Acupuncture and Herbal Medicine

Research progress regarding endocannabinoid system involvement in pain modulation and electroacupuncture analgesia

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Abstract

Pain is a subjective and unpleasant sensation that significantly impacts the daily lives of individuals. Chronic pain represents one of the most challenging public health issues, and ensuring effective pain management is a fundamental right of individuals and a sacred duty of healthcare providers. Cannabis, one of the earliest recognized medicinal plants, contains cannabinoids, which are non-opioid substances that modulate nociceptive responses. Electroacupuncture (EA), characterized by its low-risk and well-tolerated nature, is pivotal in pain management. The endocannabinoid system consists of endocannabinoids, cannabinoid receptors, and enzymes involved in endocannabinoid synthesis, degradation, and transport. Recently, the role of the endocannabinoid system in pain development and EA analgesia has attracted considerable research attention. Studies have highlighted the role of the endocannabinoid system in various types of pain, including inflammatory pain, neuropathic pain, and cancer-related pain, as well as in EA analgesia. This study aims to review the mechanisms of endocannabinoid system involvement in pain modulation and EA analgesia to provide insights to inform clinical approaches to pain management.

Keywords: Electroacupuncture, Endocannabinoid receptors, Inflammatory pain, Neuropathic pain

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Pain is a subjective and unpleasant sensation that significantly impacts the daily lives of individuals. The danger of pain to human health should not be underestimated, and it is a long-term focus of major global healthcare concerns. Chronic pain seriously affects the normal lives of individuals and causes a huge economic burden[1–2]. Western therapies are ineffective for analgesia. Inflammatory pain is a common clinical type of chronic pain resulting from many diseases, including osteoarthritis, rheumatoid arthritis, and fibromyalgia. Currently, clinical treatment of inflammatory pain is dominated by nonsteroidal drugs and opioids. Nonsteroidal drugs cause gastrointestinal and cardiovascular side effects, and opioids can lead to drug tolerance and addiction, limiting their scope of application in the clinic[3–4]. The analgesic effects of acupuncture are related to opioid peptides, adenosine, cannabinoids, and many other neurotransmitters[5]. Electroacupuncture (EA) is effective for relieving inflammatory pain of knee osteoarthritis, fibrous tissue myalgia, myofascial pain, and other types of pain[6–7]. EA combined with medication is more effective than Western medicine alone for rheumatoid arthritis pain[8]. Cannabis, one of the earliest recognized medicinal plants, contains cannabinoids, which are non-opioid substances that modulate nociceptive responses[9]. The endocannabinoid system (eCBs), as an important target in pain research, is closely related to inflammatory pain, neuropathic pain, and cancer pain, and it is involved in the mechanism of EA analgesia[10]. This study aims to review the roles and mechanisms of endocannabinoid receptors involved in pain modulation to provide insights to inform clinical approaches to pain management with acupuncture. In this article, eCBs involvement in pain modulation and EA analgesia are discussed by reviewing published Chinese and English literature from China National Knowledge Infrastructure (CNKI), Pubmed (2010–2024). The keywords for searcher were eCBs, acupuncture, EA analgesia, inflammatory pain, neuropathic pain, cancer pain, visceral pain. The articles that met the following criteria were included: a) the studies were written in Chinese or English; b) basic research on inflammatory pain, neuropathic pain, cancer pain, and visceral pain modeling; c) study subjects received EA or CB1R/CB2R agonist/antagonist treatment; and d) the studies

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evaluated the mechanism of the endogenous cannabinoid system on pain models or EA analgesia.

Types, distribution, and function of endocannabinoid receptors

Endocannabinoid receptor types and distribution

Two main types of cannabinoid receptors exist in organisms, including cannabinoid receptor-1 (CB1R) and cannabinoid receptor-2 (CB2R), both of which are G protein-coupled receptors[11]. CB1R is the subtype of G protein-coupled receptor with the highest expression abundance in the central nervous system. Therefore, it is known as the central-type cannabinoid receptor. CB1R is abundantly distributed in the basal ganglia and most tissues and organs of the body, such as the heart, lungs, thymus, and spleen[12].

CB2R is primarily distributed in the periphery, particularly in tissues and cells related to the immune system, such as the splenic limbic area, immune cells, tonsils, and thymus[12]. Moreover, it mediates the immunosuppressive effects of Δ9-tetrahydrocannabinol (Δ-THC)[13], and therefore it is referred to as the peripheral cannabinoid receptor.

Physiologic functions of endocannabinoid receptors

Endocannabinoids act by binding to and activating cannabinoid receptors. Upon appropriate external stimulation, endocannabinoids are released from the postsynaptic membrane and diffuse to the presynaptic membrane, where they bind to receptors. This binding inhibits neurotransmitter release and contributes to the regulation of higher functions, including sensation, movement, cognition, and memory[14].

