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Receptor mechanisms underlying the CNS effects of cannabinoids: CB_1 receptor and beyond

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Abstract

Cannabis legalization continues to progress in many US states and other countries. Δ^9-tetrahydrocannabinol (Δ^9-THC) is the major psychoactive constituent in cannabis underlying both its abuse potential and the majority of therapeutic applications. However, the neural mechanisms underlying cannabis action are not fully understood. In this chapter, we first review recent progress in cannabinoid receptor research, and then examine the acute CNS effects of Δ^9-THC or other cannabinoids (WIN55212-2) with a focus on their receptor mechanisms. In experimental animals, Δ^9-THC or WIN55212-2 produces classical pharmacological effects (analgesia, catalepsy, hypothermia, hypolocomotion), biphasic changes in affect (reward vs. aversion, anxiety vs. anxiety relief), and cognitive deficits (spatial learning and memory, short-term memory). Accumulating evidence indicates that activation of CB_1Rs underlies the majority of Δ^9-THC or WIN55121-2's pharmacological and behavioral effects. Unexpectedly, glutamatergic CB_1Rs preferentially underlie cannabis action relative to GABAergic CB_1Rs. Functional roles for CB_1Rs expressed on astrocytes and mitochondria have also been uncovered. In addition, Δ^9-THC or WIN55212-2 is an agonist at CB_2R, GPR55 and PPARγ receptors and recent studies implicate these receptors in a number of their CNS effects. Other receptors (such as serotonin, opioid, and adenosine receptors) also modulate Δ^9-THC's actions and their contributions are detailed. This chapter describes the neural mechanisms underlying cannabis action, which may lead to new discoveries in cannabis-based medication development for the treatment of cannabis use disorder and other human diseases.

1. Introduction

Cannabis is the most commonly abused drug worldwide and accounts for half of all drug seizures by law enforcement (WHO, 2021). Since the 2000s, the general public has reported less perceived risk from cannabis, while diagnoses of cannabis use disorder (CUD) climb (Carliner, Brown, Sarvet, & Hasin, 2017). An estimated 147 million people in the world are cannabis users WHO, 2021. Recreational use remains the most prevalent (53.4%), but a growing community of individuals report purely medical use (10.5%) or a combination

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Conflict of interest

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of medical and recreational use (36.1%; Schauer, King, Bunnell, Promoff, & McAfee, 2016). Therapeutic use of cannabis has a long history and an accumulating body of work has supported cannabinoids in the treatment of chronic spasticity and pain (Whiting et al., 2015). In this chapter, we explore the acute effects of cannabis from a neurobiological viewpoint. The majority of work in this vein has focused on Δ^9-tetrahydrocannabinol (Δ^9-THC), the primary psychoactive phytocannabinoid in cannabis that underlies its rewarding effects, but also the majority of therapeutic uses. Δ^9-THC was first isolated from hashish by Rafael Mechoulam in 1964 (Gaoni & Mechoulam, 1964). This compound produces a number of physiological and behavioral changes in preclinical animal models including the classic tetrad effects (analgesia, catalepsy, hypothermia, hypolocomotion), a change in affective state either positive (reward, anxiety relief) or negative (aversion, anxiogenesis), and deleterious effects on cognition. Systemic reviews on the endocannabinoid system, pharmacology of cannabinoids, and their involvement and implications in various human diseases have previously been conducted and are beyond the scope of this chapter (Alexander, 2016; Leung, 2011; Mechoulam & Parker, 2013; Pertwee, 2005, 2006). Here we focus on research progress investigating the neural mechanisms underlying the behavioral effects of Δ^9-THC and other cannabinoids in experimental animals. We first describe the receptor systems where cannabinoids bind followed by detailed region- and cell type-specific receptor mechanisms underlying Δ^9-THC's CNS effects.

2. Cannabinoid receptors

There are at least two types of cannabinoid receptors (CB_1R and CB_2R) identified. Δ^9-THC, synthetic cannabinoids (WIN55,212-2, CP55940, HU-210), and the endocannabinoids (anandamide, AEA; 2-arachidonoyl glycerol, 2-AG) have high binding affinities at both the GPCR-coupled receptors. Cannabinoids also bind and activate other putative cannabinoid receptors, including G protein-coupled receptor 55 (GPR55), transient receptor potential vanilloid 1 (TRPV1) channel, and peroxisome proliferator-activated nuclear receptors (PPARs) (Fig. 1). In addition, cannabinoids may also indirectly act on other receptor systems such as opioid, adenosine, and serotonin receptors by diverse ways.

Table 1 shows the receptor binding profiles of those commonly used cannabinoids to both CB_1 and CB_2 receptors and other putative receptors as shown in Fig. 1. In brief, these compounds are classified into four categories based on their chemical structures: classical, nonclassical, eicosanoid, and aminoalkylindole (Pertwee, 2008a, 2008b; Pertwee et al., 2010). The classical category includes dibenzopyran derivatives such as Δ^9-THC and HU-210. Δ^9-THC is a weak partial agonist at both the CB_1R and CB2R with greater CB1R affinity and activity at GPR55 and PPARγ (Pertwee, 2008a, 2008b). HU-210 is a synthetic analog of Δ^8-THC with 100–800-fold greater potency than Δ^9-THC at the CB_1R and CB_2R, a prolonged duration of action, and activity at GPR55 and TRPV1 (Devane et al., 1992; Pertwee et al., 2010). CP55940 fits within the nonclassical nomenclature, containing compounds that are Δ^9-THC derivatives and lack a pyran ring (Howlett et al., 2002). CP55940 has marginally lower affinity than HU-210 at the CB_1R and CB_2Rs and binds to GPR55, TRPV1 and PPARγ (Pertwee et al., 2010). Within the eicosanoid classification are the two main endocannabinoids: 2-AG and AEA. AEA is a partial agonist at both the cannabinoid receptors with even lower CB_2R affinity than Δ^9-THC (Pertwee, 2005).

2-AG has high affinity at the CB_1R and somewhat less at the CB_2R with greater efficacy observed at CB_1Rs than CP55940. Both AEA and 2-AG bind to GPR55, TRVP1, and PPARγ (Pertwee et al., 2010). The fourth and final category, the aminoalkylindoles, have the most distinct chemical structures relative to the other subtypes (Ferraro et al., 2001). The aminoalkylindole WIN 55,212-2 is a full agonist at both the $CB_1R$and $CB_2R$with greater affinity than Δ^9-THCattheCB$_1$R andactivity at TRVP1, PPARα and PPARγ (Howlett et al., 2002).

2.1 CB_1 receptor

As stated above, Δ^9-THC acts as a partial agonist at G-protein coupled CB_1R (Iwamura, Suzuki, Ueda, Kaya, & Inaba, 2001). This receptor recruits $G_{i/o}$ proteins and inhibits adenylate cyclase while increasing mitogen-activated protein kinase (Howlett, 2005; Pertwee, 2008a, 2008b). CB_1R can also inhibit N-type and P/Q-type calcium currents, stimulate A-type outward potassium channels, and use G_s proteins to signal (Howlett et al., 2002; Jarrahian, Watts, & Barker, 2004).

Regional distribution of CB_1R: The first CB_1R distribution studies used autoradiography with [^{3}H]-CP55,940, a tritiated CB_1R agonist (Herkenham et al., 1991, 1990) and found extraordinarily high levels of CB1Rs in the substantia nigra, globus pallidus, hippocampus, cerebellum, and cortex (Fig. 2). Autoradiographic studies using [^{3}H]-WIN55,212-2 further confirmed this pattern in rat (Jansen, Haycock, Ward, & Seybold, 1992) and human brains (Glass, Faull, & Dragunow, 1997; Mato, Del Olmo, & Pazos, 2003). *In situ* hybridization (ISH) and immunohistochemistry (IHC) assays corroborated the autoradiographic reports and revealed that CB_1Rs are highly expressed in a restricted set of forebrain neurons, particularly in the cortex, amygdala, and hippocampus (see reviews by Galaj & Xi, 2019; Hu & Mackie, 2015). These neurons project widely throughout the CNS, resulting in a dense network of CB_1-positive axons (Bodor et al., 2005; Mackie, 2008). Double-label immunostaining and ISH experiments revealed that the cells expressing CB1Rs in the forebrain are primarily GABAergic and CCK-positive interneurons (Katona et al., 1999; Tsou, Mackie, Sañudo-Peña, & Walker, 1999).

Neuronal CB_1R: RNAscope ISH is a highly sensitive and selective assay that we and others have used to characterize the cellular distributions of CB_1Rs in the brain. High densities of CB_1 mRNA have been detected in the cell bodies of both GABA and glutamate neurons in multiple brain regions including the cortex, thalamus, midbrain and cerebellum (Fig. 3; Han et al., 2017; Humburg et al., 2021; Vickstrom et al., 2021). This CB_1 mRNA signal is highly specific as selective deletion of CB_1Rs from either GABAergic neurons or glutamatergic neurons abolished CB_1 mRNA staining in the corresponding cell types. Functional studies provide further information regarding cellular localization of CB_1R. For example, electrophysiological assays demonstrate that CB_1R activation inhibits GABA release in the midbrain, which may lead to postsynaptic (dopamine) neuron disinhibition (or activation; Lupica & Riegel, 2005; Szabo, Siemes, & Wallmichrath, 2002). This suggests that activation of GABAergic CB1Rs has functional consequences. Electrophysiological assays also demonstrate functional CB1R expression in glutamatergic neurons or their terminals in the midbrain and many other brain regions (Melis, Gessa, & Diana, 2000; Melis

et al., 2004). We have examined CB_1R expression in midbrain dopamine (DA) neurons. Under high magnification, CB_1-immunostaining was found mainly in cell membranes and nerve fibers, but not in neuronal cell bodies (Han et al., 2017). Since nerve fibers from different neuronal types are always intertwined, IHC assays alone are not sufficient to identify whether midbrain DA neurons express CB_1Rs. However, RNAscope ISH assays indicate that a subpopulation of midbrain DA neurons expresses CB_1 mRNA (Fig. 3).

Endocannabinoids regulate physiological functions in the brain mainly through activation of CB_1Rs that inhibit presynaptic GABA or glutamate release via a retrograde endocannabinoid-CB_1R mechanism (Castillo, Younts, Chávez, & Hashimotodani, 2012; Piomelli, 2003). Specifically, presynaptic neuronal excitation increases glutamate release at excitatory synapses by activation of voltage-dependent Ca^{++} channels, which subsequently activates postsynaptic AMPA and NMDA receptors and depolarizes post-synaptic neurons. Meanwhile, glutamate may also activate postsynaptic mGluR1 or mGluR5, causing an increase in 2-AG synthesis in postsynaptic neurons. Postsynaptic neuronal depolarization may also elevate intracellular Ca^{++} and elicit 2-AG production. After being released from postsynaptic neurons, 2-AG retrogradely travels across the synapse to activate presynaptic CB_1Rs. Presynaptic CB1Rs are $G_{i/o}$ protein-coupled receptors (Howlett, 2005; Pertwee, 2008a, 2008b). Their activation leads to inhibition of presynaptic glutamate or GABA release (Hoffman, Laaris, Kawamura, Masino, & Lupica, 2010; Howlett et al., 2002; Howlett, Blume, & Dalton, 2010; Jarrahian et al., 2004; Laaris, Good, & Lupica, 2010). This neuronal CB_1R-mediated inhibition leads to several types of short-term or long-term synaptic plasticity, such as depolarization-induced suppression of excitation at excitatory synapses, depolarization-induced suppression of inhibition at inhibitory synapses, or long-term depression, which are associated with endocannabinoid involvement in various brain functions (Galaj & Xi, 2019).

Glial CB_1R: CB_1R has also been detected on non-neuronal cells such as astrocytes (Djeungoue-Petga & Hebert-Chatelain, 2017; Han et al., 2012; Oliveira da Cruz, Robin, Drago, Marsicano, & Metna-Laurent, 2016; Stella, 2010). Astrocytes were traditionally thought to provide nutrients to neurons and to maintain a functional homeostasis for neuronal functions. However, recent studies have indicated that astrocytes can regulate synaptic transmission and brain functions. For example, electrical stimulation of adjacent neurons can increase intracellular Ca^{++} levels in hippocampal astrocytes that express CB_1R (Navarrete & Araque, 2008). This effect is mediated by a $G\alpha q$ protein-phospholipase C signal pathway, rather than the $G\alpha_{i/o}$ protein-cAMP signal pathway observed in neurons. The increase in astrocyte Ca^{++} induces gliotransmitter release (Metna-Laurent & Marsicano, 2015; Mothet et al., 2000) and results in hetero-synaptic potentiation at excitatory or inhibitory synapses. Thus, glial CB_1R-mediated neuronal excitation differs significantly from neuronal CB_1R-mediated homosynaptic inhibition.

Less is known regarding CB_1R present on microglia and mitochondria. Microglia are the immune cells of the CNS. They act as macrophages and can change phenotype based on their microenvironment. Microglia in an activated state dispense a substantial amount of nitric oxide (NO). Interestingly, administration of a CB_1R agonist blocks this effect (Waksman, Olson, Carlisle, & Cabral, 1999) and microglia contain an anandamide binding

site coupled to NO release (Stefano, Liu, & Goligorsky, 1996). As such, changes in NO production may mediate the effects of cannabinoids via microglial CB_1Rs. On the other hand, mitochondria are organelles responsible for a cell's energy production. They support basic brain functioning primarily via the process of mitochondrial respiration i.e., the conversion of oxygen and nutrients into ATP. CB_1R on mitochondria (mtCB_1Rs) modulates mitochondrial respiration (Bénard et al., 2012) and are neuroprotective (Ma et al., 2015). Further, mtCB_1R mediates depolarization-induced suppression of inhibition, a form of short term synaptic plasticity in which glutamatergic neurons in the hippocampus are depolarized leading to the release of endocannabinoids and subsequent CB_1R activation and decreased GABAergic activity (Bénard et al., 2012).

2.2 CB_2 receptor

The cannabinoid CB_2R was cloned in 1993 from human leukemia cells (Munro, Thomas, & Abu-Shaar, 1993). CB2R has 44% sequence homology with CB_1Rs (Pertwee, 1997). They are G-protein coupled ($G_{i/o}$) and inhibit adenylate cyclase, leading to a decrease in cAMP signaling and neuronal inhibition (Patel, Davison, Pittman, & Sharkey, 2010). CB_2R activation can also stimulate p42/p44 MAP kinase and elevate intracellular calcium (Cabral & Griffin-Thomas, 2008). Δ^9-THC is a partial agonist at CB_2R with relatively high affinity (Table 1; Iwamura et al., 2001).

Regional distribution of CB_2R: CB_2R was initially referred to as "peripheral cannabinoid receptors" due to their predominant expression in peripheral tissues including immune cells, spleen, tonsils, lymph nodes, liver, and the gastrointestinal tract (Galiègue et al., 1995; Onaivi et al., 1999) and the failure to detect CB_2R in the CNS. However, more advanced techniques such as RNAscope ISH and fluorescence-activated cell sorting (FACS) followed by RT-PCR assays have unearthed CB_2R expression in the CNS including the spinal cord (Nent, Nozaki, Schmöle, Otte, & Zimmer, 2019), brain stem (Van Sickle et al., 2005), hippocampus (Li & Kim, 2015), ventral tegmental area (Zhang et al., 2017), and cerebellum (Gong et al., 2006).

Cellular distribution of CB_2R: The specific cell types within the CNS that express CB_2R are somewhat controversial. The majority of work assumes that CB_2Rs are expressed on microglia although more direct anatomical evidence is still needed. Recent studies have revealed neuronal CB_2R expression on DA neurons in the midbrain (Zhang et al., 2015; Zhang et al., 2017), glutamate neurons in the red nucleus and hippocampus (Li & Kim, 2015; Stempel et al., 2016; Zhang et al., 2021) and GABA neurons in the striatum and cerebellum (Fig. 4; Li & Kim, 2015; Zhang, De Biase, et al., 2021) (Fig. 4). CB_2Rs in the brain are located on the postsynaptic cells (Brusco, Tagliaferro, Saez, & Onaivi, 2008a, 2008b) and are inducible, showing upregulation under neuroinflammatory conditions (Atwood & Mackie, 2010; Maresz, Carrier, Ponomarev, Hillard, & Dittel, 2005).

CB_2R transcripts: An important finding in recent research is the unique distribution patterns of CB_2 transcript (mRNA) isoforms (CB_{2A}, CB_{2B}, CB_{2C}, CB_{2D}) across species and tissue types (Liu et al., 2009; Zhang et al., 2015), which may, in part, explain why early assessments failed to detect CB_2 mRNA in the brain (Galiègue et al., 1995; Munro

et al., 1993; Schatz, Lee, Condie, Pulaski, & Kaminski, 1997). In humans and mice the CB_{2A} isoform was found primarily in the testis and brain, whereas CB_{2B} was expressed in the spleen and leukocytes (Liu et al., 2009). CB_{2C} and CB_{2D} isoforms were only detected in rats (Zhang et al., 2015). On the whole, CB_{2A} is the predominant subtype (20–30-fold higher than CB_{2B}; Zhang et al., 2014). However, in the mouse spleen CB_{2A} is only about 3-fold higher than CB_{2B} (Zhang et al., 2014). A direct comparison of brain and spleen CB_{2A} mRNA levels revealed considerably greater expression in the spleen (50–100-fold). These findings suggest that brain CB_2 mRNA is more likely to be detected with a probe that targets CB_{2A} rather than CB_{2B} transcript. However, brain CB2 expression is still detectable using riboprobes that recognize the encoding sequences on both CB_{2A} and CB_{2B} isoforms, by which CB_2 mRNA was discovered in the cortex, hippocampus, and globus pallidus of non-human primates (Lanciego et al., 2011; Sierra et al., 2015). These findings indicate that expression of the CB_2 gene is dependent on the isoform subtype and varies by species and region.

2.3 GPR55

Δ^9-THC is an agonist at the orphan receptor GPR55 (Table 1). This receptor has been put forward as a putative “CB3 cannabinoid receptor,” given that both endocannabinoids (AEA, 2-AG) and synthetic cannabinoids (HU-210, CP55,940) are also able to bind (Table 1). However, GPR55 does not contain a quintessential cannabinoid binding pocket (Baker, Pryce, Davies, & Hiley, 2006) and has minimal receptor homology with CB1R (13.5%) or CB2R (14.4%; Elbegdorj, Westkaemper, & Zhang, 2013). GPR55 couples to G_{12} and G_{13} proteins and activates RhoA and Ca^{++} (Henstidge et al., 2009; Ryberg et al., 2007). GPR55 is distributed throughout the nervous system. In the periphery, it was been uncovered in the GI tract (Li et al., 2013), liver (Romero-Zerbo et al., 2011), pancreas (McKillop, Moran, Abdel-Wahab, & Flatt, 2013), and adipose tissue (Imbernon et al., 2014). QT-PCR assays indicate GPR55 mRNA expression in the striatum, substantia nigra, frontal cortex, hippocampus and cerebellum (Celorrio et al., 2017; Ryberg et al., 2007; Wu et al., 2013). In cell cultures, GPR55 and microglia colocalize (Pietr et al., 2009). In striatal or substantia nigra (SN) brain tissues, GPR55 mRNA was detected in neurons (colocalized with a neuronal marker), but not in microglia or astrocytes (Celorrio et al., 2017).

2.4 Peroxisome proliferator-activated receptors (PPARs)

PPARs are nuclear receptors with 3 isoforms (α, β, γ) that regulate gene expression (O’Sullivan, 2016). Activated PPARs dimerize retinoid X receptors and bind to DNA sequences termed PPAR response elements (Bishop-Bailey, 2000). Δ^9-THC is an agonist at PPARγ (EC50~0.3μM; O’Sullivan, Tarling, Bennett, Kendall, & Randall, 2005) (Table 1), but does not bind to PPARα (Sun et al., 2007). However, one report demonstrated that Δ^9-THC administration increased PPARα transcriptional activity (Takeda et al., 2014). PPARs are also activated by endocannabinoids (AEA, 2-AG) and fatty acids (oleic acid, arachidonic acid) and may function as lipid sensors, monitoring metabolic activity *in vivo* (Pertwee et al., 2010). PPARγ expression predominates in adipose tissue, but is also observed in the liver, large intestine, and spleen (Lehrke & Lazar, 2005; Vidal-Puig et al., 1996; Villapol, 2018). Within the CNS, PPARγ expression has been detected in the piriform cortex, ventral pallidum, caudate putamen (Moreno, Farioli-Vecchioli, & Cerù, 2004), and to a lesser extent

the prefrontal cortex (PFC), nucleus accumbens (NAc), and amygdala (Warden et al., 2016). Immunohistochemical images showed colocalization of PPARγ in neurons, some staining in astrocytes, but not in microglia (Warden et al., 2016).

2.5 Transient receptor potential vanilloid 1 (TRPV1) channel

Six families of transient receptor potential channels (TRP) have been identified: canonical, vanilloid (TRPV), melastatin (TRPM), polycystin, mucolipin and ankyrin (TRPA). TRPs are ion channels with a nonselective cation pore and six transmembrane domains that are involved in sensory transduction. Δ^9-THC has no effect on TRPV1 functional activity at 100 μM, while AEA is a potent TRPV1 agonist with a EC_{50} value of 0.16–1.15 μM (Table 1). Δ^9-THC is a mild agonist at TRPV2 (EC_{50}: ~0.65μM) and has intermediate effects at TRPA1 (EC_{50}: ~0.23μM) and TRPM8 (IC50: ~0.16μM; De Petrocellis et al., 2011). TRPV2 is activated by elevations in temperature and inflammation (De Petrocellis, Nabissi, Santoni, & Ligresti, 2017) and distributed in the paraventricular nucleus, arcuate nucleus, nucleus of the solitary tract, locus coeruleus as well as a number of other regions in the rat forebrain and hindbrain (Nedungadi, Dutta, Bathina, Caterina, & Cunningham, 2012). TRPV2 is colocalized with neurons and to a lesser extent, astrocytes (Nedungadi et al., 2012; Shibasaki, Ishizaki, & Mandadi, 2013).

2.6 Other targets

Beyond the five main receptor systems described above, cannabinoids may also interact with other targets possibly by forming heterodimers or functioning as opioid receptor allosteric modulators. For the purposes of this book chapter, we will only discuss the few receptors implicated in cannabinoid action in later Sections 3–6.

