB1 receptor antagonist[30,31]. The cannabinoid-based antinociception is thought to occur via GABA disinhibition, which suppresses GABAergic afferent inputs in the PAG or RVM and activates the descending circuit[32]. For example, electroacupuncture could both activate postsynaptic glutamatergic neurons and inhibit presynaptic GABAergic neurons in the ventrolateral PAG (vlPAG) via CB1 receptors to exert antinociceptive effects, and specifically knock-out of CB1 receptors on presynaptic GABAergic terminals in the vlPAG abolished the electroacupuncture effect on pain hypersensitivity[33]. Of note, the transient receptor potential vanilloid-1 (TRPV1) channel-mediated modulation of presynaptic glutamatergic synaptic transmission in the PAG-RVM-spinal system could not be neglected. CB1 receptors mediate the inhibition of presynaptic glutamate release and elicit hyperalgesic action, while TRPV1 channels, which also could be activated by cannabinoids, mediate the activation of presynaptic glutamate release and elicit analgesic action[34]. Therefore, the future cannabinoid-based therapy targeting PAG-RVM-spinal system for pain control is expected to realize neuronal and receptor specificity to avoid the manifold modulation and conflicting results induced by non-specific pharmacologic treatment. Moreover, some forms of stress-induced analgesia, such as that associated with conditioned fear, also require activation of the descending PAG-RVM-spinal system and are cannabinoid-dependent[35]. It was reported that the stress-induced activation of postsynaptic type 5 metabotropic glutamate receptors (mGlu5) and diacylglycerol lipase-α (DGL-α) to trigger local retrograde 2-AG signaling acting at presynaptic CB1 receptors in the dorsolateral PAG (dlPAG) could exert analgesia[36]. To sum up, the eCB-based descending PAG-RVM-spinal system is a crucial circuit for pain modulation and stress-induced analgesia.

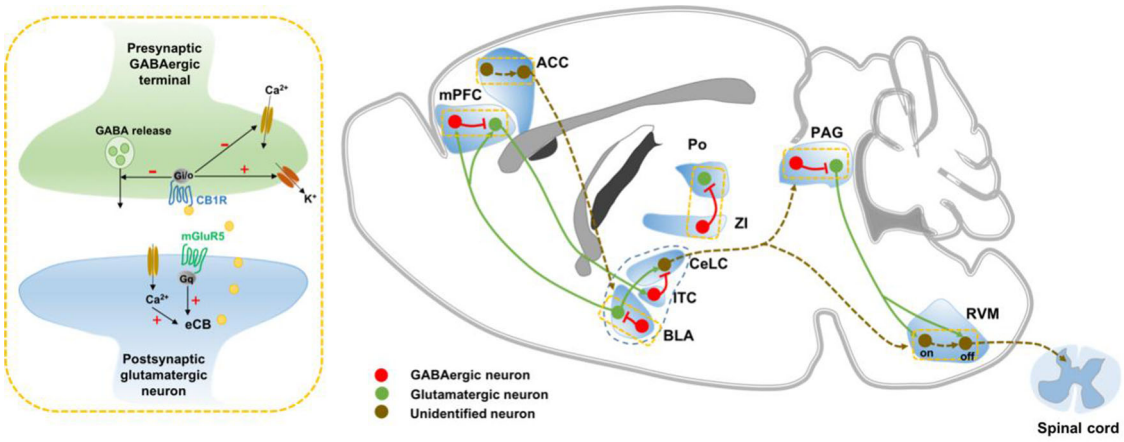

Figure 2. Cannabinoid modulation of pain-related circuits. ACC: Anterior cingulate cortex; BLA: basolateral amygdala; CB1R: cannabinoid type 1 receptor; CeLC: the laterocapsular division of the central nucleus; eCB: endocannabinoid; GABA: gamma-aminobutyric acid; ITC: the intercalated cell mass of the amygdala; mPFC: medial prefrontal cortex; PAG: periaqueductal grey; Po: the posterior complex of the thalamus; RVM: rostral ventromedial medulla; ZI: zona incerta.

Central pain modulatory circuits

The eCB-based central circuits for pain modulation remain less characterized. According to the expression of CB1 receptors in the pain-related regions, prefrontal cortex, amygdala, and thalamus have attracted more interest here.

Medial prefrontal cortex

In the medial prefrontal cortex (mPFC), CB1 receptors are exclusively expressed in GABAergic interneurons which synapse on mPFC pyramidal cells[37], and activation of CB1 receptors can inhibit synaptic inhibition of pyramidal cells, that is, disinhibition of pyramidal cells. mPFC dysfunction with decreased pyramidal cell activity and impaired mGluR5-driven eCB signaling was found in models of both inflammatory and neuropathic pain[38,39]. Restoring eCB signaling could rescue impaired postsynaptic mGluR5 function in the mPFC to overcome abnormal synaptic inhibition and increase mPFC pyramidal output, hence inhibiting pain behaviors[40]. Moreover, mPFC interacts closely with the amygdala which is also crucial in pain modulation[41]. For one thing, the basolateral amygdala (BLA) pyramidal cells target not only mPFC pyramidal cells to mediate excitation, but also mPFC interneurons to induce feedforward inhibition[42]. Abnormally enhanced feedforward inhibition at the BLA-mPFC circuit is related to decreased mPFC pyramidal output in inflammatory pain[40]. For another, mPFC pyramidal neurons project to a cluster of GABAergic neurons in the intercalated cell mass (ITC) of the amygdala, which subsequently inhibit pain-related amygdala output neurons[43]. Rescue of mGluR5-driven eCB signaling in the mPFC could inhibit abnormally enhanced amygdala output in pain. The interactions between mGluR5 and the eCB system for pain modulation also exist in the dlPAG as mentioned above.

Amygdala

Of note, amygdala also has a high density of CB1 receptors mainly distributing in the terminals of cholecystokinin (CCK)-positive interneurons and contributes to the production of cannabinoid-induced antinociception[44]. Intra-BLA administration of cannabinoid receptor agonists WIN55,212-2 could induce antinociception effects that were reversed by a CB1 receptor antagonist AM251[45]. The amygdala appears to modulate nociceptive responses by activating a descending antinociceptive pathway through the descending PAG-RVM-spinal system[41,46]. In addition, the endogenous fatty acid amide, N-palmitoylethanolamide (PEA) in the anterior cingulate cortex (ACC) could reduce inflammatory pain-related behavior, possibly via

increased AEA-induced activation on CB1 receptors and reduction of neuronal activity in the BLA[47], but the neuronal types involved in the ACC-BLA circuit was not identified. Moreover, the CB1 receptors in the ACC-BLA glutamatergic projections have been reported to regulate drinking behavior[48], which further enhances the importance of neuronal types involved in different behaviors.

