Cannabinoids and Pain: Mechanisms of Action

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Introduction

Cannabinoids act simultaneously or synergistically on multiple pain targets within the peripheral and CNS [1–3]. Alongside acting on cannabinoid receptors (CB1 and CB2), cannabinoids may modulate pain through interaction with the putative non-CB1/non-CB2 cannabinoid G protein-coupled receptor 55 (GPR55) and GPR18 which is also known as the N-arachidonoyl glycine (NAGly) receptor [4, 5], as well as other well-known G protein-coupled receptors (GPCRs) such as serotonin (5-HT) and opioid receptors [6, 7].

Moreover, cannabinoids can interact with different transient receptor potential ion channel subfamilies (TRPV, TRPA, and TRPM) [2, 3]. TRPV1 is involved with temperature control, pain transmission, and modulation, as well as the integration of diverse painful stimuli [8–10].

Cannabinoids have various effects on the cys-loop ligand-gated ion channel superfamily (e.g., nicotinic acetylcholine, glycine, $GABA_A$, $GABA_A$-ρ, $5\text{-}HT_3$ receptors) [11–19]. Anandamide, THC, and cannabidiol directly activate glycine receptors, contributing to cannabinoid-induced analgesia in inflammatory and neuropathic pain [12–15], while 2-arachidonoylglycerol (2-AG) and cannabidiol (CBD) are positive allosteric modulators mainly at the α2-containing $GABA_A$ receptor subtypes [16, 17]. On the other hand, cannabinoids (THC) negatively allosterically modulate and inhibit nicotinic and 5-HT3 receptors [11, 18, 19].

The anti-inflammatory action of cannabinoids may contribute to their analgesic effects [20, 21]. Cannabinoid (CBD) action as a CB2 inverse agonist may explain its anti-inflammatory properties [22]. Some cannabinoids modulate and activate different isoforms of the nuclear receptor peroxisome proliferator-activated receptors (PPARα, β, and γ) [23].

Additionally, non-cannabinoid constituents of the cannabis plant (e.g., terpenoids and flavonoids) may contribute to the analgesic and anti-inflammatory effects of cannabis [24, 25].

Endocannabinoids' Mechanism of Action

Anandamide (AEA)

Anandamide is a partial agonist at both CB_1 and CB_2 receptors, but a full agonist at the transient receptor potential vanilloid 1 (TRPV1) receptor. Although anandamide is a partial agonist, it has a selectivity and higher affinity to the CB_1 receptor than 2-AG [26]. Once actions are carried out at the receptor, anandamide is thought to possibly be taken up by transport proteins on both neurons

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and glia that mediate endocannabinoid uptake [27]. Anandamide can play a dual role in nociception: antinociceptive at cannabinoid receptors and pronociceptive at the TRPV1 receptor [28]. Anandamide has a noted "tetrad effect" when injected into mice. The tetrad is a combination of inhibition of motor activity, catalepsy, hypothermia, and hypoalgesia [29, 30].

Anandamide also interacts with other neurotransmitter systems that may play a role in nociception. Cannabinoids might directly inhibit 5-HT_3 receptors, leading to analgesia and neuroprotection effects [29]. Anandamide exerts part of its CNS effects through the 5-HT_3 receptors [29]. In addition, it was shown that micromolar concentrations of anandamide bind to 5-HT_1 and 5-HT_2 receptors, thus further describing the role of anandamide in other neurotransmitter systems [31].

2-Arachidonoylglycerol (2-AG)

2-AG is a full agonist at CB_1 and CB_2 receptors. 2-AG may be secreted from the postsynaptic neuron by simple diffusion or through a passive carrier protein [27]. Once bound to CB_1, activation leads to inhibition of neurotransmitter release in the presynaptic cell via inhibition of voltage-activated calcium channels and enhancement of inwardly rectifying K^+ channels in the cell [27, 32].

Subsequent to neuronal depolarization, the Ca2+-dependent release of glutamate from presynaptic vesicles activates NMDA receptors at the postsynaptic neurons leading to excitatory postsynaptic currents (EPSCs). This variation of membrane excitability quickly triggers the synthesis of 2-AG. Then, 2-AG travels retrograde to stimulate CB1 receptors on presynaptic terminals, which in turn activate K+ channels and inversely inhibit Ca2+ channels, thus inhibiting excitatory neurotransmitter release [32] (Fig. 24.1).

Endocannabinoids and Pain Modulation

Endocannabinoids are sensitized on demand. When noxious stimuli occur, there is an increase in endocannabinoid release, thus leading to pain modulation effects [30]. Animal studies show endocannabinoids to have analgesic actions in the periphery, spinal, and supraspinal pain pathways [30] (Table 24.1).

Peripheral Mechanisms

Models of inflammatory pain show elevated concentrations of anandamide and 2-AG in peripheral tissues [28]. The cannabinoid receptor, CB2, in the periphery plays a vital role in analgesia. 2-AG has been studied to show multiple mechanisms leading to pain modulation which include inhibiting production and release of reactive oxygen species and cytokines, and in addition 2-AG will release peripheral endogenous opioids [28]. There is more research describing the anti-inflammatory and antinociceptive mediated actions of 2-AG compared to anandamide. There are also CB1 receptors in the periphery that localize on sensory afferent terminals where endocannabinoids act to gate the transduction of pain from noxious stimuli [28].

Spinal Mechanisms

Endocannabinoids have antinociceptive effects at the dorsal horn in the spinal cord due to high expression of CB_1 receptors. At this level, 2-AG inhibits the release of pronociceptive neurotransmitters from primary afferent terminals mediated by CB_1 receptors [28]. In contrast, anandamide was shown to have effects on acute and chronic pain via mediation of CB_2 receptors expressed on inhibitory interneurons and glial cells [28]. In a surgical incision model, it was shown that hours