Opioid receptors: A significant amount of work indicates cross-talk between the endocannabinoid and endogenous opioid system. Opioid receptors are inhibitory GPCRs. There are four receptor subtypes: μ, δ, κ, and nociception, with endorphins, enkephalins, dynorphins, and nociceptin as the endogenous ligands, respectively. CB_1R was reported to form heterodimers with μ, δ, and κ opioid receptors and signaling at μ opioid receptors (MORs) is reduced by CB_1R agonism (Rios, Gomes, & Devi, 2006). Colocalization of CB_1Rs and MORs has also been detected in striatal medium-spiny neurons and the dorsal horn of the spinal cord (Rodriguez, Mackie, & Pickel, 2001; Salio et al., 2001). In addition, Δ^9-THC was reported to increase the rate of dissociation of MOR and δ opioid receptor (DOR) ligands from their orthosteric binding sites designating THC as an allosteric modulator at these receptors (Kathmann, Flau, Redmer, Tränkle, & Schlicker, 2006).

Adenosine receptors: Cannabinoids also have activity at the adenosine receptors, which are divided into four subtypes: A_1, A_{2A}, A_{2B} and A_3. Prior work has demonstrated that CB_1R antagonism prevents A_1R activation (Savinainen, Saario, Niemi, Järvinen, & Laitinen, 2003). Heteromeric complexes between CB_1Rs and $A_{2A}Rs$ have been detected in the striatum (Ferre et al., 2011; Ferreira et al., 2015) and hippocampus (Aso et al., 2019). The endocannabinoids (2-AG, AEA), but not synthetic cannabinoids (WIN55,212-2, CP55940), were reported to function as negative allosteric modulators at the A_3 receptor (Lane, Beukers, Mulder-Krieger, & Ijzerman, 2010).

Serotonin receptors: Additionally, a subset of serotonergic receptors is targeted by cannabinoids. There are seven families of 5-HT receptors (5-$HT_{1–7}$) and further subcategories within these classes. The majority of 5-HT receptors are GPCRs, not including the $5HT_3R$. CB_1-$5HT_{2A}$ heterodimers have been identified in the hippocampus, caudate putamen, and somatosensory cortex (Viñals et al., 2015). The Δ^9-THC metabolites, 11-hydroxy-Δ^8-THC and 11-oxo-Δ^8-THC, attenuated serotonin binding to 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{2C} receptors (Kimura, Ohta, Watanabe, Yoshimura, & Yamamoto, 1998; Kimura, Yamamoto, Ohta, Yoshida, & Watanabe, 1996). Similarly, AEA weakened radioligand binding of 5-HT to 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} (Kimura et al., 1998). On the other hand, HU210 increased 5-HT binding to 5-HT_2Rs on rat cortical membranes (Cheer, Cadogan, Marsden, Fone, & Kendall, 1999). In addition, CB_1R may also form heterodimers with dopamine D_2Rs in the striatum (Marcellino et al., 2008)

3. Cannabinoid tetrad effects

High doses of cannabinoids such as Δ^9-THC or WIN55,212-2 (a potent CB_1R and CB_2R agonist) produce classical tetrad effects—analgesia, hypothermia, catalepsy, and hypolocomotion, which are often used to determine whether a novel compound is cannabimimetic in nature. The receptor mechanisms mediating cannabinoid effects in the tetrad are not fully understood. However, transgenic mice with conditional knockouts of different cannabinoid receptors have been widely used to identify the neuronal populations that mediate Δ^9-THC or other cannabinoid effects. Significant progress has been made. Here, we discuss each assay within the tetrad and the current knowledge regarding the neural underpinnings of Δ^9-THC- or WIN55,212-2-induced changes.

3.1 Analgesia

In pre-clinical work, Δ^9-THC induces a strong antinociceptive effect across multiple behavioral tests (hot plate, tail flick test, formalin test) and models of chronic pain (inflammatory pain, neuropathic pain; Casey, Atwal, & Vaughan, 2017; Craft, Haas, Wiley, Yu, & Clowers, 2017; Finn et al., 2004; Wang et al., 2020).

CB_1R mechanisms: Early work demonstrated that pharmacological blockade or genetic deletion of CB_1Rs in CB_1-KO mice blocked Δ^9-THC- or WIN55,212-2-induced analgesia (Compton, Aceto, Lowe, & Martin, 1996; Ledent et al., 1999; Rinaldi-Carmona et al., 1994; Varvel et al., 2005; Wiley & Martin, 2003; Zimmer, Zimmer, Hohmann, Herkenham, & Bonner, 1999). To address the anatomical locus and the cell type-specific receptor mechanisms underlying cannabinoid modulation of pain, multiple cell-type specific CB_1-KO mice have been developed with CB_1R deleted from a restricted neuronal population. As stated above, CB_1Rs are highly expressed on GABA and glutamatergic neurons. However, selective deletion of CB_1Rs on cortical glutamatergic neurons (Glu-CB_1-KO, generated by crossing CB_1-floxed mice with NEX-Cre mice), forebrain GABAergic interneurons (GABA-CB_1-KO, generated by crossing CB_1-floxed mice with Dlx5/6-Cre mice), or dopamine D_1 receptor-expressing neurons (Drd_1-CB_1-KO, generated by crossing CB_1-floxed mice with D_1-Cre mice) failed to alter Δ^9-THC antinociception (Table 2; Monory et al., 2007). These

findings indicate that CB_1Rs on cortical GABAergic or glutamatergic neurons as well as D_1-expressing neurons do not mediate cannabinoid antinociception.

In a more recent report, De Giacomo and colleagues (2020) used a conditional rescue model in which CB_1Rs are restored only in distinct neuronal subpopulations in full CB_1-KO mice and compared to full CB_1R-KO mice to determine whether CB_1Rs in a given region can reproduce Δ^9-THC antinociception. In line with the findings from conditional CB_1-KO mice, the rescue of CB_1R expression in dorsal telencephalic glutamate neurons (Glu-CB_1-RS) or forebrain GABA neurons (GABA-CB_1-RS) did not re-establish Δ^9-THC-induced analgesia (De Giacomo et al., 2020), suggesting that activation of CB_1Rs in forebrain GABA or glutamate neurons is insufficient to produce analgesic effects. In contrast, mice lacking CB_1Rs on CaMKIIα-positive neurons (CaMK-CB_1-KO, generated by CB_1-floxed mice with CaMKIIα-Cre mice) demonstrated attenuated (but not abolished) Δ^9-THC-induced analgesia (Monory et al., 2007), suggesting that CB_1Rs in CaMKIIα-expressing neurons partially mediate Δ^9-THC-induced analgesia. In addition, CB_1Rs may still be expressed by GABAergic neurons in other brain regions in the forebrain of GABA-CB_1-KO mice since the *Dlx5/6* (distal-less homeobox 5 and 6) genes are expressed in progenitors of GABAergic interneurons only in developing forebrain and their expression strongly diminishes after birth (Dimidschstein et al., 2016). Moreover, in the striatum these genes are not GABA specific. Similarly, CB_1Rs may still be expressed in glutamatergic neurons in other brain regions in the forebrain Glu-CB_1-KO mice since the NEX gene is mainly expressed in pyramidal neurons of the dorsal telencephalon during embryonic development (Schwab et al., 2000). Thus, more studies are required to determine the role of CB_1Rs in GABA or glutamate neurons of other non-forebrain regions in cannabinoid antinociception.

The major site of pain perception is the sensory nervous system, to be more precise, the sensory neurons in the dorsal root ganglia (DRG) as well as the dorsal horn neurons in the spinal cord, which also contain high densities of CB1Rs (Ahluwalia, Urban, Capogna, Bevan, & Nagy, 2000; Farquhar-Smith et al., 2000). To determine the role of CB_1Rs in primary sensory neurons, a peripheral CB_1-KO mouse line was developed, in which CB1Rs in DRG nociceptive ($Na_v1.8$-expressing) sensory neurons were deleted (SNS-CB1-KO, generated by crossing CB_1-floxed mice with SNS-Cre mice; Agarwal et al., 2007). The nociceptor-specific loss of CB_1Rs substantially reduced analgesia produced by local and systemic, but not intrathecal, delivery of WIN55,212-2 (Table 2; Agarwal et al., 2007). This suggests that CB_1Rs expressed on the peripheral terminals of nociceptors (DRG sensory neurons) are critical in cannabinoid-induced analgesia (Fig. 5). These findings are consistent with work demonstrating that systemic administration of a novel peripherally acting CB_1R agonist, AZ11713908, produced robust analgesia (Yu et al., 2010). Interestingly, CaMKIIα is also highly expressed in DRG neurons (Carlton & Hargett, 2002), suggesting that a peripheral CB_1R mechanism could also contribute to the reduction of Δ^9-THC-induced analgesia observed in CaMK-CB_1-KO mice. Thus, CB1R mechanisms in peripheral sensory neurons appear to be the primary mechanism underlying cannabinoid analgesic effects (Fig. 5).

CB_2R mechanisms: Although CB_1R activation appears to be the primary mechanism underlying Δ^9-THC's analgesic effects, other targets have been discovered. For instance,

CB_2R agonists have been demonstrated to produce potent analgesic effects in animal models of chronic inflammatory and neuropathic pain (Maldonado, Baños, & Cabañero, 2016; Shang & Tang, 2017). Further, we have recently reported that deletion of CB_2Rs in CB_2-KO mice significantly reduces Δ^9-THC- or WIN55,212-2-induced analgesia, implicating CB_2Rs in cannabinoid antinociception (Wang et al., 2020). However, the anatomical substrates underlying CB_2R-mediated analgesia are still unclear. Recently, it was reported that mice can learn to self-administer the CB_2R agonist JWH133 to inhibit neuropathic pain (Cabañero et al., 2020). This behavior was blocked by global CB_2-KO mice, suggesting a CB_2R-mediated effect. Interestingly, selective deletion of CB_2R from neurons in neuronal CB_2-KO mice (CB_2-floxed X Syn-Cre) caused an increase in JWH133 self-administration, while selective deletion of CB_2R from immune cells in monocyte-specific CB_2-KO mice (CB_2-floxed X LysM-Cre) did not alter JWH133 self-administration, suggesting that increased spontaneous pain occurs in neuronal CB_2-KO mice and high doses of JWH133 are required to relieve neuropathic pain (Cabañero et al., 2020) (Table 2). These findings provide clear evidence supporting a neuronal CB_2R mechanism underlying CB2R-induced analgesia. However, selective deletion of CB_2R from DGR neurons in peripheral neuronal CB_2-KO mice (CB_2-loxed X Nav1.8-Cre) did not significantly alter JWH133-produced analgesic effects, suggesting that a neuronal CB_2R mechanism in the brain play a dominant role in JWH133- or other cannabinoid-induced analgesia (Fig. 5).

Other mechanisms: Additionally, the TRPA1 channel is a receptor critically involved in thermal pain perception. Evidence has shown that TRPA1 is implicated in cannabinoid antinociception. Specifically, Akopian et al. (2008) found that WIN55,212-2 induces analgesia in a peripheral capsaicin pain model, which is absent in TRPA1-KO mice. JWH133 produced a significant reduction in either mechanical or thermal hypernociception in a neuropathic pain model (Cabañero et al., 2020). Genetic deletion of TRPA1 blocked JWH133-induced reduction in thermal, but not, mechanical, pain, suggesting possible involvement of TRPA1 in cannabinoid analgesia. In addition, the opioid system was reported to be involved in cannabinoid analgesia. Specifically, κ-opioid receptors (KORs) are involved in Δ^9-THC-induced analgesia as the κ agonist dynorphin was increased by Δ^9-THC administration and mice with a genetic deletion of dynorphin showed attenuated Δ^9-THC-induced analgesia (Houser, Eads, Embrey, & Welch, 2000; Zimmer et al., 2001). However, KOR-KO mice displayed no change in Δ^9-THC antinociception (Ghozland et al., 2002). Given that Δ^9-THC does not bind to KORs, dynorphin may indirectly alter Δ^9-THC's action against pain. Unexpectedly, genetic deletion of GPR55 produced an opposite enhancement in WIN55,212-2-induced analgesia (Wang et al., 2020), suggesting involvement of GPR55 mechanism in cannabinoid analgesia.

3.2 Hypothermia

Intermediate to high doses of Δ^9-THC produce a drop in body temperature across different routes of administration and species (Hayakawa et al., 2007; McMahon, Amin, & France, 2005; Taffe, Kevin, Creehan, & Vandewater, 2015; Taffe, Creehan, Vandewater, Kerr, & Cole, 2021; Varvel et al., 2006).

CB_1R mechanism: CB_1Rs mediate the hypothermic effects of Δ^9-THC as pharmacological antagonism or genetic deletion of CB_1Rs blocks Δ^9-THC-induced decreases in temperature (Hayakawa et al., 2007; Ledent et al., 1999; McMahon et al., 2005; Varvel et al., 2005; Zimmer et al., 1999). In contrast to the analgesic effects, hypothermic responses to Δ^9-THC were significantly attenuated in CaMK-CB_1-KO and forebrain Glu-CB_1-KO mice, but not forebrain GABA-CB_1-KO mice, implicating cortical glutamatergic neurons in Δ^9-THC-induced hypothermia (Monory et al., 2007). The hypothermic effects of Δ^9-THC are likely mediated mainly by CB_1Rs expressed in the preoptic anterior hypothalamus (POAH), a major thermoregulatory brain area (Fitton & Pertwee, 1982; Rawls, Cabassa, Geller, & Adler, 2002). In forebrain Glu-CB_1-RS and GABA-CB_1-RS mice, CB_1R expression is rescued in the hypothalamus relative to full CB_1-KO mice (Gutierrez-Rodríguez et al., 2017; Remmers et al., 2017; Ruehle et al., 2013). Consistent with the data from conditional knockout mice, Glu-CB_1-RS, but not GABA-CB_1-RS, mice showed a partial rescue of Δ^9-THC hypothermia. As such, glutamatergic CB_1Rs may play a dominant role in Δ^9-THC-mediated hypothermia. Glutamate tonically increases body temperature by binding to NMDA receptors in the preoptic hypothalamus (Sengupta, Jaryal, & Mallick, 2016). One report found that the hypothermic response to WIN55,212-2 is synergistically enhanced by NMDA receptor antagonism (Rawls, Cowan, Tallarida, Geller, & Adler, 2002). Microinjections of WIN55,212-2 into the POAH induced hypothermia (Rawls, Cabassa, et al., 2002). These findings suggest that cannabinoids may act on a glutamatergic pathway in the POAH to produce hypothermia (Fig. 5).

Non-CB_1R mechanisms: Additional non-CB_1R receptor mechanisms have been implicated in Δ^9-THC-induced temperature shifts. We found that blockade or deletion of CB_2Rs in global CB_2-KO mice or selective deletion of CB2Rs in midbrain DA neurons failed to alter Δ^9-THC- or WIN55,121-2-induced hypothermia (Liu et al., 2017; Wang et al., 2020). In contrast, selective antagonism or genetic deletion of GPR55 receptors augmented hypothermia in response to Δ^9-THC or WIN55,212-2 (Wang et al., 2020), suggesting that activation of GPR55 has a suppressive effect on Δ^9-THC-induced hypothermia. No prior work has established a role for GPR55 in temperature control. However, knowledge of this receptor is limited, and future work should investigate this possibility. In addition, serotonergic 5-HT_{1A} receptors and dopamine D_2 receptors also regulate Δ^9-THC-induced hypothermia in an opposing manner such that D_2 receptor antagonists attenuate and 5-HT_{1A} receptor antagonists potentiate Δ^9-THC's hypothermic effects and vice versa with their respective agonists (Malone & Taylor, 2001; Nava, Carta, & Gessa, 2000). Although Δ^9-THC has no direct binding affinity at 5-HT_{1A} and D2 receptors, these effects could be mediated indirectly via Δ^9-THC metabolite activity at the 5-$HT_{1A}R$ and CB_1-D_2 heterodimer interactions.

3.3 Catalepsy

In rodents, Δ^9-THC induces catalepsy at high doses (10mg/kg and above; Long et al., 2010; Metna-Laurent, Mondésir, Grel, Vallée, & Piazza, 2017). The most common behavioral assay of catalepsy is the bar test in which an animals forepaws are placed on a horizontal bar and the amount of time it takes them to move out of this unusual conformation and put both paws on the ground is recorded (Sanberg, Bunsey, Giordano, & Norman, 1988).

CB_1R mechanism: As with Δ^9-THC induced hypothermia, blockage or deletion of CB_1Rs effectively abolishes Δ^9-THC's cataleptic effects (Ledent et al., 1999; Lichtman & Martin, 1997; Tseng & Craft, 2004; Varvel et al., 2005; Zimmer, Zimmer, Hohmann, Herkenham, & Bonner, 1999). An early study found that deletion of CB_1Rs on forebrain GABA or glutamate neurons failed to alter the cataleptic effects of Δ^9-THC (Monory et al., 2007), demonstrating that CB_1Rs on both neuronal cell types in the cortex do not mediate Δ^9-THC-induced catalepsy. This is consistent with findings from conditional rescue mice in which neither dorsal telencephalic glutamatergic CB_1Rs nor forebrain GABAergic CB_1Rs were sufficient to rescue the cataleptic effect of Δ^9-THC (De Giacomo et al., 2020).

Interestingly, deletion of CB_1Rs from CaMKIIα (CaMK-CB_1-KO) or D_1-expressing neurons (Drd1-CB_1-KO) abolished Δ^9-THC-induced catalepsy (Monory et al., 2007), suggesting that CB1Rs on both types of neurons play a critically important role in catalepsy produced by cannabinoids. CaMKIIα is expressed in numerous neuronal cell types that project to a myriad of brain regions. Therefore, it is unknown exactly how CB_1Rs in CaMKIIα-expressing neurons underlie cannabinoid-induced catalepsy. In contrast, D1Rs are mainly distributed in one population of GABAergic medium-spiny neurons (D_1-MSNs) in the striatum and glutamatergic neurons in the cortex. It is well known that D_1-MSNs regulate voluntary motor movements (van der Stelt & Di Marzo, 2003). Activation of CB_1Rs on D_1-MSNs likely inhibits GABAergic MSNs in the striatum, producing motor impairment. This is supported by the finding that microinjections of Δ^9-THC into the nucleus accumbens (NAc) produced catalepsy (Sano et al., 2008) that was inhibited by both serotoninergic agonists and NMDA receptor antagonists (Nobuaki Egashira et al., 2006; Kinoshita et al., 1994). These findings suggest that CB_1R expression in the striatum may be a primary brain region underlying Δ^9-THC-induced catalepsy (Fig. 5).

CB_2R mechanism: In addition to CB_1R, CB_2R also plays a role in the cataleptic effects of Δ^9-THC or WIN55212-2. Indeed, deletion and pharmacological antagonism of CB_2Rs attenuated cataleptic behavior following Δ^9-THC or WIN55,212-2 administration (Wang et al., 2020). Furthermore, selective deletion of CB_2Rs from midbrain DA neurons attenuated WIN55,212-2-induced catalepsy (Liu et al., 2017), while deletion of CB_2R from microglia (CB_2-floxed X CX3CR1-Cre) had no effect on WIN55,212-2-induced catalepsy (Liu, Canseco-Alba, Liang, Ishiguro, & Onaivi, 2020), suggesting that a neuronal, not microglial, CB_2R mechanism underlies cannabinoid-induced catalepsy. In addition, it was recently reported that CB_2Rs are highly expressed in glutamate neurons in the red nucleus of the midbrain and modulate locomotor activity (Zhang, Shen, et al., 2021). These findings together suggest that activation of CB_2Rs in the mesolimbic DA neurons and the motor circuit glutamate neurons at least in part underlies cannabinoid-induced catalepsy (Fig. 5).

GPR55 mechanism: On the other hand, it was recently reported that GPR55 receptors are densely distributed in the striatum and administration of a GPR55 agonist (abnormal-cannabidiol) has been shown to block catalepsy produced by haloperidol (Marichal-Cancino, Fajardo-Valdez, E. Ruiz-Contreras, Mendez-Díaz, & Prospero-García, 2017; Celorrio et al., 2017), while pharmacological blockade of GPR55 potentiate Δ^9-THC-induced catalepsy (Wang et al., 2020). Similarly, mice lacking GPR55 demonstrated enhanced Δ^9-THC- or

WIN55,212-2-induced catalepsy (Wang et al., 2020). These findings suggest that GPR55 activation may produce an anti-cataleptic effect. As such, the final behavioral expression of cannabinoid-induced catalepsy may depend on the respective contributions of CB_1R, CB_2R, and GPR55.

3.4 Hypolocomotion

Δ^9-THC suppresses locomotor activity at doses of 3mg/kg and above. The open field locomotion test is most often utilized to measure changes in movement. Mice are placed in a large, empty container and the distance they travel is monitored. The rotarod test is another measure of locomotor performance, particularly motor coordination, in which mice are placed on an elevated revolving rod and the time it takes them to fall is recorded.

CB_1R mechanism: Like the other assays within the tetrad, Δ^9-THC or WIN55,212-2 alters locomotor activity via activation of CB_1Rs as deletion of CB_1Rs abolished Δ^9-THC and other cannabinoids-induced locomotor impairment (Ledent et al., 1999; Nguyen et al., 2016; Taffe, Creehan, & Vandewater, 2015; Zimmer et al., 1999). Findings from three different conditional CB_1-KO mice strains (Glu-CB_1-KO, CaMK-CB_1-KO and VgluT2-CB_1-KO) implicate glutamatergic neurons in Δ^9-THC's effects on locomotion (Monory et al., 2007; Han et al., 2017). These findings parallel work with conditional rescue mice in which restoration of CB1R expression in dorsal telencephalic glutamatergic neurons (Glu-CB_1-RS mice) reestablished Δ^9-THC-induced locomotor suppression (De Giacomo et al., 2020). In contrast, deletion of CB_1Rs in forebrain GABA neurons failed to alter Δ^9-THC-induced locomotor impairment (Monory et al., 2007). Similarly, GABA-CB_1-RS mice with CB_1R expression rescued in forebrain GABAergic neurons showed no evidence of Δ^9-THC locomotor inhibition (De Giacomo et al., 2020). Previous work has demonstrated that cannabinoids attenuate excitatory glutamatergic input in the striatum (Brown, Brotchie, & Fitzjohn, 2003). Thus, CB_1Rs on corticostriatal glutamatergic projection neurons likely mediate hypolocomotion produced by Δ^9-THC (Monory et al., 2007) (Fig. 5).

