

Cannabis *versus* neuromodulators in chronic pain

Cannabis versus neuromoduladores na dor crônica

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ABSTRACT

BACKGROUND AND OBJECTIVES: The change of paradigm in relation to the medical use of cannabis and its components in the treatment of pain is undeniable nowadays. Understanding the functioning of the endocannabinoid system and its interaction with drugs already available on the market is necessary for professionals who care for patients with chronic pain. The aim of this study was to show the mechanisms by which cannabinoids act, not only on CB1 and CB2 receptors, but also on various other receptors, modulating chronic pain, and encourage health professionals to recognize the need to expand the knowledge about its functioning and synergism with several medications so that the safe use of cannabis occurs in the treatment of multiple diseases, especially chronic pain.

CONTENTS: The action of cannabinoids on the endocannabinoid system has the ability to neuro and immunomodulate pain transmission in a multifactorial and extremely complex way, acting simultaneously on multiple targets, in the peripheral, spinal and supraspinal nervous system. The analgesia mechanisms determined by cannabinoids include the inhibition of the release of neurotransmitters and neuropeptides in presynaptic nerve terminals, modulation of postsynaptic neuronal excitability, activation of the descending inhibitory pathway and reduction of neural inflammation. There is also the possibility that the interaction of cannabi-

noids with opioid and serotonergic receptors has an amplifying effect on the analgesic effect of drugs belonging to the opioid class.

CONCLUSION: The endocannabinoid system plays a key role in pain control and its pathophysiology. It is expected that this system will continue to be studied for a better understanding of its signaling pathways and metabolism, and also that more clinical trials of greater size and duration will be carried out to understand to what extent this approach can be beneficial in the treatment of chronic pain.

Keywords: *Cannabis sativa*, Chronic pain, Endocannabinoids.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A mudança de paradigma, em nível mundial, em relação ao uso medicinal de cannabis e seus respectivos componentes no tratamento da dor é indiscutível nos tempos atuais. Entender o funcionamento do sistema endocanabinoide e sua interação com fármacos já disponíveis no mercado se faz necessário aos profissionais que cuidam de pacientes com dor crônica. O objetivo deste estudo foi mostrar os mecanismos pelos quais os canabinoides atuam, não somente nos receptores CB1 e CB2, mas também em diversos outros receptores, agindo na modulação da dor crônica, bem como incentivar os profissionais da saúde a reconhecerem a necessidade de ampliar o conhecimento acerca desse funcionamento e sinergismo com diversos fármacos para que ocorra o uso seguro da cannabis no tratamento de múltiplas doenças, sobretudo dores crônicas.

CONTEÚDO: A ação dos canabinoides no sistema endocanabinoide tem a capacidade de neuro e imunomodulação da transmissão da dor de forma multifatorial e extremamente complexa, atuando simultaneamente em múltiplos alvos, no sistema nervoso periférico, espinhal e supraespinhal. Os mecanismos de analgesia determinados pelos canabinoides incluem a inibição de liberação de neurotransmissores e neuropeptídeos nos terminais nervosos pré-sinápticos, a modulação da excitabilidade neuronal pós-sináptica, a ativação da via inibitória descendente e a redução da inflamação neural. Existe ainda a possibilidade de que a interação dos canabinoides com receptores opioides e serotoninérgicos tenha uma ação amplificadora do efeito analgésico de fármacos pertencentes à classe opioide.

CONCLUSÃO: O sistema endocanabinoide desempenha um papel fundamental no controle da dor e na sua fisiopatologia. Espera-se que esse sistema continue a ser estudado para uma melhor compreensão das suas vias de sinalização e metabolismo. É preciso também que se realizem mais ensaios clínicos, de maior dimensão e duração, para compreender até que ponto essa abordagem poderá ser benéfica no tratamento da dor crônica.

Descritores: *Cannabis sativa*, Dor crônica, Endocanabinoides.

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HIGHLIGHTS

- The endocannabinoid system is a defense against excitotoxicity in situations of neuronal hyperactivity and can mitigate the chronification of pain.
- The system works in an antidromic way. In chronic pain, exogenous doses can restore more effective conditions of functioning and modulation.
- Anandamide, tetrahydrocannabinol (THC) and cannabidiol (CBD) directly activate glycine receptors, contributing to cannabinoid-induced analgesia in inflammatory and neuropathic pain, while 2-arachidonoylglycerol (2-AG) and CBD are positive allosteric modulators, mainly in the $\alpha 2$ subunits of the GABA_A receptor. The 2-AG signaling cascades in microglial cells mediate the effects of persistent pain.

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INTRODUCTION

The interest in *Cannabis sativa* has been demonstrated, with current scientific research, for the most different and growing therapeutic applications.