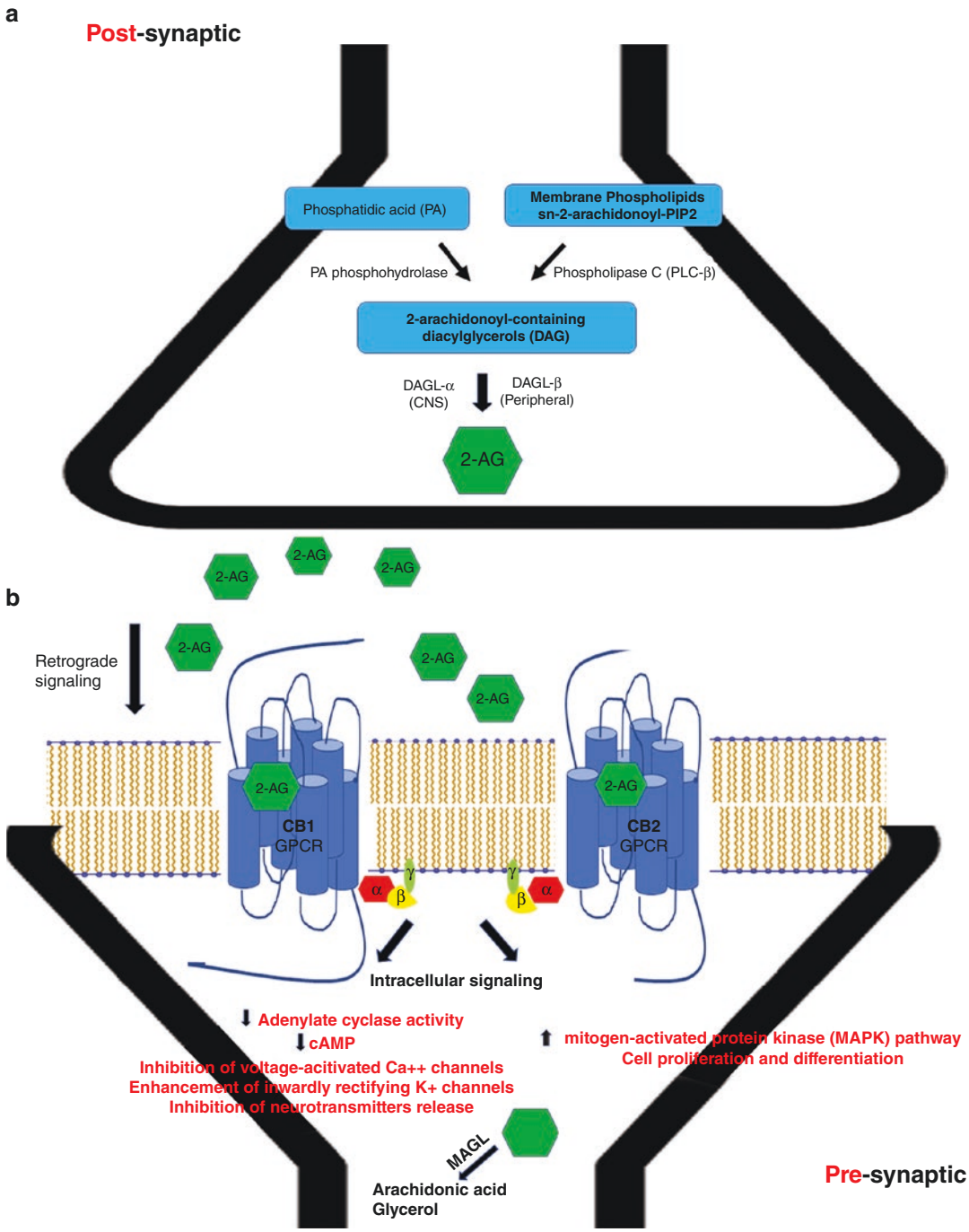

Fig. 24.1 Synthesis of 2-AG and the retrograde signaling. (**a**) The variation of postsynaptic membrane excitability triggers the synthesis of 2-AG. (**b**) 2-AG travels retrograde to stimulate CB1 receptors on presynaptic terminals, which in turn activate K+ channels and inversely inhibit Ca2+ channels, thus inhibiting excitatory neurotransmitter release. 2-AG is metabolized in the presynaptic neuron with MAGL into arachidonic acid and glycerol. 2-AG, 2-arachidonoylglycerol; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; COX2, cyclooxygenase 2; DAG, diacylglycerol; DAGL-α and DAGL-β, diacylglycerol lipase-α or diacylglycerol lipase-β; MAGL, monoacylglycerol lipase; PA, phosphatidic acid; PLCβ, phospholipase Cβ; PLD, phospholipase D; PIP2, sn-2-arachidonoyl-phosphatidylinositol-4,5-bisphosphate. (Used with permission from ©Samer Narouze, MD, PhD)

Table 24.1 Cannabinoid multimodal analgesic mechanisms of action

Cannabinoid antinociception pathways	
Peripheral	
	Peripheral CB2 receptor activation can lead to pain modulation by inhibiting production and release of inflammatory mediators (reactive oxygen species and cytokines) Endocannabinoids can release peripheral endogenous opioids Peripheral CB1 receptors act to gate the transduction of pain from noxious stimuli
Spinal	
	CB1 receptors are highly expressed on dorsal horn and DRG. CB1 activation leads to inhibition of pronociceptive neurotransmitter release from primary afferent terminals CB2 receptors expressed on spinal inhibitory interneurons and glial cells Anandamide exerts its actions at the onset of pain, whereas 2-AG plays a role in the resolution of pain
Supraspinal	
	Cannabinoids modulate: Ascending pain signals in the thalamus Descending signals in the brain stem Pain sensation in the frontal-limbic circuits (THC targets preferentially the affective qualities of pain) Anandamide has a "biphasic effect." On-demand release during acute pain causes antinociceptive effects. High concentration of anandamide due to prolonged stimulation leads to pronociceptive responses via TRPV1 binding

CB1 cannabinoid receptor type 1, *CB2* cannabinoid receptor type 2, *DRG* dorsal root ganglion, *THC* Δ^9-tetrahydrocannabinol, *CBD* cannabidiol, *AEA* anandamide, *2-AG* 2-arachidonoylglycerol, *TRPV1* transient receptor potential vanilloid type 1. (By ©Samer Narouze, MD, PhD, used with permission)

after a peripheral surgical incision, there was a marked decrease in anandamide concentrations, whereas there were no changes in 2-AG concentration [28]. Anandamide concentrations returned to baseline as nociceptive behavior subsides. 2-AG concentrations increased later in conjunction with glial cell activation, CB_2 receptor upregulation, and resolution of the pain state [28]. Endocannabinoids have different effects on pain modulation. Anandamide exerts its action at the onset of pain, whereas 2-AG plays a role in the resolution of pain.

Supraspinal Mechanisms

Endocannabinoids modulate ascending pain signals in the thalamus, descending signals in the brain stem, and pain sensation in the frontal-limbic circuits [28]. Anandamide has a biphasic effect on the supraspinal level of pain modulation. Anandamide is released due to stimulation of the periaqueductal gray (PAG) or peripheral inflammatory insult [27]. In acute pain, anandamide that is released causes antinociceptive actions. When high concentrations of anandamide occur due to prolonged stimulation, anandamide modulates pronociceptive responses via TRPV1 binding [27].

Anandamide and 2-AG Synergistic Effect

Anandamide and 2-AG have synergistic yet different roles in pain modulation at the spinal and supraspinal levels. Stress-induced analgesia exhibits a synergistic effect of anandamide and 2-AG through induction of descending inhibitory GABAergic signaling to the spinal cord, thus mediating stress-induced analgesia [27]. In a prolonged foot shock modulation study, both endocannabinoids were found to be released in the ipsilateral lumbar V dorsal root ganglion upon stimulation [33]. The CB_1 receptors at the dorsal root ganglion and CB_2 receptors at the periphery involve a synergistic interplay between anandamide and 2-AG [33]. Both endocannabinoids levels were enhanced after 3 and 7 days of chronic constriction injury at the sciatic nerve of a rat [33]. After the 3-day mark, endocannabinoid levels were increased only at the spinal cord and PAG. However, after 7 days, elevated concentrations were detected in the rostral ventral medulla as well [33]. This study provides evidence of endocannabinoid cooperation regarding synergistic involvement in the regulation of pain.