The basal ganglia contains two major GABAergic neuronal populations—D_1-MSNs and D_2-MSNs. Both populations of neurons express CB_1Rs (Hermann, Marsicano, & Lutz, 2002) and control basal ganglia motoric output (Graybiel, 2000). Activation of D_1-MSNs enhances, while activation of D_2-MSNs inhibits locomotion (Calabresi, Picconi, Tozzi, Ghiglieri, & Di Filippo, 2014; Kravitz et al., 2010). The D_1-expressing MSNs have become a locus of interest since Δ^9-THC treatment may directly inhibit this locomotor-enhancing population of neurons. However, CB_1R deletion from D_1-MSNs had no effect on Δ^9-THC-induced hypolocomotion (Monory et al., 2007). Interestingly, the effects of Δ^9-THC on overall locomotor activity (open field test) vs. motor coordination (rotarod) may have distinct neural underpinnings. Indeed, Blazquez and colleagues (2020) found that Glu-CB_1-KO and WT mice had comparable deficits in motor coordination following Δ^9-THC in direct contrast to the findings described above using the open-field. Further, the motor dyscoordinating effects of Δ^9-THC were absent in Drd1-CB_1-KO mice, indicating that D_1-MSNs are critical for Δ^9-THC-induced deficits in motor coordination (Blázquez et al., 2020) (Fig. 5).

CB_2R mechanism: In addition to CB_1R mechanisms, dopaminergic CB_2Rs may also underlie Δ^9-THC-induced locomotor depression. We have previously reported that CB_1 and CB_2 receptors modulate locomotor activity in opposite directions (Li et al., 2021; Li et al., 2009; Wang et al., 2020; Xi et al., 2011). Specifically, genetic deletion of CB_1Rs decreased basal locomotor activity, while genetic deletion of CB_2Rs produced a moderate increase, indicating that activation of CB_2Rs inhibits locomotor behavior (Li et al., 2021; Wang et al., 2020). Systemic or intra-NAc administration of JWH133, a selective CB_2R agonist, inhibits basal level locomotion and decreases cocaine's locomotor activating effects in a dose-dependent manner (Xi et al., 2011). Further, genetic deletion of CB_2Rs blocked the Δ^9-THC-induced reduction in open-field locomotion (Li et al., 2021; Wang et al., 2020), implicating CB2Rs in Δ^9-THC's locomotor suppressant effects. When CB_2Rs are selectively deleted from midbrain DA neurons, mice show an increase in basal locomotor activity (Canseco-Alba et al., 2019). These findings suggest that dopaminergic CB_2Rs contribute to Δ^9-THC-induced hypolocomotion (Galaj & Xi, 2019; Jordan & Xi, 2019) (Fig. 5).

GPR55 mechanism: Finally, GPR55-KO mice showed heightened Δ^9-THC or WIN55,212-2-induced deficits in motor coordination on the rotarod (Wang et al., 2020). These findings complement prior work in which administration of a GPR55 agonist improved performance on the rotarod following selective lesions of striatal DA neurons (Fatemi, Abdollahi, Shamsizadeh, Allahtavakoli, & Roohbakhsh, 2021). This work demonstrates that GPR55 agonism is involved in motor coordination and has an obverse effect on Δ^9-THC hypomotility in the tetrad, although the cell types and brain regions responsible are unknown.

In summary, Δ^9-THC and other cannabinoids produce classical tetrad effects through multiple receptor mechanisms, including CB_1R, CB_2R and GPR55 with CB_1R predominant (Table 2). Technical advances in detecting low level gene expression and the development of conditional transgenic animals have begun to uncover the region and cell type-specific subpopulations that underlie Δ^9-THC's effects in the tetrad. In brief, CB_1R in peripheral primary sensory neurons of the DRG and CB_2R in super-spinal neurons appear to be the major targets underlying THC-induced analgesia, while glutamatergic CB_1Rs in the preoptic anterior hypothalamus are not only necessary, but also sufficient for Δ^9-THC-induced hypothermia. The cataleptic and locomotor suppressant effects of Δ^9-THC are likely mediated mainly by activation of CB_1Rs on corticostriatal glutamatergic projection neurons and CB_2Rs on midbrain DA neurons and red nucleus glutamate neurons (Fig. 5).

4. Cannabinoid subjective effects

The subjective experience of cannabis varies on the affective spectrum from person to person. The majority of human users report enjoyment, relaxation and laughter, while others describe paranoia, anxiety and depression (Green, Kavanagh, & Young, 2003). In preclinical work, negative or aversive effects of Δ^9-THC are most commonly observed, particularly at high doses, whereas reward is rarer, difficult to replicate and only observed with low doses. A number of preclinical models of drug reward are utilized in addiction research. The gold standard is intravenous self-administration where animals are implanted with a jugular catheter and trained to make operant responses for drug infusions. Another commonly

used model is place conditioning in which the amount of time spent in a context formerly associated with drug exposure is used as a measure of reward. Aversion can also be assessed in this model if time in the drug paired context drops considerably after conditioning. Lastly, intracranial self-stimulation (ICSS) is a behavioral test that assesses how drugs of abuse alter operant responding for electrical stimulation of the median forebrain bundle or optical stimulation of a specific phenotype of neurons such as DA neurons or glutamate neurons. A decrease or increase in brain-stimulation reward (BSR) thresholds denotes a rewarding or aversive drug effect, respectively. The following section will walk through studies investigating the neural mechanisms underlying Δ^9-THC reward *versus* aversion using these behavioral models.

4.1 Cannabinoid reward

Self-administration of Δ^9-THC has been demonstrated in squirrel monkeys at low doses (4μg/kg/infusion), but not in rhesus monkeys, an effect that can be blocked by rimonabant, a selective CB1R blocker (John et al., 2018; Justinova, Tanda, Redhi, & Goldberg, 2003; Mansbach, Nicholson, Martin, & Balster, 1994; Tanda, Munzar, & Goldberg, 2000). However, in rodents (rats and mice), Δ^9-THC or WIN55,212-2 alone cannot maintain reliable self-administration possibly due to the limited reinforcing efficacy and anxiogenic effects of cannabinoids (Lefever, Marusich, Antonazzo, & Wiley, 2014; Takahashi & Singer, 1979). Interestingly, it was recently reported that passive Δ^9-THC pre-exposure or co-administration of Δ^9-THC with cannabidiol (CBD), a phytocannabinoid devoid of psychotomimetic effects, improved cannabinoid self-administration in rats (Spencer et al., 2018). A small number of studies have demonstrated Δ^9-THC-induced place preferences and decreases in BSR thresholds at the low end of the dose range (0.075–1mg/kg), which are absent in the presence of a CB_1R antagonist or in CB_1-KO mice (Braida, Iosue, Pegorini, & Sala, 2004; Foll, Wiggins, & Goldberg, 2006; Gardner et al., 1988; Ghozland et al., 2002; Katsidoni, Kastellakis, & Panagis, 2013; Lepore, Liu, Savage, Matalon, & Gardner, 1996; Lepore, Vorel, Lowinson, & Gardner, 1995; Li et al., 2021; Soria et al., 2004; Valjent & Maldonado, 2000). Microinjections of Δ^9-THC directly into the NAc shell and posterior ventral tegmental area (VTA) also support place preferences in rats, implicating these brain regions in Δ^9-THC-induced reward (Zangen, Solinas, Ikemoto, Goldberg, & Wise, 2006).

GABAergic CB_1R mechanism: Δ^9-THC administration produces a rise in DA concentration in the NAc (Tanda, Pontieri, & Chiara, 1997) and increases the firing rate of dopaminergic neurons in the VTA (French, Dillon, & Wu, 1997). Thus, it was hypothesized that CB_1Rs on GABA neurons mediate the rewarding effects of Δ^9-THC via disinhibition of VTA DA neurons (Fig. 6). This hypothesis is supported by electrophysiological data demonstrating decreased GABA activity in midbrain slices in the presence of Δ^9-THC and WIN55,212-2 (Friend et al., 2017; Szabo et al., 2002). Additionally, transgenic $FAAH^{C/A}$ knock-in mice, which recapitulate the FAAH (fatty acid amide hydrolase) polymorphism and display decreased FAAH expression and elevated circulating AEA, produced an enhanced place preference in adolescent female $FAAH^{C/A}$ mice relative to controls (Burgdorf et al., 2020). Importantly, this increase in cannabinoid reward was accompanied by greater expression of GABAergic CB_1Rs and lower expression of glutamatergic CB_1Rs in the VTA (Burgdorf et al., 2020).

Non-CB_1R mechanisms: Other work has evaluated whether non-cannabinoid receptor systems are involved in the rewarding effects of Δ^9-THC. In one report, the MOR antagonist, naltrexone, decreased Δ^9-THC self-administration (Justinova, Tanda, Munzar, & Goldberg, 2004) and Δ^9-THC place preferences were absent in MOR-KO mice (Ghozland et al., 2002). Δ^9-THC increases β-endorphin release in the VTA, which could explain the lack of rewarding effects when MORs are antagonized or deleted (Solinas, Zangen, Thiriet, & Goldberg, 2004). Another series of studies implicated A_{2A} adenosine receptors (A_{2A}Rs) in the rewarding effects of Δ^9-THC. CB_1Rs form heterodimers with A_{2A}Rs on presynaptic cells and activation of A_{2A}Rs counteracts the inhibitory effects of CB_1Rs on glutamate release in corticostriatal terminals (Ferreira et al., 2015; Köfalvi et al., 2020). Antagonism of presynaptic A_{2A}Rs was shown to reduce Δ^9-THC self-administration in squirrel monkeys, indicating that a decrease in cortical striatal glutamate attenuates Δ^9-THC reward (Justinová et al., 2011). Similarly, inhibition of postsynaptic A_{2A}Rs potentiated Δ^9-THC self-administration (Justinová, Redhi, Goldberg, & Ferre, 2014). These findings suggest that excess glutamate in corticostriatal brain regions, perhaps the NAc, may also contribute to the rewarding effects of Δ^9-THC likely by stimulating dopamine release in the striatum. Finally, α7 nicotinic acetylcholine receptors (α7nAChRs) also play a role in Δ^9-THC reward. Kynurenic acid (KYNA) acts as a negative allosteric modulator of α7nAChRs and increased levels of KYNA inhibit Δ^9-THC-induced increases in NAc dopamine and Δ^9-THC self-administration in squirrel monkeys (Justinova et al., 2013). α7nAChRs are located on glutamatergic neurons that project to the NAc shell (Dani & Bertrand, 2007; Secci et al., 2019). As such, suppression of glutamatergic activity by KYNA and subsequent decreases in NAc DA likely underlie the decrease in Δ^9-THC reward. This work by Justinova and colleagues provides further evidence in support of a glutamatergic accumbal mechanism meditating Δ^9-THC's rewarding properties perhaps in conjunction with disinhibition of GABAergic tone in the VTA.

4.2 Cannabinoid aversion

The aversive effects of Δ^9-THC are well documented in preclinical work. Subjects develop robust place aversions and increases in BSR thresholds in ICSS particularly at intermediate to high doses (3–20mg/kg; Braida et al., 2004; Hempel, Clasen, Nelson, Woloshchuk, & Riley, 2018; Katsidoni et al., 2013; Li et al., 2021; Mallet & Beninger, 1998a, b; Schramm-Sapyta et al., 2007; Spiller et al., 2019; Valjent & Maldonado, 2000; Vann et al., 2008; Wiebelhaus et al., 2015). We have recently tested cannabinoids in a new assay, optogenetic ICSS (oICSS), to further evaluate the rewarding (or reward-enhancing) *versus* aversive (or reward-attenuating) effects of a given drug (Han et al., 2017; Jordan et al., 2019; Newman et al., 2019). In this procedure, an adeno-associated virus (AAV) carrying a Cre-dependent channelrhodopsin 2 (ChR2) gene is microinjected into the VTA to express light-sensitive ChR2 in DA neurons of transgenic DA transporter (DAT)-Cre mice or glutamatergic neurons in VgluT2-Cre mice. Using this assay, we found that systemic administration of Δ^9-THC or WIN55,212-2 dose-dependently inhibited oICSS maintained by optical stimulation of VTA DA neurons and shifted the stimulation-response curve rightward or downward (Humburg et al., 2021), suggesting that cannabinoids are aversive in mice.

Glutamatergic CB_1R mechanism: The receptor mechanisms underlying Δ^9-THC's aversive effects are not fully understood. In prior work, cannabinoid-induced reductions in BSR thresholds were prevented by CB_1R antagonism (SR141716A or AM251; Katsidoni, Kastellakis, & Panagis, 2013; Spiller et al., 2019), pointing to a CB_1R mechanism in cannabinoid-induced aversion. To determine the specific cell types involved, we have recently used optogenetics to stimulate VTA glutamate neurons in VgluT2-Cre mice (Han et al., 2017). Unexpectedly, Δ^9-THC significantly inhibited oICSS maintained by optical stimulation of VTA glutamatergic neurons, but this effect was absent in VgluT2-CB_1-KO mice. Similarly, deletion of CB_1Rs on glutamate neurons prevented the expression of Δ^9-THC place aversions (Han et al., 2017). These findings suggest that CB_1Rs on VTA glutamate neurons are involved in Δ^9-THC-induced aversion (Fig. 6). This fits with the model of Δ^9-THC's affective properties described above wherein increased expression of CB_1Rs on GABA neurons and lower expression of CB_1Rs on glutamate neurons shifts the affective properties of Δ^9-THC towards reward (Burgdorf et al., 2020).

Dopaminergic CB_2R mechanism: Beyond CB_1Rs, Δ^9-THC's aversive effects were also blocked by CB_2R antagonism, as assessed by an increase in BSR thresholds in rats (Spiller et al., 2019). Additionally, genetic deletion of CB_2Rs shifted Δ^9-THC place conditioning from a place aversion in wildtype mice to a place preference in CB_2-KO mice (Li et al., 2021), indicating that CB_2Rs play a role in the initial aversive effects of Δ^9-THC. CB_2Rs are expressed on VTA dopaminergic neurons (Zhang et al., 2014; Zhang et al., 2017; Zhang et al., 2019) and can decrease the firing rate of these cells as well as diminish DA release in the NAc (Ma et al., 2019; Zhang et al., 2014; Zhang et al., 2017). These findings implicate CB_2Rs on mesolimbic DA neurons in THC-induced aversion (Fig. 6).

PPAR mechanisms: Little is known regarding the role of PPARs in cannabinoid action. However, we have recently explored the function of PPARs in Δ^9-THC induced aversion using oICSS (Hempel, Bi, Klein, & Xi, 2021). Administration of Δ^9-THC decreased responding for optical stimulation of VTA DA neurons in DAT-cre mice and this effect was attenuated by administration of a PPARα or PPARγ antagonist. As previously stated, Δ^9-THC is a potent PPARγ agonist (Table 1), which delineates how PPARγ antagonism reduced Δ^9-THC action on oICSS. PPARα receptors have been detected in the VTA and NAc at low levels (Warden et al., 2016). However, the mechanism through which PPARα modulates Δ^9-THC's aversive effects is still unclear. While Δ^9-THC administration does produce changes in PPARα gene transcription, it does not bind to the α isoform.

Kappa opioid receptor mechanism: Finally, κ-opioid receptors (KORs) have been investigated as a potential receptor target mediating Δ^9-THC aversion. Mice with elevated expression of the opioid encoding gene prodynorphin, a precursor of the KOR agonist dynorphin, demonstrated enhanced Δ^9-THC place aversions relative to controls (Cheng, Laviolette, van der Kooy, & Penninger, 2004). In the same vein, dynorphin-deficient and KOR-KO mice developed attenuated Δ^9-THC place aversions as did mice administered a KOR antagonist prior to assessments of Δ^9-THC aversion (Clasen et al., 2017; Ghozland et al., 2002; Zimmer et al., 2001). Microinjections of Δ^9-THC into the posterior NAc shell produced a significant place aversion that was attenuated by KOR antagonism, implicating

NAc KORs in the expression of Δ^9-THC aversion (Norris, Szkudlarek, Pereira, Rushlow, & Laviolette, 2019).

5. Cannabinoid effects on anxiety

One of the most commonly cited reasons for cannabis use in humans is the relaxing effects of the drug (Ewusi Boisvert et al., 2020; Green, Kavanagh, & Young, 2003); however, some individuals experience anxiety under the influence (Spindle et al., 2018). In preclinical models, Δ^9-THC has a biphasic effect on anxiety: anxiolytic at low doses and anxiogenic at high doses. The elevated plus maze (EPM) is a frequently used animal model in which rodents are placed on a raised apparatus containing two crossed arms – one of which is enclosed by walls and the other is open. Greater time spent in the open arms is a measure of decreased anxiety. The light dark test is another assay of anxiety that takes advantage of rodents' preference for dark, enclosed spaces. Subjects have access to two compartments separated by a door – one compartment is open and well-lit and the other is dark and enclosed. Anxiolytic drugs increase the proportion of time spent in the light compartment. The following subsections will update the current understanding of the receptor mechanisms underlying the anxiolytic and anxiogenic effects of Δ^9-THC.

5.1 Anxiolytic

As with the majority of cannabinoid effects on the central nervous system, administration of a CB_1 antagonist blocks Δ^9-THC-induced anxiolytic properties (Berrendero & Maldonado, 2002; Rubino et al., 2007). CB_1Rs in the amygdala and prefrontal cortex (PFC) underlie this effect (Tiziana Rubino et al., 2007). CP55,940 also produces an anxiolytic-like response at a low dose (1μg/kg), which is absent in Glu-CB_1-KO, but not GABA-CB_1-KO mice (Rey, Purrio, Viveros, & Lutz, 2012), suggesting that glutamatergic CB_1Rs in the PFC and amygdala mediate the initial anxiolytic effects of Δ^9-THC. However, further work is needed to confirm this.

CB_1R and CB_2R mechanisms: One study found that brief exposure to a predator odor produced an anxiety-like state in rats that was blocked by the selective monoacylglycerol lipase (MGL) inhibitors, KML29 and JZL184 (Ivy et al., 2020). MGL inhibitors prevent 2-AG degradation and elevate brain 2-AG concentrations, indicating that increased levels of 2-AG were anxiolytic in this model. Unexpectedly, the behavioral response to JZL184 was abolished by a CB_2R, but not CB_1R, antagonist. Specifically, the selective CB_2R agonist, JWH133, produced anxiolytic-like effects in rats exposed to a predator odor stressor and this response was blocked by the CB_2R antagonist AM630 (Ivy et al., 2020). However, early studies demonstrated that JZL184 produced marked anti-anxiety effects that were prevented by administration of the CB_1R antagonist SR141716A (Kinsey, O'Neal, Long, Cravatt, & Lichtman, 2011; Sciolino, Zhou, & Hohmann, 2011). Thus, 2-AG relieves anxiety potentially through activation of both CB_1Rs and CB_2Rs.

Other receptor mechanisms: Outside of the cannabinoid receptor family, other systems also modulate Δ^9-THC's anti-anxiety effect (Table 3). For instance, antagonism of the MOR and DOR suppressed the anxiolytic response to Δ^9-THC, although no

additional work has investigated this neurobiological mechanism (Berrendero & Maldonado, 2002). Additionally, serotonergic receptors are known to regulate anxiety and have been investigated in this context. Administration of a 5-HT_{1A} receptor antagonist abolished the anxiolytic effect of Δ^9-THC (Braida, Limonta, Malabarba, Zani, & Sala, 2007). Similarly, genetic deletion of 5-HT_{2A} receptors (5-HT_{2A}Rs) blocked the anxiolytic response to Δ^9-THC (Viñals et al., 2015). Viñals et al. (2015) further demonstrated that CB1Rs form heterodimeric complexes with 5-HT_{2A}Rs and perturbation of this relationship via transmembrane helix interference peptides suppressed the anti-anxiety effect of Δ^9-THC. These heterodimers were found in the cortex, hippocampus and striatum, although it's unknown exactly which regions mediate the anxiolytic effects of Δ^9-THC.

5.2 Anxiogenic

CB_1Rs in the basolateral amygdala mediate the anxiogenic effects of Δ^9-THC, as prior work has demonstrated that microinjections of Δ^9-THC into this brain region produced anxiety that was attenuated by pretreatment with the CB_1R antagonist AM251 (Rubino et al., 2008). Interestingly, mice lacking CB_1Rs on GABAergic, but not glutamatergic neurons, failed to demonstrate anxiety in response to CP55,940 (50μg/kg; Rey, Purrio, Viveros, & Lutz, 2012). A $GABA_B$ receptor-related mechanism may also contribute to the anxiogenic effect as positive allosteric modulation of $GABA_B$ receptors blocked CP55,940-induced anxiety. Whether these findings extend to Δ^9-THC's anxiogenic response is unknown. In addition, we have recently discovered that inhibition of PPARα can attenuate the anxiety produced by 5mg/kg Δ^9-THC (Hempel et al., 2021). PPARα is expressed brain regions that regulate anxiety including the amygdala and hippocampus (Kainu, Wikström, Gustafsson, & Pelto-Huikko, 1994; Warden et al., 2016). However, the function of PPARα in the CNS is still being explored and very little is currently known.

A number of studies have demonstrated that co-administration of CBD can inhibit the anxiogenic effects of Δ^9-THC (Liu, Scott, & Burnham, 2021; Murphy et al., 2017; Szkudlarek et al., 2019; Todd & Arnold, 2016; Zuardi, Shirakawa, Finkelfarb, & Karniol, 1982). CBD targets a number of receptors, but could suppress the effects of Δ^9-THC on anxiety via negative allosteric modulation of the CB1R or 5-HT_{1A}R activation (Campos & Guimarães, 2008; Galaj & Xi, 2021; Laprairie, Bagher, Kelly, & Denovan-Wright, 2015; Russo, Burnett, Hall, & Parker, 2005). Prior work has demonstrated that CBD can block anxiety caused by restraint stress via activity at the 5-HT_{1A}R (Resstel et al., 2009). Along these lines, Szkudlarek et al. (2019) found that intra-PFC injections of CBD suppressed Δ^9-THC-induced anxiety in the EPM and 5-HT_{1A}Rs are highly expressed in PFC neurons. Further work is needed to ascertain if direct 5-HT_{1A}R activation mediates CBD's inhibitory effect on Δ^9-THC in preclinical models of anxiety (for a summary see Table 3).

6. Cannabinoid cognitive effects

Acute exposure to cannabis impairs executive functions in human users across a number of domains such as attention, inhibitory control, psychomotor control, short term episodic memory, working memory and spatial memory (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Crean, Crane, & Mason, 2011; Ranganathan & D'Souza, 2006). In animals,

deficits in learning and memory are observed in spatial learning and memory, short term memory, repeated acquisition, habit formation, and fear conditioning (Goodman & Packard, 2015; Kangas et al., 2016; Prini et al., 2020; Resstel, Moreira, & Guimarães, 2009). A comprehensive review of the literature regarding the neurobiology of cannabinoids and cognition is beyond the scope of the present work. Here, we will focus on the neural mechanisms underlying acute effects of the most consistent Δ^9-THC-induced neurocognitive impairments, namely spatial learning and memory and short-term memory. A number of different animal models have been used in this context. Two commonly employed tests are the Morris water maze (MWM) and the novel object recognition task (NOR). The MWM assesses spatial learning and memory and in this task, animals are placed in a tank filled with cloudy liquid and must find a hidden platform to escape. In the NOR, subjects are initially exposed to two objects and in a subsequent session they are presented with one familiar and one novel object. Time spent exploring the new object is a measure of short-term memory impairment (for a summary see Table 4).

