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The neuropharmacology of cannabinoid receptor ligands in central signaling pathways

Tibor M. Brunt[1] | **Matthijs G. Bossong**[2]

[1]Department of Psychiatry, Amsterdam Institute for Addiction Research, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[2]Department of Psychiatry, University Medical Center Utrecht Brain Center, Utrecht University, Utrecht, The Netherlands

Correspondence
Tibor M. Brunt, Amsterdam Institute for Addiction Research, Department of Psychiatry, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.
Email: orbit.biomed@gmail.com

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Abstract

The endocannabinoid system is a complex neuronal system involved in a number of biological functions, like attention, anxiety, mood, memory, appetite, reward, and immune responses. It is at the centre of scientific interest, which is driven by therapeutic promise of certain cannabinoid ligands and the changing legalization of herbal cannabis in many countries. The endocannabinoid system is a modulatory system, with endocannabinoids as retrograde neurotransmitters rather than direct neurotransmitters. Neuropharmacology of cannabinoid ligands in the brain can therefore be understood in terms of their modulatory actions through other neurotransmitter systems. The CB_1 receptor is chiefly responsible for effects of endocannabinoids and analogous ligands in the brain. An overview of the neuropharmacology of several cannabinoid receptor ligands, including endocannabinoids, herbal cannabis and synthetic cannabinoid receptor ligands is given in this review. Their mechanism of action at the endocannabinoid system is described, mainly in the brain. In addition, effects of cannabinoid ligands on other neurotransmitter systems will also be described, such as dopamine, serotonin, glutamate, noradrenaline, opioid, and GABA. In light of this, therapeutic potential and adverse effects of cannabinoid receptor ligands will also be discussed.

KEYWORDS

cannabinoid receptor ligands, CB_1 receptor, endocannabinoids, synthetic cannabinoids

1 | INTRODUCTION

The endocannabinoid system is a neurological pathway that has received much attention over the past decades, partly because it is the primary target for Δ9-tetrahydrocannabinol (THC), the main psychoactive compound in the cannabis plant (Pertwee, 2006b). In the scientific community, however, the endocannabinoid system has gained a lot of attention due to its pharmacological promise for the development of new compounds for treatment of a large variety of disorders (Bonnet & Marchalant, 2015; Chiurchiù et al., 2018; Guindon & Hohmann, 2008; Leweke et al., 2016; Pertwee, 2006b; Saito et al., 2013; Watkins & Kim, 2014). In particular, the study of existing ligands and the development of new substances that

Abbreviations: 2-AG, 2-arachidonylglycerol; AM, Alexandros Makriyannis; CBD, cannabidiol; GABA, gamma-aminobutyric acid; GPCR, G-protein-coupled receptor; JWH, John W. Huffman; LC, locus coeruleus; NAc, nucleus accumbens; SC, synthetic cannabinoids; THC, Δ9-tetrahydrocannabinol; VTA, ventral tegmental area.

are able to bind to the endocannabinoid system and to modulate its properties in the central nervous system (CNS) or the periphery seem to be at the core of this regained attention.

The endocannabinoid system consists of at least two types of receptors (CB_1 and CB_2) and endogenous ligands that bind to these receptors (Katona & Freund, 2012). CB_1 receptors are primarily found in the brain, with the highest concentrations demonstrated in the basal ganglia, cerebellum, hippocampus, and cerebral cortex (Glass & Felder, 1997; Hoffman et al., 2003; Hohmann & Herkenham, 1999; Mackie,2005; Wong et al., 2010). At nerve terminals they mediate release of both inhibitory and excitatory neurotransmitters (Katona & Freund, 2012; Maejima et al., 2001). CB_1 receptors are involved in many brain functions such as movement, coordination, sensory perception, learning and memory, and processing of reward and emotions (Bossong et al., 2014; Hill et al., 2009; Van Hell et al., 2012; Zanettini et al., 2011). CB_2 receptors occur in the periphery, like immune cells and gastrointestinal tract (Lombard et al., 2007; Lunn et al., 2006; Wright et al., 2008) and in the CNS mainly on microglia (Cabral et al., 2008; Pertwee, 2006a).

This review provides an overview of the neuropharmacology of a number of endocannabinoid receptor ligands, including endocannabinoids, the main pharmacological compounds of herbal cannabis and synthetic cannabinoid receptor ligands. This comprises not only their action on the endocannabinoid system, but also describes cannabinoid effects on other neurotransmitter systems, such as dopamine, glutamate, and GABA. Finally, in light of the action of different cannabinoid ligands, their therapeutic potential as well as neuropathology as a result of abnormal activation of the endocannabinoid system is discussed.