Zona incerta

Besides the well-known eCB-based pain-related brain circuits, recent studies have demonstrated some novel circuits. The posterior complex of the thalamus (Po) is a higher-order somatosensory nucleus. It could respond to noxious stimuli and its aberrant activity is related to nocifensive behaviors. Po is a unique region that lacks local GABAergic interneurons and mainly receives GABAergic projections from zona incerta (ZI). Wang *et al.* found that pharmacological activation of CB1 receptors at Zl-Po GABAergic terminals specifically increased the pain threshold and ameliorated chronic pain[49].

CANNABINOID MODULATION OF STRESS-RELATED EMOTIONAL CIRCUITS

In addition to pain, emotion is also closely linked to the organism's survival and life quality, and they often reinforce each other. Meanwhile, cannabinoid modulation in pain and emotion seems to share circuit mechanisms. Therefore, we further review the cannabinoid modulation of stress-related emotional circuits in the following part.

Emotional disorders affect 9%-20% of people worldwide, and a major environmental factor eliciting the lifetime prevalence of emotion disorders is cumulative life stressors[50,51]. Exposure to prolonged periods of stress and maladaptive stress coping have been reported to impact emotional processing and provoke the episodes of mental illness[51], such as anxiety and major depression, which are associated with high levels of mortality and incredible physical burden[52]. Therefore, figuring out the mechanisms underlying stress adaptation is critical for emotion disorders-related therapy. The eCB system is closely integrated within stress and emotional neural circuits, indicating that it might be crucial in the maintenance of stress adaptation and the emotional manifestations of stress[51]. For example, cannabis has been used for centuries for its mood-elevating and stress-reducing properties, predominantly via THC activating the CB1 receptors[53]. However, blockade of the CB1 receptors by the weight-reducing drug rimonabant exerts undesirable psychiatric side effects, such as depression[3]. Moreover, chronic *in vivo* augmentation of 2-AG levels could substantially reverse the anxiety-like phenotype induced by repeated restrain stress[54]. FAAH inhibitors, such as URB597, could also modulate emotion by enhancing AEA-related activation of CB1 receptors in certain emotion-related brain areas[55]. It should be noted, however, that chronic augmentation of 2-AG by inhibition of MAGL causes physical dependence, impaired eCB-mediated synaptic plasticity and CB1 receptor desensitization, which potentially limit its therapeutic potential[56]. These effects do not appear to be produced by increasing AEA with chronic inhibition of FAAH[57]. Moreover, a recent randomized clinical trial has further demonstrated that the FAAH inhibitor, JNJ-42165279, could dampen the neural response to anxiety-related processing in healthy male subjects[58]. Although eCB-based pharmacological studies have made some achievements, they still often encounter conflicting reports. For example, a number of studies have suggested CB1 receptor antagonists as potential therapeutic targets for major depressive disorders, which has been reviewed by Witkin *et al.*[50]. Unspecific global manipulation without clear circuit mechanisms impedes the therapeutic application of eCB-based medications. Thus, the adaptive changes in neural circuits accompanied by emotional disorders should be identified, such as cortex, forebrain, hippocampus, amygdala, hypothalamus, and so on[59]. Here, we aimed to review the key brain regions and circuits participating in the eCB-mediated stress responses and stress-related emotional disorders, mainly focusing on the cannabinoid modulation of presynaptic neurotransmitter release in distinct brain regions and circuits [Figure 3].

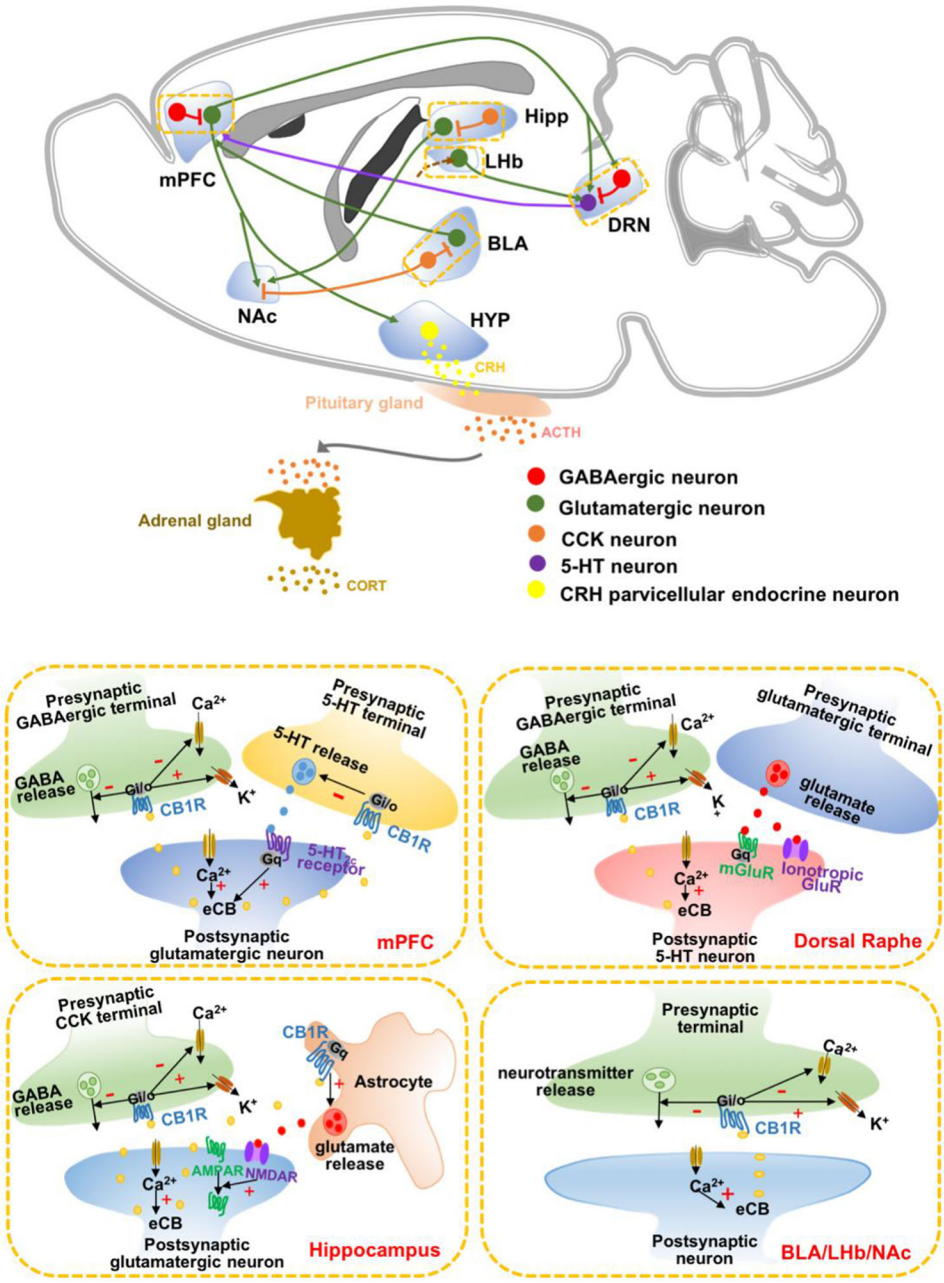

Figure 3. Cannabinoid modulation of stress-related circuits. AMPAR: α-amino-3-hydroxy-5-methyl-isoxazole propionic acid receptor; BLA: basolateral amygdala; CB1R: cannabinoid type 1 receptor; CCK: cholecystokinin; CRH: corticotropin-releasing hormone; DRN: dorsal raphe nucleus; eCB: endocannabinoid; GABA: gamma-aminobutyric acid; Hipp: hippocampus; HYP: hypothalamus; LHb: lateral habenular nucleus; mPFC: medial prefrontal cortex; NAc: nucleus accumbens; NMDAR: N methyl D asparate receptor 1; 5-HT: 5-hydroxytryptamine.