6.1 Spatial memory

CB_1Rs mediate the impairment in spatial memory after acute administration of Δ^9-THC as demonstrated by work in which CB_1Rs are antagonized or genetically deleted (Lichtman & Martin, 1996; Varvel & Lichtman, 2002). Intracerebral microinjection studies have established that CB1Rs in the hippocampus and medial PFC (mPFC) underlie this effect (Egashira, Mishima, Iwasaki, & Fujiwara, 2002). Moreover, the synthetic cannabinoid, HU210, produced deficits in spatial memory that were present in the forebrain GABA-CB_1-KO and Glu-CB_1-KO mice, but absent in mice with a conditional deletion of CB_1Rs in astrocytes (Han et al., 2012). In this report, antagonism of glutamatergic NMDA receptors (NMDARs) blocked the effects of HU210 on spatial memory and long-term synaptic depression in the hippocampus (Han et al., 2012). These findings indicate that cannabinoid-induced changes in spatial memory rely on stimulation of CB_1Rs on astrocytes and subsequent release of glutamate and changes in NMDAR signaling that induce LTD. It's unknown whether a similar pathway underlies the effects of Δ^9-THC in the MWM. However, antagonism and genetic ablation of cyclooxygenase-2 (COX-2), an enzyme responsible for the conversion of arachidonic acid to prostanoids, blocked Δ^9-THC impairments in spatial memory (Chen et al., 2013). These findings tie in with the astrocytic CB_1R mechanism as COX-2 enhances prostaglandin E_2 (PGE_2) release from astrocytes (Chen et al., 2013) and PGE_2 signaling can facilitate glutamatergic gliotransmission (Cali, Lopatar, Petrelli, Pucci, & Bezzi, 2014). Overall, astrocytic glutamate release appears to play a pivotal role in the expression of cannabinoid memory impairment.

A number of other pathways are involved in the effects of Δ^9-THC on spatial memory. For instance, pretreatment with an adenosine A_1 receptor (A_1R) agonist (caffeine) significantly elevated the Δ^9-THC-induced deficit in spatial memory (Sousa et al., 2011). A_1Rs were detected on glutamatergic terminals in the hippocampus and stimulation of A_1Rs disinhibited CB_1R suppression of hippocampal glutamatergic signaling (Sousa et al., 2011). Activation of the serotonergic system had the opposite effect on Δ^9-THC spatial memory impairments, i.e. the deficit was reversed by 5-HT_{1A} and $5HT_2$ receptor agonism (Egashira et al., 2002; Inui et al., 2004). Δ^9-THC also attenuated acetylcholine release in the dorsal

hippocampus, which was blocked by administration of a 5-HT_{1A}R agonist in agreement with prior work in which facilitation of acetylcholine release rescued Δ^9-THC-induced memory deficits (Inui et al., 2004; Mishima, Egashira, Matsumoto, Iwasaki, & Fujiwara, 2002). These systems may work in concert with astrocyte mediated glutamate release to mediate Δ^9-THC's effects on spatial memory.

6.2 Short-term memory

Unsurprisingly, activation of CB_1Rs mediates the Δ^9-THC-induced deficits in short-term memory as confirmed by CB_1R antagonism studies (Hampson & Deadwyler, 2000; Mallet & Beninger, 1998a, b). The hippocampus appears to be a locus of interest in this respect as *in vivo* recording from groups of hippocampal neurons during performance of a short-term memory task revealed attenuated firing strength following Δ^9-THC administration (Hampson & Deadwyler, 2000). One group has demonstrated that mice lacking CB_1Rs in hippocampal mitochondria fail to demonstrate a disruption in short-term memory following WIN55,212-2 administration (Hebert-Chatelain et al., 2016). CB_1Rs on mitochondria inhibit soluble-adenylyl cyclase, which decreases protein kinase A phosphorylation and has downstream impacts on mitochondrial energetic activity (Hebert-Chatelain et al., 2016). However, recent work has shown that intra-hippocampal injections of a protein kinase C inhibitor blocked Δ^9-THC's effects on short-term memory (Busquets-Garcia et al., 2018). It's not clear whether the differential activity at these two protein kinase families works in conjunction to produce cannabinoid memory deficits or if the cannabinoid agent selected drives activity at one or the other group of enzymes.

The adenosine system has also been implicated in Δ^9-THC's inhibitory effect on short-term memory. Administration of caffeine or a selective A_1R antagonist potentiated Δ^9-THC-induced short-term memory impairments (Panlilio et al., 2012). On the other hand, A_{2A}R antagonism mediated the therapeutic effect of CBD on Δ^9-THC short-term memory deficits (Aso et al., 2019). A_1 and A_{2A}R antagonists have recently been shown to differentially regulate synaptic plasticity in the hippocampus, which could underlie their opposing actions on cannabinoid memory changes (Reis et al., 2019). As described earlier, CB_1Rs form heterodimers with $5HT_{2A}$Rs and evidence of these structures has been detected in the hippocampus (Viñals et al., 2015). Both genetic deletion and pharmacological antagonism of $5HT_{2A}$Rs reversed Δ^9-THC-induced changes in short-term memory (Viñals et al., 2015). Finally, cholinergic hypofunction has been hypothesized to play a role in the cognitive deficits produced by cannabinoids. Goonawardena, Robinson, Hampson, and Riedel (2010) found that an acetylcholinesterase inhibitor blocked WIN55,212-2-induced memory impairing properties and restored the normal firing patterns of hippocampal neurons. Whether these findings can be applied to Δ^9-THC is unknown.

7. Conclusion

The majority of Δ^9-THC's pharmacological and behavioral effects are mediated by activation of CB_1Rs (Tables 2–4). However, the cell types and brain regions expressing these receptors varies depending on the behavior assessed. Despite the widespread expression of CB_1Rs on GABAergic neurons, glutamatergic CB_1Rs preferentially underlie many of

Δ^9-THC's effects including hypothermia, hypolocomotion, aversion, and anxiety relief. New research has discovered functional roles for CB_1Rs expressed on astrocytes and mitochondria in cannabinoid-induced cognitive impairments. This represents an exciting and promising area for future work, as non-neuronal CB_1R expression has been mostly ignored. Similarly, Δ^9-THC binds to a number of other targets such as CB_2R, GPR55, PPARs. The data from our lab has demonstrated that activation of these non-CB_1 receptors also modulate Δ^9-THC-induced behavior (Hempel et al., 2021; Li et al., 2021; Spiller et al., 2019; Wang et al., 2020). A host of additional non-cannabinoid receptor systems have been implicated in Δ^9-THC's behavioral effects primarily serotonergic (5-HT_{1A}Rs & 5-HT_{2A}Rs), opioidergic (MORs & KORs), and adenosinergic (A_1Rs & A_{2A}Rs) signaling. Activity at these receptors may stem from downstream activity following CB_1R or CB_2R stimulation. Given the increasing use of cannabis for both recreational and medicinal purposes, understanding the neurobiology of Δ^9-THC's CNS effects is of vital concern. Moreover, this research provides a basis for the design of pharmacotherapeutics for substance use disorders including cannabis use disorder as well as non-psychoactive alternatives for medical marijuana users.

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Abbreviations

Δ^9-THC	Δ^9-tetrahydrocannabinol
AEA	Anandamide
2-AG	2-arachidonoyl glycerol
ChR2	channelrhodopsin 2
GABA	gamma-aminobutyric acid
GPR55	G protein-coupled receptor 55
GPCR	G protein-coupled receptor
ISH	in situ hybridization
NAc	nucleus accumbens
oICSS	optical intracranial self-stimulation
PPARα	peroxisome proliferator-activated nuclear receptor alpha
PPARγ	peroxisome proliferator-activated nuclear receptor gamma
TRPV1	transient receptor potential vanilloid 1 channel
VTA	ventral tegmental area

References

Agarwal N, Pacher P, Tegeder I, Amaya F, Constantin CE, Brenner GJ, et al. (2007). Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. Nature Neuroscience, 10(7), 870–879. 10.1038/nn1916. [PubMed: 17558404]

Ahluwalia J, Urban L, Capogna M, Bevan S, & Nagy I (2000). Cannabinoid 1 receptors are expressed in nociceptive primary sensory neurons. Neuroscience, 100(4), 685–688. 10.1016/S0306-4522(00)00389-4. [PubMed: 11036202]

Akopian AN, Ruparel NB, Patwardhan A, & Hargreaves KM (2008). Cannabinoids desensitize capsaicin and mustard oil responses in sensory neurons via TRPA1 activation. The Journal of Neuroscience, 28(5), 1064–1075. 10.1523/jneurosci.1565-06.2008. [PubMed: 18234885]

Alexander SPH (2016). Therapeutic potential of cannabis-related drugs. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 64, 157–166. 10.1016/j.pnpbp.2015.07.001. [PubMed: 26216862]

Aso E, Fernández-Dueñas V, López-Cano M, Taura J, Watanabe M, Ferrer I, et al. (2019). Adenosine A_{2A}-cannabinoid CB1 receptor heteromers in the hippocampus: Cannabidiol blunts Δ_9-tetrahydrocannabinol-induced cognitive impairment. Molecular Neurobiology, 56(8), 5382–5391. 10.1007/s12035-018-1456-3. [PubMed: 30610611]

Atwood BK, & Mackie K (2010). CB2: A cannabinoid receptor with an identity crisis. British Journal of Pharmacology, 160(3), 467–479. 10.1111/j.1476-5381.2010.00729.x. [PubMed: 20590558]

Baker D, Pryce G, Davies WL, & Hiley CR (2006). In silico patent searching reveals a new cannabinoid receptor. Trends in Pharmacological Sciences, 27(1), 1–4. 10.1016/j.tips.2005.11.003. [PubMed: 16318877]

Bénard G, Massa F, Puente N, Lourenço J., Bellocchio L., Soria-Gómez E., et al. (2012). Mitochondrial CB_1 receptors regulate neuronal energy metabolism. Nature Neuroscience, 15(4), 558–564. 10.1038/nn.3053. [PubMed: 22388959]

Berrendero F, & Maldonado R (2002). Involvement of the opioid system in the anxiolytic-like effects induced by Δ9-tetrahydrocannabinol. Psychopharmacology, 163(1), 111–117. 10.1007/s00213-002-1144-9. [PubMed: 12185408]

Bishop-Bailey D (2000). Peroxisome proliferator-activated receptors in the cardiovascular system. British Journal of Pharmacology, 129(5), 823–834. 10.1038/sj.bjp.0703149. [PubMed: 10696077]

Blázquez C, Ruiz-Calvo A, Bajo-Grañeras R, Baufreton JM, Resel E, Varilh M, et al. (2020). Inhibition of striatonigral autophagy as a link between cannabinoid intoxication and impairment of motor coordination. eLife, 9, e56811. 10.7554/eLife.56811. [PubMed: 32773031]

Bodor AL, Katona I, Nyíri G, Mackie K, Ledent C, Hájos N, et al. (2005). Endocannabinoid signaling in rat somatosensory cortex: Laminar differences and involvement of specific interneuron types. The Journal of Neuroscience, 25(29), 6845–6856. 10.1523/jneurosci.0442-05.2005. [PubMed: 16033894]

Braida D, Iosue S, Pegorini S, & Sala M (2004). Delta9-tetrahydrocannabinol-induced conditioned place preference and intracerebroventricular self-administration in rats. European Journal of Pharmacology, 506(1), 63–69. 10.1016/j.ejphar.2004.10.043. [PubMed: 15588625]

Braida D, Limonta V, Malabarba L, Zani A, & Sala M (2007). 5-HT1A receptors are involved in the anxiolytic effect of Δ9-tetrahydrocannabinol and AM 404, the anandamide transport inhibitor, in Sprague–Dawley rats. European Journal of Pharmacology, 555(2), 156–163. 10.1016/j.ejphar.2006.10.038. [PubMed: 17116299]

Brown TM, Brotchie JM, & Fitzjohn SM (2003). Cannabinoids decrease corticostriatal synaptic transmission via an effect on glutamate uptake. The Journal of Neuroscience, 23(35), 11073–11077. 10.1523/jneurosci.23-35-11073.2003. [PubMed: 14657164]

Brusco A, Tagliaferro P, Saez T, & Onaivi ES (2008a). Postsynaptic localization of CB2 cannabinoid receptors in the rat hippocampus. Synapse, 62(12), 944–949. 10.1002/syn.20569. [PubMed: 18798269]

Brusco A, Tagliaferro P, Saez T, & Onaivi ES (2008b). Ultrastructural localization of neuronal brain CB2 cannabinoid receptors. Annals of the New York Academy of Sciences, 1139(1), 450–457. [PubMed: 18991892]

Burgdorf CE, Jing D, Yang R, Huang C, Hill MN, Mackie K, et al. (2020). Endocannabinoid genetic variation enhances vulnerability to THC reward in adolescent female mice. Science Advances, 6(7), eaay1502. 10.1126/sciadv.aay1502. [PubMed: 32095523]

Busquets-Garcia A, Gomis-González M, Salgado-Mendialdúa V, Galera-López L, Puighermanal E, Martín-García E, et al. (2018). Hippocampal protein kinase C signaling mediates the short-term memory impairment induced by Delta9-tetrahydrocannabinol. Neuropsychopharmacology, 43(5), 1021–1031. 10.1038/npp.2017.175. [PubMed: 28816239]

Cabañero D, Ramírez-López A, Drews E, Schmöle A, Otte DM, Wawrzczak-Bargiela A, et al. (2020). Protective role of neuronal and lymphoid canna-binoid CB2 receptors in neuropathic pain. eLife, 9, e55582. [PubMed: 32687056]

Cabral GA, & Griffin-Thomas L (2008). Cannabinoids as therapeutic agents for ablating neuroinflammatory disease. Endocrine, Metabolic & Immune Disorders Drug Targets, 8(3), 159–172. 10.2174/187153008785700118.

Calabresi P, Picconi B, Tozzi A, Ghiglieri V, & Di Filippo M (2014). Direct and indirect pathways of basal ganglia: a critical reappraisal. Nature Neuroscience, 17(8), 1022–1030. 10.1038/nn.3743. [PubMed: 25065439]

Cali C, Lopatar J, Petrelli F, Pucci L, & Bezzi P (2014). G-protein coupled receptor-evoked glutamate exocytosis from astrocytes: Role of prostaglandins. Neural Plasticity, 2014, 254574. 10.1155/2014/254574. [PubMed: 24551459]

Campos AC, & Guimarães FS (2008). Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. Psychopharmacology, 199(2), 223. 10.1007/s00213-008-1168-x. [PubMed: 18446323]

Canseco-Alba A, Schanz N, Sanabria B, Zhao J, Lin Z, Liu Q-R, et al. (2019). Behavioral effects of psychostimulants in mutant mice with cell-type specific deletion of CB2 cannabinoid receptors in dopamine neurons. Behavioural Brain Research, 360, 286–297. 10.1016/j.bbr.2018.11.043. [PubMed: 30508607]

Carliner H, Brown QL, Sarvet AL, & Hasin DS (2017). Cannabis use, attitudes, and legal status in the U.S.: A review. Preventive Medicine, 104, 13–23. 10.1016/j.ypmed.2017.07.008. [PubMed: 28705601]

Carlton SM, & Hargett GL (2002). Stereological analysis of Ca2+/calmodulin-dependent protein kinase IIα-containing dorsal root ganglion neurons in the rat: Colocalization with isolectin Griffonia simplicifolia, calcitonin gene-related peptide, or vanilloid receptor 1. Journal of Comparative Neurology, 448(1), 102–110. 10.1002/cne.10250. [PubMed: 12012376]

Casey SL, Atwal N, & Vaughan CW (2017). Cannabis constituent synergy in a mouse neuropathic pain model. Pain, 158(12), 2452–2460. 10.1097/j.pain.0000000000001051. [PubMed: 28885457]

Castillo PE, Younts TJ, Chávez AE, & Hashimotodani Y (2012). Endocannabinoid signaling and synaptic function. Neuron, 76(1), 70–81. 10.1016/j.neuron.2012.09.020. [PubMed: 23040807]

Celorrio M, Rojo-Bustamante E, Fernández-Suárez D, Sáez E, Estella-Hermoso de Mendoza A, Müller CE, et al. (2017). GPR55: A therapeutic target for Parkinson's disease? Neuropharmacology, 125, 319–332. 10.1016/j.neuropharm.2017.08.017. [PubMed: 28807673]

Cheer JF, Cadogan AK, Marsden CA, Fone KCF, & Kendall DA (1999). Modification of 5-HT2 receptor mediated behaviour in the rat by oleamide and the role of cannabinoid receptors. Neuropharmacology, 38(4), 533–541. 10.1016/S0028-3908(98)00208-1. [PubMed: 10221757]

Chen R, Zhang J, Fan N, Teng Z-Q, Wu Y, Yang H, et al. (2013). Δ9-THC-caused synaptic and memory impairments are mediated through COX-2 signaling. Cell, 155(5), 1154–1165. 10.1016/j.cell.2013.10.042. [PubMed: 24267894]

Cheng H-YM, Laviolette SR, van der Kooy D, & Penninger JM (2004). DREAM ablation selectively alters THC place aversion and analgesia but leaves intact the motivational and analgesic effects of morphine. The European Journal of Neuroscience, 19(11), 3033–3041. 10.1111/j.0953-816X.2004.03435.x. [PubMed: 15182311]

Clasen MM, Flax SM, Hempel BJ, Cheng K, Rice KC, & Riley AL (2017). Antagonism of the kappa opioid receptor attenuates THC-induced place aversions in adult male Sprague-Dawley rats. Pharmacology Biochemistry and Behavior, 163, 30–35. 10.1016/j.pbb.2017.10.010. [PubMed: 29100992]

Compton DR, Aceto MD, Lowe J, & Martin BR (1996). In vivo characterization of a specific cannabinoid receptor antagonist (SR141716A): Inhibition of delta 9-tetrahydrocannabinol-induced responses and apparent agonist activity. The Journal of Pharmacology and Experimental Therapeutics, 277(2), 586–594. [PubMed: 8627535]

Craft RM, Haas AE, Wiley JL, Yu Z, & Clowers BH (2017). Gonadal hormone modulation of △9-tetrahydrocannabinol-induced antinociception and metabolism in female versus male rats. Pharmacology Biochemistry and Behavior, 152, 36–43. 10.1016/j.pbb.2016.09.006. [PubMed: 27670094]

Crane NA, Schuster RM, Fusar-Poli P, & Gonzalez R (2013). Effects of cannabis on neurocognitive functioning: recent advances, neurodevelopmental influences, and sex differences. Neuropsychology Review, 23(2), 117–137. 10.1007/s11065-012-9222-1. [PubMed: 23129391]

Crean RD, Crane NA, & Mason BJ (2011). An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. Journal of Addiction Medicine, 5(1), 1–8. 10.1097/ADM.0b013e31820c23fa. [PubMed: 21321675]

Dani JA, & Bertrand D (2007). Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. Annual Review of Pharmacology and Toxicology, 47(1), 699–729. 10.1146/annurev.pharmtox.47.120505.105214.

De Giacomo V, Ruehle S, Lutz B, Häring M, & Remmers F (2020). Differential glutamatergic and GABAergic contributions to the tetrad effects of Δ(9)-tetrahydrocannabinol revealed by cell-type-specific reconstitution of the CB1 receptor. Neuropharmacology, 179, 108287. 10.1016/j.neuropharm.2020.108287. [PubMed: 32860777]

De Petrocellis L, Ligresti A, Moriello AS, Allarà M, Bisogno T, Petrosino S, et al. (2011). Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. British Journal of Pharmacology, 163(7), 1479–1494. 10.1111/j.1476-5381.2010.01166.x. [PubMed: 21175579]

De Petrocellis L, Nabissi M, Santoni G, & Ligresti A (2017). Chapter Eight—Actions and regulation of ionotropic cannabinoid receptors. In Kendall D, & Alexander SPH (Eds.), *Vol.* 80. Advances in pharmacology (pp. 249–289). Academic Press. [PubMed: 28826537]

Devane WA, Breuer A, Sheskin T, Jaerbe TU, Eisen MS, & Mechoulam R (1992). A novel probe for the cannabinoid receptor. Journal of Medicinal Chemistry, 35(11), 2065–2069. [PubMed: 1317925]

Dimidschstein J, Chen Q, Tremblay R, Rogers SL, Saldi GA, Guo L, et al. (2016). A viral strategy for targeting and manipulating interneurons across vertebrate species. Nature Neuroscience, 19(12), 1743–1749. [PubMed: 27798629]

Djeungoue-Petga M-A, & Hebert-Chatelain E (2017). Linking mitochondria and synaptic transmission: The CB1 receptor. BioEssays, 39(12), 1700126. 10.1002/bies.201700126.

Egashira N, Matsuda T, Koushi E, Mishima K, Iwasaki K, Shoyama Y, et al. (2006). Involvement of 5-hydroxytryptamine1A receptors in Δ9-tetrahydrocannabinol-induced catalepsy-like immobilization in mice. European Journal of Pharmacology, 550(1), 117–122. 10.1016/j.ejphar.2006.08.051. [PubMed: 17022969]

Egashira N, Mishima K, Iwasaki K, & Fujiwara M (2002). Intracerebral microinjections of delta 9-tetrahydrocannabinol: search for the impairment of spatial memory in the eight-arm radial maze in rats. Brain Research, 952(2), 239–245. 10.1016/s0006-8993(02)03247-x. [PubMed: 12376185]

Egashira N, Mishima K, Katsurabayashi S, Yoshitake T, Matsumoto Y, Ishida J, et al. (2002). Involvement of 5-hydroxytryptamine neuronal system in Δ9-tetrahydrocannabinol-induced impairment of spatial memory. European Journal of Pharmacology, 445(3), 221–229. 10.1016/S0014-2999(02)01755-7. [PubMed: 12079687]

Elbegdorj O, Westkaemper RB, & Zhang Y (2013). A homology modeling study toward the understanding of three-dimensional structure and putative pharmacological profile of the G-protein coupled receptor GPR55. Journal of Molecular Graphics and Modelling, 39, 50–60. 10.1016/j.jmgm.2012.10.005. [PubMed: 23220281]

Ewusi Boisvert E, Bae D, Pang RD, Davis JP, Kelley-Quon LI, Barrington-Trimis JL, et al. (2020). Subjective effects of combustible, vaporized, and edible cannabis: Results from a survey of adolescent cannabis users. Drug and Alcohol Dependence, 206, 107716. 10.1016/j.drugalcdep.2019.107716. [PubMed: 31718923]

Farquhar-Smith WP, Egertová M, Bradbury EJ, McMahon SB, Rice ASC, & Elphick MR (2000). Cannabinoid CB1 receptor expression in rat spinal cord. Molecular and Cellular Neuroscience, 15(6), 510–521. 10.1006/mcne.2000.0844. [PubMed: 10860578]

Fatemi I, Abdollahi A, Shamsizadeh A, Allahtavakoli M, & Roohbakhsh A (2021). The effect of intra-striatal administration of GPR55 agonist (LPI) and antagonist (ML193) on sensorimotor and motor functions in a Parkinson's disease rat model. Acta Neuropsychiatrica, 33(1), 15–21. 10.1017/neu.2020.30. [PubMed: 32967746]

Ferraro L, Tomasini MC, Gessa GL, Bebe BW, Tanganelli S, & Antonelli T (2001). The cannabinoid receptor agonist WIN 55,212-2 regulates glutamate transmission in rat cerebral cortex: An in vivo and in vitro study. Cerebral Cortex, 11(8), 728–733. 10.1093/cercor/11.8.728. [PubMed: 11459762]

Ferre S, Quiroz C, Orru M, Guitart X, Navarro G, Cortes A, et al. (2011). Adenosine A2A receptors and A2A receptor heteromers as key players in striatal function. Frontiers in Neuroanatomy, 5(36). 10.3389/fnana.2011.00036.