2 | THE ENDOCANNABINOID SYSTEM

CB_1 receptors are found mainly at the terminals of central and peripheral neurons, inhibiting or mediating release of different neurotransmitters (Bossong & Niesink, 2010; Pertwee, 2006a). They are also found on immune cells and other types of non-neuronal cells (Kaplan, 2013; Osei-Hyiaman et al., 2005). CB_2 receptors are expressed primarily on cells of the immune system and are able to modulate immune cell migration and cytokine release, both outside and within the brain (Turcotte et al., 2016). However, CB_2 receptors are also expressed by some neurons, but the function of these neuronal CB_2 receptors is yet to be elucidated (Den Boon et al., 2012; Stempel et al., 2016). It is believed that both cannabinoid receptor types are involved in both central and peripheral functions, including neuronal development, inflammatory responses, cardiovascular, respiratory and reproductive functions, hormone release and action (Pacher & Kunos, 2013). The expression level of both cannabinoid receptors and endocannabinoids changes following physiological and pathological stimuli.

Cannabinoid receptors are G-protein-coupled receptors (GPCRs; Gyombolai et al., 2012). CB_1 and CB_2 receptors both signal through G proteins, by doing so, they inhibit adenylyl cyclase and activate mitogen-activated protein kinases (Howlett & Abood, 2017). It has been established that the endocannabinoid system is activated by other GPCRs throughout the CNS, which can trigger release of endocannabinoids and subsequently modulate neurotransmitter release via the CB_1 receptors at the presynaptic terminals (Gyombolai et al., 2012). Release of endocannabinoids only happens when GPCRs are activated on specific cells or by specific agonists (Pertwee, 2008). Cannabinoid receptor activation, both in brain synapses and in peripheral tissue, leads to 'retrograde endocannabinoid signaling' (Hashimotodani et al., 2011). In principle, presynaptic glutamate release activates both ionotropic and metabotropic (mGluR) glutamate receptors postsynaptically and leads to release of endocannabinoids. The released endocannabinoids activate presynaptically localized CB_1 receptors. In addition, CB_1 receptor G proteins can mediate activation of A-type inwardly rectifying potassium channels, and inhibition of N- and P/Q-type calcium currents.

Metabotropic glutamatergic GPCRs (mGluR) were among the first documented to trigger the release of endocannabinoids (Kreitzer & Regehr, 2001; Maejima et al., 2001). Endocannabinoid release upon mGluR activation occurs in many areas of the brain, which suggests a physiologically important signaling mechanism (Izumi & Zorumski, 2012). Likewise, muscarinic acetylcholine receptors (mAChRs) modulate synaptic transmission through release of endocannabinoids (Kim et al., 2002). So, both postsynaptically localized G-coupled mAChRs and mGluRs modulate synaptic transmission through endocannabinoid signaling in the brain. In addition, activation of the serotoninergic G-coupled $5HT_2A$ and $5HT_2C$ receptors have also been shown to release endocannabinoids and activate the endocannabinoid system (Pertwee, 2015). Furthermore, serotonergic functionality through $5HT_2A$ and $5HT_2C$ receptors is impaired in CB_1 receptor-deficient mice (Aso et al., 2009; Mato et al., 2007). Endocannabinoid-serotonin system interaction was shown in human studies (Lazary et al., 2009; Salaga et al., 2019). Finally, activation of angiotensin G-coupled AT_1 receptors with angiotensin can lead to stimulation of CB_1 receptors, thereby regulating blood pressure in the hypothalamus (Argiolas & Melis, 2005).

3 | LIGANDS

3.1 | Endocannabinoids

Most abundant endogenous ligands of the endocannabinoid receptor system are anandamide and 2-arachidonylglycerol

(2-AG; Figure 1). Synthesized and released postsynaptically, they bind to the presynaptic cannabinoid receptors, thereby modulating neurotransmitter release. Both endocannabinoids are synthesized on demand in response to elevations of intracellular calcium, due to GPCR activation as mentioned above or to other cellular processes (Bossong & Niesink, 2010; Pertwee, 2006b). Anandamide is synthesized via a two step-pathway, involving N-acyltranferase and phospholipase D, 2-AG through diacylglycerol lipase and phospholipase C. Both endocannabinoids have a limited timeframe of action because of their rapid degradation. Degradation occurs via phospholipid-dependent pathways. Anandamide is degraded primarily by the fatty acid amide hydrolase (FAAH) enzyme, which converts anandamide into ethanolamine and arachidonic acid (Pertwee, 2006a). Evidence has also emerged for the existence of additional endocannabinoids, although research on their pharmacology and function is still in its infancy.

