Endocannabinoid System: Role in Depression, Recompense, And Pain Control (Review)

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Abstract
Nearly 80% of patients have depression and pain, which are linked to poor health-related quality of life and frequently raise death rates. However, most patients with co-occurring depression and pain do not benefit from drug therapies that treat either pain or depression, making this co-occurring illness a severe problem for both people and society. Historically, *Cannabis sativa* plant extracts, now known as marijuana, were used to treat this depression-pain comorbidity. With the discoveries of cannabinoid receptor type 1 (CB1) and CB2, the mechanism of action of 9-tetrahydrocannabinol, the potent cannabinoid component of marijuana, has only lately been discovered. Subsequent studies led to the discovery of anandamide and 2-arachidonoylglycerol as endocannabinoids, which have cannabinomimetic effects via the CB1 and CB2 receptors, which are positioned on presynaptic membranes in the CNS and peripheral tissues, respectively. These endocannabinoids are lipophilic compounds created on demand from membrane lipids and quickly removed after hydrolysing enzyme use. Patients with persistent pain had altered endocannabinoid signaling, according to clinical investigations. There was much evidence that the endocannabinoid system was responsible for depression and chronic pain-related derangements of neurotransmission, neuroendocrine, and inflammatory processes. For the treatment of pain and depression, several synthetic cannabinomimetic medicines are being created.

Keywords: Endocannabinoids, anandamide, depression, 2-arachidonoylglycerol

1 INTRODUCTION

The utmost prevalent psychiatric and neurological illnesses that have a significant negative impact on society as a whole are pain and sadness [1]. Nearly 80% of patients have both depression and pain [2], and these two conditions are linked to decreased health-related quality of life [3], which frequently increases mortality [4]. Inflammatory and neuropathic pain patients are nearly five times more likely than the general population to experience depression or anxiety disorders [5]. The majority of individuals with comorbid pain and depression, however, do not respond to pharmacological therapies that target either the pain or the depression [6], making these comorbidity disorders a significant problem for both society and patients [7]. Numerous animal models of depression and long-term pain based on lesion, genetics, stress, and pharmaceutical intervention that show modified nociceptors responses have been used to substantiate these clinical observations on the connection between depression and pain [8]. Given the importance of the intricate relationship between depression and pain and its effects on society, a more profound comprehension of the molecular causes of this correlation is required to create more potent treatments [9]. In the past, marijuana, or the Cannabis Sativa plant, was used to treat the comorbidity of sadness and pain [10]. The use of marijuana to treat pain for various causes has become a hot topic because of the potential for addiction, drug abuse, and regulatory concerns [11]. The principal psychoactive component of marijuana, Δ9-tetrahydrocannabinol (Δ9-THC), has been used medicinally since around 2000 BC, although its

biological effects have only lately been discovered. In recent years, the natural Δ 9-THC receptor on cell surfaces has been found and described [12]. Understanding the MOA of Δ9-THC, which underpins its broad range of therapeutic effects, including euphoria, tranquillity, hunger stimulation, sensory changes, and analgesia, was made possible by the characterization of this receptor [13]. The discovery of anandamide, the first cannabinoid-like endogenous chemical, in the pig brain has served as a reminder of the function that the endogenous ligands of the infamous cannabinoid receptor play in a variety of biological processes [14]. The term "anandamide" refers to the properties of the N-cannabinomimetic arachidonoylethanolamine and is derived from the Sanskrit word "ananda," which means bliss [15]. A different endogenous cannabinomimetic substance called 2arachidonoylglycerol (2AG) has been discovered [16]. Significantly, the two endocannabinoids came from arachidonic acid. These substances are called endocannabinoids since they are cannabinomimetic and endogenous and act on cannabinoid receptors [17].

2 THE ENDOCANNABINOID SYSTEM

Other endogenously generated chemicals besides anandamide and 2-AG probably also affect how CB receptors work [18]. These compounds include oleamide, O-arachidonoyl ethanolamine [19], noladin ether or 2-AG ether [20], and N-arachidonoyldopamine [21]. Their physiological function is unclear; hence, whether they genuinely are endocannabinoids. Nearly 80 additional phytocannabinoids with a structure resembling that of Δ 9-THC are also present in the cannabis extracts, in addition to Δ9-THC [22]. THC is the most researched of these, and research has revealed that it affects a variety of pathophysiological processes, including anti-nociception, via activating receptors of cannabinoid type 1 (CB1) and type 2 CB2 [23].

However, Δ9-THC's clinical value is constrained by its CB1-mediated adverse CNS actions [24]. Later research showed that another phytocannabinoid called cannabidiol, which has a shallow empathy to link to receptors of CB1 and CB2, exerts beneficial therapeutic effects without producing any psychoactivity, including anti-diabetic, inflammatory, anti-bacterial, anti-anti-anxiety, anti-cancer, and anti-epileptic properties [25].