Ferreira SG, Gonçalves FQ., Marques JM., Tomé ÂR., Rodrigues RJ., Nunes-Correia I., et al. (2015). Presynaptic adenosine A2A receptors dampen cannabinoid CB1 receptor-mediated inhibition of corticostriatal glutamatergic transmission. British Journal of Pharmacology, 172(4), 1074–1086. 10.1111/bph.12970. [PubMed: 25296982]

Finn DP, Beckett SR, Roe CH, Madjd A, Fone KC, Kendall DA, et al. (2004). Effects of coadministration of cannabinoids and morphine on nociceptive behaviour, brain monoamines and HPA axis activity in a rat model of persistent pain. The European Journal of Neuroscience, 19(3), 678–686. 10.1111/j.0953-816x.2004.03177.x. [PubMed: 14984418]

Fitton AG, & Pertwee RG (1982). Changes in body temperature and oxygen consumption rate of conscious mice produced by intrahypothalamic and intracerebroventricular injections of Δ9-tetrahydrocannabinol. British Journal of Pharmacology, 75(2), 409–414. 10.1111/j.1476-5381.1982.tb08802.x. [PubMed: 6313110]

Foll BL, Wiggins M, & Goldberg SR (2006). Nicotine pre-exposure does not potentiate the locomotor or rewarding effects of Δ-9-tetrahydrocannabinol in rats. Behavioural Pharmacology, 17(2). Retrieved from http://journals.lww.com/behaviouralpharm/Fulltext/2006/03000/Nicotine_pre_exposure_does_not_potentiate_the.10.aspx.

Freels TG, Baxter-Potter LN, Lugo JM, Glodosky NC, Wright HR, Baglot SL, et al. (2020). Vaporized cannabis extracts have reinforcing properties and support conditioned drug-seeking behavior in rats. The Journal of Neuroscience, 40(9), 1897–1908. 10.1523/jneurosci.2416-19.2020. [PubMed: 31953372]

French ED, Dillon K, & Wu X (1997). Cannabinoids excite dopamine neurons in the ventral tegmentum and substantia nigra. Neuroreport, 8(3). Retrieved from http://journals.lww.com/neuroreport/Fulltext/1997/02100/Cannabinoids_excite_dopamine_neurons_in_the.14.aspx.

Friend L, Weed J, Sandoval P, Nufer T, Ostlund I, & Edwards JG (2017). CB1-dependent long-term depression in ventral tegmental area GABA neurons: A novel target for marijuana. The Journal of Neuroscience, 37(45), 10943–10954. 10.1523/jneurosci.0190-17.2017. [PubMed: 29038246]

Galaj E, & Xi Z-X (2019). Potential of cannabinoid receptor ligands as treatment for substance use disorders. CNS Drugs, 33(10), 1001–1030. 10.1007/s40263-019-00664-w. [PubMed: 31549358]

Galaj E, & Xi Z-X (2021). Possible receptor mechanisms underlying cannabidiol effects on addictive-like behaviors in experimental animals. International Journal of Molecular Sciences, 22(1), 134. Retrieved from https://www.mdpi.com/1422-0067/22/1/134.

Galiègue S, Mary S, Marchand J, Dussossoy D, Carrière D, Carayon P, et al. (1995). Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. European Journal of Biochemistry, 232(1), 54–61. 10.1111/j.1432-1033.1995.tb20780.x. [PubMed: 7556170]

Gaoni Y, & Mechoulam R (1964). Isolation, structure, and partial synthesis of an active constituent of hashish. Journal of the American Chemical Society, 86(8), 1646–1647.

Gardner EL, Paredes W, Smith D, Donner A, Milling C, Cohen D, et al. (1988). Facilitation of brain stimulation reward by delta 9-tetrahydrocannabinol. Psychopharmacology, 96(1), 142–144. [PubMed: 2852376]

Ghozland S, Matthes HWD, Simonin F, Filliol D, Kieffer BL, & Maldonado R (2002). Motivational effects of cannabinoids are mediated by mu-opioid and kappa-opioid receptors. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 22(3), 1146–1154. [PubMed: 11826143]

Glass M, Faull RLM, & Dragunow M (1997). Cannabinoid receptors in the human brain: A detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience, 77(2), 299–318. 10.1016/S0306-4522(96)00428-9. [PubMed: 9472392]

Gong J-P, Onaivi ES, Ishiguro H, Liu Q-R, Tagliaferro PA, Brusco A, et al. (2006). Cannabinoid CB2 receptors: Immunohistochemical localization in rat brain. Brain Research, 1071(1), 10–23. 10.1016/j.brainres.2005.11.035. [PubMed: 16472786]

Goodman J, & Packard MG (2015). The influence of cannabinoids on learning and memory processes of the dorsal striatum. Neurobiology of Learning and Memory, 125, 1–14. 10.1016/j.nlm.2015.06.008. [PubMed: 26092091]

Goonawardena AV, Robinson L, Hampson RE, & Riedel G (2010). Cannabinoid and cholinergic systems interact during performance of a short-term memory task in the rat. Learning & Memory, 17(10), 502–511. [PubMed: 20876271]

Graybiel AM (2000). The basal ganglia. Current Biology, 10(14), R509–R511. [PubMed: 10899013]

Green B, Kavanagh D, & Young R (2003). Being stoned: A review of self-reported cannabis effects. Drug and Alcohol Review, 22(4), 453–460. 10.1080/09595230310001613976. [PubMed: 14660135]

Gutierrez-Rodríguez A, Puente N, Elezgarai I, Ruehle S, Lutz B, Reguero L, et al. (2017). Anatomical characterization of the cannabinoid CB1 receptor in cell-type–specific mutant mouse rescue models. Journal of Comparative Neurology, 525(2), 302–318. 10.1002/cne.24066. [PubMed: 27339436]

Hampson RE, & Deadwyler SA (2000). Cannabinoids reveal the necessity of hippocampal neural encoding for short-term memory in rats. The Journal of Neuroscience, 20(23), 8932–8942. 10.1523/jneurosci.20-23-08932.2000. [PubMed: 11102504]

Han X, He Y, Bi G-H, Zhang H-Y, Song R, Liu Q-R, et al. (2017). CB1 receptor activation on VgluT2-expressing glutamatergic neurons underlies Δ 9-tetrahydrocannabinol (Δ 9-THC)-induced aversive effects in mice. Scientific Reports, 7(1), 1–15. [PubMed: 28127051]

Han J, Kesner P, Metna-Laurent M, Duan T, Xu L, Georges F, et al. (2012). Acute cannabinoids impair working memory through astroglial CB1 receptor modulation of hippocampal LTD. Cell, 148(5), 1039–1050. 10.1016/j.cell.2012.01.037. [PubMed: 22385967]

Hayakawa K, Mishima K, Nozako M, Hazekawa M, Ogata A, Fujioka M, et al. (2007). Δ9-tetrahydrocannabinol (Δ9-THC) prevents cerebral infarction via hypothalamic-independent hypothermia. Life Sciences, 80(16), 1466–1471. 10.1016/j.lfs.2007.01.014. [PubMed: 17289082]

Hebert-Chatelain E, Desprez T, Serrat R, Bellocchio L, Soria-Gomez E, Busquets-Garcia A, et al. (2016). A cannabinoid link between mitochondria and memory. Nature, 539(7630), 555–559. 10.1038/nature20127. [PubMed: 27828947]

Hempel B, Bi GH, Klein B, & Xi ZX (2021). Peroxisome proliferator-activated receptors modulate optical brain-stimulation reward in DAT-Cre mice. Under review.

Hempel BJ, Clasen MM, Nelson KH, Woloshchuk CJ, & Riley AL (2018). An assessment of concurrent cannabidiol and Δ^9-tetrahydrocannabinol administration in place aversion and taste avoidance conditioning. Experimental and Clinical Psychopharmacology, 26(2), 205–213. 10.1037/pha0000188. [PubMed: 29648861]

Henstidge CM, Balenga NAB, Ford LA, Ross RA, Waldhoer M, & Irving AJ (2009). The GPR55 ligand L-α-lysophosphatidylinositol promotes RhoA-dependent Ca2+ signaling and NFAT activation. The FASEB Journal, 23(1), 183–193. 10.1096/fj.08-108670. [PubMed: 18757503]

Herkenham M, Lynn A, Johnson M, Melvin L, de Costa B, & Rice K (1991). Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. The Journal of Neuroscience, 11(2), 563–583. 10.1523/jneurosci.11-02-00563.1991. [PubMed: 1992016]

Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, et al. (1990). Cannabinoid receptor localization in brain. Proceedings of the National Academy of Sciences, 87(5), 1932–1936. Retrieved from https://www.pnas.org/content/pnas/87/5/1932.full.pdf.

Hermann H, Marsicano G, & Lutz B (2002). Coexpression of the cannabinoid receptor type 1 with dopamine and serotonin receptors in distinct neuronal subpopulations of the adult mouse forebrain. Neuroscience, 109(3), 451–460. 10.1016/S0306-4522(01)00509-7. [PubMed: 11823058]

Hoffman AF, Laaris N, Kawamura M, Masino SA, & Lupica CR (2010). Control of cannabinoid CB_1 receptor function on glutamate axon terminals by endogenous adenosine acting at A_1 receptors. The Journal of Neuroscience, 30(2), 545–555. 10.1523/jneurosci.4920-09.2010. [PubMed: 20071517]

Houser SJ, Eads M, Embrey JP, & Welch SP (2000). Dynorphin B and spinal analgesia: induction of antinociception by the cannabinoids CP55,940, Delta(9)-THC and anandamide. Brain Research, 857(1–2), 337–342. 10.1016/s0006-8993(00)01981-8. [PubMed: 10700588]

Howlett AC (2005). Cannabinoid receptor signaling. In Pertwee RG (Ed.), Cannabinoids (pp. 53–79). Berlin, Heidelberg: Springer Berlin Heidelberg.

Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, et al. (2002). International union of pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacological Reviews, 54(2), 161–202. 10.1124/pr.54.2.161. [PubMed: 12037135]

Howlett AC, Blume LC, & Dalton GD (2010). CB1 cannabinoid receptors and their associated proteins. Current Medicinal Chemistry, 17(14), 1382–1393. [PubMed: 20166926]

Hu SS-J, & Mackie K (2015). Distribution of the endocannabinoid system in the central nervous system. In Pertwee RG (Ed.), Endocannabinoids (pp. 59–93). Cham: Springer International Publishing.

Humburg BA, Jordan CJ, Zhang H-Y, Shen H, Han X, Bi G-H, et al. (2021). Optogenetic brain-stimulation reward: A new procedure to re-evaluate the rewarding versus aversive effects of cannabinoids in dopamine transporter-Cre mice. Addiction Biology, 26(4), e13005. 10.1111/adb.13005. [PubMed: 33538103]

Imbernon M, Whyte L, Diaz-Arteaga A, Russell WR, Moreno NR, Vazquez MJ, et al. (2014). Regulation of GPR55 in rat white adipose tissue and serum LPI by nutritional status, gestation, gender and pituitary factors. Molecular and Cellular Endocrinology, 383(1), 159–169. 10.1016/j.mce.2013.12.011. [PubMed: 24378736]

Inui K, Egashira N, Mishima K, Yano A, Matsumoto Y, Hasebe N, et al. (2004). The serotonin1A receptor agonist 8-OHDPAT reverses delta 9-tetrahydrocannabinol-induced impairment of spatial memory and reduction of acetylcholine release in the dorsal hippocampus in rats. Neurotoxicity Research, 6(2), 153–158. 10.1007/bf03033218. [PubMed: 15325968]

Ivy D, Palese F, Vozella V, Fotio Y, Yalcin A, Ramirez G, et al. (2020). Cannabinoid CB2 receptors mediate the anxiolytic-like effects of monoacylglycerol lipase inhibition in a rat model of predator-induced fear. Neuropsychopharmacology, 45(8), 1330–1338. 10.1038/s41386-020-0696-x. [PubMed: 32375160]

Iwamura H, Suzuki H, Ueda Y, Kaya T, & Inaba T (2001). In vitro and in vivo pharmacological characterization of JTE-907, a novel selective ligand for cannabinoid CB_2 receptor. Journal of Pharmacology and Experimental Therapeutics, 296(2), 420–425. Retrieved from https://jpet.aspetjournals.org/content/jpet/296/2/420.full.pdf. [PubMed: 11160626]

Jansen EM, Haycock DA, Ward SJ, & Seybold VS (1992). Distribution of cannabinoid receptors in rat brain determined with aminoalkylindoles. Brain Research, 575(1), 93–102. 10.1016/0006-8993(92)90428-C. [PubMed: 1504787]

Jarrahian A, Watts VJ, & Barker EL (2004). D2 dopamine receptors modulate Galpha-subunit coupling of the CB1 cannabinoid receptor. The Journal of Pharmacology and Experimental Therapeutics, 308(3), 880–886. 10.1124/jpet.103.057620. [PubMed: 14634050]

John WS, Martin TJ, Solingapuram Sai KK, Nader SH, Gage HD, Mintz A, et al. (2018). Chronic Δ^9-THC in rhesus monkeys: Effects on cognitive performance and dopamine D2/D3 receptor availability. Journal of Pharmacology and Experimental Therapeutics, 364(2), 300–310. 10.1124/jpet.117.244194. [PubMed: 29203575]

Jordan CJ, Humburg B, Rice M, Bi G-H, You Z-B, Shaik AB, et al. (2019). The highly selective dopamine D3R antagonist, R-VK4-40 attenuates oxycodone reward and augments analgesia in rodents. Neuropharmacology, 158, 107597. 10.1016/j.neuropharm.2019.04.003. [PubMed: 30974107]

Jordan CJ, & Xi ZX (2019). Progress in brain cannabinoid CB(2) receptor research: From genes to behavior. Neuroscience and Biobehavioral Reviews, 98, 208–220. 10.1016/j.neubiorev.2018.12.026. [PubMed: 30611802]

Justinová Z, Ferre S, Redhi GH, Mascia P, Stroik J, Quarta D, et al. (2011). Reinforcing and neurochemical effects of cannabinoid CB1 receptor agonists, but not cocaine, are altered by an adenosine A2A receptor antagonist. Addiction Biology, 16(3), 405–415. 10.1111/j.1369-1600.2010.00258.x. [PubMed: 21054689]

Justinova Z, Mascia P, Wu H-Q, Secci ME, Redhi GH, Panlilio LV, et al. (2013). Reducing cannabinoid abuse and preventing relapse by enhancing endogenous brain levels of kynurenic acid. Nature Neuroscience, 16(11), 1652. [PubMed: 24121737]

Justinová Z, Redhi GH, Goldberg SR, & Ferre S (2014). Differential effects of presynaptic versus postsynaptic adenosine A2A receptor blockade on Δ9-tetrahydrocannabinol (THC) self-administration in squirrel monkeys. The Journal of Neuroscience, 34(19), 6480–6484. 10.1523/jneurosci.5073-13.2014. [PubMed: 24806674]

Justinova Z, Tanda G, Munzar P, & Goldberg SR (2004). The opioid antagonist naltrexone reduces the reinforcing effects of Delta 9 tetrahydrocannabinol (THC) in squirrel monkeys. Psychopharmacology, 173(1–2), 186–194. 10.1007/s00213-003-1693-6. [PubMed: 14668977]

Justinova Z, Tanda G, Redhi GH, & Goldberg SR (2003). Self-administration of delta9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. Psychopharmacology, 169(2), 135–140. 10.1007/s00213-003-1484-0. [PubMed: 12827345]

Kainu T, Wikström AC, Gustafsson JA, & Pelto-Huikko M (1994). Localization of the peroxisome proliferator-activated receptor in the brain. Neuroreport, 5(18), 2481–2485. 10.1097/00001756-199412000-00019. [PubMed: 7696585]

Kangas BD, Leonard MZ, Shukla VG, Alapafuja SO, Nikas SP, Makriyannis A, et al. (2016). Comparisons of Δ_9-tetrahydrocannabinol and anandamide on a battery of cognition-related behavior in nonhuman primates. Journal of Pharmacology and *Experimental Therapeutics*, 357(1), 125–133. 10.1124/jpet.115.228189. [PubMed: 26826191]

Kathmann M, Flau K, Redmer A, Tränkle C, & Schlicker E (2006). Cannabidiol is an allosteric modulator at mu-and delta-opioid receptors. Naunyn-Schmiedeberg's Archives of Pharmacology, 372(5), 354–361. [PubMed: 16489449]

Katona I, Sperlágh B, Sík A, Käfalvi A, Vizi ES, Mackie K, et al. (1999). Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. The Journal of Neuroscience, 19(11), 4544–4558. 10.1523/jneurosci.19-11-04544.1999. [PubMed: 10341254]

Katsidoni V, Kastellakis A, & Panagis G (2013). Biphasic effects of Delta9-tetrahydrocannabinol on brain stimulation reward and motor activity. The international journal of neuropsychopharmacology/official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP), 16(10), 2273–2284. 10.1017/S1461145713000709.

Kimura T, Ohta T, Watanabe K, Yoshimura H, & Yamamoto I (1998). Anandamide, an endogenous cannabinoid receptor ligand, also interacts with 5-hydroxytryptamine (5-HT) receptor. Biological and Pharmaceutical Bulletin, 21(3), 224–226. [PubMed: 9556149]

Kimura T, Yamamoto I, Ohta T, Yoshida H, & Watanabe K (1996). Changes in 5-HT receptor binding induced by tetrahydrocannabinol metabolites in bovine cerebral cortex. Research Communications in Alcohol and Substances of Abuse, 17(1–2), 57–69.

Kinoshita H, Hasegawa T, Katsumata Y, Kameyama T, Yamamoto I, & Nabeshima T (1994). Effect of dizocilpine (MK-801) on the catalepsy induced by Δ9-tetrahydrocannabinol in mice. Journal of Neural Transmission/General Section JNT, 95(2), 137–143. 10.1007/BF01276432.

Kinsey SG, O'Neal ST, Long JZ, Cravatt BF, & Lichtman AH (2011). Inhibition of endocannabinoid catabolic enzymes elicits anxiolytic-like effects in the marble burying assay. Pharmacology Biochemistry and Behavior, 98(1), 21–27. 10.1016/j.pbb.2010.12.002. [PubMed: 21145341]

Köfalvi A, Moreno E, Cordomí A., Cai N-S., Fernández-Dueñas V., Ferreira SG., et al. (2020). Control of glutamate release by complexes of adenosine and cannabinoid receptors. BMC Biology, 18(1), 9. 10.1186/s12915-020-0739-0. [PubMed: 31973708]

Kravitz AV, Freeze BS, Parker PRL, Kay K, Thwin MT, Deisseroth K, et al. (2010). Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature, 466(7306), 622–626. 10.1038/nature09159. [PubMed: 20613723]

Laaris N, Good CH, & Lupica CR (2010). Δ9-tetrahydrocannabinol is a full agonist at CB1 receptors on GABA neuron axon terminals in the hippocampus. Neuropharmacology, 59(1), 121–127. 10.1016/j.neuropharm.2010.04.013. [PubMed: 20417220]

Lanciego JL, Barroso-Chinea P, Rico AJ, Conte-Perales L, Callén L, Roda E, et al. (2011). Expression of the mRNA coding the cannabinoid receptor 2 in the pallidal complex of Macaca fascicularis. Journal of Psychopharmacology, 25(1), 97–104. 10.1177/0269881110367732. [PubMed: 20488834]

Lane JR, Beukers MW, Mulder-Krieger T, & Ijzerman AP (2010). The endocannabinoid 2-arachidonylglycerol is a negative allosteric modulator of the human A3 adenosine receptor. Biochemical Pharmacology, 79(1), 48–56. 10.1016/j.bcp.2009.07.024. [PubMed: 19665453]

Laprairie RB, Bagher AM, Kelly MEM, & Denovan-Wright EM (2015). Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. British Journal of Pharmacology, 172(20), 4790–4805. 10.1111/bph.13250. [PubMed: 26218440]

Ledent C, Valverde O, Cossu G, Petitet F, Aubert JF, Beslot F, et al. (1999). Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. Science, 283(5400), 401–404. 10.1126/science.283.5400.401. [PubMed: 9888857]

Lefever TW, Marusich JA, Antonazzo KR, & Wiley JL (2014). Evaluation of WIN 55,212-2 self-administration in rats as a potential cannabinoid abuse liability model. Pharmacology, Biochemistry, and Behavior, 118, 30–35. 10.1016/j.pbb.2014.01.002. [PubMed: 24412835]

Lehrke M, & Lazar MA (2005). The many faces of PPARγ. Cell, 123(6), 993–999. 10.1016/j.cell.2005.11.026. [PubMed: 16360030]

Lepore M, Liu X, Savage V, Matalon D, & Gardner EL (1996). Genetic differences in Δ9-tetrahydrocannabinol-induced facilitation of brain stimulation reward as measured by a rate-frequency curve-shift electrical brain stimulation paradigm in three different rat strains. Life Sciences, 58(25), PL365–PL372. 10.1016/0024-3205(96)00237-8. [PubMed: 8649214]

Lepore M, Vorel SR, Lowinson J, & Gardner EL (1995). Conditioned place preference induced by !D–9-tetrahydrocannabinol: Comparison with cocaine, morphine, and food reward. Life Sciences, 56(23–24), 2073–2080. 10.1016/0024-3205(95)00191-8. [PubMed: 7776834]

Leung L (2011). Cannabis and its derivatives: Review of medical use. The Journal of the American Board of Family Medicine, 24(4), 452–462. 10.3122/jabfm.2011.04.100280. [PubMed: 21737770]

Li K, Fichna J, Schicho R, Saur D, Bashashati M, Mackie K, et al. (2013). A role for O-1602 and G protein-coupled receptor GPR55 in the control of colonic motility in mice. Neuropharmacology, 71, 255–263. 10.1016/j.neuropharm.2013.03.029. [PubMed: 23603203]

Li X, Hempel BJ, Yang H-J, Han X, Bi G-H, Gardner EL, et al. (2021). Dissecting the role of CB_1 and CB_2 receptors in cannabinoid reward versus aversion using transgenic CB1- and CB2-knockout mice. European Neuropsychopharmacology, 43, 38–51. 10.1016/j.euroneuro.2020.11.019. [PubMed: 33334652]

Li X, Hoffman AF, Peng XQ, Lupica CR, Gardner EL, & Xi ZX (2009). Attenuation of basal and cocaine-enhanced locomotion and nucleus accumbens dopamine in cannabinoid CB1-receptor-knockout mice. Psychopharmacology, 204(1), 1–11. 10.1007/s00213-008-1432-0. [PubMed: 19099297]

Li Y, & Kim J (2015). Neuronal expression of CB2 cannabinoid receptor mRNAs in the mouse hippocampus. Neuroscience, 311, 253–267. 10.1016/j.neuroscience.2015.10.041. [PubMed: 26515747]

Lichtman AH, & Martin BR (1996). Delta 9-tetrahydrocannabinol impairs spatial memory through a cannabinoid receptor mechanism. Psychopharmacology, 126(2), 125–131. 10.1007/bf02246347. [PubMed: 8856831]

Lichtman AH, & Martin BR (1997). The selective cannabinoid antagonist SR 141716A blocks cannabinoid-induced antinociception in rats. Pharmacology Biochemistry and Behavior, 57(1), 7–12. 10.1016/S0091-3057(96)00121-9. [PubMed: 9164547]

Liu QR, Canseco-Alba A, Liang Y, Ishiguro H, & Onaivi ES. (2020). Low basal CB2R in dopamine neurons and microglia influences cannabinoid tetrad effects. International Journal of Molecular Sciences, 21(24), 9763. 10.3390/ijms21249763. [PubMed: 33371336]

Liu QR, Canseco-Alba A, Liang Y, Ishiguro H, & Onaivi ES (2020). Low Basal CB2R in Dopamine Neurons and Microglia Influences Cannabinoid Tetrad Effects. International Journal of Molecular Sciences, 21(24). 10.3390/ijms21249763.