In the 20th century, when the first chemical components of the plant were identified, there were increasing efforts to understand their mechanism of action and their interaction with human physiology, which led to the discovery of specific receptors for cannabinoids and endogenous ligands, called endocannabinoids. Their metabolic pathways were also identified, which gave rise to what is now known as the endocannabinoid system¹. Subsequently, alterations in signaling, modified concentrations of endocannabinoids and alterations in the expression of cannabinoid receptors were found and associated with various diseases, which led to an effort to modulate this system in order to obtain therapeutic results. It is now known that the endocannabinoid system plays a fundamental role in pain control and its pathophysiology¹.

The interest in investigating the relationship between the endocannabinoid system and chronic pain is due to the fact that this type of pain, in addition to being a complex condition that intensely compromises quality of life, is associated with a high economic cost and lower labor productivity. Chronic pain is defined by the International Association for the Study of Pain (IASP) as pain that persists or recurs for more than 3 months². It represents one of the most prevalent health problems, affecting around 20% of people worldwide. Chronic pain is multifactorial: biological, psychological and social factors contribute to the pain syndrome. The pathophysiological mechanisms of chronic pain are complex and there is a lack of effective drugs to treat it, which leads to the need to discover new therapeutic strategies.

Cannabinoids act simultaneously or synergistically on multiple pain-related targets in the central nervous system (CNS) and peripheral nervous system (PNS)³. In addition to acting on cannabinoid receptors (CB1 and CB2), cannabinoids can modulate pain by interacting with G protein-coupled receptor 55 (GPR55) and G protein-coupled receptor 18 (GPR18), which is also known as the N-arachidonyl glycine receptor (NAGly), as well as other well-known G protein-coupled receptors (GPCRs), such as serotonin (5-HT) and opioid receptors³.

Cannabinoids can interact with different transient receptor potential ion channels (TRPV, TRPA and TRPM)^{3,4}. TRPV1 is involved in temperature control, pain transmission and modulation, as well as in the integration of various painful stimuli³. It also has various effects on the cyst-loop receptor superfamily of ligand-activated ion channels (e.g. nicotinic acetylcholine, glycine, GABA_A, GABA_{A-p}, 5-HT₃ receptors)³. Anandamide, tetrahydrocannabinol (THC) and cannabidiol (CBD) directly activate glycine receptors, contributing to cannabinoid-induced analgesia in inflammatory and neuropathic pain, while 2-arachidonoylglycerol (2-AG) and CBD are positive allosteric modulators, mainly in the $\alpha 2$ subunits of the GABA_A receptor³. On the other hand, THC is a negative allosteric modulator and inhibits nicotinic and 5-HT₃ receptors^{3,5}. Cannabinoids

can exert other non-CB1/non-CB2 receptor-mediated antinociceptive effects by interacting with 5HT₃ and N-methyl-d-aspartate (glutamatergic) receptors⁴.

The anti-inflammatory action of cannabinoids may contribute to their analgesic effects. CBD's action as an inverse CB2 agonist may explain its anti-inflammatory properties. Some cannabinoids modulate and activate different isoforms of peroxisome proliferator-activated nuclear receptors (PPAR α , β and γ)³. In addition, the non-cannabinoid components of the cannabis plant (for example, terpenoids and flavonoids) can contribute to the analgesic and anti-inflammatory effects of cannabis³.

The endocannabinoid system (ECS) is a neuromodulatory system that plays a role in CNS development, synaptic plasticity and the response to harmful endogenous and environmental stimuli.

ECS consists of:

1. endocannabinoids or endogenous cannabinoids or endogenous ligands: anandamide and 2-arachidonoylglycerol (2-AG). There are other endogenous cannabimimetic molecules being investigated that will expand the number of endocannabinoids;
2. receptors: cannabinoid receptors 1 and 2 (CB1 and CB2);
3. enzymes responsible for the synthesis, transport and degradation of endocannabinoids: NAPE-PLD, DAGL, FAAH, MAGL.

ECS is characterized by a wide distribution throughout the body. It is a ubiquitous neuromodulatory system, fundamental in basic physiology and behavioral aspects, which seems to be involved in pathophysiological conditions at both central and peripheral levels⁶.

ENDOCANNABINOIDS - MECHANISM OF ACTION

Endocannabinoids are one of the exceptions to the law of dynamic polarization, proposed by a study in 1891, which postulated that the orthodromic direction of interneural communication proceeds from pre-synaptic axon terminals to post-synaptic dendrites. Unlike classic neurotransmitters, endocannabinoids function as extracellular retrograde messengers in an antidromic direction, being released from the postsynaptic neuron to act on presynaptic CB1s in an autocrine and paracrine manner⁶.

