# Endocannabinoid system: Role in depression, reward and pain control (Review)

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**Abstract.** Depression and pain co-exist in almost 80% of patients and are associated with impaired health-related quality of life, often contributing to high mortality. However, the majority of patients who suffer from the comorbid depression and pain are not responsive to pharmacological treatments that address either pain or depression, making this comorbidity disorder a heavy burden on patients and society. In ancient times, this depression-pain comorbidity was treated using extracts of the *Cannabis sativa* plant, known now as marijuana and the mode of action of $\Delta^9$-tetrahydrocannabinol, the active cannabinoid ingredient of marijuana, has only recently become known, with the identification of cannabinoid receptor type 1 (CB1) and CB2. Subsequent investigations led to the identification of endocannabinoids, anandamide and 2-arachidonoylglycerol, which exert cannabinomimetic effects through the CB1 and CB2 receptors, which are located on presynaptic membranes in the central nervous system and in peripheral tissues, respectively. These endocannabinoids are produced from membrane lipids and are lipohilic molecules that are synthesized on demand and are eliminated rapidly after their usage by hydrolyzing enzymes. Clinical studies revealed altered endocannabinoid signaling in patients with chronic pain. Considerable evidence suggested the involvement of the endocannabinoid system in eliciting potent effects on neurotransmission, neuroendocrine, and inflammatory processes, which are known to be deranged in depression and chronic pain. Several synthetic cannabinomimetic drugs are being developed to treat pain and depression. However, the precise mode of action of endocannabinoids on different targets in the body and whether their effects on pain and depression follow the same or different pathways, remains to be determined.

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## 1. Introduction

The most common debilitating disorders affecting society at large are pain and depression, which are the most prevalent among neurological and psychiatric disorders. Depression and pain co-exist in almost 80% of patients (1) and are associated with impaired health-related quality of life, often contributing to high mortality (2,3). It has been observed that patients suffering from inflammatory and neuropathic pain are almost 5 times more prone to develop depression or anxiety disorder as compared to the general population (4-6). However, the majority of patients who suffer from comorbid depression and pain are not responsive to pharmacological treatments that address the pain or depression, making this comorbidity disorder a heavy burden on patients and society (7). These clinical observations on the association of pain and depression have been confirmed in several animal models of depression and chronic pain based on genetics, stress, lesion, and pharmacological manipulation that show altered nociceptive response (8,9). Considering the significance of the complex interaction between pain and depression and its societal impact, a better understanding of the molecular basis for this association is needed for developing more effective therapeutics.

In ancient times, this depression-pain comorbidity was treated through the use of extracts of the *Cannabis sativa* plant, commonly known now as marijuana. Use of marijuana for addressing pain due to various reasons has become a hot topic in terms of possible addiction, drug abuse as well as regulatory issues. Although historically, the use of marijuana dates back to over 2000 BC, the biological action of the main psychoactive ingredient of marijuana, $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) has only recently been identified. The biological receptor of $\Delta^9$-THC on the cell surface has recently been identified and described (10,11). Characterization of this receptor led to understanding of the mode of action of $\Delta^9$-THC that underlies its wide spectrum of pharmacological effects, which encompass euphoria, calmness, appetite stimulation, sensory

alterations and analgesia (10,11). Identification of the first endogenous cannabinoid-like substance, anandamide, in pig brain reiterated the significance of the so-called cannabinoid receptor and its endogenous ligands in the control of a wide variety of biological activities (12). The name 'anandamide', derived from Sanskrit ('ananda' meaning bliss) is given to *N*-arachidonoylethanolamine, for its cannabinomimetic effects. Another endogenous cannabinomimetic compound known as 2-arachidonoylglycerol (2-AG) was identified (13,14). Of note, the two endocannabinoids were derivatives of arachidonic acid. Considering that these compounds are cannabinomimetic and endogenous, acting on the cannabinoid receptors, they are known as endocannabinoids.