Endogenous cannabinoid ligands have been implicated in a number of physiological relevant functions, modulating sleeping, feeding, and reward behavior as well as immunomodulatory and antinociceptive properties (Pacher et al., 2006). Both inflammatory and anti-inflammatory properties have been linked to the peripheral CB_2 endocannabinoid system, like the downregulation of inflammatory mediators and cells upon activation of the CB_2 receptor (Turcotte et al., 2016). Antinociceptive properties are mediated via CB_1 receptors that are located throughout the pain circuits peripherally and centrally. Endocannabinoid effects on appetite and reward are complex, but involves regulation via the CB_1 receptor of GABAergic and glutamatergic input to the dopaminergic regions in the brain,

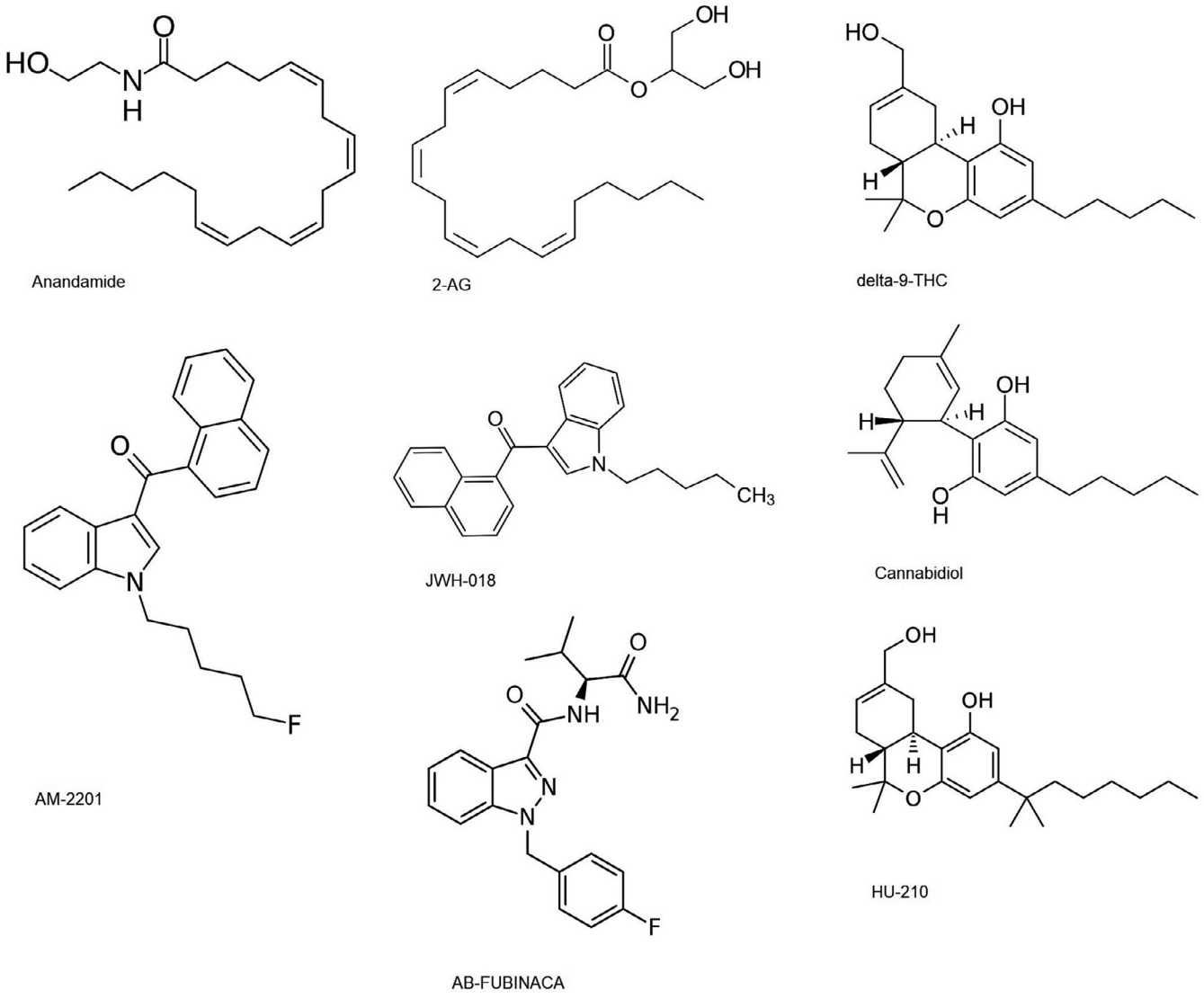

FIGURE 1 Molecular structures of some well-known cannabinoid receptor ligands, including endocannabinoids, phytocannabinoids and synthetic cannabinoids. 2-AG, 2-arachidonylglycerol; delta-9-THC, delta-9-tetrahydrocannabinol; JWH-018, 1-pentyl-3-(1-naphthoyl)indole; AM-2201, 1-(5-fluoropentyl)-3-(1-naphthoyl)indole; HU-210, (6aR)[-trans-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6Hdibenzo[b,d]pyran-9-methanol; ABFUBINACA, N-[(2S)-1-Amino-3-methyl-1-oxo-2-butanyl]-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide

resulting in decreased avoidance behavior and increased appetitive responding to a rewarding stimulus, like food or substances of abuse (Parsons & Hurd, 2015).