Endocannabinoids are derived from phospholipid precursors in the cell membrane and are produced on demand in postsynaptic neurons, so they are not synthesized in presynaptic endings or stored in vesicles like classic neurotransmitters⁶.

Endocannabinoid synthesis occurs in response to an increase in the intracellular concentration of calcium (Ca²⁺) due to neuronal depolarization or mobilization of intracellular deposits (via stimulation of receptors coupled to Gq/G11 proteins) and/or direct enzymatic activation by Gq/G11 proteins. After synthesis, they are transported across the cell membrane and reach the binding sites, located on the helices of the receptors that cross and exceed the internal and external limits of the membrane (transmembrane), diffusing laterally between its layers. The resulting influx of Ca²⁺ (via VCC - voltage-dependent calcium channels and NMDA, NMDA-R type receptors) acts as a

second messenger, modulating the release of other neurotransmitters⁶, which are inactivated mainly by reuptake (neurons and glia), then hydrolyzed by specific enzymes. Anandamide is metabolized by fatty acid amide hydroxylase (FAAH) into ethanolamine and arachidonic acid, and 2-AG by a monoacylglycerol lipase (although also by FAAH)⁶. The endocannabinoid system constitutes a cellular defense against excitotoxicity in situations of acute hyperactivity in neuronal pathways.

Anandamide (AEA)

AEA (N-arachidonyl ethanolamide), a conjugation of “ananda” (Sanskrit for “eternal happiness”) and “amide”, was the first endocannabinoid discovered. It is a partial agonist of CB1 and CB2 receptors, but a full agonist (with low affinity) of the transient receptor potential vanilloid 1 (TRPV1). Although AEA is a partial agonist, it has greater selectivity and affinity for the CB1 receptor than 2-AG and appears to be the main endocannabinoid^{3,6}.

AEA can play a dual role in nociception: antinociceptive on cannabinoid receptors and pronociceptive on TRPV1 receptor. It has a remarkable “tetrad effect” when injected into mice. The tetrad is a combination of inhibition of motor activity, catalepsy, hypothermia and hypoalgesia, also interacting with other

neurotransmitter systems that may play a role in nociception. Cannabinoids can directly inhibit 5-HT₃ receptors, leading to analgesia and neuroprotective effects. Anandamide exerts part of its effects on the CNS via 5-HT₃ receptors. In addition, micromolar concentrations of anandamide have been shown to bind to 5-HT₁ and 5-HT₂ receptors, thus describing anandamide’s role in other neurotransmitter systems³.

2-Araquidonoilglicerol (2-AG)

2-AG is a full agonist at CB1 and CB2 receptors that can be released from the postsynaptic neuron by simple diffusion and/or through a process facilitated by a carrier protein. Once bound to CB1, activation leads to inhibition of neurotransmitter release in the presynaptic cell via voltage-dependent Ca²⁺ channels and stimulation of the cell’s inward rectifier K⁺ channels. After neuronal depolarization, the release of glutamate from Ca²⁺-dependent presynaptic vesicles activates NMDA receptors in postsynaptic neurons, leading to postsynaptic currents. This change in membrane excitability rapidly triggers the synthesis of 2-AG. 2-AG then goes retrograde to the presynaptic terminals to stimulate CB1 receptors which, in turn, activate K⁺ channels and inversely inhibit Ca²⁺ channels, thus inhibiting the release of excitatory neurotransmitters (figure 1).