The use of nabiximols, a cannabis extract with a 1:1 ratio of cannabidiol and Δ9-THC, has been licensed to treat multiple sclerosis-related spasticities, neuropathic pain, and intractable cancer pain [26]. In complement to natural cannabinoids, synthetic cannabinoids such as dronabinol and its analog nabilone have been developed to treat various types of pain [27]. For case, nabilone and dronabinol are presently prescribed in Canada and the United States for chemotherapy-related emesis, while nabilone is suggested for loss of appetite linked to weight loss related to AIDS [28]. Additionally, the results of a clinical investigation demonstrated nabilone's effectiveness in treating diabetic neuropathy [29]. Rimonabant, a different synthetic medication initially licensed for the treatment of smoking cessation and obesity, was later discovered to have depressive actions and was withdrawn. Rimonabant is an inhibitor of the CB1 receptor [30].

2.1 Biosynthesis of endocannabinoids

Endocannabinoids are lipophilic compounds produced from membranes "on demand" and liberated immediately without being stored in vesicles. Post-synaptic neurons have anandamide and 2-AG [31]. The membrane phospholipid phosphatidylethanolamine (NAPE) is first N-arachidonoylated by a calcium-dependent N-acyltransferase to produce N-arachidonoyl phosphatidy-lethanolamine (NAPE), which is then hydrolyzed by a NAPE-selective phosp-holipase D (NAPE-PLD) to produce N-arachidonoylethanolamine (anandamide) [32]. The PLC first creates diacylglycerol (DAG) from inositol phospholipids, and then DAG is hydrolyzed to 2-AG by plasma membrane-associated sn1-DAG lipase in a two-step process (DAGL) [33]. Once 2-AG has been produced, it is regulated by

monoacylglycerol lipase (MAGL), which accounts for 85% of the hydrolysis, and α/β hydrolase domain containing 6 (ABHD6) and ABHD12, which also hydrolyze 2-AG to arachidonic acid and glycerol [34]. Cyclooxygenase-2 and lipoxygenase [35], in addition to hydrolysis, operate on 2-AG to produce prostaglandin glyceryl esters and other related bioactive chemicals [36]

Figure 1.