In the mPFC, eCB-mediated circuits modulate stress and emotion mainly via monoaminergic systems and HPA axis. For one thing, stress stimulates mPFC-projecting serotonergic neurons in DRN and promotes 5-HT release in mPFC, which further increases the production of 2-AG via activation of postsynaptic 5-HT_{2c} receptors. Then, 2-AG could retrogradely stimulate presynaptic CB1 receptors and inhibit 5-HT release. Acute 5-HT stimulation causes anxiety by stimulation of 5-HT_{2c} receptors. Chronic elevation of extracellular 5-HT concentration has an antidepressant effect by downregulating 5-HT_{2c} receptors and other

5-HT receptors. For another, stress-induced release of glucocorticoid could increase eCB signaling within the mPFC, and then activate CB1 receptors on GABAergic neurons to disinhibit mPFC glutamatergic projection neurons, in turn terminates the release of glucocorticoid, which further prevent the stress-induced emotion disorders. In the BLA, eCB could inhibit the presynaptic inhibitory inputs, disinhibit BLA pyramidal neurons, and prevent anxiety-like behaviors. Selective inhibition of the NAc-projecting BLA CCK terminals by cannabinoids could induce antidepressant-like effects. In the LHb, activation of CB1 receptors could restore the impaired LFS-LTD by acute stress exposure and decrease the susceptibility to depression. In the hippocampus, eCB could not only activate GABAergic presynaptic CB1R to produce pro-depressant effects on acutely stressed mice or antidepressant effects on chronically stressed mice, but also activate astroglia CB1R to induce antidepressant effects on acutely stressed mice without significant effects on chronically stressed mice.

The prefrontal cortex

The prefrontal cortex (PFC) is closely involved in emotion, especially depression[60,61]. Clinic studies have identified dysfunction in the PFC and its linked brain regions in patients with major depression[62], including decreased glucose metabolism and reduced neuronal activity and volume[63,64], but treatment of depression seems to reverse some of these deficits[65]. Therefore, the PFC might be a critical area involved in eCB-based emotional brain circuitry.

According to the literature, eCB-mediated PFC circuits modulate stress and emotion mainly via monoaminergic systems and HPA axis. For one thing, monoaminergic systems, including 5-hydroxytryptamine (5-HT), dopamine (DA), and norepinephrine, have been reported to be a potential target for depression treatment[66]. Therefore, most studies focused on the role of PFC-related monoaminergic pathways in depression, particularly 5-HT pathways[67]. The dorsal raphe nucleus (DRN) is rich in serotonergic neurons releasing 5-HT[68]. Stress stimulates mPFC-projecting serotonergic neurons in DRN and promotes 5-HT release in mPFC, which further increases the production of 2-AG via activation of postsynaptic 5-HT2c receptors[69]. Then, 2-AG could retrogradely stimulate presynaptic CB1 receptors and inhibit 5-HT release. Moreover, the top-down control exerted by the mPFC over the DRN is also of particular importance in stress processing and depression. mPFC directly projects to both serotoninergic and GABAergic neurons in the DRN, and mainly mediates a GABAergic feedforward inhibition on DRN 5-HT neurons. Interestingly, specific eCB-mediated synaptic inhibition targeting DRN GABAergic neurons was uncovered to favor the excitation of 5-HT neurons by mPFC axons[70]. For another, activation of projection neurons from the mPFC is necessary for the termination of the hypothalamic-pituitary-adrenal (HPA) axis activity[71]. Glucocorticoid release induced by stress could also increase eCB signaling within the mPFC, and subsequently activate CB1 receptors on GABAergic neurons to disinhibit mPFC glutamatergic projection neurons, which in turn terminates the release of glucocorticoid[72]. Thus, eCB signaling could suppress stress-induced glucocorticoid release by inhibiting GABAergic transmission in the mPFC, which further prevents stress-induced emotion disorders.

In addition to modulating PFC-related monoaminergic transmission during stress, CB1 receptors also regulate glutamate release and plasticity at PFC-BLA synapses to promote extinction after stress. It has been reported that eCB signaling at mPFC-BLA synapses dynamically tracks extinction learning and mutation of CB1 receptors in PFC-BLA terminals could impair extinction memory formation[73]. Moreover, chronic exposure to Δ9-THC during adolescence could inhibit the expression and function of NMDA receptors in the mature PFC neuronal dendrites, which might cause emotional disorders in teens[74]. These results indicated that eCB system might be a therapeutic target for both stress-related emotion disorders and extinction-deficient disorders via multiple circuits and neurotransmissions.

Amygdala

The amygdala is also critically involved in stress responses and aversive emotions[75-77]. Exposure to acute stress could reduce the level of AEA in the amygdala, which subsequently enables the activation of the HPA axis and increases glucocorticoid release. Additionally, increased synthesis of the eCBs and subsequent activation of Cnr1, a cannabinoid receptor, in the amygdala is generally known to mediate fear extinction, potentially via inhibition of the anxiogenic neuropeptide CCK and/or modulation of the GABAergic system[78]. Of several anatomically and functionally distinct nuclei, CB1 receptors are particularly abundant in the BLA, a central node mediating stress and anxiety[79]. In the BLA, CB1 receptors are mainly expressed in CCK-positive interneurons[80,81] and 2-AG preferentially inhibits presynaptic GABAergic transmission to disinhibit BLA pyramidal neurons[82], which might project to other brain regions, such as mPFC, and further modulate emotion[83]. Increased phasic 2-AG-mediated synaptic suppression in BLA also promotes stress adaptation[84]. Moreover, augmenting amygdala AEA also promotes stress coping in humans[57]. Gene deletion or pharmacological inhibition of FAAH, a degradation enzyme of AEA, could prevent dendritic hypertrophy in BLA and decrease anxiety-like behaviors. In addition, intra-BLA administration of FAAH inhibitors could rescue stress-related deficient fear extinction[75]. The above results all suggest restoring deficient eCB signaling in BLA as a target to resist stress. Furthermore, BLA dysfunction has also been clinically implicated in depression. It was demonstrated that selective inhibition of the NAc-projecting BLA CCK terminals by intra-NAc administration of synthetic cannabinoids sufficiently produced antidepressant-like effects[85]. Moreover, amygdala cannabinoids also control stress-related behaviors, such as eating disorders. It has been reported that CB1 receptors in central nucleus of amygdala (CeA)-parabrachial nucleus (PBN) inhibitory projections could induce long-term depression and mediate fear-induced feeding suppression. Dysfunction of CB1 receptors in CeA neurons could prevent such stress-related eating disorders[86].