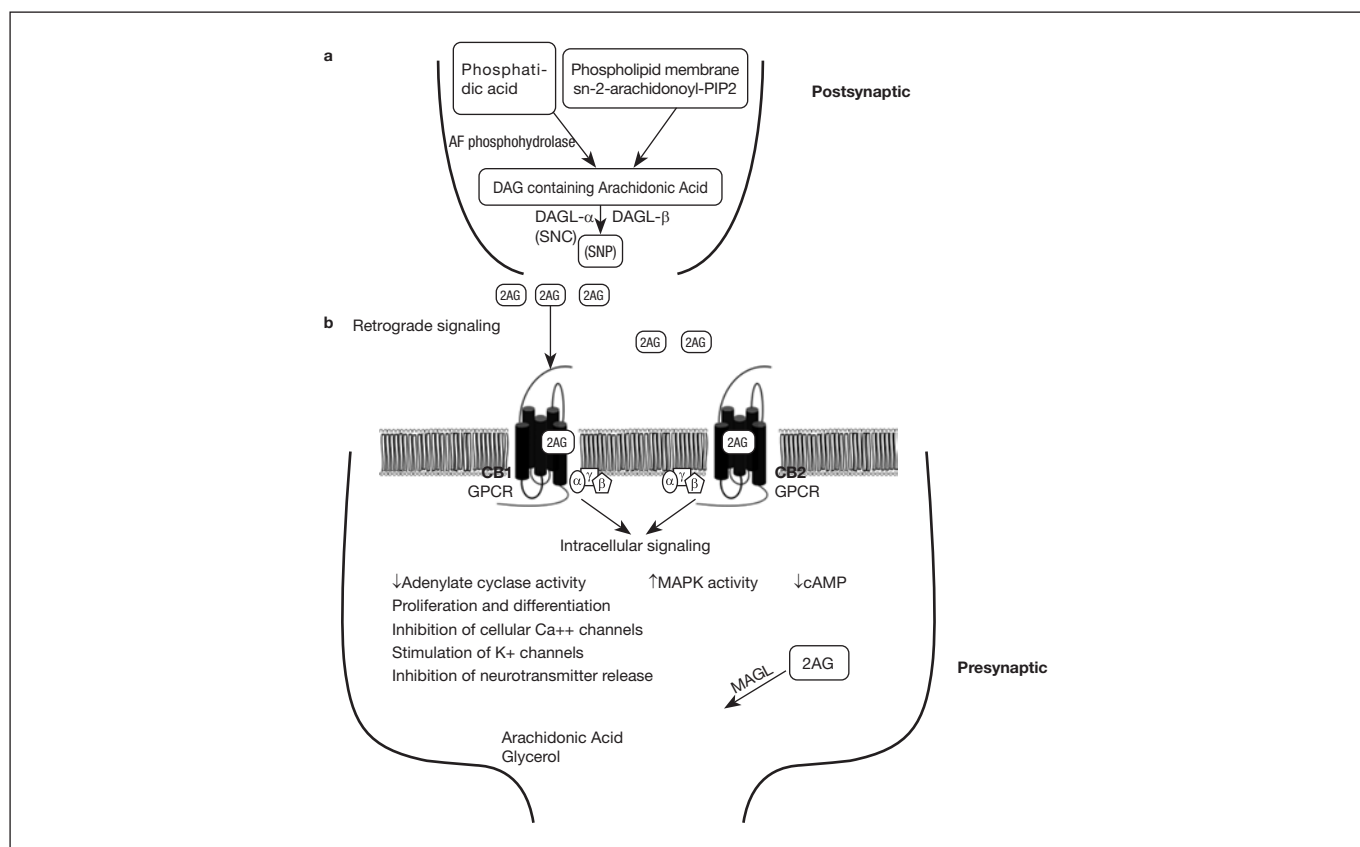


Figure 1. 2-AG synthesis and retrograde signaling.

(a) The variation of postsynaptic membrane excitability triggers the synthesis of 2-AG. (b) 2-AG travels retrograde to stimulate CB1 receptors on presynaptic terminals, which in turn activate K⁺ channels and inversely inhibit Ca⁺⁺ channels, thus inhibiting excitatory neurotransmitter release. 2-AG is metabolized in the presynaptic neuron with MAGL into arachidonic acid and glycerol. The concept shown in the figure is defended by a study³ and does not include glial participation (especially astroglia). 2-AG, 2-arachidonoylglycerol; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; DAG, diacylglycerol; DAGL- α and DAGL- β , diacylglycerol lipase- α or diacylglycerol lipase- β ; MAGL, monoacylglycerol lipase; PA, phosphatidic acid; PLC β , phospholipase C β ; PIP₂, sn-2-arachidonoyl-phosphatidylinositol-4,5-bisphosphate; MAPK, mitogenactivated protein kinase; GPCR, G protein-coupled receptors.

ENDOCANNABINOIDS - PAIN MODULATION

Pain is characterized by the detection of noxious stimuli by specific sensory receptors, the nociceptors, anatomically presented as free nerve endings of A δ and C axonal fibers, each with its own particularities, with the ability to detect painful stimuli and conduct them to the cerebral cortex, where they are interpreted as pain¹. In chronic pain (CP), the pathophysiological mechanisms have not been fully elucidated, making treatment difficult and the results not always satisfactory.

Neurophysiological studies have helped to clarify the pathophysiology of the disease, revealing, for example, increased activity in somatosensory nerve fibers or changes in the endogenous control of nociception¹.

The pathophysiological mechanisms underlying CP include complex processes of peripheral and central sensitization. Antinociceptive actions from the endocannabinoid system have been demonstrated in numerous animal pain models⁷. Endocannabinoids are produced on demand (without storage in synaptic vesicles) in postsynaptic neurons. When nociceptive stimuli occur, there is an increase in the release of endocannabinoids, leading to pain-modulating effects. Animal research shows that endocannabinoids have analgesic actions in the peripheral, spinal and supraspinal pain pathways³.