CB1R has been observed to be involved in the regulation of downstream pain pathways and negative emotion-related loops such as fear, anxiety, and stress[15], as well as playing a key role in sleeping regulation[16]. One study reported that cannabidiol (CBD) administration in CB1R knockout mice did not produce anxiolytic effects, whereas administration of the CB1R antagonist SR141716A after CBD administration in normal mice blocked the anxiolytic effects of CBD[17]. Hartmann et al.[18] observed that CBD reduces external aggression in mice, and the CB1R antagonist AM251 impairs the anti-aggressive effects of CBD. This highlights the important value of CB1R in regulating emotions. Meanwhile, CB1R is involved in other physiological and pathological processes. Kang and Ma[19] reported that CB1R ameliorated spinal cord injury by inhibiting microglia activation and inflammatory response. Yang et al.[20] suggested that CB1R could promote intestinal motility in mice by improving the mitochondrial function of enteric neurons. Moreover, the involvement of CB1R in the regulation of cardiovascular diseases such as hypertension and atherosclerosis has been documented[21]. In recent years, the involvement of the eCBs in various neurological disorders has received widespread attention, particularly the study of the role of cannabinoid receptors in pain and acupuncture analgesia[22].

CB2R activation can stimulate immunosuppression and alleviate the development of inflammation and associated tissue damage, suggesting that CB2R may exert an anti-inflammatory effect[23]. Hui-Wen et al.[24] identified that activating CB2R could help protect experimental sepsis rat lungs from acute lung injury by blocking the P38 mitogen-activated protein kinase signaling pathway, lowering the release of inflammatory factors from lung tissues, and increasing the expression of tight junction proteins[24]. Pacher et al.[25] observed that mice lacking CB2R developed endothelial formation, an increased proliferation rate of smooth muscle cells, elevated expression of adhesion molecules and pro-inflammatory substances, and heightened inflammatory changes. CB2R is involved in many other diseases, including those related to the central nervous system. Selective CB2R agonists attenuate post-stroke injury and improve memory in mice[26], while transgenic mice overexpressing CB2R exhibit relatively less depressive behavior in related tests[27]. CB2R agonists protect against the injurious sensations of thermal stimuli, exert anti-inflammatory effects, modulate inflammatory cellular phenotypes, and are involved in analgesic mechanisms both peripherally and centrally in different manners. CB2R will likely be a potential target for the treatment of chronic pain[28].

Endocannabinoid receptors involved in inflammatory pain and EA analgesia

CB1 receptors are primarily distributed in the central nervous system and expressed on neurons and astrocytes[29–30]. Previous studies highlight the pivotal role of CB1R in inflammatory pain modulation. Systemic application of CB-13, a peripherally restricted CB1/CB2R dual agonist, significantly relieved pain in complete Freund's adjuvant (CFA)-induced inflammatory pain in mice. However, either the use of the CB1R antagonist AM6545 or CB1R knockdown markedly compromised the analgesic effects of CB-13, suggesting that CB-13 exerts analgesic effects through peripheral CB1R activation[31]. The analysis by Klinger-Gratz et al.[32] of the dose-dependent analgesic effect of acetaminophen in inflammatory pain mice revealed that intrathecal injection of AM404 (an endocannabinoid reuptake inhibitor) to indirectly activate CB1R mimicked this effect. Both compounds lost their analgesic effect in CB1R knockout mice, confirming CB1R involvement in inflammatory pain[32]. Moreover, intranasal administration of melanin-concentrating hormone (MCH) significantly increased mechanical and thermal pain thresholds in mice. AM251 (a CB1R antagonist) reversed the analgesic effect of MCH in models of nerve injury (partial sciatic nerve ligation) and CFA-induced inflammatory pain, while MCH increased CB1R expression and activation in specific brain regions. These findings collectively underscore the involvement of CB1R in inflammatory pain analgesia[33].

However, CB1R activation may cause associated psychiatric side effects. Therefore, a possible potential pain therapeutic mechanism targeting CB2R primarily located in the periphery has received attention[34]. An experimental study by Donatello et al.[35] demonstrated

that lavender essential oil attenuated mechanical nociceptive sensitization induced by inflammation and neuropathic pain through inhalation involving opioid and cannabinoid receptors. The anti-inflammatory and analgesic effects of lavender essential oil were reversed by AM630, a selective CB2R antagonist[35]. Continuous intrathecal infusion of polysaccharide peptides significantly alleviated mechanical nociceptive hypersensitivity and thermal pain sensitization in arthritic pain morphine-tolerant rats by upregulating CB2R[36]. Other studies have reported that linderane can bind to CB2R and regulate the polarization of microglia in the anterior cingulate cortex to exert analgesic effects[37]. These findings demonstrate the analgesic effect of CB2R selective agonists.