## 2. The endocannabinoid system

Besides anandamide and 2-AG, there are other endogenously produced molecules that also likely influence the function of CB receptors. These molecules include oleamide (15), O-arachidonoyl ethanolamine, also termed virodhamine (16), 2-AG ether or noladin ether (17), and *N*-arachidonoyl-dopamine (18). However, their physiological role is not clear and thus whether they are true endocannabinoids has yet to be ascertained. In addition to $\Delta^9$-THC, almost 80 other phytocannabinoids are found in the cannabis extracts, with a structure similar to that of THC. Of these, THC is the most studied and was shown to activate cannabinoid receptor type 1 (CB1) and CB2 and affect many pathophysiological processes, including anti-nociception (19). However, because of its CB1-mediated unwanted CNS effects, the clinical utility of THC is limited (19). Subsequent studies revealed that another phytocannabinoid, cannabidiol, with very low affinity to bind to CB1 and CB2 receptors, exerts positive pharmacological effects, such as anti-anxiety, anti-epileptic, anti-bacterial, anti-inflammatory, anticancer and also anti-diabetic properties without any psychoactivity (20). Nabiximols, a cannabis extract containing THC and cannabidiol at a 1:1 ratio, has been approved for the treatment of neuropathic pain, spasticity associated with multiple sclerosis and intractable cancer pain (21). In addition to the natural cannabinoids, synthetic cannabinoids, such as dronabinol, and its analogue nabilone, have been developed to address various types of pain. For instance, dronabinol and nabilone are currently used for chemotherapy-associated emesis in Canada and USA and nabilone is indicated for anorexia associated with AIDS-related weight loss (22). In addition, findings of a clinical trial showed the efficacy of nabilone in diabetic neuropathy (23). Another synthetic drug, an antagonist/inverse agonist of CB1 receptor, rimonabant, initially approved for obesity and smoking cessation, was found to have depressive effects and was subsequently withdrawn.

*Biosynthesis of endocannabinoids.* Endocannabinoids are lipophilic molecules synthesized 'on demand' from membrane phospholipids, and released immediately, without storage in vesicles. Anandamide and 2-AG are produced at post-synaptic neurons. Anandamide is produced in a two-step process involving *N*-arachidonoylation of the membrane phospholipid, phosphatidylethanolamine, to form *N*-arachidonoyl phosphatidylethanolamine (NAPE) by a calcium-dependent *N*-acyltransferase, followed by hydrolysis
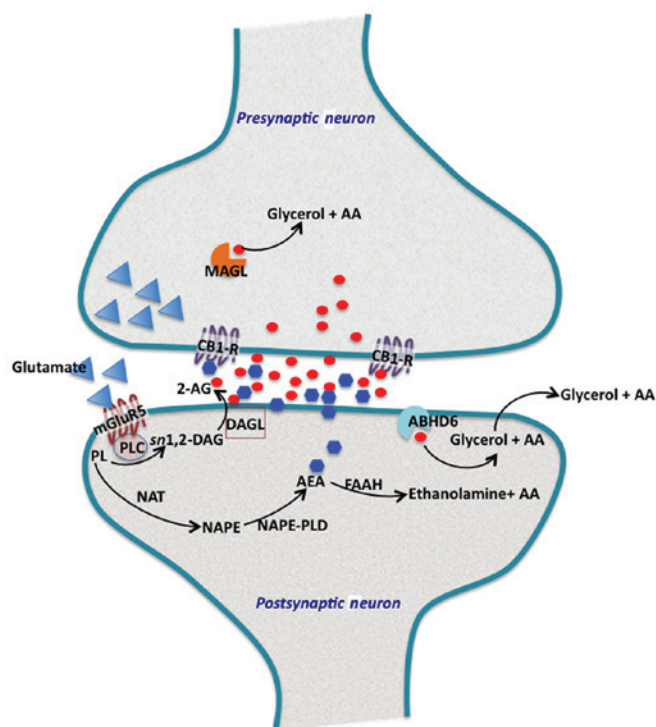


Figure 1. Endocannabinoid biosynthesis and signalling at synapse. In the perisynaptic zone of the dendritic spine, the three main proteins involved in 2-arachidonoylglycerol (2-AG) production are located in the postsynaptic neurons (28,29). Activation of mGluR5 metabotropic glutamate receptors, leads to the hydrolysis of membrane phosphatidylinositols (PL) by phospholipase C (PLC)-β to form sn1,2-diacylglycerol (sn1,2-DAG), which contains arachidonic acid at position-2. The sn1,2-DAG is then hydrolyzed by plasma membrane bound to DAG lipase-α (DAGL), to generate 2-AG. The concerted action of these protein components located proximal to each other on the postsynaptic membrane, allows for the rapid accumulation of 2-AG. 2-AG then enters the the synaptic cleft to activate cannabinoid receptor type 1 (CB1), present on the presynaptic axon terminals. 2-AG that reaches into presynaptic terminals, is hydrolyzed by monoacylglycerol lipase (MAGL). Excess 2-AG in the postsynaptic terminals is degraded by α/β hydrolase domain containing 6 (ABHD6), which is a MAG hydrolase. By contrast, arachidonoylethanolamine or anandamide (AEA) is also produced in the postsynaptic terminals by the action of *N*-acyltransferase, which synthesizes *N*-arachidonoyl phosphatidylethanolamine (NAPE). NAPE is further hydrolyzed by a specific PLD (NAPE-PLD) to generate AEA. AEA also traverses the postsynaptic membrane and reaches the CB1 receptors at the presynaptic axon terminals. Most of the excess and unused AEA is rapidly eliminated in postsynaptic terminals by fatty acid amide hydrolase (FAAH).