3.2 | Components in herbal cannabis

More than 100 phytocannabinoids have been characterized so far in the Cannabis *Sativa* plant (McPartland et al., 2015). The best known are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD; Figure 1). THC and CBD are biosynthesized by enzymes, which are expressed by alleles located at the same gene locus in the Cannabis plant (De Meijer et al., 2003). In cannabis plants that are grown for recreational consumption, the ratio of THC:CBD was about 14 in 1995, but this has since then increased to about 80 (ElSohly et al., 2016). Both THC and CBD are partial agonists of the CB_1 and CB_2 receptors, with moderate binding affinity of THC and low binding affinity of CBD (Pertwee, 2008). In comparison to the endocannabinoids anandamide and 2-AG, THC displays a lower binding affinity for cannabinoid receptors. THC mimics endocannabinoids as a partial agonist at CB_1 and CB_2 receptors (Mechoulam et al., 1998). Besides being ligands for the endocannabinoid receptors, cannabis and its many constituents have a more complex mechanism of action and activate the endocannabinoid system through several different pathways (McPartland et al., 2015). THC is the prominent psychoactive cannabinoid and mediates the subjective mental properties of cannabis, like reward (Pertwee, 2008). CBD does not have rewarding and reinforcing effects or abuse potential (Wenzel & Cheer, 2018).

The positive subjective effects of smoked cannabis are largely blocked by inverse CB_1 receptor agonists, like rimonabant, demonstrating that the subjective pleasurable effects of THC is mediated by the CB_1 receptor (Pertwee, 2008). THC modulates the mesolimbic dopamine system by increasing baseline firing rate of dopamine neurons in the ventral tegmental area (VTA) and it increases phasic dopamine release in the nucleus accumbens (NAc) by the CB_1 receptor in rodents (Cheer et al., 2004). It is thought that during periods of burst firing, GABAergic terminals expressing CB_1 receptors are modulated by cannabinoids, decreasing GABAergic inhibition, thereby causing disinhibition of dopamine release (Zlebnik & Cheer, 2016). However, in the human brain, this increase in dopamine release in the striatum seems more modest (Bossong et al., 2009, 2015). It is products mainly containing natural THC, like cannabis, and products containing synthetic THC, like dronabinol and nabilone, that have been approved for the treatment of nausea as well as for appetite stimulation in cancer and acquired immunodeficiency syndrome (AIDS; Hill et al., 2012). The effects of THC on the reward system and appetite stimulation have also led to the development of CB_1 antagonists such as rimonabant to treat addiction disorders and weight loss in obesity (Christensen et al., 2007; Pertwee, 2010). However, rimonabant was withdrawn from the market, because it caused severe psychiatric side effects (McPartland et al., 2015).

CBD is a non-intoxicating cannabinoid compound that may attenuate some of the acute as well as long-term effects associated with cannabis use (Freeman et al., 2019; McPartland et al., 2015; Pertwee, 2008). Although the mode of action of CBD is not fully understood, there are indications that it acts as either a cannabinoid CB_1/CB_2 receptor inverse agonist (Laprairie et al., 2015; Thomas et al., 2007) or a negative allosteric modulator of the cannabinoid CB_1 receptor (Laprairie et al., 2015). It may also act as an indirect agonist and antagonist at the CB_1 receptor, by increasing endocannabinoid availability through inhibition of the hydrolytic enzyme that breaks down anandamide (Di Marzo & De Petrocellis, 2012) and as non-competitive antagonist at CB_1 (Thomas et al., 2007). Furthermore, CBD inhibits adenosine uptake and is a 5-hydroxytryptamine 1A ($5\text{-}HT_{1A}$) receptor agonist. CBD is also able to modulate opioid, dopamine D_2, $GABA_A$, and glycine receptors. When CBD and THC are co-administered, it appears that CBD reduces the subjective intoxication and anxiety effects of THC (Zlebnik & Cheer, 2016). For instance, CBD reduced the fear response of THC in humans in functional MRI studies (Bhattacharyya et al., 2010; Fusar-Poli et al., 2009). CBD is also proposed to counteract the rewarding, anxiogenic, and psychosis-like properties of THC, although the attenuating impact of CBD is largely dependent on dose, route of administration, and THC:CBD ratio (Freeman et al., 2019; Iseger & Bossong, 2015; Zlebnik & Cheer, 2016).