EA, characterized by its low-risk and well-tolerated nature, is pivotal in pain management[38]. The analgesic mechanism of EA is closely linked to CB1R. In a rat migraine model, EA was demonstrated to upregulate CB1 receptor expression in the trigeminal ganglion and reduce the release of calcitonin gene-related peptide (a pro-inflammatory nociceptive substance), and the administration of the antagonist ACOMPLIA inhibited this. This suggests that EA can exert anti-inflammatory and analgesic effects by upregulating and activating trigeminal ganglion CB1 receptor expression[39]. In addition, in the morphine-induced hyperalgesia (MIH) model, intrathecal injection of the CB1R agonist WIN-55,212-2 inhibited the phosphorylation level of extracellular signal-regulated kinase 1/2(ERK1/2) in the spinal cord and significantly increased the antinociceptive effect of EA compared with the EA group, whereas CB1R antagonists induced the opposite result. Activation of spinal CB1 receptors by EA therapy may exert anti-inflammatory and analgesic effects by inhibiting the activation of ERK1 and ERK2 signaling pathway[40]. In addition, EA downregulates gamma-aminobutyric acid (GABA) levels in the midbrain ventrolateral periaqueductal gray (vlPAG), a process inhibited by the CB1R antagonist AM251, suggesting a modulation of presynaptic inhibitory transmitter release as part of its analgesic mechanism[41]. In a knee osteoarthritis pain (KOA) model, EA upregulated the level of CB1R expression on GABAergic neurons in the vlPAG and inhibited the KOA-induced decrease in the level of 5-HT in the medulla, suggesting that endocannabinoid (2-AG)-CB1R-GABA-5-HT might be a novel signaling pathway that is involved in the inhibition of chronic pain by EA[42].

CB2R contributes significantly to EA analgesia for inflammatory pain[43]. At the peripheral level, the mechanism of inflammatory pain likely involves the accumulation of inflammatory factors released by non-neural cells, sensitizing nociceptive nerve fibers following tissue injury. Peripheral immune cells release various substances, including inflammatory cytokines and lipid degradation products (eg, interleukin-5, 5-hydroxytryptamine, nerve growth factor, and prostaglandin E_2) that stimulate and bind to corresponding receptors at the nerve endings. This binding results in nociceptive sensitization of these receptors that transmit pain signals through the dorsal root ganglion to the dorsal horn of the spinal cord[44–46]. EA suppresses inflammatory cytokine production through various pathways, including the release of opioids, cannabinoids, and adenosine from immune cells. By binding to μ-opioid receptors, CB2R, and adenosine receptors on neurons or immune cells, EA inhibits central sensitization and the release of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1β, thereby alleviating pain[47–48]. In a KOA mouse model, EA activated CB2R in knee meniscus fibroblasts, inhibiting the level of pro-inflammatory cytokine IL-1β and alleviating osteitis pain. EA was observed to alleviate cartilage degradation *via* CB2R[49]. Activation of CB2R by EA may be involved in analgesic modulation by enhancing the efficacy of the endogenous opioid peptide analgesic system. EA increases β-endorphin expression in inflammatory skin tissue[50]. CB2R activation by EA activates Gi/o proteins and causes them to release Gβγ. The βγ subunit activates the MAPK signaling pathway, and this causes an increase in the intracellular Ca2+ concentration and ultimately facilitates the release of β-endorphin to inhibit pain (Figure 1), and MAPK inhibitors significantly inhibit the above results. The MAPK pathway is involved in the peripheral analgesic effects of CB2R agonists[51]. Some studies suggesting EA can ameliorate neuropathic or inflammatory pain by reducing NLRP3 inflammasome activation which can regulate autophagic process[52–55]. We further studied and determined that the involvement of CB2R in EA for anti-inflammatory pain was related to cellular autophagy function[56]. Damaged mitochondria produce reactive oxygen species (ROS) that may induce activation of the NLRP3 inflammatory vesicles[57] and increase secretion of IL-1β maturation fragments[58–59], thereby sensitizing peripheral nociceptors and leading to inflammatory pain[60]. In this study, the CB2R agonist AM1241 was used to simulate the effect of EA, and it was determined that the activation of CB2R by EA could effectively enhance the autophagy function of NR8383 macrophages in inflamed skin tissues, promote the removal of damaged mitochondria and reduce the release of related inflammatory factors, thus relieving inflammatory pain (Figure 1). These findings collectively underscore the vital role of CB2R in mitigating inflammatory pain.

We used concise images to represent the roles of CB1R and CB2R in EA analgesia (Figure 2).

Endocannabinoid receptors involved in neuropathic pain and EA analgesia

Neuropathic pain manifests as nociceptive hypersensitivity and spontaneous pain[61], often arising after nerve injury, leading to deleterious changes in injured neurons and downstream regulatory pathways in the central nervous system[62]. Various nerve injuries in the peripheral or central nervous system, such as those affecting the spinal cord posterior roots, peripheral nerves, or certain central nervous system regions, can induce neuropathic pain[63].