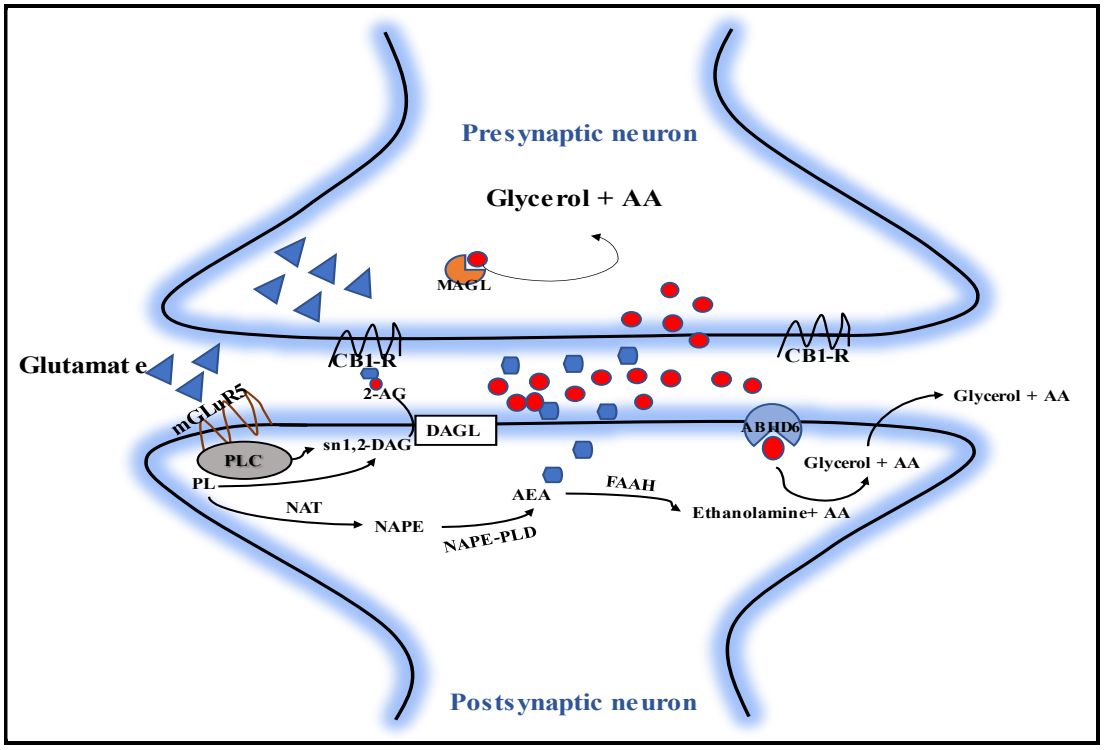

Figure 1 Endocannabinoid signaling and production at synapses. The three significant proteins in the 2-arachidonoylglycerol (2-AG) synthesis are localized in the post-synaptic neurons in the pri-synaptic zone of the dendritic spine. When the mGluR5 metabotropic glutamate receptors are activated, phospholipase C (PLC)-β hydrolyses the membrane phosphatidylinositols (PL) to create sn1,2-diacylglycerol (sn1,2-DAG), which has arachidonic acid at position 2. The plasma membrane-bound DAG lipase-α (DAGL) then hydrolyses the sn1,2-DAG to produce 2-AG. The rapid build-up of 2-AG is made possible by the coordinated activity of these protein elements, which are close to one another on the post-synaptic membrane. To stimulate the cannabinoid receptor type 1 (CB1) found on the terminals of the presynaptic axon, 2-AG then enters the synaptic cleft. Monoacylglycerol lipase hydrolyses 2-AG, which enters presynaptic terminals (MAGL). ABC hydrolase domain containing 6 (ABHD6), a MAG hydrolase, breaks down an extra 2-AG in post-synaptic terminals. In contrast, N-acyltransferase, which creates N-arachidonoyl phosphatidy-lethanolamine, produces arachidonoy lethanolamine, also known as anandamide (AEA), in the post-synaptic terminals (NAPE). A particular PLD (NAPEPLD) further hydrolyses NAPE to produce AEA. Additionally, AEA crosses the post-synaptic membrane to reach the presynaptic axon terminal CB1 receptors. Fatty acid amide hydrolase rapidly eliminates the majority of extra and unusable AEA in post-synaptic terminals (FAAH) [37].

Table 1 Pain and depression therapy based on cannabinoids [11]

Condition	Cannabinoid-based drug	Outcomes for pain	Outcomes for depression and anxiety
HIV	Marijuana	Decrease in muscle and nerve pain	Decrease in Anxiety
Cancer	Nabilone	Decrease in pain score	Decrease in Overall stress
Fibromyalgia	Nabilone	Decrease in Pain	Decrease in Anxiety
Offenders with psychiatric disorders	Nabilone	Decrease in Pain	Decrease in Post-traumatic stress disorder symptoms
Chronic neuropathic pain	Δ9-THC	Decrease in Pain and pain intensity	Decrease in Anxiety
Diabetic neuropathy	Sativex (Δ9-THC, cannabidiol)	Decrease in Pain	Increase in quality of life

Δ9-THC, Δ9-tetrahydrocannabinol.

3 CANNABINOID RECEPTORS

CB1 and CB2, two cannabinoid receptor subtypes, have been cloned and studied [38]. While CB2 receptors are more prevalent in peripheral organs with immunological activities, such as the spleen, CB1 receptors are more prevalent in the CNS [39].

CB1 receptors are widely dispersed throughout the central nervous system (CNS), with concentrations highest in the motor and limbic systems and the spinal cord dorsal horn, rostral ventromedial medulla, and periaqueductal grey [40]. On the terminals and axons of neurons, CB1 receptors exhibit presynaptic location in synapses [41]. In the Gi/Go class of GPCR, the CB1 and CB2 binding sites suppress neurotransmitter release [18]. Endocannabinoids can link to CB1 receptors in the presynaptic membrane after discharge [42]. Adenylate cyclase is inhibited by these CB receptors [43].

Only CB1 receptor stimulation, not CB2 receptor stimulation, results in the stimulation of potassium channels and MAP kinase to block voltage-dependent N- and P/Q-type calcium channels [44]. Although CB2 binding sites are primarily found in peripheral organs and immune cells, some neuron subsets in the brain have been found to express these receptors, suggesting that they may also be involved in the regulation of neurotransmission [45]. Endocannabinoids bind to other receptors, including GPR55 [46], peroxisome proliferator-activated receptors, transient receptor potential vanilloid 1, and GPR119 [32]. Some cannabinoid agonists and pharmaceutical endocannabinoid tone modulators have different effects because of the endocannabinoids' non-CB1/2 receptor action [47]. Once their receptors are active, cellular absorption and subsequent hydrolysis remove endocannabinoids from the synaptic junction and extracellular environment [48]. It has been proposed that a particular "endocannabinoid membrane transporter," which has not yet been characterized, likely mediates the uptake of anandamide [49]. How 2AG uptake is mediated is unclear [50]. Contrary to 2-AG, which is removed in presynaptic neurons by MAGL after CB1 receptor activation, anandamide is hydrolyzed in post-synaptic neurons by FAAH, halting anandamide activity at the time of its creation [51]. Lipoxygenase and cycloxygenase break down anandamide into oxygenated metabolites that act on non-cannabinoid targets [52].