CBD has gained much attention as molecule without the typical psychiatric side effects of rimonabant or THC, because of its low affinity for the CB_1 receptor (McPartland et al., 2015). Therefore, the development of cannabinoid-based therapeutics has shifted toward CBD and herbal cannabis formulations with a low THC:CBD ratio (Freeman et al., 2019). At the moment CBD is viewed as a phytocannabinoid with great therapeutic promise, due to its potential anxiolytic, antidepressant, antipsychotic, anti-inflammatory, and anti-carcinogenic effects (Pellati et al., 2018; Zlebnik & Cheer, 2016; Iseger & Bossong, 2015). For example, fhe first clinical trials with CBD treatment of schizophrenia patients show the potential of CBD as an effective, safe, and well-tolerated antipsychotic compound (Batalla et al., 2019; Iseger & Bossong, 2015). The first randomized clinical trial of CBD for cannabis use disorder demonstrated that CBD was safe and more efficacious than placebo at reducing cannabis use (Freeman et al., 2020). Furthermore, Sativex®, a whole cannabis extract with a THC:CBD ratio of 1 has been developed for treatment of pain and spasticity in multiple sclerosis (Barnes, 2006) and has shown potential in the treatment of cannabis use disorder (Batalla et al., 2019).

3.3 | Synthetic cannabinoids (SC)

Synthetic cannabinoids (SC) were originally designed and manufactured in the 1970s and 1980s to study the cannabinoid receptors in the brain, such as the cyclohexylphenols (CP), like (6aR)[-trans-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6Hdibenzo[b,d]pyran-9-methanol (HU-210), a structural analogue of THC, with a potency that is >100 times higher at the CB_1 and CB_2 receptors (De Fonseca et al., 1994; Mechoulam et al., 1988). Later on, aminoalkylindoles were developed as possible safe therapeutic alternatives for THC, like 1-pentyl-3-(1-naphthoyl)indole (JWH-018) and the other SC series created by John W. Huffman (JWH), AM-series (created by Alexandros Makriyannis) SC (Castaneto et al., 2014) and indazole-carboxamide derivatives, like N-[(2S)-1-Amino-3-methyl-1-oxo-2-butanyl]-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (AB-FUBINACA; Banister et al., 2015; Figure 1). To date several hundred SC are known, belonging to various chemical classes (EMCDDA, 2017). They can be non-selective or highly selective agonists at the CB_1 or CB_2 receptor, or at both (Pertwee, 2010). In general, SC are lipophilic molecules and almost all of them have a much greater binding affinity to the cannabinoid receptors than THC or endocannabinoids (Table 1).

Whereas the therapeutic use, originally intended for SC, seems virtually non-existent, SC were increasingly synthesized in clandestine laboratories to be marketed and sold as legal cannabis alternatives, since the early 2000s (United Nations Office on Drugs & Crime, 2020). They are sold through the Internet, either on webshops or on the dark-web, but also in head shops, under slang names as "Spice" or "K2". They can be purchased as tablets, pure powder, smokable herbal blends (whereby the SC are sprayed over plant like material) or even in liquids that can be vaped via an electronic cigarette (Karila et al., 2016). As they often do not show up on routine toxicology screenings and are accessible with relative ease, popularity of SC has risen in some parts of the world that have a strict cannabis legislation. Even though some countries have banned many SC (Drug Enforcement Agency,2020), many new SC keep emerging, sometimes not covered by the current legislations. Legislation is often bypassed by modification of chemical structures, leading to an ever-growing plethora of new analogues (Karila et al., 2016).

Because of their high affinity and selectivity to the cannabinoid receptors, use of SC tends to cause much more intense and severe effects than endocannabinoids and herbal cannabinoids (Castaneto et al., 2014; Le Boisselier et al., 2017). Whereas severity of adverse effects with herbal cannabis is considered low and fatalities are virtually absent, this is not the case with SC (Tait et al., 2016; Van Amsterdam, Brunt, et al., 2015; Van Amsterdam, Brunt, et al., 2015). SC use is frequently associated with hospitalizations and deaths. SC are known to cause mental adverse effects, like panic attacks, anxiety, paranoia, hallucinations, and psychosis (Tait et al., 2016; Van Amsterdam, Brunt, et al., 2015; Van Amsterdam, Brunt, et al., 2015). This is not surprising, given the fact that high doses of THC, present in strong herbal cannabis formulations, have been long known to increase the risk of adverse mental effects and psychosis (Englund et al., 2017). In chronic SC users, studies have found increased anxiety, depression, and an impairment in executive functioning (Cohen et al., 2017, 2020), reduced grey matter density and impairments in working memory (Livny et al., 2018).