In the cerebral cortex, CB1R plays an important role in neuropathic pain. Wu et al.[64] demonstrated that the selective elimination of CB1R from GABAergic neurons in the prefrontal ventral-lateral orbital cortex completely abrogates the analgesic effects induced by HU210. This finding underscores the indispensable role of CB1R in mediating analgesia in neuropathic pain conditions[64]. The medial prefrontal cortex (mPFC) contributes to

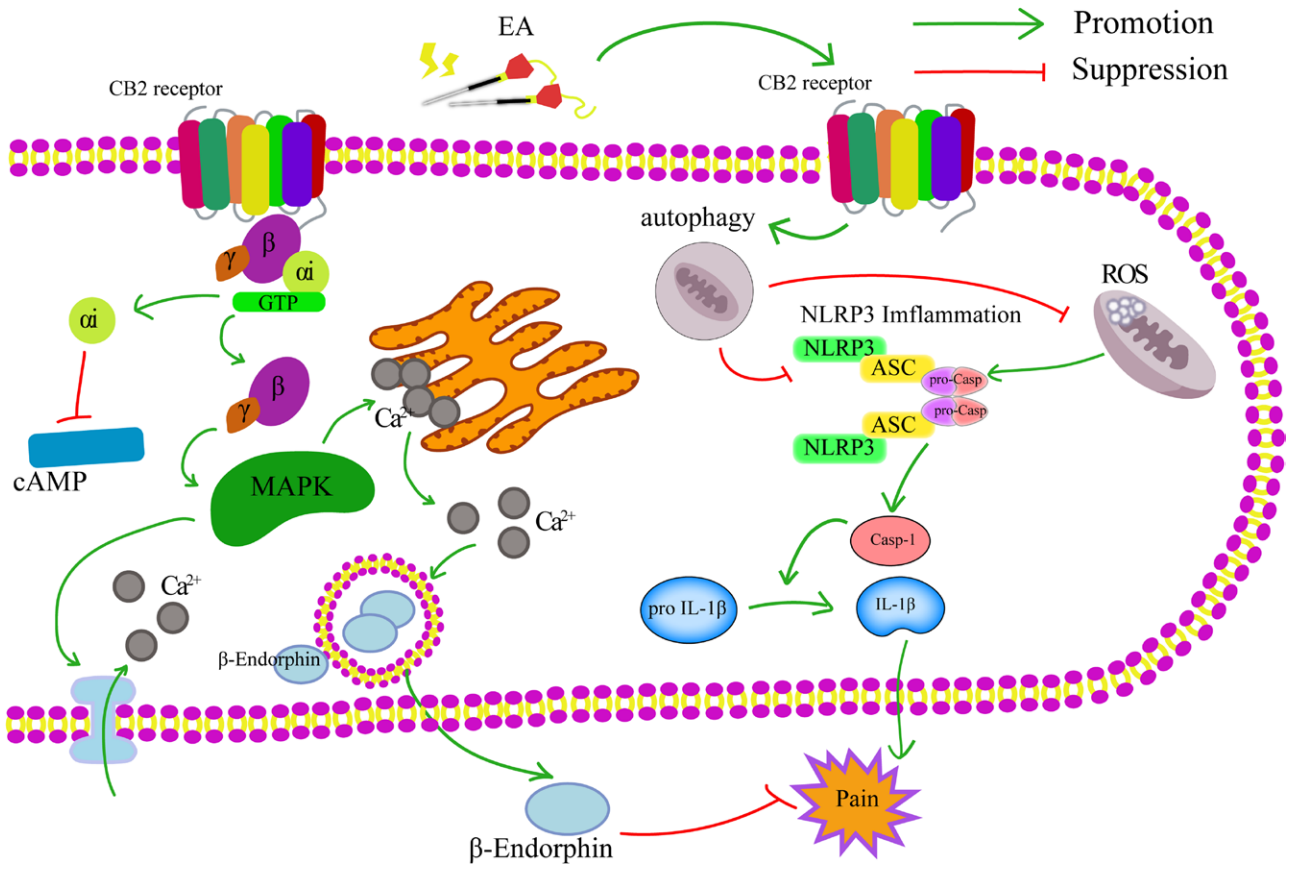

Figure 1. Mechanism of EA in treating inflammatory pain by inhibiting the activation of NLRP3 inflammasome and promoting the release of β-endorphin through the CB2 receptor. CB2R activation by EA activates Gi/o proteins and causes them to release Gβγ. The βγ subunit activates the MAPK signaling pathway, and this causes an increase in the intracellular Ca[2]⁺ concentration and ultimately facilitates the release of β-endorphin to inhibit pain. Damaged mitochondria produce ROS that may induce activation of NLRP3 inflammatory vesicles and increase secretion of IL-1β maturation fragments, thereby sensitizing peripheral nociceptors and leading to inflammatory pain. The activation of CB2R by EA could effectively enhance the autophagy function of NR8383 macrophages in inflamed skin tissues, promote the removal of damaged mitochondria, and reduce the release of related inflammatory factors, thus relieving inflammatory pain. cAMP: Cyclic adenosine monophosphate; CB1/2 receptor: Endocannabinoid receptor 1/2; EA: Electroacupuncture; IL-1β: Interleukin-1β; MAPK: Mitogen-activated protein kinase; NLRP3: NOD-like receptor thermal protein domain-associated protein 3; ROS: Reactive oxygen species.

pain processing[65]. Endocannabinoids inhibit inhibitory inputs to GABAergic neurons in the mPFC *via* presynaptic CB1R in pyramidal neurons (PNs), thus maintaining mPFC excitatory activity[66]. Activation of CB1R in the mPFC through injection of the CB1R agonist WIN-55, 212-2 (WIN) temporarily alleviates pain behavior during the chronic phase of neuropathic pain. Conversely, injection of the CB1R antagonist AM4113 attenuates pain behavior during the same phase in mice[67].