Peripheral mechanisms

In the periphery, CB1 receptors are located in sensory afferent terminals where endocannabinoids act to control the transduction of pain from nociceptive stimuli, while CB2 receptors, located in cells of the immune system and keratinocytes, intervene in the release of endorphins, acting on the opioid receptors of primary afferent neurons, thus inhibiting nociception^{1,3,8}. Inflammatory pain models show high concentrations of anandamide and 2-AG in peripheral tissues^{3,8}. The CB2 cannabinoid receptor in the periphery plays a vital role in analgesia.

Studies show that 2-AG participates in multiple mechanisms that lead to pain modulation, including inhibiting the production and release of reactive oxygen species (ROS) and cytokines, as well as the release of peripheral endogenous opioids^{3,8}. There is more research describing the anti-inflammatory and antinociceptive actions mediated by 2-AG compared to anandamide.

This action in the periphery holds considerable promise for separating therapeutic effects from unwanted adverse effects on the CNS⁷.

Spinal mechanisms

Endocannabinoids have antinociceptive effects in the spinal cord due to the high expression of CB1 receptors in the dorsal root ganglia and nociceptive terminals of the dorsal horn, where they inhibit the release of neurotransmitters involved in pain transmission¹. At this level, 2-AG inhibits the release of pronociceptive neurotransmitters from the primary afferent terminals mediated by CB1 receptors^{13,8}.

CB2 in the spinal cord appears to modulate central immune responses, which has been implicated in the development and neuronal sensitization of neuropathic pain¹. Anandamide has shown

antinociceptive effects in acute and chronic pain through CB2 receptors expressed on inhibitory interneurons and glial cells^{3,8}. These effects were shown in an experimental model, in which hours after a peripheral surgical incision, there was a marked decrease in anandamide concentrations, while there were no changes in the concentration of 2-AG^{3,8}. Anandamide concentrations returned to baseline as nociceptive behavior decreased. 2-AG concentrations subsequently increased in conjunction with glial cell activation, up-regulation of the CB2 receptor and resolution of the pain state^{3,8}.

Endocannabinoids have different effects on pain modulation. Anandamide acts at the onset of pain, while 2-AG plays a role in pain resolution³.

Supraspinal mechanisms

Several studies have attributed an important role to the endocannabinoid system in the modulation of painful stimuli at the supraspinal level. CB1 inhibits ascending nociceptive transmission, mainly in the thalamus and brainstem, modifies the subjective interpretation of pain by modulating neuronal activity in fronto-limbic circuits (more specifically in the amygdala) and cortical areas, and activates the descending inhibitory pathway by inhibiting the release of gamma-aminobutyric acid (GABA) in the periaqueductal gray (PAG) and raphe nuclei^{1,3,8}. Anandamide has a biphasic effect on the supraspinal level of pain modulation, being released due to stimulation of the periaqueductal gray (PAG) or the presence of peripheral inflammation⁹. In acute pain, the anandamide released causes antinociceptive actions. When high concentrations of anandamide occur due to prolonged stimulation, it modulates pronociceptive responses by binding to TRPV¹⁹.

Synergic effect of anandamide and 2-AG

In the modulation of pain at the spinal and supraspinal levels, anandamide and 2-AG have synergistic but different roles. Stress-induced analgesia exhibits a synergistic effect of anandamide and 2-AG through the induction of descending inhibitory GABAergic signaling to the spinal cord, thus mediating stress-induced analgesia⁹. In a prolonged modulation study with shock application to the foot, both endocannabinoids were released in the ipsilateral L5 dorsal root ganglion after stimulation^{3,10}. CB1 receptors in the dorsal root ganglion and CB2 receptors in the periphery involved a synergistic interaction between anandamide and 2-AG^{3,10}. Both endocannabinoid levels were shown to be increased after 3 and 7 days of chronic constriction injury in the sciatic nerve of a rat^{3,10}. After 3 days, endocannabinoid levels increased only in the spinal cord and PAG. However, after 7 days, high concentrations were also detected in the rostral ventral bulb^{3,10}. This study provided evidence of endocannabinoid cooperation in relation to synergistic involvement in pain regulation.

CP increases the endocannabinoid signaling effects of both anandamide and 2-AG. Positive regulation of CB2 receptors found in such pain states would benefit from endocannabinoid agonism^{3,9}. 2-AG signaling cascades in microglial cells mediate the effects on persistent pain^{3,9}.

ENDOCANNABINOID RECEPTORS

CB1 receptors

Central CB1

CB1 receptor is the most abundant GPCR in mammalian brains. It is therefore referred to as the “brain’s cannabinoid receptor”³. These receptors are expressed centrally in all brain structures and in decreasing density, from the olfactory bulb, cerebellum, hippocampus, basal nuclei, cortex and amygdala to the hypothalamus, thalamus and brainstem.