Hippocampus

Hippocampal dysfunction is a common pathological feature in emotion deficits[87]. The CB1 receptors in hippocampus are also highly expressed in CCK-positive terminals[88], and mediate disinhibition of glutamatergic projection neurons which further control mesolimbic regions, such as the NAc, and underline hippocampal-mediated emotion disorders[89,90]. Acute stress induced by acute exposure to glucocorticoids increases eCB modulation of GABA, whereas chronic stress induced by prolonged exposure to glucocorticoids reduces CB1 receptors and eCBs in the hippocampus, indicating a biphasic effect of stress on eCB system in the hippocampus[91]. Moreover, a low dose of MAGL inhibitors could induce antidepressant effects on acute stress-exposed mice but not on chronic stress-exposed mice, through long-term depression (LTD) of excitatory glutamatergic synapses in hippocampus probably mediated by CB1 receptors in astroglial cells and postsynaptic glutamate receptors[92]. In contrast, a high dose of MAGL inhibitors could produce pro-depression effects on acutely stressed mice, but antidepressant effects on chronic corticosterone-exposed mice, through disinhibition of GABAergic synapses mediated by GABAergic presynaptic CB1 receptors in hippocampus[92]. The above results indicate MAGL inhibitors as a new class of rapid-acting and long-lasting antidepressants[92].

In addition, multiple cannabinoid signaling cascades in the hippocampus have been reported to modulate neuropsychiatric behaviors. For example, CB1 receptor agonists could activate the mammalian target of rapamycin (mTOR) signaling, the activation of which is required for rapid antidepressant action of NMDA receptor antagonist ketamine. It was reported that chronic unpredictable mild stress decreased eCB-mTOR signaling in the hippocampus and further induced depressive-like behaviors, whereas MAGL inhibitor JZL184 could produce antidepressant-like effects by enhancing hippocampal eCB-mTOR signaling[93]. These results indicated that the eCB-mTOR signaling pair might mediate the antidepressant-like effect of MAGL inhibitors. Moreover, the growth-associated protein of 43 kDa (GAP43) has been reported to be a synapse

type-specific regulatory partner of CB1 receptors that could hamper CB1 receptors-mediated effects on hippocampal circuit function, such as convulsion[94]. Then, excitatory mossy cells (MCs) in the hippocampus express high levels of CB1 receptors, which could inhibit excitatory MCs inputs into dentate granule cells (GCs) via βγ signaling during induction and via αi/o signaling before induction in the form of presynaptic metaplasticity[95]. In addition, NECAB1 and NECAB2 have been newly found distributed as predominant calcium-binding proteins in CB1/CCK-positive interneurons, which needs functional investigation[96]. Therefore, the interaction between CB1 receptors with intracellular proteins in different neuronal types might diversely modulate neuropsychiatric behaviors, which deserves further investigation.

Habenula

Habenula has emerged as an appealing therapeutic target for stress-related emotion disorders, partly because of its unique position at the center of the mesolimbic stress/reward circuit[97,98]. Habenula has been divided into two subregions, including medial habenula (MHb) and lateral habenula (LHb). Both of these two subregions show a robust eCB system, which modulates local synaptic transmission during stress.

The MHb receives sole identified GABAergic inputs from the medial septum and nucleus of the diagonal band (MSDB), and the MSDB-MHb GABAergic inputs express obvious CB1 receptors. It has been reported that MHb neurons could release 2-AG and retrogradely inhibit presynaptic GABA release from MSDB, and this eCB-mediated depolarized-induced suppression of inhibition (DSI) could be blocked by MAGL. Moreover, manipulation of CB1 receptors or MAGL in MSDB-MHb GABAergic inputs could bidirectionally regulate anxiety- and depressive-like behaviors, which might be a potential mechanism underlying cannabinoid anxiolytic and antidepressant effects[99].

The LHb receives inputs from the basal ganglia and limbic system, and sends outputs to midbrain dopaminergic in the ventral tegmental area (VTA) and serotoninergic neurons in the DRN, which have been implicated in the behavioral response to stress[100]. CB1 receptors are widely expressed in the LHb, not only on presynaptic but also on postsynaptic, astrocytic, and mitochondrial membranes. Slice electrophysiology experiments have recently shown that a CB1 receptor-dependent decrease in presynaptic neurotransmitter release mediated the low-frequency stimulation (LFS)-induced LTD (LFS-LTD) in LHb synapses. Acute stress exposure selectively impaired LFS-LTD and greatly facilitated the induction of LTP in the LHb[101]. Therefore, stress exposure may facilitate LTP while masking LTD in the LHb, leading to the abnormal potentiation of LHb synapses overall, which has been suggested to mediate depression-like behaviors. Pharmacological activation of CB1 receptors could restore LTD in the LHb, which may reverse the stress exposure-induced imbalanced bidirectional synaptic plasticity and contribute to determining the threshold for the onset of depression[101]. However, contrary to the above report, it is also shown that exposure to chronic stress increases the 2-AG level and burst firing in the LHb, while CB1 receptors blockade in LHb promotes proactive coping strategies in the forced swimming test and reduces anxiety-like behavior in the elevated plus maze[100]. Thus, chronic stress enhances eCB signaling in the LHb, while disruption of stress-induced eCB signaling could promote a more proactive strategy that favors exploration over avoidance. An alternative explanation for the two discrepant reports is that the CB1 receptors mediating LFS-LTD or stress-coping are located on different presynaptic terminals and modulate different synaptic neurotransmission, and they have different responsiveness under various conditions. Following studies further found that eCB could simultaneously depress GABA release via circuit-specific presynaptic CB1 receptors and potentiate glutamate release via astrocytic CB1 receptors, which suggested a potential cellular mechanism underlying eCB-mediated activation of LHb neurons and subsequent anxious- and depressive-like states[102]. Therefore, future studies might be helpful to explore the relative roles of eCB system in gating excitatory and inhibitory transmission from both neuronal and glial cells in the LHb.