At the level of the spinal cord, CB1R is a major receptor involved in neuropathic pain. Cheng et al.[68] reported that the CB1R pathway regulates spinal dorsal horn synapses in rats with neuropathic pain at different ages. In neonatal rats, CB1R inhibits spinal dorsal horn field potential (PS) and exerts analgesic effects primarily by regulating N-methyl-D-aspartic acid receptor (NMDAR) activity, while in juvenile and adult rats, this analgesic effect is mediated by NMDAR and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR), respectively[68].

At the peripheral level, CB2 receptors are the main receptors regulating neuropathic pain. CB2 receptors are predominantly located in peripheral tissues, with a minor presence in microglia within the central nervous system. Microglia activation plays a pivotal role in pain development, becoming activated at the onset of pain induced by spinal cord injury and maintaining dorsal horn neuron excitability by releasing various factors such as IL-1β, IL-6, TNF-α, and ATP that induce pain[69]. Early studies have demonstrated the neuropathic pain-relieving properties of CB2R on microglia using CB2R-selective agonist (NESS400) treatment and CB2R knockout mice, respectively[70–71]. Following peripheral nerve injury, bivalent histone modifications enhance the expression of CB2 receptors in primary sensory neurons at the peripheral level. This upregulation of CB2Rs reduces nociceptive transmission to the spinal cord, thereby mitigating neuropathic pain[68]. Another study demonstrated that in spared nerve injury modeling, continuous intrathecal injection of the CB2R agonist PM226 effectively attenuates mechanical and cold hyperalgesia in mice while blocking the shift of microglia to a pro-inflammatory phenotype[72]. P2X7 is a member of the purinergic receptor family that is primarily expressed by immune cells. When it is activated, inflammatory factors such as IL-1β and IL-6 are released[73]. Meanwhile, CB2R activation downregulates P2X7 expression, inhibiting further microglial activation and inflammatory factor release and thereby exerting neuroprotective effects[72]. CB2R prevents