In addition, SC can cause major physiological side effects such as hypertension, hypotension, bradycardia, tachycardia, agitation, nausea, and vomiting (Castaneto et al., 2014). Cannabinoid receptors are present in the heart, and, upon activation, they may lead to undesirable cardiac effects (Ozturk et al., 2019). In moderate doses, THC is known to cause cardiac effects, like tachycardia, and together with myocardial oxygen demand can contribute to arrhythmia development, whereas at high doses THC causes bradycardia (Pacher et al., 2018). Use of SC has been linked to serious adverse cardiovascular effects such as stroke, myocardial infarction, cardiomyopathy, and cardiac arrest (Ozturk et al., 2019; Pacher et al., 2018). Most prominently, cardiac arrhythmia was seen in hospitalized cases. However, the interaction between cardiac contractility and cannabinoid receptors is complex and

TABLE 1 Affinities of some well-known cannabinoid receptor ligands for the Cb_1 and CB_2 receptors

Compound	CB_1 Ki (nM)	CB_2 Ki (nM)	Reference
AB-FUBINACA	0.9	—	Castaneto et al. (2014)
AM2201	1.0	2.6	Castaneto et al. (2014)
CP47,497	0.8	—	Castaneto et al. (2014)
HU210	0.2	0.4	Castaneto et al. (2014)
JWH-018	9.0	2.9	Castaneto et al. (2014)
JWH-073	8.9	38.0	Castaneto et al. (2014)
JWH-210	0.5	0.7	Castaneto et al. (2014)
XLR-144	29.0	2.1	Castaneto et al. (2014)
THC	41.0	36.0	Castaneto et al. (2014)
CBD	842.0	203.0	Howlett et al. (2002)
Anandamide	32.0	1932.0	Vemuri et al. (2008)
2-AG	472.0	1,400.0	Vemuri et al. (2008)

includes both the central nervous system and local physiological cardiac systems. Possibly, a distorted autonomic nervous system control by SC disrupts the cardiovascular system at several levels, leading to cardiac arrhythmia.

4 | ENDOCANNABINOID SYSTEM AND NEUROTRANSMISSION IN THE BRAIN

The endocannabinoid system is present throughout the whole brain, with particular high CB_1 concentrations in the basal ganglia, the putamen, hypothalamus, and nucleus accumbens (Shu-Jung Hu & Mackie, 2015). In addition, at a lower density, CB_1 receptors are located in the cortex, cerebellum, amygdala, spinal cord, and brainstem, where also CB_2 receptors are located as they are on microglial cells. In accordance to its brain topography, the endocannabinoid system displays actions at various brain neuronal pathways and modifies their specific functions (Di Marzo, 2009). The endocannabinoid system modulates neurotransmission indirectly, with endocannabinoids acting as retrograde neurotransmitters instead of direct neurotransmitters. The mechanism of action of endocannabinoids and analogous ligands can therefore be understood in terms of their modulatory actions on other neurotransmitter systems.

It has been proposed that cannabinoids increase the risk of both psychosis and addiction, and that their actions at the striatal dopamine system contribute to this (Bossong et al., 2015; Daniju et al., 2020; Sami et al., 2015). It seems that chronic cannabis users have lower baseline dopamine levels (D'Souza et al., 2008; Bloomfield et al., 2016; van de Giessen et al., 2017). Especially, the age of onset of cannabis use was associated with lower striatal dopamine release (Urban et al., 2012). This lower dopamine activity might be responsible for increased addiction potential of cannabis (Bloomfield et al., 2016). Also, decreased cognitive functioning in cannabis-dependent users might also be due to lower baseline dopamine levels (Sami et al., 2015). On the other hand, the increase in striatal dopamine after acute cannabis administration might underlie the increased risk for psychosis (Bossong et al., 2009). For instance, SC produce profound increases in dopamine levels, in the nucleus accumbens for instance (Canazza et al., 2016; De Luca et al., 2015; Ossato et al., 2017), most likely via inhibition of GABAergic and glutamatergic neurotransmission (Le Boisselier et al., 2017). In addition, reduced dopamine activity was seen in chronic cannabis users that were prone to develop psychotic symptoms after exposure to cannabis or other substances of abuse (Mizrahi et al., 2014). However, the relevance of cannabis exposure was obscured in all of these studies because of other risk factors that might play a role, like genetic predisposition or environment.

Cannabinoid signaling also influences the serotonin system. Activation of the CB_1 receptors by ligands inhibits serotonin release in the prefrontal cortex, while blockade of these receptors increased serotonin release (Cohen et al., 2019; Haj-Dahmane & Shen, 2009). Chronic cannabis use also seems to lower the serotonin levels in the raphe nuclei (Bambico et al., 2010) and high doses of cannabis or high affinity CB_1 agonists cause aversive mood effects, anxiety, and depression (Castaneto et al., 2014; Leweke & Koethe, 2008). Cannabinoid ligands also regulate expression of serotonergic receptors and this contributes to the side effects on mood of cannabinoids (Le Boisselier et al., 2017). Recently, for example, it was found that SC upregulated the 5-HT_{2A} receptors via the CB_1 receptor (Fantegrossi et al., 2018; Franklin & Carrasco, 2012). This upregulation was hypothesized to underlie proneness for psychotic symptoms or mood disorders. Also, an interaction was shown between the serotonin and the endocannabinoid systems in the treatment of mood disorders with CBD (Schier et al., 2014).