4 ENDOCANNABINOIDS IN PAIN AND DEPRESSION

Individuals have different experiences with pain, an integrated experience involving cognitive, emotional, and physiological aspects [53]. Because humans and other animals cannot express pain, most basic pain research is undertaken on laboratory animals [54]. To monitor pain in animals, it is usually necessary to distinguish between the subjective experience of pain and the observable neural activity that underlies it [55]. Nociceptive pathways are engaged when noxious signals, including heat and mechanical damage, are translated into neuronal action potentials by sensory afferent neurons, like mechanoreceptors in the PNS [56]. Through the cell body and axon of the significant afferent neuron, these action potentials travel from a synapse in the superficial dorsal horn of the spinal cord [57].

Contributions from several spinal cord cell types are combined and sent up ascending routes to the brainstem and then to the thalamus [58]. The higher brain areas that control the sensory (such as the somatosensory cortex) and affective (cingulate cortex and amygdala) aspects of pain get a signal from the thalamus [59]. Because of the bridge between supra-spinal nociceptive regions, descent modulatory channels from the brain to the spinal cord can either strengthen or reduce arriving nociceptive signals [60]. Since the endocannabinoid system is dispersed across the supraspinal and spinal regions, it can efficiently control neurophysiological processes, including processing effects and pain [61]. In patients with long-term pain as well as in individuals with psychiatric disorders, clinical trials have revealed altered endocannabinoid signaling [62]. Major depression and bipolar illness have been linked to specific genetic variants in the CB1 and CB2 receptors, and treatment resistance has been seen in depression patients with single nucleotide polymorphisms in the CB1 receptor [63]. The endocannabinoid system was active in osteoarthritis patients, including plasma levels of 2-AG and CB1 and CB2 mRNA. They also demonstrated a good relationship between 2-AG levels, discomfort, and melancholy [64]. Nevertheless, it is unknown whether these modifications represent compensatory attempts to lessen osteoarthritis sufferers' discomfort [65]. To fully comprehend the relationship between the endocannabinoid system and pain and depression, more research is required [66].

Although, to the best of our knowledge, only a small number of clinical studies have specifically addressed the role of endocannabinoids in pain-depression interactions, patients with HIV have reported reduced muscle and nerve pain after consuming cannabis, along with reduced anxiety and depressive symptoms [67]. For 30 days, daily supplementary Cesamet (nabilone, a Δ9-THC analog) treatment for cancer patients reduced overall stress and discomfort [68]. In a double-blind, randomized, placebo-controlled trial involving fibromyalgia pain management and quality of life enhancement was proven [69]

Table 1. Studies utilizing Δ9-THC (dronabinol) in patients with fibromyalgia or chronic neuropathic pain produced similar outcomes [70].

The research above and others demonstrate that when present concurrently in a range of patients, depression or anxiety and pain respond to exogenously administered cannabis, even though the underlying mechanism is yet unknown [71].

It has been established that the amygdala's increased activity and decreased functional connections with the somatosensory cortex are related to the Δ9-THC-mediated reductions in pain [72]. As a result, the amygdala is probably the brain circuit that connects emotional reactions to pain. It is yet unknown exactly how the endocannabinoids affect behavior, emotion, and nociceptive processing [73]. There is currently a lot of research [74] showing that the endocannabinoid system has powerful impacts on neuroendocrine, neurotransmission, and inflammatory processes- all known to be out of whack in depression and chronic pain [75].

5 CONCLUSION

Most patients have both depression and pain, which frequently increases mortality. Most people with comorbid depression and pain do not respond to therapeutic therapies that treat either the pain or the depression, exacerbating the comorbidity problem. The main element in marijuana, Δ9-THC, exerts its action by activating CB1 and CB2 receptors. Cannabis contains cannabinoids, commonly known to manage feelings of grief and pain. Anandamide and 2-AG, two naturally occurring endocannabinoids with cannabinomimetic properties, activate these receptors. The neuroendocrine, neurotransmission and inflammatory mechanisms that are known to be out of whack in depression and long-term pain are affected in significant ways by the endocannabinoid system. The precise mechanism by which endocannabinoids act on numerous biological sites, as well as whether or not their impacts on pain and depression employ the same or different pathways, will require further study.

Credit authorship contribution statement

Himanshu Sharma: Data curation, Writing-original draft, Methodology, Software.
Rashmi Pathak: Conceptualization, Methodology, Writing-review & editing.
Lipi Nogai: Conceptualization, Methodology
Riya Mishra: Conceptualization, Methodology
Maulshree Bhandari: Conceptualization, Methodology
Manju Koli: Conceptualization, Methodology
Nitin kumar: Conceptualization, Methodology
Priya Pandey: Conceptualization, Methodology

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Conflicts of interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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