CB1 receptors are expressed in most areas of the brain in presynaptic terminals of glutamatergic and GABAergic neurons³. In addition, CB1 receptors can also be expressed postsynaptically and can form heterodimers in association with other GPCRs, including dopamine D2, adenosine A2 or orexin type 13 receptors³.

The intracellular region of CB1 is more regularly coupled to Gi/o proteins. Consequently, activation of CB1 receptors inhibits the activity of adenylate cyclase with a subsequent reduction in the level of intracellular cyclic adenosine monophosphate (cAMP) or promotes the activity of mitogen-activated protein kinase (MAPK) (figure 2). The decrease in the level of cAMP leads to the activation of voltage-dependent K⁺ channels and the inhibition of Ca²⁺ channels, thus decreasing the release of neurotransmitters. In neurons, CB1 activation of Gi/o can also directly inhibit voltage-dependent Ca²⁺ channels¹¹.

The intracellular region of CB1 is most regularly coupled to Gi/o proteins. The activation of CB1 receptors by binding to a ligand (2-AG) inhibits adenylate cyclase activity with subsequent reduction of intracellular cyclic adenosine monophosphate (cAMP) level or enhances mitogen-activated protein kinase (MAPK) activity. Decreased cAMP level leads to activation of voltage-gated K⁺ and inhibition of Ca²⁺ channels, thus inhibiting neurotransmitter release. The concept shown in the figure is defended by a study³. 2-AG, 2-arachidonoylglycerol; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; MAPK, mitogenactivated protein kinase; GPCR, G protein-coupled receptors.

Neuronal depolarization rapidly triggers the synthesis of endocannabinoids, particularly 2-AG, in postsynaptic neurons.

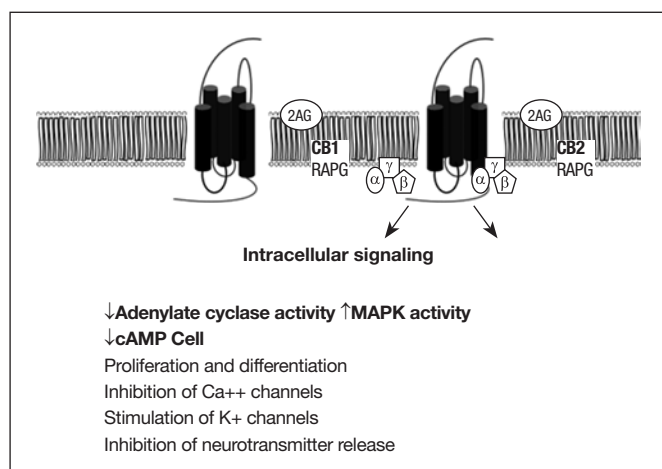


Figure 2. CB1 receptor activation

Subsequently, 2-AG acts retrogradely on CB1 receptors in the presynaptic terminals and is then inactivated by hydrolytic enzymes. This “on-demand” synthesis of endocannabinoids leads to CB1-mediated activation of K⁺ channels and inhibition of Ca²⁺ channels, thus controlling the release of excitatory and inhibitory neurotransmitters, which eventually tune the duration of synaptic activity and synaptic plasticity¹². CB1 is also found in non-neuronal brain cells, predominantly in astrocytes, where its activation stimulates the release of neurotransmitters. Activation of the astroglial CB1 receptor appears to induce intracellular Ca²⁺ levels, triggering the release of glutamate and the subsequent activation of presynaptic metabotropic glutamate receptors¹³.

Peripheral CB1

CB1 receptors are also expressed in PNS and in almost all mammalian tissues and organs, including the adrenal glands, smooth and skeletal muscle, heart, lungs, gastrointestinal tract, liver, male and female reproductive tract, bones, adipose tissue and skin³. CB1 receptors play a vital role in maintaining homeostasis and regulating adrenal, cardiovascular, pulmonary, gastrointestinal and reproductive functions, among others. They are mainly located in the afferent sensory terminals, where endocannabinoids act to control the transduction of nociceptive stimuli, thus playing an important role in the sensitization of peripheral pain³.

CB2 receptors

Central CB2

The function of CB2 in the brain is still controversial. In contrast to CB1, CB2 receptors are limited in the brain, their expression is restricted to specific neuronal cells and they become abundant in activated microglia and astrocytes. These receptors play an important role in immune function, inflammation and pain modulation, especially in states of allodynia and hyperalgesia. In order to identify the role of the CB2 receptor in regulating the central immune responses that lead to the development of neuropathic CP, a group of researchers used genetically modified mice without CB2 expression and with CB2 overexpression in a model of induced neuropathic pain. The elimination of CB2 receptors led to an increase in the manifestations (hyperalgesia and allodynia) of neuropathic pain. On the other hand, overexpression of CB2 receptors attenuated these manifestations. These findings have encouraged interest in studying agonists of this receptor for the treatment of neuropathic pain¹⁴.