Liu Q-R, Canseco-Alba A, Zhang H-Y, Tagliaferro P, Chung M, Dennis E, et al. (2017). Cannabinoid type 2 receptors in dopamine neurons inhibits psychomotor behaviors, alters anxiety, depression and alcohol preference. Scientific Reports, 7(1), 17410. 10.1038/s41598-017-17796-y. [PubMed: 29234141]

Liu Q-R, Pan C-H, Hishimoto A, Li C-Y, Xi Z-X, Llorente-Berzal A, et al. (2009). Species differences in cannabinoid receptor 2 (CNR2 gene): Identification of novel human and rodent CB2 isoforms, differential tissue expression and regulation by cannabinoid receptor ligands. Genes, Brain and Behavior, 8(5), 519–530. 10.1111/j.1601-183X.2009.00498.x. [PubMed: 19496827]

Liu J, Scott BW, & Burnham WM (2021). Effects of cannabidiol and Δ9-tetrahydrocannabinol in the elevated plus maze in mice. Behavioural Pharmacology. 10.1097/fbp.0000000000000636. Publish Ahead of Print.

Long LE, Chesworth R, Huang X-F, McGregor IS, Arnold JC, & Karl T (2010). A behavioural comparison of acute and chronic Delta9-tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice. The international journal of neuropsychopharmacology/official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP), 13(7), 861–876. 10.1017/S1461145709990605.

Lupica CR, & Riegel AC (2005). Endocannabinoid release from midbrain dopamine neurons: a potential substrate for cannabinoid receptor antagonist treatment of addiction. Neuropharmacology, 48(8), 1105–1116. 10.1016/j.neuropharm.2005.03.016. [PubMed: 15878779]

Ma Z, Gao F, Larsen B, Gao M, Luo Z, Chen D, et al. (2019). Mechanisms of cannabinoid CB(2) receptor-mediated reduction of dopamine neuronal excitability in mouse ventral tegmental area. eBioMedicine, 42, 225–237. 10.1016/j.ebiom.2019.03.040. [PubMed: 30952618]

Ma L, Jia J, Niu W, Jiang T, Zhai Q, Yang L, et al. (2015). Mitochondrial CB1 receptor is involved in ACEA-induced protective effects on neurons and mitochondrial functions. Scientific Reports, 5(1), 12440. 10.1038/srep12440. [PubMed: 26215450]

Mackie K (2008). Cannabinoid receptors: where they are and what they do. Journal of Neuroendocrinology, 20(Suppl 1), 10–14. 10.1111/j.1365-2826.2008.01671.x. [PubMed: 18426493]

Maldonado R, Baños JE, & Cabañero D (2016). The endocannabinoid system and neuropathic pain. Pain, 157, S23–S32. 10.1097/j.pain.0000000000000428. [PubMed: 26785153]

Mallet PE, & Beninger RJ (1998a). The cannabinoid CB1 receptor antagonist SR141716A attenuates the memory impairment produced by Δ9-tetrahydrocannabinol or anandamide. Psychopharmacology, 140(1), 11–19. 10.1007/s002130050733. [PubMed: 9862397]

Mallet PE, & Beninger RJ (1998b). Δ9-Tetrahydrocannabinol, but not the endogenous cannabinoid receptor ligand anandamide, produces conditioned place avoidance. Life Sciences, 62(26), 2431–2439. 10.1016/S0024-3205(98)00226-4. [PubMed: 9651110]

Malone DT, & Taylor DA (2001). Involvement of somatodendritic 5-HT1A receptors in Δ9-tetrahydrocannabinol-induced hypothermia in the rat. Pharmacology Biochemistry and Behavior, 69(3), 595–601. 10.1016/S0091-3057(01)00567-6. [PubMed: 11509221]

Mansbach RS, Nicholson KL, Martin BR, & Balster RL (1994). Failure of Delta(9)-tetrahydrocannabinol and CP 55,940 to maintain intravenous self-administration under a fixed-interval schedule in rhesus monkeys. Behavioural Pharmacology, 5(2), 219–225. [PubMed: 11224271]

Marcellino D, Carriba P, Filip M, Borgkvist A, Frankowska M, Bellido I, et al. (2008). Antagonistic cannabinoid CB1/dopamine D2 receptor interactions in striatal CB1/D2 heteromers. A combined neurochemical and behavioral analysis. Neuropharmacology, 54(5), 815–823. 10.1016/j.neuropharm.2007.12.011. [PubMed: 18262573]

Maresz K, Carrier EJ, Ponomarev ED, Hillard CJ, & Dittel BN (2005). Modulation of the cannabinoid CB2 receptor in microglial cells in response to inflammatory stimuli. Journal of Neurochemistry, 95(2), 437–445. 10.1111/j.1471-4159.2005.03380.x. [PubMed: 16086683]

Marichal-Cancino BA, Fajardo-Valdez A, Ruiz-Contreras AE, Mendez-Díaz M, & Prospero-García O (2017). Advances in the physiology of GPR55 in the central nervous system. Current Neuropharmacology, 15(5), 771–778. 10.2174/1570159X14666160729155441. [PubMed: 27488130]

Mato S, Del Olmo E, & Pazos A (2003). Ontogenetic development of cannabinoid receptor expression and signal transduction functionality in the human brain. European Journal of Neuroscience, 17(9), 1747–1754. 10.1046/j.1460-9568.2003.02599.x. [PubMed: 12752773]

McKillop AM, Moran BM, Abdel-Wahab YHA, & Flatt PR (2013). Evaluation of the insulin releasing and antihyperglycaemic activities of GPR55 lipid agonists using clonal beta-cells, isolated pancreatic islets and mice. British Journal of Pharmacology, 170(5), 978–990. 10.1111/bph.12356. [PubMed: 23992544]

McMahon LR, Amin MR, & France CP (2005). SR 141716A differentially attenuates the behavioral effects of Δ9-THC in rhesus monkeys. Behavioural Pharmacology, 16(5–6), 363–372. Retrieved from https://journals.lww.com/behaviouralpharm/Fulltext/2005/09000/SR_141716A_differentially_attenuates_the.8.aspx. [PubMed: 16148440]

Mechoulam R, & Parker LA (2013). The endocannabinoid system and the brain. Annual Review of Psychology, 64(1), 21–47. 10.1146/annurev-psych-113011-143739.

Melis M, Gessa GL, & Diana M (2000). Different mechanisms for dopaminergic excitation induced by opiates and cannabinoids in the rat midbrain. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 24(6), 993–1006. 10.1016/S0278-5846(00)00119-6. [PubMed: 11041539]

Melis M, Perra S, Muntoni AL, Pillolla G, Lutz B, Marsicano G, et al. (2004). Prefrontal Cortex Stimulation Induces 2-Arachidonoyl-Glycerol-Mediated Suppression of Excitation in Dopamine Neurons. The Journal of Neuroscience, 24(47), 10707–10715. 10.1523/jneurosci.3502-04.2004. [PubMed: 15564588]

Metna-Laurent M, & Marsicano G (2015). Rising stars: Modulation of brain functions by astroglial type-1 cannabinoid receptors. Glia, 63(3), 353–364. 10.1002/glia.22773. [PubMed: 25452006]

Metna-Laurent M, Mondésir M, Grel A, Vallée M, & Piazza P-V (2017). Cannabinoid-Induced Tetrad in Mice. Current Protocols in Neuroscience, 80(1), 9.59.51–59.59.10. 10.1002/cpns.31.

Mishima K, Egashira N, Matsumoto Y, Iwasaki K, & Fujiwara M (2002). Involvement of reduced acetylcholine release in Δ9-tetrahydrocannabinol-induced impairment of spatial memory in the 8-arm radial maze. Life Sciences, 72(4), 397–407. 10.1016/S0024-3205(02)02274-9. [PubMed: 12467880]

Monory K, Blaudzun H, Massa F, Kaiser N, Lemberger T, Schütz G, et al. (2007). Genetic Dissection of Behavioural and Autonomic Effects of Δ9-Tetrahydrocannabinol in Mice. PLoS Biology, 5(10), e269. 10.1371/journal.pbio.0050269. [PubMed: 17927447]

Moreno S, Farioli-Vecchioli S, & Cerù MP (2004). Immunolocalization of peroxisome proliferator-activated receptors and retinoid x receptors in the adult rat CNS. Neuroscience, 123(1), 131–145. 10.1016/j.neuroscience.2003.08.064. [PubMed: 14667448]

Mothet J-P, Parent AT, Wolosker H, Brady RO, Linden DJ, Ferris CD, et al. (2000). d-Serine is an endogenous ligand for the glycine site of the N-methyl-d-aspartate receptor. Proceedings of the National Academy of Sciences, 97(9), 4926–4931. 10.1073/pnas.97.9.4926.

Munro S, Thomas KL, & Abu-Shaar M (1993). Molecular characterization of a peripheral receptor for cannabinoids. Nature, 365(6441), 61–65. 10.1038/365061a0. [PubMed: 7689702]

Murphy M, Mills S, Winstone J, Leishman E, Wager-Miller J, Bradshaw H, et al. (2017). Chronic adolescent Δ9-tetrahydrocannabinol treatment of male mice leads to long-term cognitive and behavioral dysfunction, which are prevented by concurrent cannabidiol treatment. Cannabis and Cannabinoid Research, 2(1), 235–246. [PubMed: 29098186]

Nava F, Carta G, & Gessa GL (2000). Permissive Role of Dopamine D2 Receptors in the Hypothermia Induced by Δ9-Tetrahydrocannabinol in Rats. Pharmacology Biochemistry and Behavior, 66(1), 183–187. 10.1016/S0091-3057(00)00231-8. [PubMed: 10837859]

Navarrete M, & Araque A (2008). Endocannabinoids mediate neuron-astrocyte communication. Neuron, 57(6), 883–893. 10.1016/j.neuron.2008.01.029. [PubMed: 18367089]

Nedungadi TP, Dutta M, Bathina CS, Caterina MJ, & Cunningham JT (2012). Expression and distribution of TRPV2 in rat brain. Experimental Neurology, 237(1), 223–237. 10.1016/j.expneurol.2012.06.017. [PubMed: 22750329]

Nent E, Nozaki C, Schmöle A-C, Otte D, & Zimmer A (2019). CB2 receptor deletion on myeloid cells enhanced mechanical allodynia in a mouse model of neuropathic pain. Scientific Reports, 9(1), 7468. 10.1038/s41598-019-4-3858-4.31097758. [PubMed: 31097758]

Newman AH, Cao J, Keighron JD, Jordan CJ, Bi G-H, Liang Y, et al. (2019). Translating the atypical dopamine uptake inhibitor hypothesis toward therapeutics for treatment of psychostimulant use disorders. Neuropsychopharmacology, 44(8), 1435–1444. 10.1038/s41386-019-0366-z. [PubMed: 30858517]

Nguyen JD, Aarde SM, Vandewater SA, Grant Y, Stouffer DG, Parsons LH, et al. (2016). Inhaled delivery of Δ9-tetrahydrocannabinol (THC) to rats by e-cigarette vapor technology. Neuropharmacology, 109, 112–120. 10.1016/j.neuropharm.2016.05.021. [PubMed: 27256501]

Norris C, Szkudlarek HJ, Pereira B, Rushlow W, & Laviolette SR (2019). The bivalent rewarding and aversive properties of Δ9-tetrahydrocannabinol are mediated through dissociable opioid receptor substrates and neuronal modulation mechanisms in distinct striatal sub-regions. Scientific Reports, 9(1), 9760. 10.1038/s41598-019-46215-7. [PubMed: 31278333]

O'Sullivan SE, Tarling EJ, Bennett AJ, Kendall DA, & Randall MD (2005). Novel time-dependent vascular actions of Δ9-tetrahydrocannabinol mediated by peroxisome proliferator-activated receptor gamma. Biochemical and Biophysical Research Communications, 337(3), 824–831. 10.1016/j.bbrc.2005.09.121. [PubMed: 16213464]

Oliveira da Cruz JF, Robin LM, Drago F, Marsicano G, & Metna-Laurent M (2016). Astroglial type-1 cannabinoid receptor (CB1): A new player in the tripartite synapse. Neuroscience, 323, 35–42. 10.1016/j.neuroscience.2015.05.002. [PubMed: 25967266]

Onaivi ES, Chaudhuri G, Abaci AS, Parker M, Manier DH, Martin PR, et al. (1999). Expression of cannabinoid receptors and their gene transcripts in human blood cells. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 23(6), 1063–1077. 10.1016/S0278-5846(99)00052-4. [PubMed: 10621950]

O'Sullivan SE (2016). An update on PPAR activation by cannabinoids. British Journal of Pharmacology, 173(12), 1899–1910. 10.1111/bph.13497. [PubMed: 27077495]

Panlilio LV, Ferre S, Yasar S, Thorndike EB, Schindler CW, & Goldberg SR (2012). Combined effects of THC and caffeine on working memory in rats. British Journal of Pharmacology, 165(8), 2529–2538. 10.1111/j.1476-5381.2011.01554.x. [PubMed: 21699509]

Patel KD, Davison JS, Pittman QJ, & Sharkey KA (2010). Cannabinoid CB2 Receptors in Health and Disease. Current Medicinal Chemistry, 17(14), 1394–1410. 10.2174/092986710790980041.

Pertwee RG (1997). Pharmacology of cannabinoid CB1 and CB2 receptors. Pharmacology & Therapeutics, 74(2), 129–180. [PubMed: 9336020]

Pertwee R (2005). Pharmacological actions of cannabinoids. In Pertwee RG (Ed.), Cannabinoids (pp. 1–51). Berlin, Heidelberg: Springer Berlin Heidelberg.

Pertwee R (2006). Cannabinoid pharmacology: The first 66 years. British Journal of Pharmacology, 147(Suppl. 1), S163–S171. 10.1038/sj.bjp.0706406. [PubMed: 16402100]

Pertwee RG (2008a). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. British Journal of Pharmacology, 153(2), 199–215. 10.1038/sj.bjp.0707442. [PubMed: 17828291]

Pertwee RG (2008b). Ligands that target cannabinoid receptors in the brain: from THC to anandamide and beyond. Addiction Biology, 13(2), 147–159. 10.1111/j.1369-1600.2008.00108.x. [PubMed: 18482430]

Pertwee RG, Howlett AC, Abood ME, Alexander SPH, Di Marzo V, Elphick MR, et al. (2010). International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid Receptors and

Their Ligands: Beyond CB1 and CB2. Pharmacological Reviews, 62(4), 588–631. 10.1124/pr.110.003004. [PubMed: 21079038]

Pietr M, Kozela E, Levy R, Rimmerman N, Lin YH, Stella N, et al. (2009). Differential changes in GPR55 during microglial cell activation. FEBS Letters, 583(12), 2071–2076. 10.1016/j.febslet.2009.05.028. [PubMed: 19464294]

Piomelli D (2003). The molecular logic of endocannabinoid signalling. Nature Reviews Neuroscience, 4(11), 873–884. 10.1038/nrn1247. [PubMed: 14595399]

Prini P, Zamberletti E, Manenti C, Gabaglio M, Parolaro D, & Rubino T (2020). Neurobiological mechanisms underlying cannabis-induced memory impairment. European Neuropsychopharmacology, 36, 181–190. 10.1016/j.euroneuro.2020.02.002. [PubMed: 32139186]

Ranganathan M, & D'Souza DC (2006). The acute effects of cannabinoids on memory in humans: a review. Psychopharmacology, 188(4), 425–444. 10.1007/s00213-006-0508-y. [PubMed: 17019571]

Rawls SM, Cabassa J, Geller EB, & Adler MW (2002). CB_1 receptors in the preoptic anterior hypothalamus regulate WIN 55212-2 [(4,5-dihydro-2-methyl-4 (4-morpholinylmethyl))-1-(1-naphthalenyl-carbonyl)-6H-pyrrolo[3,2,1ij]quinolin-6-one]-induced hypothermia. Journal of Pharmacology and Experimental Therapeutics, 301(3), 963–968. 10.1124/jpet.301.3.963. [PubMed: 12023525]

Rawls SM, Cowan A, Tallarida RJ, Geller EB, & Adler MW (2002). N-methyl-d-aspartate antagonists and WIN 55212-2 [4,5-dihydro-2-methyl-4(4-morpholinyl-methyl)-1-(1-naphthalenyl-carbonyl)-6H-pyrrolo[3,2,1-ij]quinolin-6-one], a cannabinoid agonist, interact to produce synergistic hypothermia. Journal of Pharmacology and Experimental Therapeutics, 303(1), 395–402. 10.1124/jpet.102.037473. [PubMed: 12235276]

Reis SL, Silva HB, Almeida M, Cunha RA, Simões AP, & Canas PM (2019). Adenosine A1 and A2A receptors differently control synaptic plasticity in the mouse dorsal and ventral hippocampus. Journal of Neurochemistry, 151(2), 227–237. 10.1111/jnc.14816. [PubMed: 31274188]

Remmers F, Lange MD, Hamann M, Ruehle S, Pape H-C, & Lutz B (2017). Addressing sufficiency of the CB1 receptor for endocannabinoid-mediated functions through conditional genetic rescue in forebrain GABAergic neurons. *Brain Structure* and Function, 222(8), 3431–3452. 10.1007/s00429-017-1411-5. [PubMed: 28393261]

Resstel LBM, Moreira FA, & Guimarães FS (2009). Chapter 16 Endocannabinoid System and Fear Conditioning. In *Vol.* 81. Vitamins & Hormones (pp. 421–440). Academic Press. [PubMed: 19647121]

Resstel LBM, Tavares RF, Lisboa SFS, Joca SRL, Corrêa FMA, & Guimarães FS (2009). 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. British Journal of Pharmacology, 156(1), 181–188. 10.1111/j.1476-5381.2008.00046.x. [PubMed: 19133999]

Rey AA, Purrio M, Viveros M-P, & Lutz B (2012). Biphasic Effects of Cannabinoids in Anxiety Responses: CB1 and GABAB Receptors in the Balance of GABAergic and Glutamatergic Neurotransmission. Neuropsychopharmacology, 37(12), 2624–2634. 10.1038/npp.2012.123. [PubMed: 22850737]

Rinaldi-Carmona M, Barth F, Heaulme M, Shire D, Calandra B, Congy C, et al. (1994). SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Letters, 350(2–3), 240–244. 10.1016/0014-5793(94)00773-x. [PubMed: 8070571]

Rios C, Gomes I, & Devi LA (2006). μ opioid and CB1 cannabinoid receptor interactions: reciprocal inhibition of receptor signaling and neuritogenesis. British Journal of Pharmacology, 148(4), 387–395. 10.1038/sj.bjp.0706757. [PubMed: 16682964]

Rodriguez JJ, Mackie K, & Pickel VM (2001). Ultrastructural localization of the CB1 cannabinoid receptor in mu-opioid receptor patches of the rat Caudate putamen nucleus. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 21(3), 823–833. 10.1523/JNEUROSCI.21-03-00823.2001. [PubMed: 11157068]

Romero-Zerbo S, Rafacho A, Díaz-Arteaga A, Suárez J, Quesada I, Imbernón M, et al. (2011). A role for the putative cannabinoid receptor GPR55 in the islets of Langerhans. The Journal of Endocrinology, 211(2), 177–185. [PubMed: 21885477]

Rubino T, Guidali C, Vigano D, Realini N, Valenti M, Massi P, et al. (2008). CB1 receptor stimulation in specific brain areas differently modulate anxiety-related behaviour. Neuropharmacology, 54(1), 151–160. 10.1016/j.neuropharm.2007.06.024. [PubMed: 17692344]

Rubino T, Sala M, Viganò D, Braida D, Castiglioni C, Limonta V, et al. (2007). Cellular mechanisms underlying the anxiolytic effect of low doses of peripheral [Delta]9-tetrahydrocannabinol in rats. Neuropsychopharmacology, 32(9), 2036–2045. 10.1038/sj.npp.1301330. [PubMed: 17287821]

Ruehle S, Remmers F, Romo-Parra H, Massa F, Wickert M, Wörtge S, et al. (2013). Cannabinoid CB1 receptor in dorsal telencephalic glutamatergic neurons: Distinctive sufficiency for hippocampus-dependent and amygdala-dependent synaptic and behavioral functions. The Journal of Neuroscience, 33(25), 10264–10277. 10.1523/jneurosci.4171-12.2013. [PubMed: 23785142]