CONCLUSION

As outlined in this review, the eCB system is characterized as a synaptic circuit breaker with highly conserved molecular architecture throughout the central nervous system. Although some eCB-mediated circuit mechanisms underlying neurological behaviors and disorders have been reviewed above, most of the presently available evidence depends on the local pharmacological studies with agonists and antagonists of cannabinoid receptors or eCB metabolic enzymes, which cannot directly demonstrate the precise causality among eCB, specific circuits and behaviors. Therefore, new technological approaches are urgently needed to address the limitation. The advent of optogenetics and pharmacogenetics has allowed the investigation of the direct causal relationship between the activity of specific circuits and behaviors in freely moving animals[103,104]. However, the technology for cell-type manipulation of eCB system components in specific circuits and synapses is still under development. The good news is that eCB sensor has been developed and it can dynamically monitor the release of eCB in specific circuits and certain behavioral conditions[105], which greatly promoted the study of circuit mechanisms underlying cannabinoid effects. We expect that the technology for cell-type manipulation of eCB system components in specific circuits is not far away. Moreover, the pivotal role of astroglia CB1 receptors, peripheral CB1 receptors and CB2 receptors in the regulation of neurobiological processes can not be neglected[101]. It has been known that astrocytes express low levels of Gq-coupled CB1 receptors[11]. Contrary to the neuronal CB1 receptors that mediate suppression of neurotransmitter release from presynaptic terminals, astroglia CB1 receptors seem to potentiate gliotransmitter release, especially glutamate, which might profoundly influence synaptic activity and brain function[106,107]. Additionally, the deletion of CB2 receptors has a relation with emotion disorders[108]. The M4-mediated antipsychotic-like effect was found to require CB2 receptor signaling[109]. Therefore, selective manipulation of CB2 receptor-mediated circuits might be a potential treatment of neurological processes. In addition, CB1 receptors are also present in peripheral and modulate multiple functions[110]. For instance, microinjection of highly selective CB1 agonists such as arachidonoyl-2-chloroethylamide into the affected paw of low doses of cannabinoids caused analgesia[111]. Moreover, CB1 receptors are expressed in adipocytes, where their activity modulates the expression and release of adiponectin, an adipokine that promotes energy expenditure[112]. Selective targeting of peripheral CB1 receptors might help to minimize the psychoactive effects in the case of clinical use of CB1 agonists. Therefore, it is worthy of further investigation about eCB-mediated modulation of the periphery and their potential therapeutic value in related disorders.

In the end, this review not only provides a better understanding of eCB-mediated synaptic plasticity, but also raises future therapeutic interventions to tackle related disorders, which makes the study of the eCB system a highly fascinating aspect of neuroscience. There is no doubt that future research will surely bring new and exciting discoveries and concepts in the next decades.

DECLARATIONS

Authors' contributions

Performed the literature search and wrote the manuscript: Wang Y, Wang Q, Tang L
Initiated the concept, gave administrative supervision, and helped edit this manuscript: Zhang X

Availability of data and materials

Not applicable.

Financial support and sponsorship

This work was supported by Grants from the National Natural Science Foundation of China (81830035, 82003729) and the Natural Science Foundation of Shandong Province (ZR2020QH357, ZR2019ZD35).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

REFERENCES

1. Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids as novel therapeutic agents in CNS disorders. *Pharmacol Ther* 2012;133:79-97. DOI PubMed
2. Xue B, Zhang X, Wang Y. Bench to bedside: Multiple facets of cannabinoid control in epilepsy. *Neurochem Int* 2020;141:104898. DOI
3. Hill MN, Gorzalka BB. Impairments in endocannabinoid signaling and depressive illness. *JAMA* 2009;301:1165-6. DOI PubMed
4. Howlett AC, Barth F, Bonner TI, et al. International union of pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev* 2002;54:161-202. DOI PubMed
5. Nakazi M, Bauer U, Nickel T, Kathmann M, Schlicker E. Inhibition of serotonin release in the mouse brain via presynaptic cannabinoid CB_1 receptors. *Naunyn-Schmiedeberg's Arch Pharmacol* 2000;361:19-24. DOI PubMed
6. Maejima T, Ohno-Shosaku T, Kano M. Endogenous cannabinoid as a retrograde messenger from depolarized postsynaptic neurons to presynaptic terminals. *Neurosci Res* 2001;40:205-10. DOI PubMed
7. Schlicker E, Kathmann M. Modulation of transmitter release via presynaptic cannabinoid receptors. *Trends Pharmacol Sci* 2001;22:565-72. DOI PubMed
8. Skupio U, Welte J, Serrat R, et al. Mitochondrial cannabinoid receptors gate corticosterone impact on novel object recognition. *Neuron* 2023;111:1887-97.e6. DOI
9. Soria-Gomez E, Pagano Zottola AC, Mariani Y, et al. Subcellular specificity of cannabinoid effects in striatonigral circuits. *Neuron* 2021;109:1513-26.e11. DOI
10. Buckley NE, McCoy KL, Mezey E, et al. Immunomodulation by cannabinoids is absent in mice deficient for the cannabinoid CB_2 receptor. *Eur J Pharmacol* 2000;396:141-9. DOI PubMed
11. Stella N. Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas. *Glia* 2010;58:1017-30. DOI PubMed PMC
12. Van Sickle MD, Duncan M, Kingsley PJ, et al. Identification and functional characterization of brainstem cannabinoid CB_2 receptors. *Science* 2005;310:329-32. DOI PubMed
13. Zhang HY, Gao M, Liu QR, et al. Cannabinoid CB_2 receptors modulate midbrain dopamine neuronal activity and dopamine-related behavior in mice. *Proc Natl Acad Sci U S A* 2014;111:E5007-15. DOI PubMed PMC
14. Castillo PE, Younts TJ, Chávez AE, Hashimotodani Y. Endocannabinoid signaling and synaptic function. *Neuron* 2012;76:70-81. DOI PubMed PMC
15. Kilaru A, Chapman KD. The endocannabinoid system. *Essays Biochem* 2020;64:485-99. DOI PubMed
16. Lutz B, Marsicano G, Maldonado R, Hillard CJ. The endocannabinoid system in guarding against fear, anxiety and stress. *Nat Rev Neurosci* 2015;16:705-18. DOI PubMed PMC
17. Coghill RC. The distributed nociceptive system: a framework for understanding pain. *Trends Neurosci* 2020;43:780-94. DOI PubMed PMC
18. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. *JAMA* 2015;313:2474-83. DOI PubMed
19. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015;313:2456-73. DOI
20. Aggarwal SK. Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain* 2013;29:162-71. DOI PubMed
21. Martin BR, Lichtman AH. Cannabinoid transmission and pain perception. *Neurobiol Dis* 1998;5:447-61. DOI PubMed
22. Donvito G, Nass SR, Wilkerson JL, et al. The endogenous cannabinoid system: a budding source of targets for treating inflammatory and neuropathic pain. *Neuropsychopharmacology* 2018;43:52-79. DOI PubMed PMC
23. Foadi N, Berger C, Pilawski I, et al. Inhibition of voltage-gated Na^+ channels by the synthetic cannabinoid ajulemic acid. *Anesth Analg* 2014;118:1238-45. DOI PubMed