by a NAPE-selective phospholipase D (NAPE-PLD) to form *N*-arachidonoylethanolamine (anandamide) (24,25). Anandamide levels are regulated by its breakdown through the action of fatty acid amide hydrolase (FAAH) (26). 2-AG is synthesized in a two-step process, in which diacylglycerol (DAG) is first produced by the PLC from inositol phospholipids, followed by the hydrolysis of DAG to 2-AG by plasma membrane-associated sn1-DAG lipase (DAGL) (14). Once formed, 2-AG levels are regulated by monoacylglycerol lipase (MAGL), which accounts for ~85% of the hydrolysis and by α/β hydrolase domain containing 6 (ABHD6) and ABHD12, which also hydrolyze 2-AG to arachidonic acid and glycerol (27). In addition to hydrolysis, 2-AG is acted on by cyclooxygenase-2 (28) and lipoxygenase (29), to form prostaglandin glyceryl esters and other related bioactive compounds (Fig. 1).

Table I. Cannabinoid-based therapies to treat pain and depression.

| Condition | Cannabinoid-based drug | Outcomes for pain | Outcomes for depression and anxiety |
|---|---|---|---|
| HIV | Marijuana | ↓Muscle, nerve pain | ↓Anxiety |
| Cancer | Nabilone | ↓Pain score | ↓Overall stress |
| Fibromyalgia | Nabilone | ↓Pain | ↓Anxiety |
| Offenders with psychiatric disorders | Nabilone | ↓Pain | ↓Post-traumatic stress disorder symptoms |
| Chronic central neuropathic pain | $\Delta^9$-THC | ↓Pain and pain intensity | ↓Anxiety |
| Diabetic peripheral neuropathy | Sativex ($\Delta^9$-THC, cannabidiol) | ↓Pain | ↑Quality of life |

$\Delta^9$-THC, $\Delta^9$-tetrahydrocannabinol.

*Cannabinoid receptors.* Two subtypes of cannabinoid receptors, CB1 and CB2, have been cloned and characterized (11,30). CB1 receptors are most abundant in the central nervous system (CNS), whereas CB2 receptors are present mostly in peripheral tissues with immune functions, and most densely in the spleen (31). In the CNS, CB1 receptors are distributed densely in motor and limbic regions, in areas involved in pain transmission and modulation (e.g., periaqueductal grey, rostral ventromedial medulla, and spinal cord dorsal horn), as well as in the periphery (32). In the synapses, CB1 receptors show pre-synaptic localization on axons and terminals of neurons. The CB1 and CB2 receptors are G-protein coupled receptors of Gi/Go subtype, and mediate the inhibition of neurotransmitter release. Once released, endocannabinoids bind to CB1 receptors located in the presynaptic membrane. These CB receptors inhibit adenylate cyclase. Only CB1 receptor activation, but not that of CB2 receptors, causes blockage of voltage-dependent N- and P/Q-type calcium channels through the activation of potassium channels and mitogen-activated protein kinase. Although CB2 receptors are mostly localized in immune cells and peripheral tissues, their presence has been observed in some subsets of neurons in brain and thus these receptors likely participate in the modulation of neurotransmission (33). Endocannabinoids also bind to other receptors including transient receptor potential vanilloid 1, peroxisome proliferator-activated receptors, GPR55, and GPR119 (34-36) and this non-CB1/2 receptor activity of endocannabinoids accounts for the differential effects of certain cannabinoid agonists and pharmacological modulators of endocannabinoid tone.

Following activation of their receptors, endocannabinoids are removed from the synaptic junction/extracellular space by a process of cellular uptake and then their hydrolysis. It has been suggested that the uptake of anandamide is probably mediated via a specific 'endocannabinoid membrane transporter', which is yet to be identified (37,38). It is not clear how 2-AG uptake is mediated. Anandamide is hydrolyzed in post-synaptic neurons by FAAH, thus terminating the anandamide action at the time of its synthesis, whereas 2-AG is hydrolyzed in pre-synaptic neurons by MAGL, following CB1 receptor activation. Metabolism of anandamide by lipoxygenase and cycloxygenase enzymes yields oxygenated products with activity on non-cannabinoid targets (39).