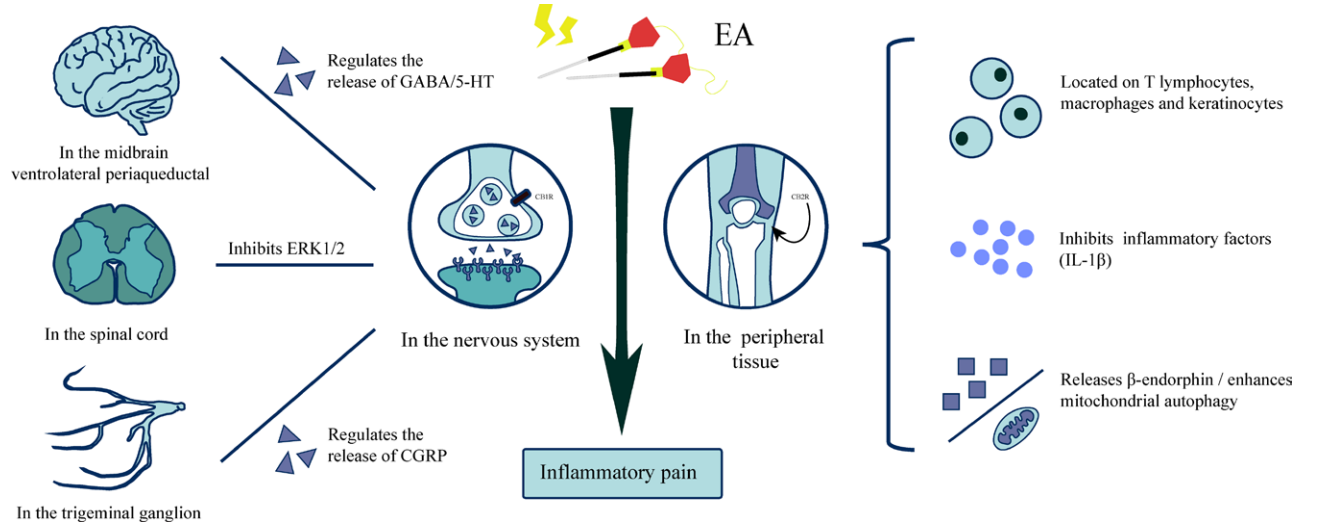

Figure 2. Mechanisms of CB1R and CB2R involvement in EA analgesia in inflammatory pain. The CB1R receptor is predominantly located in the central nervous system, with particularly high concentrations in various regions of the brain. It plays a crucial role in modulating the release of neurotransmitters such as GABA and 5-HT, thereby exerting significant influence over mood, sleep patterns, appetite, and pain perception. In addition, CB1R inhibits the activation of ERK1/2, a process that is vital for cell proliferation, differentiation, and apoptosis. Furthermore, it is implicated in the regulation of CGRP, a peptide associated with pain, inflammation, and vasodilation. CB2R is mainly distributed in immune cells and peripheral tissues and inhibits the release of the inflammatory factor IL-1β, reducing inflammatory responses. It also affects the immune response by regulating immune cell function, such as the proliferation, differentiation, and function of T lymphocytes and macrophages. In addition, CB2R promotes the release of β-endorphin, which has analgesic effects and enhances cellular autophagy, promoting cellular self-renewal and repair to maintain cellular health and function. CGRP: Calcitonin gene-related peptide; EA: Electroacupuncture; ERK1/2: Extracellular signal-regulated kinase 1/2; GABA: Gamma-aminobutyric acid; IL-1β: Interleukin-1β.

chemotherapy-induced neuropathic pain by activating spinal cord Toll-like receptor type 4[74]. For example, paclitaxel (PTX), an antitumor medication, is known to trigger neuropathic pain[75]. However, the application of CBD has been demonstrated to prevent the onset of neuropathic pain associated with PTX treatment. The preventive effect of CBD is negated by the cannabinoid CB2 receptor antagonist AM630, suggesting that CB2R signaling may be involved in the protective mechanism against PTX-induced neuropathic pain[74,76].

EA exerts analgesic effects by modulating the expression of CB1R in key brain regions, regulating the excitability of relevant neurons, and thus inhibiting the transmission of pain signals. For example, in the gray matter surrounding the vlPAG, EA simultaneously inhibits GABAergic neurons and activates glutamatergic neurons *via* CB1 receptors, thus exerting an analgesic effect[77]. EA activates CB1R in the primary somatosensory cortex (S1), and this leads to presynaptic inhibition of GABAergic vasoactive intestinal peptide-positive interneurons (VIP-INs) axon terminals and subsequent enhancement of abnormally lowered somatostatin-positive interneurons (SST-INs) activity. This significantly reduces abnormally elevated excitatory PNs activity, thus revealing the involvement of CB1R in the cortex of the EA in alleviating neuropathic pain[78] (Figure 3).

EA can promote the repair of adductor nerve injury by activating the polarization of microglia to the inflammation-suppressive M2 morphology in an adductor nerve injury model in beagles. Immunofluorescence indicated that the expression level of CB2R on microglia was significantly increased, suggesting that CB2R was primarily involved in the neuroprotective effect induced by EA[79]. Similar to CB2R agonists, EA can relieve chemotherapy-induced pain, and in a PTX-induced neuropathic pain model, EA was observed to activate peripheral sciatic nerve CB2R and inhibit the activation of NLRP3 inflammasome, thereby reducing inflammatory factor release and relieving pain. In the CB2R knockout mouse model, EA could not exert these effects, further confirming the idea[80].

Endocannabinoid receptors involved in cancer pain and EA analgesia

Cancer pain, defined by the American Society of Anesthesiologists as pain arising from the cancer itself or during cancer treatment, is a complex symptom severely impacting patient quality of life, physical well-being, psychological state, and social interactions[81]. Cannabinoids, with a longstanding history of use in alleviating cancer pain, nausea, and cachexia due to cancer treatment, have garnered increasing interest for their potential role in cancer pain management[82–83].

Numerous cancers exhibit a predilection for invading the skeleton[84], leading to excruciating bone pain[85]. Thompson et al.[86] demonstrated the efficacy of the novel monoacylglycerol lipase inhibitor MJN110 for alleviating this pain by indirectly activating CB1R and CB2R. Peripheral administration of the CB1R agonist PrNMI provided effective analgesia without inducing dose-dependent central side effects, as evidenced by a study conducted by Khasabova et al. examining mice with tumor pain[87–88]. Similarly, activation of peripheral CB1R and CB2R by arachidonic acid cyclopropionamide and the CB2R agonist AM1241, respectively, reduced tumor-associated mechanical nociceptive hypersensitivity in mice[88]. In addition, activation of spinal CB1R with arachidonoyl-2-chloroacetamide effectively mitigated