The presence of CB2 receptors on microglia within the nervous system may explain the role of cannabinoids in modulating neuropathic pain by reducing cytokine-mediated neuroinflammation¹⁵.

Like CB1, CB2 receptor is a GPCR and is coupled to the Gi/Go α protein. Thus, its stimulation inhibits adenylate cyclase activity and activates MAPK.

Selective CB2 agonists suppress neuronal activity in the dorsal horn by reducing C-fiber activity and shutdown involving wide dynamic range (WDR) neurons. There is increased peripheral expression of CB2 receptor protein or mRNA in inflamed tissues and in the dorsal root ganglion in neuropathic states³.

Peripheral CB2

CB2 is expressed mainly in immune system cells such as monocytes, macrophages, B and T cells and mast cells. Activation of the CB2 receptor reduces the release of pro-inflammatory cytokines and lymphoangiogenic factors³. In addition, CB2 receptors are also present in other peripheral organs that play a role in the immune response, including the spleen, tonsils, thymus and keratinocytes, as well as in the digestive tract. Thus, CB2 receptors represent the main regulators of inflammatory and nociceptive responses and may control the activation and migration of immune cells³.

PUTATIVE ENDOCANNABINOID RECEPTORS: TRPV1 AND GPR55

TRPV1

The vanilloid receptor type 1 (TRPV1), also known as the capsaicin receptor, was the first member of the TRPV channel sub-family to be discovered and cloned. TRPV1 channels are activated by capsaicin, endocannabinoids and phytocannabinoids³ and have a pre-synaptic and, above all, post-synaptic intracellular localization. These channels are phylogenetically related to cannabinoid receptors and are putative receptors⁶.

The function of TRPV1 is strongly dependent on the binding of regulatory proteins that induce changes in its phosphorylation state. Phosphorylation induced by adenosine triphosphate (ATP), protein kinase A (PKA) and C (PKC), phosphoinositide binding protein (PIRT) and phosphatidylinositol 4,5-bisphosphate (PIP2) is necessary for the activation of TRPV1 and cation channels. TRPV1 activation contributes to pain transmission, neurogenic inflammation, synaptic plasticity, neuronal overexcitability and neurotoxicity^{3,16}.

TRPV1 “desensitization” occurs when increased intracellular Ca²⁺, following TRPV1 stimulation, activates the protein (i.e. calmodulin) that stabilizes the channel in a closed conformational state or by Ca²⁺-dependent phosphatase (i.e. calcineurin), which dephosphorylates and inactivates TRPV1. This rapid process of desensitization and inactivation of TRPV1 is believed to be the basis of the paradoxical analgesic, anti-inflammatory and anticonvulsant effects of TRPV1 agonists^{13,16}.

TRPV1 channels are widely expressed in the dorsal root ganglia and in type A δ and C nerve fibers. In sensory neurons, TRPV1 channels function as molecular integrators for various types of sensory inputs that contribute to generating and transmitting pain. In central neurons, smaller amounts of TRPV1 channels are expressed both pre-synaptically and post-synaptically, thus acting to regulate synaptic strength. They generally affect pain, anxiety and depression by inducing effects opposite to those exerted by CB1 receptors in the same context¹⁷.

In addition, there is intracellular crosstalk between TRPV1 and CB1 or CB2, as they are co-localized in peripheral and central neurons (sensory neurons, dorsal root ganglia, spinal cord, brain neurons). Recently, a multitude of interactions have been discovered between cannabinoid, opioid and TRPV1 receptors in the modulation of pain¹⁸. This offers a great opportunity for the development of new multi-target ligands for pain control with improved efficacy and adverse effect profile.

GPR55

GPR55 belongs to the large family of GPCRs, and its endogenous ligand is lysophosphatidylinositol (LPI). It is considered by some experts to be the third cannabinoid receptor, CB3. GPR55 is activated by Δ^9 -THC when antagonized by CBD. There are conflicting data on the likelihood that low concentrations of endocannabinoids can activate GPR55. These controversies can be explained by biased signaling, depending on the type and condition of the cell or the formation of heteromers between GPR55 and CB1 receptors. GPR55 activation may play a role opposite to that of CB1, increasing the release of neurotransmitters. GPR55 may play a role in the mechanical hyperalgesia associated with inflammatory and neuropathic pain³.