Chronic pain enhances the endocannabinoid signaling effects of both anandamide and 2-AG. An upregulation of CB_2 receptors found in such pain states would benefit from endocannabinoid agonism [27]. 2-AG signaling cascades from microglial cells mediate effects in persistent pain [27].

Endocannabinoid Receptors

CB1 Receptors

Central CB1 Receptors

CB1 receptor is the most abundant GPCR in the mammalian brain; thus it is referred to as the "brain cannabinoid receptor" [34]. CB1 receptors are expressed centrally in all brain structures and in decreasing density from the olfactory bulb, cerebellum, hippocampus, basal ganglia, cortex, and amygdala to the hypothalamus, thalamus, and brain stem [35].

They are expressed in most brain areas on presynaptic terminals of both glutamatergic and gamma aminobutyric acid (GABA)-ergic neurons [36]. Moreover, CB1 receptors can also be expressed postsynaptically where it can form heterodimers in association with other GPCRs including the dopamine D2, adenosine A2, or orexin type-1 receptors [37–39].

The intracellular region of CB1 is most regularly coupled to Gi/o proteins. Consequently, the activation of CB1 receptors inhibits adenylate cyclase activity with subsequent reduction of intracellular cyclic adenosine monophosphate (cAMP) level or promotes mitogen-activated protein kinase (MAPK) activity [34] (Fig. 24.2). Decreased cAMP level leads to activation of voltage-gated K+ and inhibition of Ca2+ channels, thus inhibiting neurotransmitter release [40–42]. In neurons, CB1 activation of Gi/o can also directly inhibit voltage-activated Ca2+ channels [32].

Neuronal depolarization rapidly triggers the synthesis of endocannabinoids, particularly 2-AG, at postsynaptic neurons. Subsequently, 2-AG travel backward to stimulate CB1 receptors on presynaptic terminals, and then after it is inactivated by hydrolytic enzymes. This "on-demand"

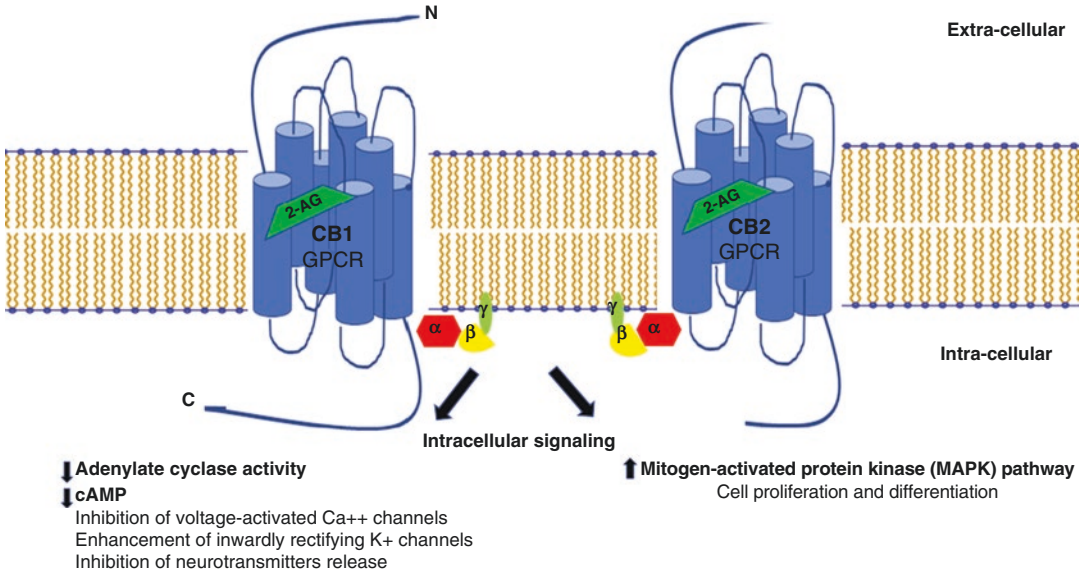

Fig. 24.2 CB1 receptor activation. The intracellular region of CB1 is most regularly coupled to Gi/o proteins. The activation of CB1 receptors by binding to a ligand (2-AG) inhibits adenylate cyclase activity with subsequent reduction of intracellular cyclic adenosine monophosphate (cAMP) level or enhances 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. (Used with permission from ©Samer Narouze, MD, PhD)

synthesis of endocannabinoids leads to CB1-mediated activation of K+ and inhibition of Ca2+ channels, thus controlling both excitatory and inhibitory neurotransmitter releases, which eventually tunes the duration of synaptic activity and synaptic plasticity [43, 44].

CB1 is also found in non-neuronal cells of the brain, predominately in astrocytes, where its activation stimulates the release of neurotransmitters. Unexpectedly, astroglial CB1 receptor activation seems to induce intracellular Ca2+ levels, triggering the release of glutamate and the subsequent activation of presynaptic metabotropic glutamate receptors [45–47] (Table 24.2).

Peripheral CB1 Receptors

CB1 receptors are also expressed in the peripheral nervous system and in almost all mammal tissues and organs including the adrenal glands, smooth and skeletal muscle, heart, lung, gastrointestinal tract, liver, male and female reproductive systems, bone, adipose tissue, and skin [32]. The CB1 receptors play a vital role in the maintenance of homeostasis and regulating adrenal, cardiovascular, lung, gastrointestinal, and reproduction functions, among others.

Peripheral CB1 receptors are mainly localized on sensory afferent terminals where endocannabinoids act to gate the transduction of pain