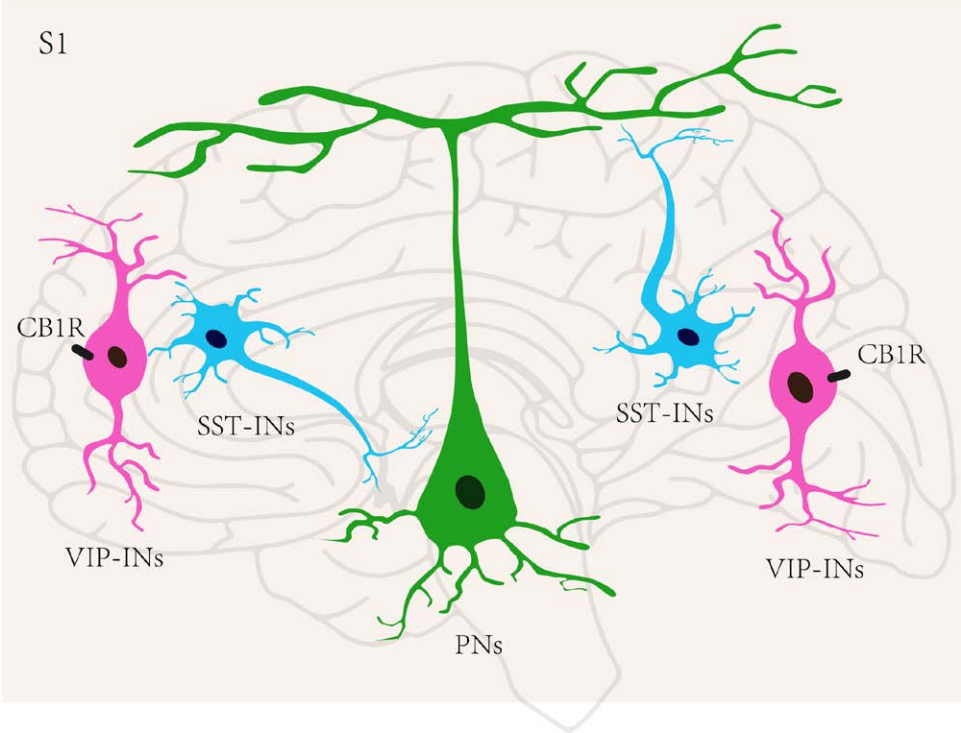

Figure 3. Cortical microcircuits for CB1R-based EA intervention in neuropathic pain. Peripheral nociceptors upload nociceptive signals to the somatosensory cortex *via* the dorsal root ganglia of the spinal cord, culminating in nociceptive perception. The somatosensory cortex acts directly on the dorsal roots of the spinal cord through corticospinal conduction tracts to modulate nociceptive input thresholds. In the pain model, neurons in the somatosensory cortex were overactivated. EA can suppress axonal presynaptic inhibition within this neuronal circuit by increasing the expression of CB1R on VIP-Ins neurons. This upregulation enhances the activity of SST-Ins neurons, which are typically diminished during pathological conditions. Consequently, the overall activity of PNs is reduced, effectively mitigating neuropathic pain. EA: Electroacupuncture; CB1/2 receptor: Endocannabinoid receptor 1/2; PNs: Pyramidal neuron; S1: The primary somatosensory cortex; SST-INs: Somatostatin-positive interneurons; VIP-INs: Vasoactive intestinal peptide-positive interneurons.

pain behaviors associated with bone cancer in mice[89–90]. Moreover, the study by de Oliveira et al.[91] examining a mouse model of cancer pain revealed that transcutaneous electrical nerve stimulation (TENS)-induced analgesia could be reversed by the CB1R antagonist AM251, implicating CB1R involvement in TENS-induced pain relief.

Furthermore, CB2R activation has emerged as a promising avenue for cancer pain management. Wang et al.[92] demonstrated that intrathecal administration of the CB2R agonist JWH015 alleviated nociceptive hypersensitivity in a bone cancer pain model. Experimental findings of Lozano et al.[93] underscored the efficacy of timely CB2R agonist AM1241 administration in suppressing bone cancer-induced pain and mitigating cancer-induced bone loss in mice without the adverse effects associated with conventional analgesic therapies. In addition, the study by Zhang et al. highlighted the potential of CB2R agonists (AM1241) for enhancing analgesia and attenuating morphine tolerance in cancer pain through modulation of MAPK signaling pathways[94–95]. Furthermore, the study by Khasabova et al.[96] revealed the involvement of CB2R in the antinociceptive effects induced by ResolvinD1 in a mouse model of bone cancer, further highlighting the therapeutic potential of CB2R activation in cancer pain management.

EA has been remarkably effective in the field of treating cancer pain[97], but the potential role and mechanism of action of the eCBs in this context remain unknown.

Endocannabinoid receptors involved in visceral pain and EA analgesia

The causes of visceral pain are complex, primarily caused by pathologic damage to internal organs, and most commonly observed in digestive system-related diseases such as inflammatory bowel disease (IBD). EA has exhibited significant results for relieving visceral pain. As determined by protein blotting and immunohistochemistry, EA has been reported to reduce chronic pain caused by IBD by activating CB2R, inhibiting macrophage activation, and thereby reducing the expression of IL-1β and inducible nitric oxide synthase (iNOS)[98]. When assessing 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced visceral hypersensitivity in goats, EA effectively relieved symptoms through the eCBs in the gut[99]. Patients with visceral hypersensitivity are also often associated with emotional problems such as anxiety and depression. Emotional stress may interact with the gut microbiota through the gut-brain axis and influence the development of visceral hyperalgesia[100]. In addition, Hu et al.[101] used TNBS to induce visceral pain and anxiety behaviors in IBD mice, while EA inhibited CB1R overexpression on GABAergic neurons in the ventral hippocampus (vHPC), thus alleviating pain and anxiety in the mice. The anxiolytic effect was reversed if CB1R on glutamatergic neurons was knocked down. This suggests that EA exerts anxiolytic effects by downregulating CB1R in GABAergic neurons and activating CB1R in glutamatergic neurons in vHPC[101].