Glutamatergic synaptic transmission is affected via chronic CB_1 activation and this disrupts glutamate synaptic plasticity, ultimately affecting cognitive abilities and development of the brain during vulnerable periods, like adolescence (Bossong & Niesink, 2010; Colizzi et al., 2016). For instance, repeated administration of THC or SC are able to down-regulate expression of glutamate AMPA and NMDA receptors in the rat cerebellum (Fan et al., 2010; Li et al., 2010,). Cannabinoid receptor agonists reduce glutamatergic synaptic transmission in several brain areas, like the hippocampus, prefrontal cortex, and nucleus accumbens via pre-synaptic modulation of glutamatergic neurons (Cohen et al., 2019). Magnetic resonance spectroscopy (MRS) is able to visualize the activity of the glutamatergic system and through this method it was found that chronic exposure to cannabinoid receptor agonists resulted in a decreased activity of the glutamatergic system in the basal ganglia and anterior cingulate cortex (Fan et al., 2010; Newman et al., 2019; Prescot et al., 2013). Reduction of glutamatergic activity in the prefrontal cortex was also found in chronic cannabis users with psychotic symptomatology and this was accompanied with impairments of working memory (Rigucci et al., 2018). Effects of cannabinoids on the glutamatergic system have also been associated in the development of schizophrenia (Cohen et al., 2019).

The endocannabinoid system is also able to potentiate $GABA_A$ mediated currents, as was demonstrated by application of endocannabinoids and phytocannabinoids, especially CBD (Bakas et al., 2017). CBD has a binding affinity to the $GABA_A$ receptor and showed comparable efficacy as the benzodiazepine flunitrazepam at increasing $GABA_A$ receptor mediated currents, suggesting CBD has a therapeutic potential for treating anxiety disorders (Cifelli et al., 2020). In addition to binding affinity for the $GABA_A$

receptors, cannabinoid agonists also modulate GABAergic neurotransmission through the presynaptic CB_1 receptors on GABA neurons, in the basal ganglia and thalamus for instance (Szabó et al., 2014). This mechanism of action on the GABA system has led to the study of cannabinoid receptor agonists in neurological conditions, like Alzheimer Disease, Parkinson's Disease, and epilepsy (Cifelli et al., 2020). For example, CBD was effective at reducing seizure frequency and severity in epileptic patients, without adverse side effects (Elliott et al., 2020; Herlopian et al., 2020; Lattanzi et al., 2018). Alzheimer Disease is characterized by disturbances in glutamatergic and GABAergic transmission and recent studies found that cannabinoids were able to recover the cognitive impairment in patients (Cassano et al., 2020; Schubert et al., 2019).

Interactions between the opioid and cannabinoid systems has been long thought to exist (Fattore et al., 2004; Pertwee, 2001; Starowicz & Di Marzo, 2013). For instance, the antinociceptive effects of cannabinoid receptor agonists are mediated through the release of endogenous opioids (Smith et al., 1994). The endogenous cannabinoid and opioid systems show large overlap in distribution, both in the brain and the spinal cord (Salio et al., 2001). Treatment with cannabinoid receptor agonists triggered the release of dynorphin B in the rat's spinal cord (Mason et al., 1999). Interestingly, treatment with CB_1 receptor antagonist AM251 reversed antinociceptive effects of morphine (Da Fonseca Pacheco et al., 2009). Several experimental animal studies have also shown that cannabinoid receptor agonists, mainly SC, are able to increase the rewarding properties of opioids, like morphine and heroin, supporting the interaction between the opioid and cannabinoid systems. Cannabis also induces locus coeruleus (LC) neuronal activity, which is thought to underlie cannabis-induced anxiety and panic disorders (Carvalho & Van Bockstaele, 2012). On the other hand, endocannabinoids also inhibit KCL-evoked excitation of the LC, showing some functional role in attenuating noradrenaline-mediated anxiety. The application of exogenous cannabinoid receptor agonists leads to too much inhibitory action on the noradrenaline system and disrupts attention processes (Solowij et al., 2002). Administration of cannabinoids alters the release of noradrenaline in specific areas of the brain, like the prefrontal cortex, LC, hippocampus, hypothalamus, and cerebellum (Moranta et al., 2004). CB_1 receptor antagonists are capable of increasing noradrenaline release, in the prefrontal cortex and hypothalamus for instance (Carvalho & Van Bockstaele, 2012). Since there is an interaction between cannabinoid and noradrenaline systems, it might be that certain highly specific cannabinoid receptor ligands might be beneficial in treating noradrenaline-related disorders, like post-traumatic stress disorder for instance.