Table 24.2 Cannabinoids mechanism of action in chronic pain

Cannabinoids' mechanism of action in chronic pain	
CB1 receptors	
Central	Expressed abundantly centrally (CNS and spinal) On presynaptic terminals of both glutamatergic and gamma aminobutyric acid (GABA) neurons GPCR receptors, coupled to Gi/Go α proteins CB1 receptor activation inhibits adenylate cyclase activity and reduces intracellular cAMP Activation of voltage-gated K+ and inhibition of Ca2+ channels, inhibiting neurotransmitter release
Peripheral	Peripheral CB1 receptors are mainly localized on sensory afferent terminals, modulating the transduction of pain from noxious stimuli, an important role in peripheral pain sensitization
CB2 receptors	
Central	The role of CB2 in the brain is still controversial Expressed in activated spinal microglia and astrocytes Like CB1, CB2 receptor is a GPCR and is coupled to Gi/Go α proteins. Thus, its stimulation inhibits adenylate cyclase activity
Peripheral	CB2 receptors are abundantly expressed in the immune system cells CB2 receptor activation reduces the release of pro-inflammatory cytokines and lymphoangiogenic factors CB2 receptors represent key regulators of inflammatory and nociceptive responses CB2 receptors can control the activation and migration of immune cells
TRPV1	
	TRPV1 channels are largely expressed in dorsal root ganglia and sensory nerve fibers (Aδ and C-type) TRPV1 has paradoxical effect on pain TRPV1 activation contributes to pain transmission and neurogenic inflammation TRPV1 "desensitization" occurs following TRPV1 stimulation due to increase of intracellular Ca2+ (see text) This fast process of TRPV1 desensitization and inactivation leads to the paradoxical analgesic and anti-inflammatory effects of TRPV1 agonists There is intracellular cross talk between TRPV1 and CB1 or CB2 as they are colocalized in peripheral and central neurons
GPR55	
	GPR55 is activated by THC while antagonized by CBD There are heteromers between GPR55 and CB1 receptors GPR55 activation may play an opposite role to CB1 by enhancing neurotransmitter release GPR55 also involved in mechanical hyperalgesia resulted from neuropathic and inflammatory pain

Table 24.2 (continued)

Cannabinoids' mechanism of action in chronic pain	
Other receptors	
	THC activates 5-HT7, 5-HT2A, and alpha-2 adrenoceptors (descending inhibitory pathway) THC, CBD, and anandamide directly activate glycine receptors, contributing to cannabinoid-induced analgesia in inflammatory and neuropathic pain 2-AG and CBD are positive allosteric modulators at the α2-containing GABAA receptor subtypes Cannabinoids (THC) inhibit nicotinic, 5-HT3, andNMDA receptors contributing to analgesia THC, CBD, and endocannabinoids activate PPARα and PPARγ receptors contributing to the analgesic, anti-inflammatory, and neuroprotective effects
Opioid receptors	
	Cross talk and heteromers between cannabinoids and opioids receptors (see text) Synergistic interactions between cannabinoid and opioid analgesia CB2 activation triggers the release of beta-endorphin
Transport proteins and metabolizing enzymes	
	CBD augments anandamide effects by inhibiting its uptake and metabolizing enzyme, FAAH This is an area of ongoing research

CB1 cannabinoid receptor type 1, *CB2* cannabinoid receptor type 2, *cAMP* cyclic adenosine monophosphate, *THC* Δ^9-tetrahydrocannabinol, *CBD* cannabidiol, *AEA* anandamide, *2-AG* 2-arachidonoylglycerol, *GPCR* G protein-coupled receptor, *GPR55* G protein-coupled receptor 55, *TRPV1* transient receptor potential vanilloid type 1, *NMDA* N-methyl-D-aspartate, *FAAH* fatty acid amide hydrolase. (By ©Samer Narouze, MD, PhD, used with permission)

from noxious stimuli [3], thus playing an important role in peripheral pain sensitization.

Central CB2 Receptors

The role of CB2 in the brain is still controversial. In contrast to CB1, CB2 receptors in the brain are limited, and its expression is restricted to specific neuronal cells and becomes abundant in activated microglia and astrocytes [45, 48].

Like CB1, CB2 receptor is a GPCR and is coupled to Gi/Go α proteins. Thus, its stimulation inhibits adenylate cyclase activity and activates MAPK [32].

Peripheral CB2 Receptors

In contrast, CB2 receptors are abundantly expressed in the immune system cells such as monocytes, macrophages, B and T cells, and mast cells. CB2 receptor activation reduces the release of pro-inflammatory cytokines and lymphoangiogenic factors [49–51]. Moreover, CB2 receptors are also present in other peripheral organs playing a role in the immune response, including the spleen, tonsils, thymus gland, and keratinocytes, as well as in the gastrointestinal system [32].

Accordingly, CB2 receptors represent key regulators of inflammatory and nociceptive responses and can control the activation and migration of immune cells [52, 53].

Other Putative Endocannabinoid Receptors: TRPV1 and GPR55

TRPV1

The transient receptor potential vanilloid type 1 (TRPV1) channel, also known as the capsaicin receptor, was the first member of the TRPV channel subfamily to be discovered and cloned [54]. TRPV1 channels are activated by capsaicin, endocannabinoids, and phytocannabinoids [55–57].

TRPV1 function is heavily dependent on the binding of key regulatory proteins that induce changes in its phosphorylation state. The phosphorylation induced by adenosine triphosphate (ATP), protein kinase A (PKA), PKC, phosphoinositide-binding protein (PIRT), and phosphatidylinositol 4,5-bisphosphate (PIP2) is required for TRPV1 activation and cation gating. TRPV1 activation contributes to pain transmission, neurogenic inflammation, synaptic plasticity, neuronal overexcitability, and neurotoxicity [57–60].

TRPV1 "desensitization" occurs as the rise of intracellular Ca2+ following TRPV1 stimulation activates proteins (i.e., calmodulin) that stabilize the channel in a closed conformational state or Ca2+-dependent phosphatases (i.e., calcineurin), which dephosphorylate and inactivate TRPV1 [59–63]. This fast process of TRPV1 desensitization and inactivation is thought to underlie the paradoxical analgesic, anti-inflammatory, and anti-convulsant effects of TRPV1 agonists [57, 64, 65].

TRPV1 channels are largely expressed in dorsal root ganglia and sensory nerve fibers (Aδ and C-type) [66]. In sensory neurons, TRPV1 channels work as molecular integrators for multiple types of sensory inputs that contribute to generate and transmit pain. In central neurons, lower amounts of TRPV1 channels are expressed both pre- and postsynaptically, where they act to regulate synaptic strength [66–68]. They usually affect pain, anxiety, and depression by inducing effects opposite to those exerted by CB1 receptors in the same context [32].

Moreover, there is intracellular cross talk between TRPV1 and CB1 or CB2 as they are colocalized in peripheral and central neurons (sensory neurons, dorsal root ganglia, spinal cord, brain neurons) [67, 69]. Recently, a multiplicity of interactions between cannabinoid, opioid, and TRPV1 receptors in pain modulation was discovered [70]. This provides a great opportunity for the development of new multiple target ligands for pain control with improved efficacy and side effects profile [71].

GPR55

GPR55 is considered by some experts as the third cannabinoid receptor, CB3. GPR55 belongs to the large family of GPCRs, and its endogenous ligand is lysophosphatidylinositol (LPI) [72, 73].

GPR55 is activated by Δψ-THC while antagonized by cannabidiol (CBD). Conflicting data exist regarding the likelihood that low concentrations of endocannabinoids may activate GPR55 [74, 75]. These controversies might be explained by biased signaling depending on the cell type and condition or the formation of heteromers between GPR55 and CB1 receptors [76, 77]. Activation of GPR55 might play an opposite role to CB1 by enhancing neurotransmitter release [32]. GPR55 may play a role in mechanical hyperalgesia associated with inflammatory and neuropathic pain [78].