PHYTOCANNABINOIDS (THC AND CBD)

THC

Δ^9 -tetrahydrocannabinol (THC) is an analog of the endocannabinoid anandamide (AEA). It is responsible for most of the pharmacological actions of cannabis, including psychoactive, memory, analgesic, anti-inflammatory, antioxidant, antipruritic, bronchodilatory, antispasmodic and muscle relaxant activities. THC acts as a partial agonist at CB1 and CB2¹⁹ receptors. THC has a very high binding affinity for the CB1 receptor, which mediates its psychoactive properties. Interestingly, most of the negative effects of THC - psychic effects, memory impairment, anxiety and immunosuppression - can be reversed by other constituents of the cannabis plant (other cannabinoids, CBD, terpenoids and flavonoids)³.

Cannabidiol (CBD)

CBD is the other important cannabinoid in the cannabis plant. It is the non-psychoactive analog of THC. It has significant analgesic, anti-inflammatory, anticonvulsant and anxiolytic activities without the psychoactive effect of THC. CBD has little binding affinity for CB1 or CB2 receptors, but can antagonize them in the presence of THC. CBD behaves as a non-competitive negative allosteric modulator of the CB1 receptor and reduces the efficacy of THC and AEA²⁰. This may explain the “entourage effect” that CBD exhibits, as it improves the tolerability and safety of THC, reducing the likelihood of psychoactive effects and other adverse effects, such as tachycardia, sedation and anxiety.

PHYTOCANNABINOIDS - PAIN MODULATION

The phytocannabinoids THC and CBD are lipophilic substances that readily cross the blood-brain barrier and interact with receptors in both the central and peripheral nervous systems, exerting analgesic effects especially in hyperalgesia and inflammatory states.

THC

THC provides CB1 receptor-mediated antinociception through activation of supraspinal levels and descending serotonergic and noradrenergic pain-modulating pathways to produce antinociceptive effects via spinal activation of 5-HT₇, 5-HT_{2A} and alpha-2 adrenoceptor²¹.

The fronto-limbic distribution of cannabinoid receptors explains the central mechanism of THC analgesia, as it preferentially targets the affective qualities of pain. A functional magnetic resonance imaging study revealed that amygdala activity contributes to the dissociative effect of THC on pain perception related to continuous cutaneous pain and hyperalgesia that were temporarily induced by capsaicin²². THC reduced reported discomfort, but not intensity of continuous pain and hyperalgesia. THC also reduced functional connectivity between the amygdala and primary sensory-motor areas during the ongoing pain state. The authors concluded that peripheral mechanisms alone cannot explain the dissociative effects of THC on observed pain and amygdala activity contributes to the interindividual response to cannabinoid analgesia.

The analgesic effects of THC are mediated by mechanisms distinct from those responsible for the psychoactive effects. THC has an additional analgesic effect with kappa opioid receptor agonists. This effect is blocked by kappa antagonism, but opioid receptor antagonism does not alter the psychoactive effects of THC³.

CBD

CBD regulates pain perception, mainly through non-CB1/non-CB2 mechanisms. CBD interacts with a significant number of other targets, including non-cannabinoid GPCR (e.g. 5-HT_{1A}), ion channels (TRPV1, TRPA1, TRPM8, GlyR) and PPAR. In addition, CBD increases the effects of AEA by inhibiting its absorption, as well as its hydrolysis by the enzyme fatty acid amide hydrolase (FAAH)³.

CBD can act synergistically with THC and contribute to its analgesic effect, providing an “entourage effect”, minimizing the negative psychoactive effects of THC. This depends on the differences in THC/CBD concentration in the cannabis chemotype. Although CBD as a monotherapy has not been clinically evaluated in pain management, its anti-inflammatory and antispasmodic effects and good safety profile suggest that it can be a safe and effective analgesic³.

CONCLUSION

Pre-clinical trials have amply demonstrated the potential interest of the endocannabinoid system in pain treatment, highlighting that receptors such as CB1, CB2, and the enzymes FAAH and MAGL, among others, have been identified as possible new targets for developing more selective drugs devoid of the classic adverse effects.

With regard to clinical trials, although they don't always demonstrate efficacy, they do show that it is possible that drugs that act on the endocannabinoid system have an effect on controlling CP. In the future, it is hoped that this system will continue to be studied in order to gain a better understanding of its signaling pathways and metabolism, and also that more clinical trials of greater size and duration will be carried out in order to understand the extent to which this approach could be beneficial in CP treatment.

AUTHORS' CONTRIBUTIONS

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Data Collection, Conceptualization, Project Management, Methodology, Writing - Preparation of the Original, Writing - Review and Editing

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Writing - Review and Editing

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