24. Liktor-Busa E, Keresztes A, LaVigne J, Streicher JM, Largent-Milnes TM. Analgesic potential of terpenes derived from cannabis sativa. *Pharmacol Rev* 2021;73:98-126. DOI PubMed
25. Mlost J, Wąsik A, Starowicz K. Role of endocannabinoid system in dopamine signalling within the reward circuits affected by chronic pain. *Pharmacol Res* 2019;143:40-7. DOI PubMed
26. Monory K, Blaudzun H, Massa F, et al. Genetic dissection of behavioural and autonomic effects of Δ^9-tetrahydrocannabinol in mice. *PLoS Biol* 2007;5:e269. DOI PubMed PMC
27. Agarwal N, Pacher P, Tegeder I, et al. Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. *Nat Neurosci* 2007;10:870-9. DOI PubMed PMC
28. Cabañero D, Ramírez-López A, Drews E, et al. Protective role of neuronal and lymphoid cannabinoid CB_2 receptors in neuropathic pain. *Elife* 2020;9:e55582. DOI PubMed PMC
29. Bouchet CA, Ingram SL. Cannabinoids in the descending pain modulatory circuit: role in inflammation. *Pharmacol Ther* 2020;209:107495. DOI PubMed PMC
30. Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. *Nature* 1998;395:381-3. DOI PubMed
31. Lau BK, Drew GM, Mitchell VA, Vaughan CW. Endocannabinoid modulation by FAAH and monoacylglycerol lipase within the analgesic circuitry of the periaqueductal grey. *Br J Pharmacol* 2014;171:5225-36. DOI PubMed PMC
32. Lau BK, Vaughan CW. Descending modulation of pain: the GABA disinhibition hypothesis of analgesia. *Curr Opin Neurobiol* 2014;29:159-64. DOI PubMed
33. Zhu H, Xiang HC, Li HP, et al. Inhibition of GABAergic neurons and excitation of glutamatergic neurons in the ventrolateral periaqueductal gray participate in electroacupuncture analgesia mediated by cannabinoid receptor. *Front Neurosci* 2019;13:484. DOI PubMed PMC
34. Kawahara H, Drew GM, Christie MJ, Vaughan CW. Inhibition of fatty acid amide hydrolase unmasks CB_1 receptor and TRPV1 channel-mediated modulation of glutamatergic synaptic transmission in midbrain periaqueductal grey. *Br J Pharmacol* 2011;163:1214-22. DOI PubMed PMC
35. Olango WM, Roche M, Ford GK, Harhen B, Finn DP. The endocannabinoid system in the rat dorsolateral periaqueductal grey mediates fear-conditioned analgesia and controls fear expression in the presence of nociceptive tone. *Br J Pharmacol* 2012;165:2549-60. DOI PubMed PMC
36. Gregg LC, Jung KM, Spradley JM, et al. Activation of type 5 metabotropic glutamate receptors and diacylglycerol lipase-α initiates 2-arachidonoylglycerol formation and endocannabinoid-mediated analgesia. *J Neurosci* 2012;32:9457-68. DOI PubMed PMC
37. Wedzony K, Chocyk A. Cannabinoid CB1 receptors in rat medial prefrontal cortex are colocalized with calbindin- but not parvalbumin- and calretinin-positive GABA-ergic neurons. *Pharmacol Rep* 2009;61:1000-7. DOI PubMed
38. Ji G, Neugebauer V. CB1 augments mGluR5 function in medial prefrontal cortical neurons to inhibit amygdala hyperactivity in an arthritis pain model. *Eur J Neurosci* 2014;39:455-66. DOI PubMed PMC
39. Zhang Z, Gadotti VM, Chen L, Souza IA, Stemkowski PL, Zamponi GW. Role of prelimbic GABAergic circuits in sensory and emotional aspects of neuropathic pain. *Cell Rep* 2015;12:752-9. DOI PubMed
40. Kiritoshi T, Ji G, Neugebauer V. Rescue of impaired mGluR5-driven endocannabinoid signaling restores prefrontal cortical output to inhibit pain in arthritic rats. *J Neurosci* 2016;36:837-50. DOI PubMed PMC
41. Maire JJ, Close LN, Heinricher MM, Selden NR. Distinct pathways for norepinephrine- and opioid-triggered antinociception from the amygdala. *Eur J Pain* 2016;20:206-14. DOI PubMed PMC
42. Ji G, Sun H, Fu Y, et al. Cognitive impairment in pain through amygdala-driven prefrontal cortical deactivation. *J Neurosci* 2010;30:5451-64. DOI PubMed PMC
43. Ren W, Kiritoshi T, Grégoire S, et al. Neuropeptide S: a novel regulator of pain-related amygdala plasticity and behaviors. *J Neurophysiol* 2013;110:1765-81. DOI PubMed PMC
44. Manning BH, Martin WJ, Meng ID. The rodent amygdala contributes to the production of cannabinoid-induced antinociception. *Neuroscience* 2003;120:1157-70. DOI
45. Hasanein P, Parviz M, Keshavarz M, Javanmardi K. CB1 receptor activation in the basolateral amygdala produces antinociception in animal models of acute and tonic nociception. *Clin Exp Pharmacol Physiol* 2007;34:439-49. DOI PubMed
46. McGaraughty S, Heinricher MM. Microinjection of morphine into various amygdaloid nuclei differentially affects nociceptive responsiveness and RVM neuronal activity. *Pain* 2002;96:153-62. DOI PubMed
47. Okine BN, Madasu MK, McGowan F, et al. N-palmitoylethanolamide in the anterior cingulate cortex attenuates inflammatory pain behaviour indirectly via a CB_1 receptor-mediated mechanism. *Pain* 2016;157:2687-96. DOI
48. Zhao Z, Soria-Gómez E, Varilh M, et al. A novel cortical mechanism for top-down control of water intake. *Curr Biol* 2020;30:4789-98.e4. DOI
49. Wang H, Dong P, He C, et al. Incerta-thalamic circuit controls nocifensive behavior via cannabinoid type 1 receptors. *Neuron* 2020;107:538-51.e7. DOI
50. Witkin JM, Tzavara ET, Davis RJ, Li X, Nomikos GG. A therapeutic role for cannabinoid CB_1 receptor antagonists in major depressive disorders. *Trends Pharmacol Sci* 2005;26:609-17. DOI PubMed
51. Gorzalka BB, Hill MN, Hillard CJ. Regulation of endocannabinoid signaling by stress: implications for stress-related affective disorders. *Neurosci Biobehav Rev* 2008;32:1152-60. DOI PubMed

52. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:617-27. DOI PubMed PMC
53. Hindley G, Beck K, Borgan F, et al. Psychiatric symptoms caused by cannabis constituents: a systematic review and meta-analysis. *Lancet Psychiatry* 2020;7:344-53. DOI PubMed PMC
54. Sumislawski JJ, Ramikie TS, Patel S. Reversible gating of endocannabinoid plasticity in the amygdala by chronic stress: a potential role for monoacylglycerol lipase inhibition in the prevention of stress-induced behavioral adaptation. *Neuropsychopharmacology* 2011;36:2750-61. DOI PubMed PMC
55. Gobbi G, Bambico FR, Mangieri R, et al. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proc Natl Acad Sci U S A* 2005;102:18620-5. DOI PubMed PMC
56. Schlosburg JE, Blankman JL, Long JZ, et al. Chronic monoacylglycerol lipase blockade causes functional antagonism of the endocannabinoid system. *Nat Neurosci* 2010;13:1113-9. DOI PubMed PMC
57. Gunduz-Cinar O, MacPherson KP, Cinar R, et al. Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity. *Mol Psychiatry* 2013;18:813-23. DOI PubMed PMC
58. Paulus MP, Stein MB, Simmons AN, Risbrough VB, Halter R, Chaplan SR. The effects of FAAH inhibition on the neural basis of anxiety-related processing in healthy male subjects: a randomized clinical trial. *Neuropsychopharmacology* 2021;46:1011-9. DOI PubMed PMC
59. Rubino T, Guidali C, Vigano D, et al. CB1 receptor stimulation in specific brain areas differently modulate anxiety-related behaviour. *Neuropharmacology* 2008;54:151-60. DOI
60. Vinod KY, Hungund BL. Role of the endocannabinoid system in depression and suicide. *Trends Pharmacol Sci* 2006;27:539-45. DOI PubMed
61. Covington III HE, Lobo MK, Maze I, et al. Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex. *J Neurosci* 2010;30:16082-90. DOI PubMed PMC
62. Sibille E, Arango V, Galfalvy HC, et al. Gene expression profiling of depression and suicide in human prefrontal cortex. *Neuropsychopharmacology* 2004;29:351-61. DOI
63. Drevets WC. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. *Prog Brain Res* 2000;126:413-31. DOI PubMed
64. Geuze E, Vermetten E, Bremner JD. MR-based *in vivo* hippocampal volumetrics: 2. findings in neuropsychiatric disorders. *Mol Psychiatry* 2005;10:160-84. DOI PubMed
65. Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur Neuropsychopharmacol* 2002;12:527-44. DOI PubMed
66. Mann JJ. Neurobiology of suicidal behaviour. *Nat Rev Neurosci* 2003;4:819-28. DOI PubMed
67. Dayan P, Huys QJ. Serotonin in affective control. *Annu Rev Neurosci* 2009;32:95-126. DOI PubMed
68. Pollak Dorocic I, Fürth D, Xuan Y, et al. A whole-brain atlas of inputs to serotonergic neurons of the dorsal and median raphe nuclei. *Neuron* 2014;83:663-78. DOI
69. Lazary J, Juhasz G, Hunyady L, Bagdy G. Personalized medicine can pave the way for the safe use of CB_1 receptor antagonists. *Trends Pharmacol Sci* 2011;32:270-80. DOI PubMed
70. Geddes SD, Assadzada S, Lemelin D, et al. Target-specific modulation of the descending prefrontal cortex inputs to the dorsal raphe nucleus by cannabinoids. *Proc Natl Acad Sci U S A* 2016;113:5429-34. DOI PubMed PMC
71. Crowe MS, Nass SR, Gabella KM, Kinsey SG. The endocannabinoid system modulates stress, emotionality, and inflammation. *Brain Behav Immun* 2014;42:1-5. DOI PubMed
72. Hill MN, McLaughlin RJ, Pan B, et al. Recruitment of prefrontal cortical endocannabinoid signaling by glucocorticoids contributes to termination of the stress response. *J Neurosci* 2011;31:10506-15. DOI PubMed PMC
73. Gunduz-Cinar O, Castillo LI, Xia M, et al. A cortico-amygdala neural substrate for endocannabinoid modulation of fear extinction. *Neuron* 2023:S0896-6273(23)00482-8. DOI PubMed
74. Pickel VM, Bourie F, Chan J, Mackie K, Lane DA, Wang G. Chronic adolescent exposure to Δ9-tetrahydrocannabinol decreases NMDA current and extrasynaptic plasmalemmal density of NMDA GluN1 subunits in the prelimbic cortex of adult male mice. *Neuropsychopharmacology* 2020;45:374-83. DOI PubMed PMC
75. Gunduz-Cinar O, Hill MN, McEwen BS, Holmes A. Amygdala FAAH and anandamide: mediating protection and recovery from stress. *Trends Pharmacol Sci* 2013;34:637-44. DOI PubMed PMC
76. LeDoux J. The emotional brain, fear, and the amygdala. *Cell Mol Neurobiol* 2003;23:727-38. DOI PubMed
77. Jenniches I, Ternes S, Albayram O, et al. Anxiety, stress, and fear response in mice with reduced endocannabinoid levels. *Biol Psychiatry* 2016;79:858-68. DOI
78. Bowers ME, Ressler KJ. Interaction between the cholecystokinin and endogenous cannabinoid systems in cued fear expression and extinction retention. *Neuropsychopharmacology* 2015;40:688-700. DOI PubMed PMC
79. Ganon-Elazar E, Akirav I. Cannabinoid receptor activation in the basolateral amygdala blocks the effects of stress on the conditioning and extinction of inhibitory avoidance. *J Neurosci* 2009;29:11078-88. DOI PubMed PMC
80. McDonald AJ. Expression of the type 1 cannabinoid receptor (CB1R) in CCK-immunoreactive axon terminals in the basolateral amygdala of the rhesus monkey (*Macaca mulatta*). *Neurosci Lett* 2021;745:135503. DOI PubMed PMC
81. Katona I, Rancz EA, Acsady L, et al. Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of