Phytocannabinoids (THC and CBD)

THC

Δ^9-tetrahydrocannabinol (THC) is an analog to the endocannabinoid, anandamide (AEA). It is responsible for most of the pharmacological actions of cannabis, including the psychoactive, memory, analgesic, anti-inflammatory, antioxidant, antipruritic, bronchodilator, antispasmodic, and muscle relaxant activities [79, 80]. THC acts as a partial agonist at CB1 and CB2 receptors [22]. THC has a very high binding affinity to CB1 receptor which mediates its psychoactive properties. Interestingly, most of the negative effects of THC, psychogenic effects, impaired memory, anxiety, and immunosuppression, can be reversed by other constituents of the cannabis plant (other cannabinoids, CBD, terpenoids, and flavonoids) [24, 80].

CBD

Cannabidiol (CBD) is the other important cannabinoid in the cannabis plant. It is the non-psychoactive analog of THC. CBD have

significant analgesic, anti-inflammatory, anticonvulsant, and anxiolytic activities without the psychoactive effect of THC [81]. CBD has little binding affinity for either CB1 or CB2 receptors, but it can antagonize them in the presence of THC. CBD behaves as a non-competitive negative allosteric modulator of CB1 receptor, and it reduces the efficacy of THC and AEA [82]. This may explain the "entourage effect" that CBD displays, as it improves the tolerability and safety of THC by reducing the likelihood of psychoactive effects and other adverse effects such as tachycardia, sedation, and anxiety [80, 83].

Mechanisms of Action in 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 [84, 85] (Table 24.3).

THC

THC exhibits CB1 receptor-mediated antinociception through activation of supraspinal sites and descending serotonergic and noradrenergic pain modulatory pathways to produce antinociceptive effects via spinal 5-HT7, 5-HT2A, and alpha-2 adrenoceptor activation [86, 87].

The frontal-limbic distribution of cannabinoid receptors explains the central mechanism of THC analgesia as it targets preferentially the affective qualities of pain. Functional magnetic resonance imaging revealed that amygdala activity contributes to the dissociative effect of THC on pain perception related to cutaneous ongoing pain and hyperalgesia that were temporarily induced by capsaicin [88]. THC reduced the reported unpleasantness, but not the intensity of ongoing pain and hyperalgesia. THC also reduced func-

Table 24.3 THC and CBD mechanisms of action in pain modulation

THC and CBD mechanisms of action in pain modulation	
THC	
	Partial agonist at CB1 and CB2 receptors (see Table 24.2) High binding affinity to CB1 receptor The frontal-limbic distribution of CB1 receptors explains the central mechanism of THC analgesia as it targets preferentially the affective qualities of pain Activation of supraspinal descending serotonergic and noradrenergic pain modulatory pathways Spinal 5-HT7, 5-HT2A, and alpha-2 adrenoceptor activation CB2 receptor activation reduces cytokine-mediated neuro-inflammation Non-CB1/non-CB2 receptor-mediated antinociception by inhibiting nicotinic, 5HT3, and NMDA receptors Activation of glycine receptors, contributing to analgesia in inflammatory and neuropathic pain
CBD	
	Weak binding affinity for either CB1 or CB2 receptors. However, antagonist of CB1 and CB2, in the presence of THC Non-competitive negative allosteric modulator of the CB1 Act synergistically with THC and contribute to its analgesic effect while providing an "entourage effect" Regulates the perception of pain through non-CB1/non-CB2 mechanisms Modulation of non-cannabinoid GPCRs (5-HT1A), ion channels (TRPV1, TRPA1, TPRM8, NAGlyR), and PPARs Activation of glycine receptors, contributing to analgesia in inflammatory and neuropathic pain Augments anandamide (AEA) effects by inhibiting its uptake as well as its metabolizing enzyme, FAAH

CB1 cannabinoid receptor type 1, *CB2* cannabinoid receptor type 2, *THC*, Δ^9-tetrahydrocannabinol, *CBD* cannabidiol, *AEA* anandamide, *2-AG* 2-arachidonoylglycerol, *GPCR* G protein-coupled receptor, *GPR55* G protein-coupled receptor 55, *TRPV1* transient receptor potential vanilloid type 1, *NMDA* N-methyl-D-aspartate, *PPAR* peroxisome proliferator-activated receptors, *NAGlyR* N-arachidonoyl glycine receptor, *FAAH* fatty acid amide hydrolase. (By ©Samer Narouze, MD, PhD, used with permission)

tional connectivity between the amygdala and primary sensorimotor areas during the ongoing pain state. The authors concluded that peripheral mechanisms alone cannot account for the dissociative effects of THC on the pain that was observed and amygdala activity contributes to inter-individual response to cannabinoid analgesia [88].

The analgesic effects of THC are mediated through mechanisms distinct from those responsible for the psychoactive effects. THC has additive 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 THC [89].

Cannabinoids may exert other non-CB1/non-CB2 receptor-mediated antinociceptive effects by interacting with 5HT3 and N-methyl-d-aspartate receptors [89, 90].

CB2 receptors serve an important role in immune function, inflammation, and pain modulation specially in allodynia and hyperalgesia states [91, 92]. The presence of CB2 receptors on microglia within the nervous system may explain the cannabinoids' role in neuropathic pain modulation by reducing cytokine-mediated neuroinflammation [91, 92].

CB2 receptor expression has been demonstrated in areas of the peripheral and central nervous system relevant to pain perception and modulation, including the dorsal root ganglion, spinal cord, and microglia. This explains the analgesic effects produced by CB2 agonists [93–97].

CB2-selective agonists suppress neuronal activity in the dorsal horn via reduction in C-fiber activity and wind-up involving wide dynamic range (WDR) neurons [98, 99]. There is increase in peripheral CB2 receptor protein or mRNA expression in inflamed tissues and in the dorsal root ganglion in neuropathic states [100–102].

CBD

CBD regulates the perception of pain mainly through non-CB1/non-CB2 mechanisms. CBD interacts with a significant number of other targets, including non-cannabinoid GPCRs (e.g., 5-HT1A), ion channels (TRPV1, TRPA1, TPRM8, GlyR), and PPARs. Moreover, CBD augments anandamide (AEA) effects by inhibiting its uptake as well as its hydrolysis by the enzyme fatty acid amide hydrolase (FAAH) [3, 78, 103].

CBD can act synergistically with THC and contribute to its analgesic effect while providing an "entourage effect," minimizing the negative psychoactive effects of THC [80]. This depends on the differences in concentration of THC/CBD in the cannabis chemovar. Although CBD as a monotherapy has not been evaluated clinically in the management of pain, its anti-inflammatory and anti-spasmodic effects and good safety profile suggest that it could be a safe and effective analgesic [104, 105].