Russo EB, Burnett A, Hall B, & Parker KK (2005). Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochemical Research, 30(8), 1037–1043. 10.1007/s11064-005-6978-1. [PubMed: 16258853]

Ryberg E, Larsson N, Sjögren S, Hjorth S, Hermansson NO, Leonova J, et al. (2007). The orphan receptor GPR55 is a novel cannabinoid receptor. British Journal of Pharmacology, 152(7), 1092–1101. 10.1038/sj.bjp.0707460. [PubMed: 17876302]

Salio C, Fischer J, Franzoni MF, Mackie K, Kaneko T, & Conrath M (2001). CB1-cannabinoid and μ-opioid receptor co-localization on postsynaptic target in the rat dorsal horn. Neuroreport, 12(17), 3689–3692. Retrieved from https://journals.lww.com/neuroreport/Fulltext/2001/12040/CB1_cannabinoid_and___opioid_receptor.17.aspx. [PubMed: 11726775]

Sanberg PR, Bunsey MD, Giordano M, & Norman AB (1988). The catalepsy test: its ups and downs. Behavioral Neuroscience, 102(5), 748–759. 10.1037//0735-7044.102.5.748. [PubMed: 2904271]

Sano K, Mishima K, Koushi E, Orito K, Egashira N, Irie K, et al. (2008). Δ9-Tetrahydrocannabinol-induced catalepsy-like immobilization is mediated by decreased 5-HT neurotransmission in the nucleus accumbens due to the action of glutamate-containing neurons. Neuroscience, 151(2), 320–328. 10.1016/j.neuroscience.2007.10.026. [PubMed: 18083311]

Savinainen JR, Saario SM, Niemi R, Järvinen T, & Laitinen JT (2003). An optimized approach to study endocannabinoid signaling: Evidence against constitutive activity of rat brain adenosine A1 and cannabinoid CB1 receptors. British Journal of Pharmacology, 140(8), 1451–1459. 10.1038/sj.bjp.0705577. [PubMed: 14623770]

Schatz AR, Lee M, Condie RB, Pulaski JT, & Kaminski NE (1997). Cannabinoid receptors CB1 and CB2: a characterization of expression and adenylate cyclase modulation within the immune system. Toxicology and Applied Pharmacology, 142(2), 278–287. 10.1006/taap.1996.8034. [PubMed: 9070350]

Schauer GL, King BA, Bunnell RE, Promoff G, & McAfee TA (2016). Toking, vaping, and eating for health or fun: marijuana use patterns in adults, U.S., 2014. American Journal of Preventive Medicine, 50(1), 1–8. 10.1016/j.amepre.2015.05.027. [PubMed: 26277652]

Schramm-Sapyta N, Cha Y, Chaudhry S, Wilson W, Swartzwelder HS, & Kuhn C (2007). Differential anxiogenic, aversive, and locomotor effects of THC in adolescent and adult rats. Psychopharmacology, 191(4), 867–877. 10.1007/s00213-006-0676-9. [PubMed: 17211649]

Schwab MH, Bartholomae A, Heimrich B, Feldmeyer D, Druffel-Augustin S, Goebbels S, et al. (2000). Neuronal basic helix-loop-helix proteins (NEX and BETA2/Neuro D) regulate terminal granule cell differentiation in the hippocampus. Journal of Neuroscience, 20(10), 3714–3724. [PubMed: 10804213]

Sciolino NR, Zhou W, & Hohmann AG (2011). Enhancement of endocannabinoid signaling with JZL184, an inhibitor of the 2-arachidonoylglycerol hydrolyzing enzyme monoacylglycerol lipase, produces anxiolytic effects under conditions of high environmental aversiveness in rats. Pharmacological Research, 64(3), 226–234. 10.1016/j.phrs.2011.04.010. [PubMed: 21600985]

Secci ME, Mascia P, Sagheddu C, Beggiato S, Melis M, Borelli AC, et al. (2019). Astrocytic mechanisms involving kynurenic acid control Δ9-tetrahydrocannabinol-induced increases in glutamate release in brain reward-processing areas. Molecular Neurobiology, 56(5), 3563–3575. 10.1007/s12035-018-1319-y. [PubMed: 30151725]

Sengupta T, Jaryal AK, & Mallick HN (2016). Effects of NMDA and non-NMDA ionotropic glutamate receptors in the medial preoptic area on body temperature in awake rats. Journal of Thermal Biology, 61, 1–7. 10.1016/j.jtherbio.2016.07.020. [PubMed: 27712650]

Shang Y, & Tang Y (2017). The central cannabinoid receptor type-2 (CB2) and chronic pain. International *Journal of Neuroscience*, 127(9), 812–823. 10.1080/00207454.2016.1257992. [PubMed: 27842450]

Shibasaki K, Ishizaki Y, & Mandadi S (2013). Astrocytes express functional TRPV2 ion channels. Biochemical and Biophysical Research Communications, 441(2), 327–332. 10.1016/j.bbrc.2013.10.046. [PubMed: 24161738]

Sierra S, Luquin N, Rico AJ, Gómez-Bautista V, Roda E, Dopeso-Reyes IG, et al. (2015). Detection of cannabinoid receptors CB1 and CB2 within basal ganglia output neurons in macaques: changes following experimental parkinsonism. Brain Structure and Function, 220(5), 2721–2738. 10.1007/s00429-014-0823-8. [PubMed: 24972960]

Solinas M, Zangen A, Thiriet N, & Goldberg SR (2004). β-Endorphin elevations in the ventral tegmental area regulate the discriminative effects of Δ-9-tetrahydrocannabinol. European Journal of Neuroscience, 19(12), 3183–3192. 10.1111/j.0953-816X.2004.03420.x. [PubMed: 15217374]

Soria G, Castañe A, Berrendero F, Ledent C, Parmentier M, Maldonado R, et al. (2004). Adenosine A2A receptors are involved in physical dependence and place conditioning induced by THC. European Journal of Neuroscience, 20(8), 2203–2213. 10.1111/j.1460-9568.2004.03682.x. [PubMed: 15450100]

Sousa VC, Assaife-Lopes N, Ribeiro JA, Pratt JA, Brett RR, & Sebastião AM (2011). Regulation of hippocampal cannabinoid CB1 receptor actions by adenosine A1 receptors and chronic caffeine administration: Implications for the effects of Δ9-tetrahydrocannabinol on spatial memory. Neuropsychopharmacology, 36(2), 472–487. 10.1038/npp.2010.179. [PubMed: 20927050]

Spencer S, Neuhofer D, Chioma VC, Garcia-Keller C, Schwartz DJ, Allen N, et al. (2018). A model of Δ9-tetrahydrocannabinol self-administration and reinstatement that alters synaptic plasticity in nucleus accumbens. Biological Psychiatry, 84(8), 601–610. 10.1016/j.biopsych.2018.04.016. [PubMed: 29861097]

Spiller KJ, Bi GH, He Y, Galaj E, Gardner EL, & Xi ZX (2019). Cannabinoid CB(1) and CB(2) receptor mechanisms underlie cannabis reward and aversion in rats. British Journal of Pharmacology, 176(9), 1268–1281. 10.1111/bph.14625. [PubMed: 30767215]

Spindle TR, Cone EJ, Schlienz NJ, Mitchell JM, Bigelow GE, Flegel R, et al. (2018). Acute effects of smoked and vaporized cannabis in healthy adults who infrequently use cannabis: A crossover trial. JAMA Network Open, 1(7), e184841. 10.1001/jamanetworkopen.2018.4841.30646391. [PubMed: 30646391]

Stefano GB, Liu Y, & Goligorsky MS (1996). Cannabinoid receptors are coupled to nitric oxide release in invertebrate immunocytes, microglia, and human monocytes*. Journal of Biological Chemistry, 271(32), 19238–19242. 10.1074/jbc.271.32.19238. [PubMed: 8702604]

Stella N (2010). Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas. Glia, 58(9), 1017–1030. 10.1002/glia.20983. [PubMed: 20468046]

Stempel AV, Stumpf A, Zhang H-Y, Özdoğan T, Pannasch U, Theis A-K, et al. (2016). Cannabinoid type 2 receptors mediate a cell type-specific plasticity in the hippocampus. Neuron, 90(4), 795–809. 10.1016/j.neuron.2016.03.034. [PubMed: 27133464]

Sun Y, Alexander SPH, Garle MJ, Gibson CL, Hewitt K, Murphy SP, et al. (2007). Cannabinoid activation of PPAR alpha; a novel neuroprotective mechanism. British Journal of Pharmacology, 152(5), 734–743. 10.1038/sj.bjp.0707478. [PubMed: 17906680]

Szabo B, Siemes S, & Wallmichrath I (2002). Short communication: Inhibition of GABAergic neurotransmission in the ventral tegmental area by cannabinoids. European Journal of Neuroscience, 15(12), 2057–2061. 10.1046/j.1460-9568.2002.02041.x. [PubMed: 12099913]

Szkudlarek HJ, Desai SJ, Renard J, Pereira B, Norris C, Jobson CEL, et al. (2019). Δ-9-Tetrahydrocannabinol and Cannabidiol produce dissociable effects on prefrontal cortical executive function and regulation of affective behaviors. Neuropsychopharmacology, 44(4), 817–825. 10.1038/s41386-018-0282-7. [PubMed: 30538288]

Taffe MA, Creehan KM, & Vandewater SA (2015). Cannabidiol fails to reverse hypothermia or locomotor suppression induced by Δ(9)-tetrahydrocannabinol in Sprague-Dawley rats. British Journal of Pharmacology, 172(7), 1783–1791. 10.1111/bph.13024. [PubMed: 25425111]

Taffe MA, Creehan KM, Vandewater SA, Kerr TM, & Cole M (2021). Effects of Δ_9-tetrahydrocannabinol (THC) vapor inhalation in Sprague-Dawley and Wistar rats. Experimental and Clinical Psychopharmacology, 29(1), 1–13. 10.1037/pha0000373. [PubMed: 32297788]

Takahashi RN, & Singer G (1979). Self-administration of Δ9-tetrahydrocannabinol by rats. Pharmacology Biochemistry and Behavior, 11(6), 737–740. 10.1016/0091-3057(79)90274-0. [PubMed: 231789]

Takeda S, Ikeda E, Su S, Harada M, Okazaki H, Yoshioka Y, et al. (2014). Δ9-THC modulation of fatty acid 2-hydroxylase (FA2H) gene expression: Possible involvement of induced levels of PPARα in MDA-MB-231 breast cancer cells. Toxicology, 326, 18–24. 10.1016/j.tox.2014.09.011. [PubMed: 25291031]

Tanda G, Munzar P, & Goldberg SR (2000). Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. Nature Neuroscience, 3(11), 1073–1074. 10.1038/80577. [PubMed: 11036260]

Tanda G, Pontieri FE, & Chiara GD (1997). Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ_1 opioid receptor mechanism. Science, 276(5321), 2048. 10.1126/science.276.5321.2048. [PubMed: 9197269]

Todd SM, & Arnold JC (2016). Neural correlates of interactions between cannabidiol and Delta(9)-tetrahydrocannabinol in mice: implications for medical cannabis. British Journal of Pharmacology, 173(1), 53–65. 10.1111/bph.13333. [PubMed: 26377899]

Tseng AH, & Craft RM (2004). CB1 receptor mediation of cannabinoid behavioral effects in male and female rats. Psychopharmacology, 172(1), 25–30. 10.1007/s00213-003-1620-x. [PubMed: 14991224]

Tsou K, Mackie K, Sañudo-Peña MC, & Walker JM (1999). Cannabinoid CB1 receptors are localized primarily on cholecystokinin-containing GABAergic interneurons in the rat hippocampal formation. Neuroscience, 93(3), 969–975. 10.1016/S0306-4522(99)00086-X. [PubMed: 10473261]

Valjent E, & Maldonado R (2000). A behavioural model to reveal place preference to Δ9-tetrahydrocannabinol in mice. Psychopharmacology, 147(4), 436–438. 10.1007/s002130050013. [PubMed: 10672638]

van der Stelt M, & Di Marzo V (2003). The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: implications for neurological and psychiatric disorders. European Journal of Pharmacology, 480(1), 133–150. 10.1016/j.ejphar.2003.08.101. [PubMed: 14623357]

Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, et al. (2005). Identification and functional characterization of brainstem cannabinoid CB_2 receptors. Science, 310(5746), 329–332. 10.1126/science.1115740. [PubMed: 16224028]

Vann RE, Gamage TF, Warner JA, Marshall EM, Taylor NL, Martin BR, et al. (2008). Divergent effects of cannabidiol on the discriminative stimulus and place conditioning effects of Δ^9-tetrahydrocannabinol. Drug and Alcohol Dependence, 94(1–3), 191–198. 10.1016/j.drugalcdep.2007.11.017. [PubMed: 18206320]

Varvel SA, Bridgen DT, Tao Q, Thomas BF, Martin BR, & Lichtman AH (2005). Δ^9Tetrahydrocannbinol accounts for the antinociceptive, hypothermic, and cataleptic effects of marijuana in mice. Journal of Pharmacology and Experimental Therapeutics, 314(1), 329–337. 10.1124/jpet.104.080739. [PubMed: 15831444]

Varvel SA, & Lichtman AH (2002). Evaluation of CB_1 receptor knockout mice in the morris water maze. Journal of Pharmacology and Experimental Therapeutics, 301(3), 915–924. 10.1124/jpet.301.3.915. [PubMed: 12023519]

Varvel SA, Wiley JL, Yang R, Bridgen DT, Long K, Lichtman AH, et al. (2006). Interactions between THC and cannabidiol in mouse models of cannabinoid activity. Psychopharmacology, 186(2), 226–234. 10.1007/s00213-006-0356-9. [PubMed: 16572263]

Vickstrom CR, Liu X, Liu S, Hu M-M, Mu L, Hu Y, et al. (2021). Role of endocannabinoid signaling in a septohabenular pathway in the regulation of anxiety- and depressive-like behavior. Molecular Psychiatry, 26(7), 3178–3191. 10.1038/s41380-020-00905-1. [PubMed: 33093652]

Vidal-Puig A, Jimenez-Liñan M, Lowell BB, Hamann A, Hu E, Spiegelman B, et al. (1996). Regulation of PPAR gamma gene expression by nutrition and obesity in rodents. The Journal of Clinical Investigation, 97(11), 2553–2561. 10.1172/JCI118703. [PubMed: 8647948]

Villapol S (2018). Roles of peroxisome proliferator-activated receptor gamma on brain and peripheral inflammation. Cellular and Molecular Neurobiology, 38(1), 121–132. 10.1007/s10571-017-0554-5. [PubMed: 28975471]

Viñals X, Moreno E, Lanfumey L, Cordomí A, Pastor A, de La Torre R, et al. (2015). cognitive impairment induced by Delta9-tetrahydrocannabinol occurs through heteromers between cannabinoid CB1 and serotonin 5-HT2A receptors. PLoS Biology, 13(7), e1002194. 10.1371/journal.pbio.1002194. [PubMed: 26158621]

Waksman Y, Olson JM, Carlisle SJ, & Cabral GA (1999). The central cannabinoid receptor (CB1) mediates inhibition of nitric oxide production by rat microglial cells. Journal of Pharmacology and Experimental Therapeutics, 288(3), 1357–1366. Retrieved from https://jpet.aspetjournals.org/content/jpet/288/3/1357.full.pdf. [PubMed: 10027878]

Wang XF, Galaj E, Bi GH, Zhang C, He Y, Zhan J, et al. (2020). Different receptor mechanisms underlying phytocannabinoid-versus synthetic cannabinoid-induced tetrad effects: Opposite roles of CB(1)/CB(2) versus GPR55 receptors. British Journal of Pharmacology, 177(8), 1865–1880. 10.1111/bph.14958. [PubMed: 31877572]

Warden A, Truitt J, Merriman M, Ponomareva O, Jameson K, Ferguson LB, et al. (2016). Localization of PPAR isotypes in the adult mouse and human brain. Scientific Reports, 6(1), 27618. 10.1038/srep27618. [PubMed: 27283430]

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. JAMA, 313(24), 2456–2473. 10.1001/jama.2015.6358. [PubMed: 26103030]

Wiebelhaus JM, Grim TW, Owens RA, Lazenka MF, Sim-Selley LJ, Abdullah RA, et al. (2015). Δ^9-Tetrahydrocannabinol and endocannabinoid degradative enzyme inhibitors attenuate intracranial self-stimulation in mice. Journal of Pharmacology and Experimental Therapeutics, 352(2), 195–207. 10.1124/jpet.114.218677. [PubMed: 25398241]

Wiley JL, & Martin BR (2003). Cannabinoid pharmacological properties common to other centrally acting drugs. European Journal of Pharmacology, 471(3), 185–193. 10.1016/S0014-2999(03)01856-9. [PubMed: 12826237]

World Health Organization. (2021). Cannabis. Alcohol, Drugs and Addictive Behaviors Unit.

Wu C-S, Chen H, Sun H, Zhu J, Jew CP, Wager-Miller J, et al. (2013). GPR55, a G-protein coupled receptor for lysophosphatidylinositol, plays a role in motor coordination. PLoS One, 8(4), e60314. 10.1371/journal.pone.0060314. [PubMed: 23565223]

Xi ZX, Peng XQ, Li X, Song R, Zhang HY, Liu QR, et al. (2011). Brain cannabinoid CB_2 receptors modulate cocaine's actions in mice. Nature Neuroscience, 14(9), 1160–1166. 10.1038/nn.2874. [PubMed: 21785434]

Yu XH, Cao CQ, Martino G, Puma C, Morinville A, St-Onge S, et al. (2010). A peripherally restricted cannabinoid receptor agonist produces robust anti-nociceptive effects in rodent models of inflammatory and neuropathic pain. Pain, 151(2), 337–344. 10.1016/j.pain.2010.07.019. [PubMed: 20696525]

Zangen A, Solinas M, Ikemoto S, Goldberg SR, & Wise RA (2006). Two brain sites for cannabinoid reward. The Journal of Neuroscience, 26(18), 4901–4907. 10.1523/jneurosci.3554-05.2006. [PubMed: 16672664]

Zhang H-Y, Bi GH, Li X, Li J, Qu H, Zhang SJ, et al. (2015). Species differences in cannabinoid receptor 2 and receptor responses to cocaine self-administration in mice and rats. Neuropsychopharmacology, 40(4), 1037–1051. 10.1038/npp.2014.297. [PubMed: 25374096]

Zhang HY, De Biase L, Chandra R, Shen H, Liu QR, Gardner E, et al. (2021). Repeated cocaine administration upregulates CB2 receptor expression in striatal medium-spiny neurons that express dopamine D1 receptors in mice. Acta Pharmacologica Sinica. 10.1038/s41401-021-00712-6.34316031.

Zhang H-Y, Gao M, Liu Q-R, Bi G-H, Li X, Yang H-J, et al. (2014). Cannabinoid CB_2 receptors modulate midbrain dopamine neuronal activity and dopamine-related behavior in

mice. Proceedings of the National Academy of Sciences, 111(46), E5007–E5015. 10.1073/pnas.1413210111.

Zhang H-Y, Gao M, Shen H, Bi G-H, Yang H-J, Liu Q-R, et al. (2017). Expression of functional cannabinoid CB2 receptor in VTA dopamine neurons in rats. Addiction Biology, 22(3), 752–765. 10.1111/adb.12367. [PubMed: 26833913]

Zhang H-Y, Shen H, Gao M, Ma Z, Hempel BJ, Bi G-H, et al. (2021). Cannabinoid CB2 receptors are expressed in glutamate neurons in the red nucleus and functionally modulate motor behavior in mice. Neuropharmacology, 189, 108538. 10.1016/j.neuropharm.2021.108538. [PubMed: 33789118]

Zhang HY, Shen H, Jordan CJ, Liu QR, Gardner EL, Bonci A, et al. (2019). CB(2) receptor antibody signal specificity: correlations with the use of partial CB(2)-knockout mice and anti-rat CB(2) receptor antibodies. Acta Pharmacologica Sinica, 40(3), 398–409. 10.1038/s41401-018-0037-3. [PubMed: 29967455]

Zimmer A, Valjent E, König M, Zimmer AM, Robledo P, Hahn H, et al. (2001). Absence of Δ-9-tetrahydrocannabinol dysphoric effects in dynorphin-deficient mice. The Journal of Neuroscience, 21(23), 9499–9505. Retrieved from http://www.jneurosci.org/content/21/23/9499.abstract. [PubMed: 11717384]

Zimmer A, Zimmer AM, Hohmann AG, Herkenham M, & Bonner TI (1999). Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. Proceedings of the National Academy of Sciences, 96(10), 5780–5785. 10.1073/pnas.96.10.5780.

Zuardi AW, Shirakawa I, Finkelfarb E, & Karniol IG (1982). Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Psychopharmacology, 76(3), 245–250. [PubMed: 6285406]

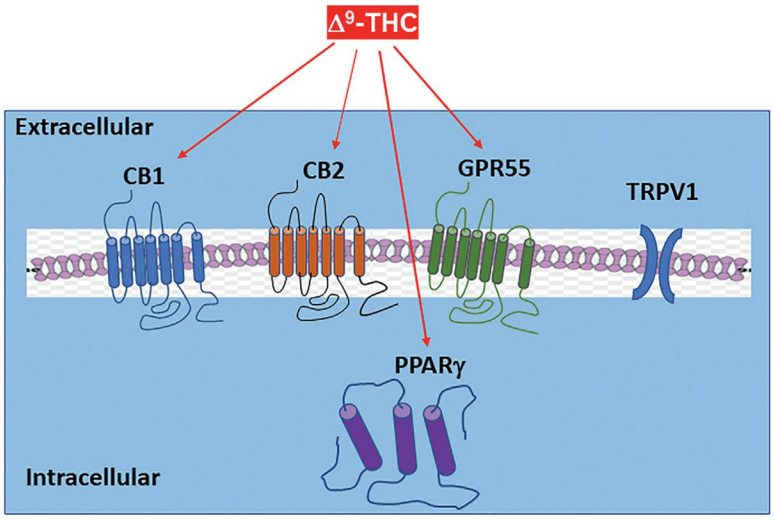

Fig. 1.

Major targets of Δ^9-THC based on their receptor binding and functional assays as shown in Table 1.