GABAergic transmission. *J Neurosci* 2001;21:9506-18. DOI PubMed PMC

82. Yoshida T, Uchigashima M, Yamasaki M, et al. Unique inhibitory synapse with particularly rich endocannabinoid signaling machinery on pyramidal neurons in basal amygdaloid nucleus. *Proc Natl Acad Sci U S A* 2011;108:3059-64. DOI PubMed PMC
83. Little JP, Carter AG. Synaptic mechanisms underlying strong reciprocal connectivity between the medial prefrontal cortex and basolateral amygdala. *J Neurosci* 2013;33:15333-42. DOI PubMed PMC
84. Bluett RJ, Báldi R, Haymer A, et al. Endocannabinoid signalling modulates susceptibility to traumatic stress exposure. *Nat Commun* 2017;8:14782. DOI PubMed PMC
85. Shen CJ, Zheng D, Li KX, et al. Cannabinoid CB_1 receptors in the amygdalar cholecystokinin glutamatergic afferents to nucleus accumbens modulate depressive-like behavior. *Nat Med* 2019;25:337-49. DOI PubMed
86. Yang B, Sanches-Padilla J, Kondapalli J, et al. Locus coeruleus anchors a trisynaptic circuit controlling fear-induced suppression of feeding. *Neuron* 2021;109:823-838.e6. DOI PubMed PMC
87. Gothelf D, Soreni N, Nachman RP, et al. Evidence for the involvement of the hippocampus in the pathophysiology of schizophrenia. *Eur Neuropsychopharmacol* 2000;10:389-95. DOI
88. Takács VT, Szőnyi A, Freund TF, Nyiri G, Gulyás AI. Quantitative ultrastructural analysis of basket and axo-axonic cell terminals in the mouse hippocampus. *Brain Struct Funct* 2015;220:919-40. DOI PubMed
89. Loureiro M, Kramar C, Renard J, Rosen LG, Laviolette SR. Cannabinoid transmission in the hippocampus activates nucleus accumbens neurons and modulates reward and aversion-related emotional salience. *Biol Psychiatry* 2016;80:216-25. DOI PubMed
90. Hwang EK, Lupica CR. Altered corticolimbic control of the nucleus accumbens by long-term Δ^9-tetrahydrocannabinol exposure. *Biol Psychiatry* 2020;87:619-31. DOI PubMed PMC
91. Wang M, Hill MN, Zhang L, Gorzalka BB, Hillard CJ, Alger BE. Acute restraint stress enhances hippocampal endocannabinoid function via glucocorticoid receptor activation. *J Psychopharmacol* 2012;26:56-70. DOI PubMed PMC
92. Wang Y, Gu N, Duan T, et al. Monoacylglycerol lipase inhibitors produce pro- or antidepressant responses via hippocampal CA1 GABAergic synapses. *Mol Psychiatry* 2017;22:215-26. DOI PubMed PMC
93. Zhong P, Wang W, Pan B, et al. Monoacylglycerol lipase inhibition blocks chronic stress-induced depressive-like behaviors via activation of mTOR signaling. *Neuropsychopharmacology* 2014;39:1763-76. DOI PubMed PMC
94. Maroto IB, Costas-Insua C, Berthoux C, et al. Control of a hippocampal recurrent excitatory circuit by cannabinoid receptor-interacting protein Gap43. *Nat Commun* 2023;14:2303. DOI PubMed PMC
95. Jensen KR, Berthoux C, Nasrallah K, Castillo PE. Multiple cannabinoid signaling cascades powerfully suppress recurrent excitation in the hippocampus. *Proc Natl Acad Sci U S A* 2021;118:e2017590118. DOI PubMed PMC
96. Miczán V, Kelemen K, Glavinics JR, et al. NECAB1 and NECAB2 are prevalent calcium-binding proteins of CB1/CCK-positive GABAergic interneurons. *Cereb Cortex* 2021;31:1786-806. DOI PubMed PMC
97. Boulos LJ, Darcq E, Kieffer BL. Translating the habenula-from rodents to humans. *Biol Psychiatry* 2017;81:296-305. DOI PubMed PMC
98. Fakhoury M. The habenula in psychiatric disorders: more than three decades of translational investigation. *Neurosci Biobehav Rev* 2017;83:721-35. DOI PubMed
99. Vickstrom CR, Liu X, Liu S, et al. Role of endocannabinoid signaling in a septohabenular pathway in the regulation of anxiety- and depressive-like behavior. *Mol Psychiatry* 2021;26:3178-91. DOI PubMed PMC
100. Berger AL, Henricks AM, Lugo JM, et al. The lateral habenula directs coping styles under conditions of stress via recruitment of the endocannabinoid system. *Biol Psychiatry* 2018;84:611-23. DOI PubMed PMC
101. Banaszkiewicz I, Biala G, Kruk-Slomka M. Contribution of CB2 receptors in schizophrenia-related symptoms in various animal models: short review. *Neurosci Biobehav Rev* 2020;114:158-71. DOI PubMed
102. Winters ND, Kondev V, Loomba N, Delpire E, Grueter BA, Patel S. Opposing retrograde and astrocyte-dependent endocannabinoid signaling mechanisms regulate lateral habenula synaptic transmission. *Cell Rep* 2023;42:112159. DOI PubMed
103. Manz KM, Coleman BC, Jameson AN, Ghose DG, Patel S, Grueter BA. Cocaine restricts nucleus accumbens feedforward drive through a monoamine-independent mechanism. *Neuropsychopharmacology* 2022;47:652-63. DOI PubMed PMC
104. Chen J, Wang Y, Chen C, et al. Activation of medial septum cholinergic neurons restores cognitive function in temporal lobe epilepsy. *Neural Regen Res* 2023;18:2459-65. DOI PubMed PMC
105. Dong A, He K, Dudok B, et al. A fluorescent sensor for spatiotemporally resolved imaging of endocannabinoid dynamics in vivo. *Nat Biotechnol* 2022;40:787-98. DOI PubMed PMC
106. Navarrete M, Araque A. Endocannabinoids potentiate synaptic transmission through stimulation of astrocytes. *Neuron* 2010;68:113-26. DOI PubMed
107. Gómez-Gonzalo M, Navarrete M, Perea G, et al. Endocannabinoids induce lateral long-term potentiation of transmitter release by stimulation of gliotransmission. *Cereb Cortex* 2015;25:3699-712. DOI
108. Ortega-Alvaro A, Aracil-Fernández A, García-Gutiérrez MS, Navarrete F, Manzanares J. Deletion of CB_2 cannabinoid receptor induces schizophrenia-related behaviors in mice. *Neuropsychopharmacology* 2011;36:1489-504. DOI PubMed PMC
109. Foster DJ, Wilson JM, Remke DH, et al. Antipsychotic-like effects of M_4 positive allosteric modulators are mediated by CB_2 receptor-dependent inhibition of dopamine release. *Neuron* 2016;91:1244-52. DOI PubMed PMC
110. Kunos G, Osei-Hyiaman D, Bátkai S, Sharkey KA, Makriyannis A. Should peripheral CB_1 cannabinoid receptors be selectively targeted for therapeutic gain? *Trends Pharmacol Sci* 2009;30:1-7. DOI PubMed PMC

111. Gutierrez T, Farthing JN, Zvonok AM, Makriyannis A, Hohmann AG. Activation of peripheral cannabinoid CB_1 and CB_2 receptors suppresses the maintenance of inflammatory nociception: a comparative analysis. *Br J Pharmacol* 2007;150:153-63. DOI PubMed PMC

112. Cota D, Marsicano G, Tschöp M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest* 2003;112:423-31. DOI PubMed PMC