References

1. Vučković S, Srebro D, Vujović KS, Vučetić Č, Prostran M. Cannabinoids and pain: new insights from old molecules. Front Pharmacol. 2018;9:1259.
2. Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, et al. International union of basic and clinical pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. Pharmacol Rev. 2010;62:588–631. https://doi.org/10.1124/pr.110.003004.
3. Morales P, Hurst DP, Reggio PH. Molecular targets of the phytocannabinoids-a complex picture. Prog Chem Org Nat Prod. 2017;103:103–31.
4. Staton PC, Hatcher JP, Walker DJ, Morrison AD, Shapland EM, Hughes JP, et al. The putative cannabinoid receptor GPR55 plays a role in mechanical hyperalgesia associated with inflammatory and neuropathic pain. Pain. 2008;139:225–36.
5. Huang SM, Bisogno T, Petros TJ, Chang SY, Zavitsanos PA, Zipkin RE, et al. Identification of a new class of molecules, the arachidonyl amino acids, and characterization of one member that inhibits pain. J Biol Chem. 2001;276:42639–44.
6. Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res. 2005;30:1037–43.
7. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. Neuroscience. 2013;248:637–54. https://doi.org/10.1016/j.neuroscience.2013.04.034.
8. Horvath G, Kekesi G, Nagy E, Benedek G. The role of TRPV1 receptors in the antinociceptive effect of

anandamide at spinal level. Pain. 2008;134:277–84. https://doi.org/10.1016/j.pain.2007.04.032.
9. Cui M, Honore P, Zhong C, Gauvin D, Mikusa J, Hernandez G, et al. TRPV1 receptors in the CNS play a key role in broad-spectrum analgesia of TRPV1 antagonists. J Neurosci. 2006;26(37):9385–93.
10. Huang SM, Bisogno T, Trevisani M, Al-Hayani A, De Petrocellis L, Fezza F, et al. An endogenous capsaicin-like substance with high potency at recombinant and native vanilloid VR1 receptors. Proc Natl Acad Sci U S A. 2002;99(12):8400–5.
11. Oz M, Al Kury L, Keun-Hang SY, Mahgoub M, Galadari S. Cellular approaches to the interaction between cannabinoid receptor ligands and nicotinic acetylcholine receptors. Eur J Pharmacol. 2014;731:100–5.
12. Hejazi N, Zhou C, Oz M, Sun H, Ye JH, Zhang L. Delta9-tetrahydrocannabinol and endogenous cannabinoid anandamide directly potentiate the function of glycine receptors. Mol Pharmacol. 2006;69:991–7.
13. Ahrens J, Demir R, Leuwer M, de la Roche J, Krampfl K, Foadi N, et al. The nonpsychotropic cannabinoid cannabidiol modulates and directly activates alpha-1 and alpha-1-Beta glycine receptor function. Pharmacology. 2009;83:217–22.
14. Xiong W, Cheng K, Cui T, Godlewski G, Rice KC, Xu Y. Cannabinoid potentiation of glycine receptors contributes to cannabis-induced analgesia. Nat Chem Biol. 2011;7:296–303.
15. Xiong W, Cui T, Cheng K, Yang F, Chen SR, Willenbring D, et al. Cannabinoids suppress inflammatory and neuropathic pain by targeting a3 glycine receptors. J Exp Med. 2012;209:1121–34. https://doi.org/10.1084/jem.20120242.
16. Sigel E, Baur R, Rácz I, Marazzi J, Smart TG, Zimmer A, et al. The major central endocannabinoid directly acts at GABA(A) receptors. Proc Natl Acad Sci U S A. 2011;108:18150–5.
17. Bakas T, van Nieuwenhuijzen PS, Devenish SO, McGregor IS, Arnold JC, Chebib M. The direct actions of cannabidiol and 2-arachidonoylglycerol at GABA(A) receptors. Pharmacol Res. 2017;119:358–70.
18. Shi B, Yang R, Wang X, Liu H, Zou L, Hu X. Inhibition of 5-HT(3) receptors-activated currents by cannabinoids in rat trigeminal ganglion neurons. J Huazhong Univ Sci Technolog Med Sci. 2012;32:265–71.
19. Barann M, Molderings G, Brüss M, Bönisch H, Urban BW, Göthert M. Direct inhibition by cannabinoids of human 5-HT3A receptors: probable involvement of an allosteric modulatory site. Br J Pharmacol. 2002;137:589–96.
20. Klein TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol. 2005;5:400–11.
21. Jesse Lo V, Fu J, Astarita G, La Rana G, Russo R, Calignano A, et al. The nuclear receptor peroxisome proliferator-activated receptor-alpha mediates the anti-inflammatory actions of palmitoylethanolamide. Mol Pharmacol. 2005;67:15–9.
22. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. Br J Pharmacol. 2008;153(2):199–215.
23. O'Sullivan SE. An update on PPAR activation by cannabinoids. Br J Pharmacol. 2016;173:1899–910.
24. Andre CM, Hausman JF, Guerriero G. Cannabis sativa: the plant of the thousand and one molecules. Front Plant Sci. 2016;7:19.
25. ElSohly MA, Radwan MM, Gul W, Chandra S, Galal A. Phytochemistry of Cannabis sativa L. Prog Chem Org Nat Prod. 2017;103:1–36.
26. Hillard CJ. Biochemistry and pharmacology of the endocannabinoids arachidonylethanolamide and 2-arachidonylglycerol. Prostaglandins Other Lipid Mediat. 2000;61(1–2):3–18.
27. Reggio PH. Endocannabinoid binding to the cannabinoid receptors: what is known and what remains unknown. Curr Med Chem. 2010;17(14):1468–86.
28. Woodhams SG, Sagar DR, Burston JJ, Chapman V. The role of the endocannabinoid system in pain. Handb Exp Pharmacol. 2015;227:119–43.
29. Mechoulam R, Fride E, Marzo VD. Endocannabinoids. Eur J Pharmacol. 1998;359(1):1–18.
30. Manzanares J, Julian MD, Carrascosa A. Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. Curr Neuropharmacol. 2006;4(3):239–57.
31. Kimura T, Ohta T, Watanabe K, Yoshimura H, Yamamoto I. Anandamide, an endogenous cannabinoid receptor ligand, also interacts with 5-hydroxytryptamine (5-HT) receptor. Biol Pharm Bull. 1998;21(3):224–6.
32. Iannotti FA, Di Marzo V, Petrosino S. Endocannabinoids and endocannabinoid-related mediators: targets, metabolism and role in neurological disorders. Prog Lipid Res. 2016;62:107–28. https://doi.org/10.1016/j.plipres.2016.02.002.
33. Luchicch A, Pistis M. Anandamide and 2-arachidonoylglycerol: pharmacological properties, functional features, and emerging specificities of the two major endocannabinoids. Mol Neurobiol. 2012;46:374–92.
34. Turu G, Hunyady L. Signal transduction of the CB1 cannabinoid receptor. J Mol Endocrinol. 2010;44:75–85.
35. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, et al. Cannabinoid receptor localization in brain. Proc Natl Acad Sci U S A. 1990;87:1932–6.
36. Elphick MR, Egertová M. The neurobiology and evolution of cannabinoid signaling. Philos Trans R Soc Lond Ser B Biol Sci. 2001;356:381–408.
37. Przybyla JA, Watts VJ. Ligand-induced regulation and localization of cannabinoid CB1 and dopamine