Table 1

The role of endocannabinoid receptors in EA analgesia in different pain types

Types of pain	Types of receptors	Role in pain modulation and EA analgesia	References
Inflammatory pain	CB1R	Activation of CB1R by EA in the trigeminal ganglion reduces the release of associated pro-inflammatory analgesic substances; activation of spinal CB1R by WIN-55,212-2 inhibits activation of the ERK1/2 signaling pathway; EA inhibits chronic pain through the 2-AG-CB1R-GABA-5-HT signaling pathway.	[39–40, 42]
	CB2R	EA inhibits peripheral sensitization and release of inflammatory cytokines such as TNF-α and IL-1β by activating CB2R; CB2R activation by EA in fibroblasts inhibits levels of the pro-inflammatory cytokine IL-1β; EA increases β-endorphin expression by activating CB2R in inflammatory skin tissue; CB2R agonist AM1241 induces β-endorphin release *via* the Gi/o-Gβγ-MAPK-Ca2+ signaling pathway; EA enhances cellular autophagy, removes damaged mitochondria, and reduces the release of associated inflammatory factors by activating CB2R.	[48, 49, 50, 51, 56–57]
Neuropathic pain	CB1R	EA exerts analgesic effects by simultaneously inhibiting GABAergic neurons and activating glutamatergic neurons *via* CB1R; activation of CB1R inhibits PS and exerts analgesic effects by modulating NMDAR activity.	[66, 68, 77–78]
	CB2R	CB2R agonist PM226/NESS400 inhibits the release of inflammatory factors such as IL-1β and IL-6 *via* microglia; EA promotes the repair of damaged nerves by activating CB2R; EA inhibits the activation of NLRP3 inflammasome through CB2R.	[70–71, 80]
Cancer pain	CB1R	CB1R is involved in inhibiting bone cancer pain.	[86, 89, 91]
	CB2R	CB2R agonist JWH015/AM1241 inhibits bone cancer pain and bone loss; CB2R agonist AM1241 promotes MAPK dephosphorylation and thus reduces morphine tolerance of cancer pain.	[92–94]
Visceral pain	CB1R	EA relieves pain and anxiety through CB1R.	[101]
	CB2R	EA inhibits macrophage activation and decreases IL-1β and iNOS expression *via* CB2R, thus reducing visceral pain.	[98]

CB1R: Cannabinoid receptor-1; CB2R: Cannabinoid receptor-2; EA: Electroacupuncture; ERK1/2: Extracellular signal-regulated kinase 1/2; iNOS: Inducible nitric oxide synthase; NMDAR: N-methyl-D-aspartic acid receptor; TNF-α: Tumor necrosis factor-alpha.

CB1R plays an important role in negative mood regulation. As research progresses, the significance of cannabinoid receptors in the realm of EA-induced analgesia is gradually emerging (Table 1). In addition, there is a deeper relationship between different EA parameters and the eCBs. Studies have demonstrated that 2 and 100 Hz EA can increase the endocannabinoid content in the inflamed tissue to the same level, and both exert analgesic effects. Concurrently, EA at 2 and 100 Hz significantly increased the number of keratinocytes, macrophages, and T lymphocytes with CB2R immunoreactivity in inflamed skin tissue[102].

Conclusion and perspective

The eCBs is regarded as an important participant in various complex physiological processes, including analgesia, repair, and mood in organisms. Among its components, CB1R and CB2R are the primary receptor types. CB1R and CB2R exhibit great application value and research potential for the inflammatory, neuropathic, and cancer pain, as well as EA analgesia. However, there are still many unanswered questions regarding cannabinoid receptors, such as the specific mechanism of cannabinoid receptor involvement in pain modulation and EA analgesia, and exploring new subtypes of endocannabinoid receptors is necessary. Currently, the combined use of CB1R and CB2R agonists and EA in the treatment of painful disorders has not been reported, and effective clinical trials are needed. Future investigative efforts within the field of neuroscience should be directed toward elucidating the intricate mechanisms underlying the role of cannabinoid receptors in the modulation of pain and the analgesic effects of EA. Such research endeavors will be instrumental in developing targeted therapeutic strategies, ultimately providing efficacious pain relief for patients suffering from various conditions.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Renjie Qin, Yisong Wu, Nuo Jin, Xingzhi Xu, Yuye Lan contributed to performing the literature search and data analysis. Xianghong Jing and Man Li drafted the manuscript. Renjie Qin made all the tables and figures. All authors contributed to the revision of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

All data generated or analyzed during this study are included in the published article.

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