## 3. Endocannabinoids in pain and depression

Pain is an integrative experience that involves physiological, emotional and cognitive aspects and this experience varies among individuals. Laboratory animals, on which most of basic pain research is conducted, cannot report pain and in animals, pain is generally monitored by differentiating between the subjective experience and nociception, the measurable neuronal events underlying the pain (?). Nociceptive pathways are triggered by the transduction of noxious stimuli, such as heat and mechanical injury, into neuronal action potentials by sensory afferent neurons, such as mechanoreceptors in the peripheral nervous system. These action potentials travel through the axon of the primary afferent neuron, and the cell body, to a synapse in the superficial dorsal horn of the spinal cord (41). Inputs, from several cells types within the spinal cord, are integrated and passed onto ascending pathways to the brainstem, and subsequently to the thalamus. The thalamus then transmits the signal to higher brain regions involved in the sensory (e.g., the somatosensory cortex) and emotional/affective (e.g., the amygdala and cingulate cortex) aspects of pain. Due to the cross-talk between supra-spinal nociceptive regions, incoming nociceptive signals can be either enhanced or dampened by descending modulatory pathways projecting from the brain to the spinal cord (40,41). The endocannabinoid system is distributed throughout the spinal and supraspinal regions, and thus is able to effectively regulate neurophysiological activities, including affective and nociceptive processing (42).

Clinical studies have shown altered endocannabinoid signaling in patients with chronic pain (43,44) as well as in psychiatric patients (45,46). Certain genetic polymorphisms in CB1 and CB2 receptors have been found to be associated with major depression and bipolar disorder (47,48) and resistance to treatment was observed in depression patients having a single nucleotide polymorphism in the CB1 receptor (49). Elevated components of the endocannabinoid system, including plasma 2-AG levels and CB1 and CB2 mRNA levels were observed in the lymphocytes in osteoarthritic patients, who also exhibited a positive correlation between 2-AG levels, pain and depression (50). However, whether these changes are compensatory to tackle the pain in osteoarthritis patients, is not known. Additional studies are necessary to better understand the association of endocannabinoid system and pain and depression.

Although, to the best of our knowledge, relatively few clinical studies have directly addressed the importance of endocannabinoids in pain-depression interactions, improved muscle and nerve pain by the intake of cannabis has been reported in HIV patients, who exhibited improved symptoms of depression and anxiety (51). In cancer patients, daily adjunctive administration of Cesamet (nabilone, a $\Delta^9$-THC analogue) for 30 days was found to improve overall anxiety and pain (52). The therapeutic efficacy of nabilone for pain management and quality of life improvement was demonstrated in a randomized, double-blind, placebo-controlled trial in patients with fibromyalgia (53) (Table I). Similar results were obtained in studies using $\Delta^9$-THC (dronabinol) in patients with chronic central neuropathic pain or fibromyalgia (54). The above and other studies (55-57) together indicate that depression/anxiety and pain, when present together in a variety of patients, respond to exogenously administered cannabinoids, although the underlying mechanism remains to be elucidated. It has been demonstrated that $\Delta^9$-THC-mediated reductions in pain are associated with enhanced amygdala activity and reduced functional connectivity between the amygdala and somatosensory cortex (58). Thus, the amygdala likely forms the common neural circuit and connecting link between emotional responding and pain. The precise mechanism(s) by which the endocannabinoids influence behavioral/emotional and nociceptive processing remains to be determined. At present, there is considerable evidence involving the endocannabinoid system in eliciting potent effects on neurotransmission, neuroendocrine, and inflammatory processes, which are all known to be deranged in depression and chronic pain.

## 4. Conclusions

Depression and pain co-exist in the majority of patients and often contribute to high mortality. Most patients who suffer from the comorbid depression and pain are not responsive to pharmacological treatments that address either the pain or depression, exacerbating this comorbidity disorder. Cannabinoids present in marijuana are well-known to contain pain and depression, and $\Delta^9$-THC, the active ingredient of marijuana, exerts its activity by activating CB1 and CB2 receptors. These receptors are activated by naturally present endocannabinoids, anandamide and 2-AG, which exert cannabinomimetic effects. The endocannabinoid system is involved in eliciting potent effects on neurotransmission, neuroendocrine, and inflammatory processes, which are known to be deranged in depression and chronic pain. Several synthetic cannabinomimetic drugs are being developed to treat pain and depression. However, the precise mode of action of endocannabinoids on different targets in the body and whether their effects on pain and depression follow the same or different pathways, remains to be determined in future studies.

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