D2L receptor heterodimers. J Pharmacol Exp Ther. 2010;332:710–9.
38. Ferré S, Lluís C, Justinova Z, Quiroz C, Orru M, Navarro G, et al. Adenosine-cannabinoid receptor interactions implications for striatal function. Br J Pharmacol. 2010;160:443–53.
39. Ward RJ, Pediani JD, Milligan G. Heteromultimerization of cannabinoid CB(1) receptor and orexin OX(1) receptor generates a unique complex in which both protomers are regulated by orexin a. J Biol Chem. 2011;286:37414–28.
40. Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptors. Pharmacol Ther. 1997;74:129–80.
41. Howlett AC, Mukhopadhyay S. Cellular signal transduction by anandamide and 2-arachidonoylglycerol. Chem Phys Lipids. 2000;108:53–70.
42. Witkowski G, Rola R, Szulczyk P. Effect of cyclic adenosine monophosphate on the G protein-dependent inward rectifier K(+)-like channel current in medial prefrontal cortex pyramidal neurons. J Physiol Pharmacol. 2012;63:457–62.
43. Mu J, Zhuang SY, Kirby MT, Hampson RE, Deadwyler SA. Cannabinoid receptors differentially modulate potassium A and D currents in hippocampal neurons in culture. J Pharmacol Exp Ther. 1999;291:893–902.
44. Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signaling at hippocampal synapses. Nature. 2001;410:588–92.
45. Stella N. Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas. Glia. 2010;58:1017–30.
46. Oliveira da Cruz JF, Robin LM, Drago F, Marsicano G, Metna-Laurent M. Astroglial type-1 cannabinoid receptor (CB1): a new player in the tripartite synapse. Neuroscience. 2015;S0306-4522(15):00434.
47. Navarrete M, Araque A. Endocannabinoids potentiate synaptic transmission through stimulation of astrocytes. Neuron. 2010;68(1):113–26.
48. Demuth DG, Molleman A. Cannabinoid signalling. Life Sci. 2006;78:549–63.
49. Matias I, Di Marzo V. Endocannabinoids and the control of energy balance. Trends Endocrinol Metab. 2007;18:27–37.
50. Staiano RI, Loffredo S, Borriello F, Iannotti FA, Piscitelli F, Orlando P, Secondo A, Pertwee RG. The pharmacology of cannabinoid receptors and their ligands: an overview. Int J Obes. 2006;30:S13–8.
51. Granata F, Lepore MT, Fiorelli A, Varricchi G, Santini M, Triggiani M, Di Marzo V, Marone G. Human lung-resident macrophages express CB1 and CB2 receptors whose activation inhibits the release of angiogenic and lymphangiogenic factors. J Leukoc Biol. 2016;99(4):531–40.
52. Malan TP Jr, Ibrahim MM, Lai J, Vanderah TW, Makriyannis A, Porreca F. CB2 cannabinoid receptor agonists: pain relief without psychoactive effects? Curr Opin Pharmacol. 2003;3:62–7.
53. Whiteside GT, Lee GP, Valenzano KJ. The role of the cannabinoid CB2 receptor in pain transmission and therapeutic potential of small molecule CB2 receptor agonists. Curr Med Chem. 2007;14:917–36.
54. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997;389:816–24.
55. De Petrocellis L, DiMarzo V. Lipids as regulators of the activity of transient receptor potential type V1 (TRPV1) channels. Life Sci. 2005;77:1651–66.
56. Di Marzo V, De Petrocellis L. Endocannabinoids as regulators of transient receptor potential (TRP) channels: a further opportunity to develop new endocannabinoid-based therapeutic drugs. Curr Med Chem. 2010;17:1430–49.
57. Iannotti FA, Hill CL, Leo A, Alhusaini A, Soubrane C, Mazzarella E, et al. Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. ACS Chem Neurosci. 2014;5:1131–41.
58. Nagy I, Friston D, Valente JS, Torres Perez JV, Andreou AP. Pharmacology of the capsaicin receptor, transient receptor potential vanilloid type-1 ion channel. Prog Drug Res. 2014;68:39–76.
59. Julius D. TRP channels and pain. Annu Rev Cell Dev Biol. 2013;29:355–84.
60. Nilius B, Mahieu F, Karashima Y, Voets T. Regulation of TRP channels: a voltage–lipid connection. Biochem Soc Trans. 2007;35:105–8.
61. Cortright DN, Szallasi A. Biochemical pharmacology of the vanilloid receptor TRPV1. An update. Eur J Biochem. 2004;271:1814–9.
62. Planells-Cases R, Garcìa-Sanz N, Morenilla-Palao C, Ferrer-Montiel A. Functional aspects and mechanisms of TRPV1 involvement in neurogenic inflammation that leads to thermal hyperalgesia. Pflugers Arch. 2005;451:151–9.
63. Mandadi S, Tominaga T, Numazaki M, Murayama N, Saito N, Armati PJ, et al. Increased sensitivity of desensitized TRPV1 by PMA occurs through PKCepsilon-mediated phosphorylation at S800. Pain. 2006;123:106–16.
64. Brederson JD, Kym PR, Szallasi A. Targeting TRP channels for pain relief. Eur J Pharmacol. 2013;716:61–76.
65. Iwaoka E, Wang S, Matsuyoshi N, Kogure Y, Aoki S, Yamamoto S, et al. Evodiamine suppresses capsaicin-induced thermal hyperalgesia through activation and subsequent desensitization of the transient receptor potential V1 channels. J Nat Med. 2016;70(1):1–7.
66. Edwards JG. TRPV1 in the central nervous system: synaptic plasticity, function, and pharmacological implications. Prog Drug Res. 2014;68:77–104.
67. Cristino L, de Petrocellis L, Pryce G, Baker D, Guglielmotti V, Di Marzo V. Immunohistochemical localization of cannabinoid type 1 and vanilloid transient receptor potential vanilloid type 1 receptors in the mouse brain. Neuroscience. 2006;139:1405–15.