5 | CONCLUSIONS

The endocannabinoid system is a complex neuronal system and is involved in a number of biological functions, like attention, anxiety, mood, memory, appetite, reward, and immune responses. Cannabinoid ligands mainly exert their actions in the brain through the CB_1 receptor and this receptor is distributed in the basal ganglia, brainstem, spinal cord, cerebellum, cortex, the putamen, hypothalamus, and NAc (Shu-Jung Hu & Mackie, 2015). Mechanism of action of cannabinoid ligands in the brain seems to depend mainly on their mediatory actions on neurotransmission. The rewarding properties of cannabinoid receptor ligands seem to be mediated through their actions at the dopamine system, as is supported by several studies (Bloomfield et al., 2016; Bossong et al., 2015; Daniju et al., 2020; Sami et al., 2015). The actions at the dopamine system is also implicated in the associated psychotic symptoms induced by exogenous cannabinoid receptor agonists (Bossong et al., 2009; Le Boisselier et al., 2017), although this has been suggested to be chiefly due to indirect effects through GABAergic and glutamatergic neurotransmission (Bossong & Niesink, 2010; Cohen et al., 2019; Rigucci et al., 2018). Other side effects of exogenous cannabinoid ligands frequently reported are anxiety and mood disorders, likely due to their actions at noradrenergic and serotonergic neurotransmission (Castaneto et al., 2014; Leweke & Koethe, 2008). The magnitude by which cannabinoid receptor ligands are able to induce these effects seems to lie in their affinity and selectivity for the CB_1 receptor (Sherif et al., 2016; Van Amsterdam, Brunt, et al., 2015; Van Amsterdam, Brunt, et al., 2015). This explains why SC are often associated with adverse side effects (Le Boisselier et al., 2017; Tait et al., 2016).

Whereas cannabinoid receptor ligands are well-known for adverse side effects and chronic cannabis use seems to be with considerable risks, like addiction or psychosis, much research centres on beneficial effects of cannabinoid ligands and their therapeutic applications (Barnes, 2006; Batalla et al., 2019; Iseger & Bossong, 2015; McPartland et al., 2015; Pellati et al., 2018; Zlebnik & Cheer, 2016). Several medical conditions seem to benefit from the antinociceptive and appetite-stimulating properties of cannabinoid receptor agonists, like symptoms of the human immunodeficiency virus (HIV), multiple sclerosis, rheumatoid arthritis and different forms of cancer (Whiting et al., 2015). But there is also a lack of robust data supporting therapeutic benefits, like controlled clinical trials. Therapeutic application of cannabinoid ligands is a careful consideration between the adverse and beneficial effects, which skews development of cannabis formulations with the right balance between agonism and antagonism at the CB_1 receptor, such as preparations containing only CBD or

with a low THC:CBD ratio (Englund et al., 2017; Freeman et al., 2019, 2020; Iseger & Bossong, 2015; Zlebnik & Cheer, 2016). Furthermore, CBD seems to counteract psychotic symptoms and addictive properties of THC (Zlebnik & Cheer, 2016). Therefore, it remains questionable whether most SC will ever reach the phase of therapeutic application in any of these disorders, because of their superior potency at the endocannabinoid receptor system and the lack of attenuating factors, like CBD (Karila et al., 2016; Pacher et al., 2018; Tait et al., 2016; Van Amsterdam, Brunt, et al., 2015; Van Amsterdam, Brunt, et al., 2015; Weinstein et al., 2017).

Taken together, the endocannabinoid system remains an interesting neurobiological avenue for study, both in terms of therapeutic promise as in the mechanistic functioning and modulation of neurotransmission in the brain. It is expected that this interest will not wane in the future, since herbal cannabis is legalized by more countries and accepted as medicine, so the debate about its positive versus negative effects continues and the consequences of chronic cannabis use in relation to psychiatric disorders (Hall et al., 2019). The hundreds of cannabinoid receptor ligands that are currently out there and the many more that will be developed will hopefully lead to an increased insight into the function of the endocannabinoid system in the brain and the development of more effective therapeutics.

METHODS: LITERATURE ASSEMBLY

Literature was researched in the Medline database on the basis of Boolean operators, “AND”, “OR” and “NOT”. MeSH terms were “endocannabinoids”, “cannabinoid”, “cannabis”, “marijuana”, “cb1 receptor”, “cb2 receptor”, “synthetic cannabinoids”, “spice”, “JWH”, “therapeutic”, “adverse effects”, “cannabinoid ligands”, “THC”, “CBD”, “anandamide”, “2-AG”, “neurotransmitters”, “dopamine”, “serotonin”, “glutamate”, “GABA”, “noradrenaline”, “opioid”, “CNS”, “brain”.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

AUTHOR CONTRIBUTIONS

TB designed and wrote the manuscript draft and the tables and figures, MB critically reviewed the manuscript and added relevant parts where necessary.

DATA AVAILABILITY STATEMENT

The reviewed literatures that support the findings of this study are available from the corresponding author, upon reasonable request.

PEER REVIEW

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ORCID

Tibor M. Brunt https://orcid.org/0000-0001-5337-9649

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