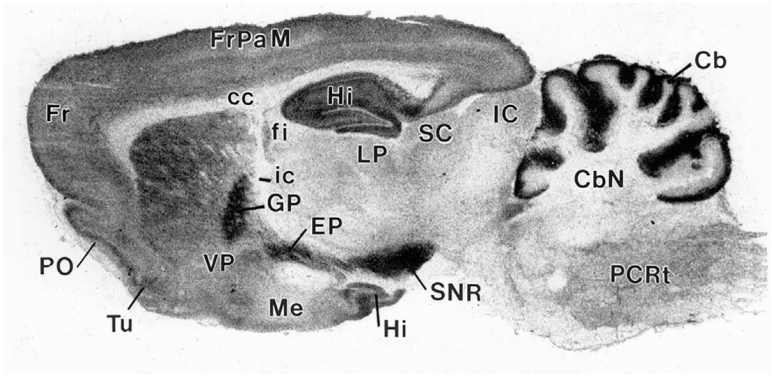

Fig. 2.

[^{3}H]CP55,940 autoradiography demonstrating CB_1R distribution in the rat brain. A high density of CB_1Rs is expressed in the SNR, GP, Hi, and cerebellum. Fr, Frontal cortex; FrPaM, frontal primary motor cortex; PO, pre-olfactory bulb; *Tu*, olfactory tubercle; Hi, hippocampus; *VP*, ventral pallidum; Me, Median eminence; fi, fimbria of the hippocampus; ic, internal capsule; LP, lateral post thalamus nuclei; SC, superior colliculus; IC, inferior colliculus; *Cb*, cerebellum; *CbN*, cerebellar nuclei; *CC*, corpus cal losum; *GP*, globus pallidus; *EP*, entopeduncular nucleus (homolog of GPi); *SNR*, substantia nigra pars reticulata; PCRt, parvicellular reticular nuclei. (This image was provided by Dr. Miles Herkenham at NIMH, USA)

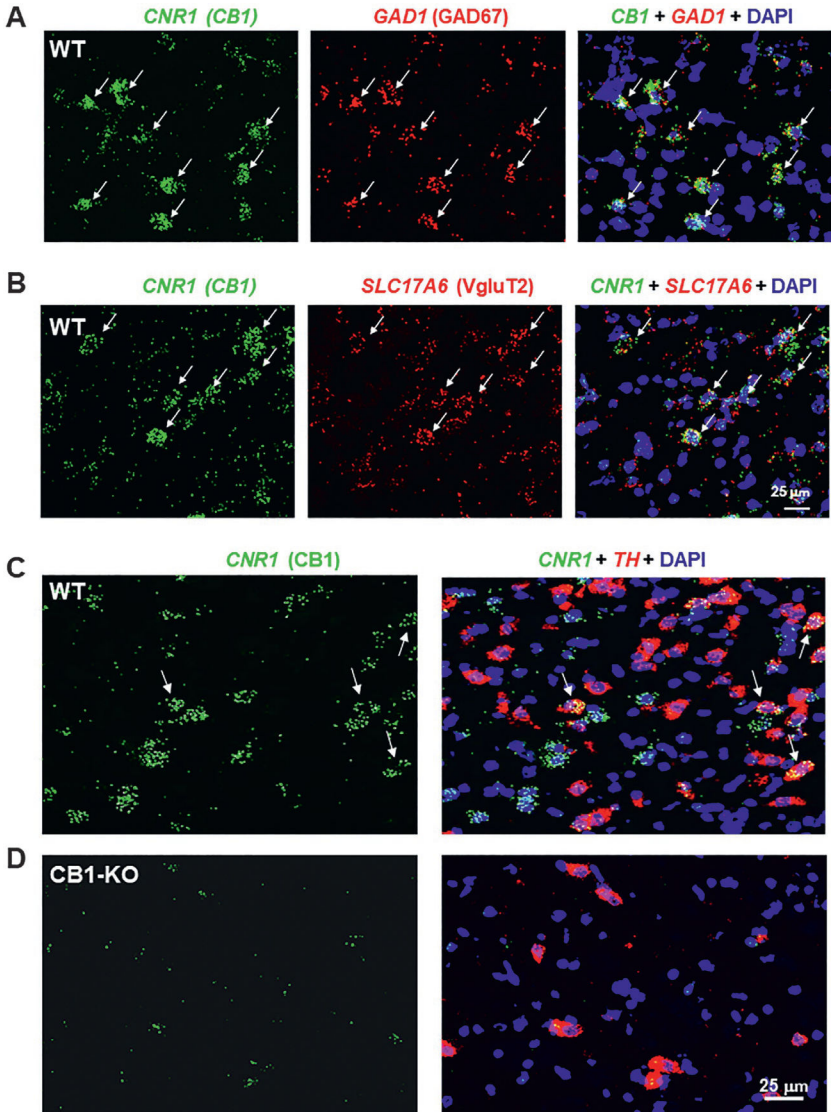

Fig. 3.

RNAscope ISH results, illustrating the cellular distributions of CB_1Rs in the midbrain ventral tegmental area. CB_1 mRNA was detected in GAD1-labeled GABAergic neurons (A), VgluT2-labeled glutamate neurons (B) and a small population of TH-labeled DA neurons (C) in the midbrain of WT, but not CB_1-KO mice (D).

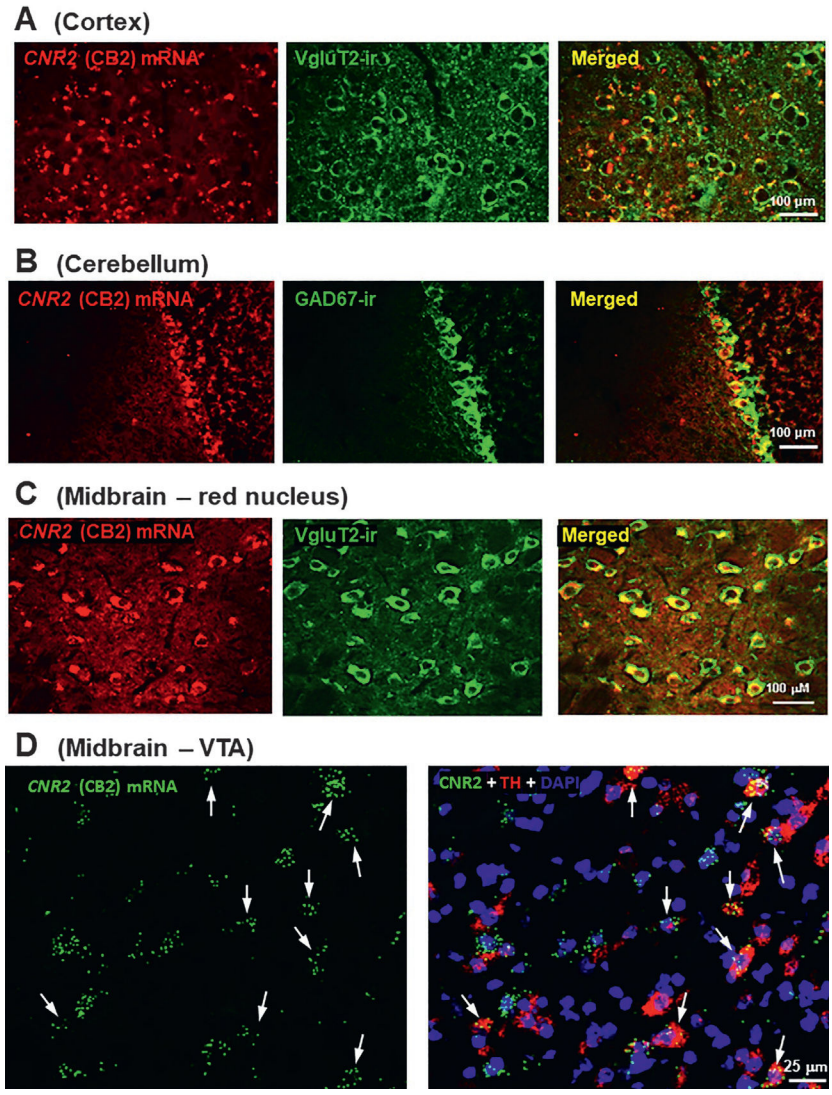

Fig. 4.

Conventional (A, B, C) and RNAscope (D) ISH results, illustrating the cellular distributions of CB_2Rs in mouse brain. CB_2 mRNA was detected in cortical VgluT2-labeled glutamatergic neurons (A), cerebellar GAD1-labeled GABAergic neurons (B), red nucleus VgluT2-labeled glutamatergic neurons (C), and VTA TH-labeled dopaminergic neurons (D).

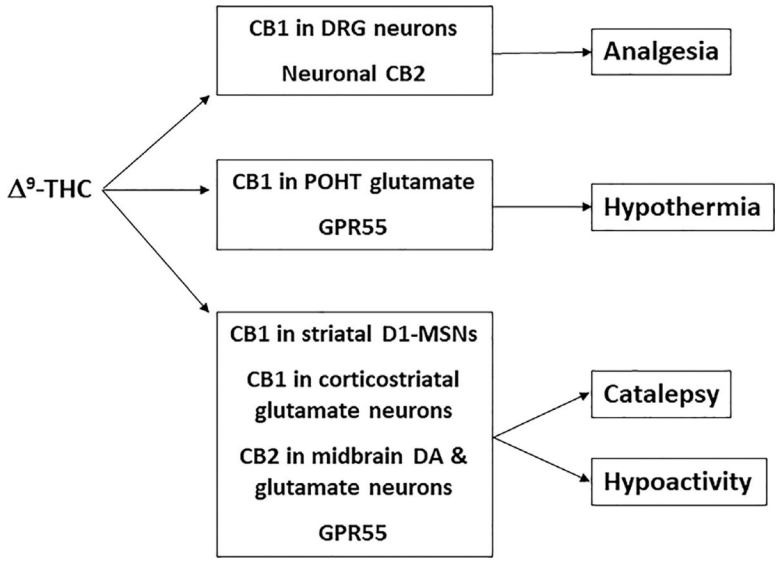

Fig. 5.

A summary of the major neural mechanisms underlying THC-induced tetrad effects.

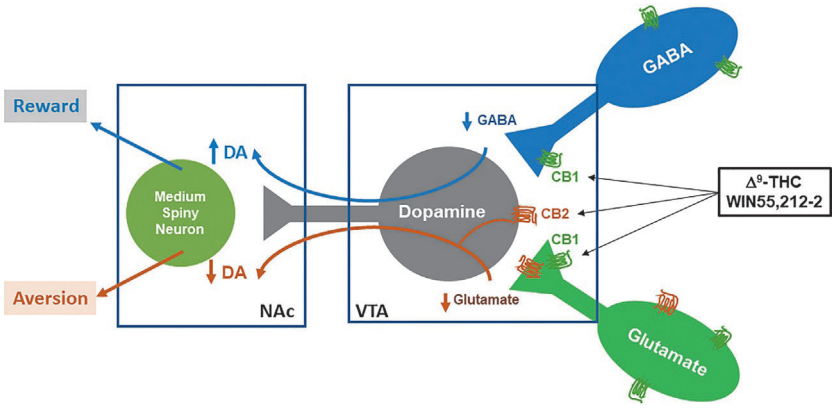

Fig. 6.

Neural mechanisms underlying cannabinoid reward vs. aversion. CB_1Rs are expressed in VTA GABAergic neurons and glutamatergic neurons as well as their afferents projected from other brain regions to VTA DA neurons (data shown). CB_2Rs are found in VTA DA neurons. Cannabinoids modulate the mesolimbic DA system via activation of brain CB_1Rs and CB_2Rs. Cannabinoids such as Δ^9-THC or WIN55,212-2 produce rewarding effects by binding to CB_1Rs on VTA GABAergic interneurons and/or their afferents, thereby reducing GABA-mediated disinhibition of VTA DA neurons and cannabinoid reward. Conversely, Δ^9-THC or WIN55,212-2 may also produce aversive effects by activating CB_1Rs on glutamatergic neurons in the VTA or glutamatergic afferents, and CB_2Rs on midbrain DA neurons, thereby inhibiting VTA DA release to the NAc. The subjective effects of cannabinoids may thus depend on the balance of opposing CB1R and CB_2R effects and individual differences in expression of cannabinoid receptors. *DA*, dopamine; GABA, γ-aminobutyric acid; *NAc*, nucleus accumbens; *VTA*, ventral tegmental area.

Table 1

Receptor binding profiles of several major cannabinoids on CB1, CB2 and other putative cannabinoid receptors.

Drug	CB_1 (Ki, nM)	CB_2 (Ki, nM)	GPR55 (EC_{50}, nM)	TRPV1 (EC_{50}, μM)	PPARγ (EC_{50}, μM)
Anandamide (AEA)	61–543	279–1940	18	0.16–1.15	8–10
2-Arachidonoylglycerol (2-AG)	58–472	145, 1400	3	8.4–26	10–30
Δ^9-Tetrahydrocannabinol (THC)	5.05–80.3	3.13–75.3	8	>100	0.3
WIN55,212-2 (WIN)	1.89–123	0.28–16.2	N.D.	>100	10
CP55940	0.5–5.0	0.69–2.8	5	>100	10
HU-210	0.06–0.73	0.17–0.52	26	1.2	N.D.

Based on Pertwee (2008a) and Pertwee et al. (2010).

Table 2

Summary of cannabinoid (THC, WIN55,212-2, JWH133)-induced tetrad effects in transgenic animals.

Transgenic mouse line	Analgesia	Hypothermia	Catalepsy	Hypoactivity	References
Wildtype	Normal THC or WIN effect	Normal effect	Normal effect	Normal effect	Monory et al. (2007) and Wang et al. (2020)
Global CB_1-KO	No effect (to THC or WIN)	No effect	No effect	No effect	Ledent et al. (1999), Monory et al. (2007), Wang et al. (2020), and Zimmer, Zimmer, Hohmann, Herkenham, and Bonner (1999)
CaMK-CB_1-KO (CB_1^{flox} xCaMK-Cre)	↓ THC effect	No effect	No effect	No effect	Monory et al. (2007)
Glu-CB_1-KO (CB_1^{flox} xNEX-Cre)	Normal THC effect	↓ THC effect	Normal effect	↓ THC effect	Monory et al. (2007)
GABA-CB_1-KO (CB_1^{flox} xDlx5/6-Cre)	Normal THC effect	Normal effect	Normal effect	Normal effect	Monory et al. (2007)
D1-CB_1-KO (CB_1^{flox} xDrd1-Cre)	Normal THC effect	↓ THC effect	↓ THC effect	Normal effect	Monory et al. (2007)
SNS-CB_1-KO (CB_1^{flox} xNav1.8-Cre)	↓ WIN effect	N/D	Normal effect	N/D	Agarwal et al. (2007)
Global CB_2-KO	↓ THC or WIN effect	Normal effect	↓ THC or WIN effect	Normal effect (rotarod) ↓ THC effect (open-field)	Wang et al. (2020) and Li et al. (2021)
DA-CB_2-KO (CB_2^{flox} xDAT-Cre)	Normal effect (to WIN)	Normal effect	↓ WIN effect	Normal effect	Liu et al. (2017))
CX3CR1-CB_2-KO (CB_2^{flox} xCX3CR1-Cre)	Normal effect (to WIN, ACEA)	Normal effect	Normal effect	Normal effect	Liu, Canseco-Alba, Liang, Ishiguro, and Onaivi (2020)
Immune-CB_2-KO ($CB2^{flox}$ xLysM-Cre)	Normal JWH133 effect	N/D	N/D	N/D	Cabañero et al. (2020)
Syn-CB_2-KO (CB_2^{flox} xSyn-Cre)	↓ JWH133 effect	N/D	N/D	N/D	Cabañero et al. (2020)
SNS-CB_2-KO (CB_2^{flox} xNav1.8-Cre)	↓ JWH133 effect in thermal pain	N/D	N/D	N/D	Cabañero et al. (2020)
GPR55-KO	Normal THC effect ↑ WIN effect	↑ THC effect	↑ THC effect	↑ THC effect	Wang et al. (2020)

Abbreviations: CaMK—Ca^{++}/calmodulin-dependent protein kinase II; $CB1^{flox}$—CB1-floxed mice; NEX—a gene encodes neuronal helix-loop-helix protein (a transcription factor), expressed in pyramidal neurons of the dorsal telencephalon during embryonic development; Dlx5/6—distal-less homeobox genes 5/6, expressed in forebrain GABAergic neurons during embryotic development; SNS—sensory neurons expressing Nav1.8 channel; DA—dopamine; LysM—lymphocytes/monocytes; Syn—Synapsin (a neuronal marker).

Table 3

Receptor mechanisms underlying Δ^9-THC's affective properties.

Assay	Target	Antagonist	Knockout mouse	Results	References
Reward					
IVSA	CB_1Rs	AM251 SR141716A	N/A	Blocked	Freels et al. (2020, Justinova, Tanda, Redhi, and Goldberg (2003), and Spencer et al. (2018)
CPP	CB_1Rs	SR141716A	CB1-KO	Blocked	Braida, Iosue, Pegorini, and Sala (2004), Li et al. (2021)
ICSS	CB_1Rs	SR141716A	N/A	Blocked	Katsidoni, Kastellakis, and Panagis (2013)
IVSA	MORs	Naltrexone	N/A	Attenuated	Justinova, Tanda, Munzar, & Goldberg, 2004
CPP	MORs	N/A	MOR-KO	Blocked	Ghozland et al. (2002)
IVSA	A_{2A}Rs	MSX-3	N/A	Attenuated	Justinová et al. (2011)
IVSA	Presynaptic A_{2A}Rs Postsynaptic A_{2A}Rs	SCH-442416 KW-6002	N/A	Attenuated Enhanced	Justinová et al. (2011) and Justinová, Redhi, Goldberg, and Ferré (2014)
IVSA	α7nAChRs	Ro 61-8048	N/A	Attenuated	Justinova et al. (2013)
Aversion					
ICSS	CB_1Rs	SR141716A	N/A	Blocked	Katsidoni, Kastellakis, and Panagis (2013)
ICSS	CB_2Rs	AM630	N/A	Blocked	Spiller et al. (2019)
oICSS	PPARα/PPARγ	GW6471 GW9662	N/A	Attenuated	Hempel et al. (2021)
oICSS CPA	Subcortical glutamate-CB1Rs	N/A	VgluT2-CB1-KO	Attenuated Blocked	Han et al. (2017)
CPA	CB_2Rs	N/A	CB2-KO	Blocked	Li et al. (2021)
CPA	Prodynorphin gene	N/A	Dream-KO	Enhanced	Cheng, Laviolette, van der Kooy, and Penninger (2004)
CPA	Prodynorphin gene	N/A	Pdyn-KO	Attenuated	Zimmer et al. (2001))
CPA	KORs	Nor-BNI	KOR-KO	Blocked	Clasen et al. (2017), Ghozland et al. (2002) and Norris, Szkudlarek, Pereira, Rushlow, and Laviolette (2019)
Anxiolytic effect					
LDB EPM	CB1Rs	SR141716A	N/A	Blocked	Berrendero and Maldonado (2002) and Rubino et al. (2007)
LDB	MORs DORs	β-funaltrexamine Naltrindole	N/A	Blocked	Berrendero and Maldonado (2002)
EPM	5-HT_{1A}Rs	WAY100635	N/A	Blocked	Braida, Limonta, Malabarba, Zani, and Sala (2007)
EPM	5-HT_{2A}Rs	N/A	5-HT_{2A}R-KO	Blocked	Viñals et al. (2015)

Assay	Target	Antagonist	Knockout mouse	Results	References
EPM	CB_2Rs	AM630	N/A	Blocked	Ivy et al. (2020)
Anxiogenic effect					
EPM	CB1Rs	AM251	N/A	Blocked	Rubino et al. (2008)
EPM	PPARα	GW6471	N/A	Attenuated	Hempel et al. (2021)
EPM Open field	Unknown	CBD	N/A	Attenuated	Liu et al. (2017), Murphy et al. (2017), and Todd and Arnold (2016)

Abbreviations: IVSA—intravenous self-administration, CPP—conditioned place preference, CPA—conditioned place aversion, ICSS—intracranial self-stimulation, oICSS—optical ICSS, LDB—Light dark box, EPM—elevated plus maze, DREAM—downstream regulatory element antagonistic modulator, Pdyn, prodynorphin.

Table 4

Receptor mechanisms underlying Δ^9-THC-induced learning and memory impairments.

Assay	Target	Antagonist	Knockout mouse	Results	References
Spatial learning and memory					
RAM	CB_1R	SR141716A	N/A	Blocked	Lichtman and Martin (1996)
MWM	CB_1R	SR141716A	CB1-KO	Blocked	Varvel and Lichtman (2002)
MWM	Cell-type specific CB_1Rs	N/A	GABA-CB1-KO Glu-CB1-KO GFAP-CB1-KO	No effect No effect Blocked	Han et al. (2012)
MWM	NDMARs	AP-5	N/A	Blocked	Han et al. (2012)
MWM	COX-2	NS-398	COX-2-KO$^-$	Blocked	Chen et al. (2013)
MWM	A_1R	Caffeine	N/A	Enhanced	Sousa et al. (2011)
RAM	5-HT	Clomipramine 5-MeODMT	N/A	Attenuated Attenuated	Egashira et al. (2002)
RAM	$5\text{-}HT_2$	DOI	N/A	Attenuated	Egashira et al. (2002)
RAM	$5\text{-}HT_{1A}$	8-OHDPAT	N/A	Reversed	Inui et al. (2004)
RAM	AchE	Physostigmine Tetrahydroaminoacridine	N/A	Attenuated Attenuated	Mishima, Egashira, Matsumoto, Iwasaki, and Fujiwara (2002)
Short-term memory					
DNMS	CB_1R	SR141617A	N/A	Blocked	Hampson and Deadwyler (2000)
DNMP	CB_1R	SR141617A	N/A	Attenuated	Hampson and Deadwyler (2000) and Mallet and Beninger (1998a, b)
NOR	Mitochondria-specific CB_1R	N/A	DN22-CB1	Blocked	Hebert-Chatelain et al. (2016)
NOR	PKC	NPC CHE	N/A	Blocked Blocked	Busquets-Garcia et al. (2018)
DNMP	A_1R	Caffeine CPT	N/A	Enhanced Enhanced	Panlilio et al. (2012)
NOR	$A_{2A}R$	SCH442416 KW-6002	N/A	Attenuated No effect	Aso et al. (2019)
NOR	$5\text{-}HT_{2A}R$	MDL 100907	N/A	Reversed	Viñals et al. (2015)
NOR	$5\text{-}HT_{2A}R$	N/A	$5\text{-}HT_{2A}R\text{-}K0$	Attenuated	Viñals et al. (2015)
DNMS	ACHe	Rivastigmine	N/A	Blocked	Goonawardena, Robinson, Hampson, and Riedel (2010)

Abbreviations: RAM—radial arm maze, MWM—Morris water maze, DNMS—delayed nonmatch to sample, DNMP—delayed nonmatch to position, NOR—novel object recognition.