68. Mori F, Ribolsi M, Kusayanagi H, Monteleone F, Mantovani V, Buttari F, et al. TRPV1 channels regulate cortical excitability in humans. J Neurosci. 2012;32:873–9.
69. Anand P, Whiteside G, Fowler CJ, Hohmann AG. Targeting CB2 receptors and the endocannabinoid system for the treatment of pain. Brain Res Rev. 2009;60:255–66. https://doi.org/10.1016/j.brainresrev.2008.12.003.
70. Zádor F, Wollemann M. Receptome: interactions between three pain-related receptors or the "triumvirate" of cannabinoid, opioid and TRPV1 receptors. Pharmacol Res. 2015;102:254–63. https://doi.org/10.1016/j.phrs.2015.10.015.
71. Reddy AS, Zhang S. Polypharmacology: drug discovery for the future. Expert Rev Clin Pharmacol. 2013;6:41–7. https://doi.org/10.1586/ecp.12.74.
72. Oka S, Nakajima K, Yamashita A, Kishimoto S, Sugiura T. Identification of GPR55 as a lysophosphatidylinositol receptor. Biochem Biophys Res Commun. 2007;362:928–34.
73. Henstridge CM, Balenga NA, Ford LA, Ross RA, Waldhoer M, Irving AJ. The GPR55 ligand L-alpha-lysophosphatidylinositol promotes RhoA-dependent Ca2+ signaling and NFAT activation. FASEB J. 2009;23:183–93.
74. Sharir H, Console-Bram L, Mundy C, Popoff SN, Kapur A, Abood ME. The endocannabinoids anandamide and virodhamine modulate the activity of the candidate cannabinoid receptor GPR55. J Neuroimmune Pharmacol. 2012;7:856–65.
75. Pertwee RG. GPR55: a new member of the cannabinoid receptor clan? Br J Pharmacol. 2007;152:984–6.
76. Kargl J, Balenga N, Parzmair GP, Brown AJ, Heinemann A, Waldhoer M. The cannabinoid receptor CB1 modulates the signaling properties of the lysophosphatidylinositol receptor GPR55. J Biol Chem. 2012;287:44234–48.
77. Martínez-Pinilla E, Reyes-Resina I, Oñatibia-Astibia A, Zamarbide M, et al. CB1 and GPR55 receptors are co-expressed and form heteromers in rat and monkey striatum. Exp Neurol. 2014;261:44–52.
78. Staton PC, Hatcher JP, Walker DJ, Morrison AD, et al. The putative cannabinoid receptor GPR55 plays a role in mechanical hyperalgesia associated with inflammatory and neuropathic pain. Pain. 2008;139(1):225–36.
79. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. Neurotherapeutics. 2009;6:713–37.
80. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 2011;163:1344–64. https://doi.org/10.1111/j.1476-5381.2011.01238.x.
81. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. Eur J Pharmacol. 2007;556:75–83. https://doi.org/10.1016/j.ejphar.2006.11.006.
82. Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol. 2015;172:4790–805. https://doi.org/10.1111/bph.13250.
83. Abrams DI, Guzman M. Cannabis in cancer care. Clin Pharmacol Ther. 2015;97:575–86. https://doi.org/10.1002/cpt.108.
84. Chin CL, Tovcimak AE, Hradil VP. Differential effects of cannabinoid receptor agonists on regional brain activity using pharmacological MRI. Br J Pharmacol. 2008;153:367–79.
85. versen L, Chapman V. Cannabinoids: a real prospect for pain relief? Curr Opin Pharmacol. 2002;2:50–5.
86. Dogrul A, Seyrek M, Yalcin B, Ulugol A. Involvement of descending serotonergic and noradrenergic pathways in CB1 receptor-mediated antinociception. Prog Neuro-Psychopharmacol Biol Psychiatry. 2012;38:97–105.
87. Seyrek M, Kahraman S, Deveci MS, Yesilyurt O, Dogrul A. Systemic cannabinoids produce CB_1-mediated antinociception by activation of descending serotonergic pathways that act upon spinal 5-HT(7) and 5-HT(2A) receptors. Eur J Pharmacol. 2010;649(1–3):183–94.
88. Lee MC, Ploner M, Wiech K, et al. Amygdala activity contributes to the dissociative effect of cannabis on pain perception. Pain. 2013;154(1):124–34. https://doi.org/10.1016/j.pain.2012.09.017.
89. Welch SP. Blockade of cannabinoid-induced antinociception by norbinaltorphimine, but not N,N-diallyl-tyrosine-Aib-phenylalanine-leucine, ICI 174,864 or naloxone in mice. J Pharmacol Exp Ther. 1993;265:633–40.
90. Pertwee RG, Howlett AC, Abood ME, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. Pharmacol Rev. 2010;62:588–631.
91. Hulsebosch CE. Special issue on microglia and chronic pain. Exp Neurol. 2012;234:253–4.
92. Beltramo M. Cannabinoid type 2 receptor as a target for chronic pain. Mini Rev Med Chem. 2009;9:11–25.
93. Beltramo M, Bernardini N, Bertorelli R, et al. CB2 receptor-mediated antihyperalgesia: possible direct involvement of neural mechanisms. Eur J Neurosci. 2006;23:1530–8.
94. Van Sickle MD, Duncan M, Kingsley PJ, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science. 2005;310:329–32.
95. Jhaveri MD, Elmes SJ, Richardson D, et al. Evidence for a novel functional role of cannabinoid CB(2) receptors in the thalamus of neuropathic rats. Eur J Neurosci. 2008;27:1722–30.
96. Anand U, Otto WR, Sanchez-Herrera D, et al. Cannabinoid receptor CB2 localisation and agonist mediated inhibition of capsaicin responses in human sensory neurons. Pain. 2008;138:667–80.

97. Jhaveri MD, Sagar DR, Elmes SJ, Kendall DA, Chapman V. Cannabinoid CB2 receptor-mediated anti-nociception in models of acute and chronic pain. Mol Neurobiol. 2007;36:26–35.
98. Nackley AG, Zvonok AM, Makriyannis A, Hohmann AG. Activation of cannabinoid CB2 receptors suppresses C-fiber responses and windup in spinal wide dynamic range neurons in the absence and presence of inflammation. J Neurophysiol. 2004;92:3562–74.
99. Quartilho A, Mata HP, Ibrahim MM, et al. Inhibition of inflammatory hyperalgesia by activation of peripheral CB2 cannabinoid receptors. Anesthesiology. 2003;99:955–60.
100. Richardson D, Pearson RG, Kurian N, et al. Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. Arthritis Res Ther. 2008;10:R43.
101. Walczak JS, Pichette V, Leblond F, Desbiens K, Beaulieu P. Behavioral, pharmacological and molecular characterization of the saphenous nerve partial ligation: a new model of neuropathic pain. Neuroscience. 2005;132:1093–102.
102. Wotherspoon G, Fox A, McIntyre P, Colley S, Bevan S, Winter J. Peripheral nerve injury induces cannabinoid receptor 2 protein expression in rat sensory neurons. Neuroscience. 2005;135:235–45.
103. Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. Bioorg Med Chem. 2015;23:1377–85. https://doi.org/10.1016/j.bmc.2015.01.059.
104. Ko GD, Bober SL, Mindra S, Moreau JM. Medical cannabis – the Canadian perspective. J Pain Res. 2016;9:735–44. https://doi.org/10.2147/JPR.S98182.
105. Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil. 2003;17:21–9. https://doi.org/10.1191/0269215503cr581oa.