Balancing the Neuroprotective Versus Neurotoxic Effects of Cannabis

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Abstract Cannabinoids are chemicals that can be endogenous, natural, and synthetic substances which has the ability to bind to the cannabinoid receptors and exhibit a plethora of pharmacological and toxicological effects. Cannabinoids, the multipotent substance has a well-defined cellular signaling pathway that leads to a diverse physiological action in the body. Based on their chemical structural attributes, these substances can cross the blood–brain barrier, and hence, can exert an effect both in the central nervous system and the peripheral system in the body. Manipulation of the cannabinoid signaling with the natural and/or synthetic ligands can result in a plethora of pharmacological effects that can be used for various prophylactic and therapeutic treatment strategies in animals and humans. However, cannabinoids also induce severe adverse effects in the central and peripheral nervous systems. Hence, in this chapter, we review the current neuropharmacological and neurotoxicological properties of cannabinoids.

Keywords Cannabinoids · Central nervous system · Neuroprotection · Neurotoxicity · Pharmacology

Abbreviations

AAN	American Academy of Neurology
ABCD	Adolescent Brain Cognitive Development
AD	Alzheimer's disease
AD	Anno Domini
AEA	Arachidonoyethanolamine (Anandamide)
AIDS	Acquired immunodeficiency syndrome
ALD	Adrenoleukodystrophy
ALS	Amyotrophic lateral sclerosis
AMA	American Medical Association
AMPAR	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
Aβ	Amyloid-β
BC	Before Christ
BDNF	Brain-derived neurotrophic factor
cAMP	3′,5′-cyclic adenosine monophosphate
CB1	Cannabinoid type 1 receptors
CB2	Cannabinoid type 2 receptors
CBD	Cannabidiol
CBG	Cannabigerol

CBN	Cannabinol
CINV	Chemotherapy-induced nausea and vomiting
CNS	Central nervous system
DGL	Diacylglycerol lipase
DSE	Depolarization-induced suppression of excitation
DSI	Depolarization-induced suppression of inhibition
eCB	Endocannabinoids
FAAH	Fatty-acid amide hydrolase
GABA	Gamma-aminobutyric acid
GI	Gastrointestinal
GM-CSF	*G*ranulocyte–macrophage colony-stimulating factor
GPCRs	G-protein coupled receptors
HD	Huntington disease
HIV	Human immunodeficiency virus
IBD	Inflammatory bowel disease
IGF-1	*Insulin-like growth factor 1*
IL-6	I*nterleukin*-6
LTD	Long-term depression
LTP	Long-term potentiation
mAChRs	Muscarinic acetylcholine receptors
MS	Multiple sclerosis
NADA	*N*-Arachidonoyl-dopamine
NAPEPLD	N-acyl phosphatidylethanolamine phospholipase D
NF-Kb	N*uclear factor* kappa-light-chain-enhancer of activated B cells
NIH	National Institutes of Health
NMDA	*N*-Methyl-D-aspartate
OCE	Oral *cannabis* extract
OMNI-CAN	Outcomes Mandate National Integration with Cannabis as Medicine
PCL-β	Phospholipase C-β
PD	Parkinson's disease
PKA	Protein kinase A
PTSD	P*osttraumatic stress disorder*
SN	Substantia nigra
THC	Tetrahydrocannabinol
TNF-α	Tumor necrosis factor-α
TRPV1	Transient receptor potential vanilloid 1
VGCC	Voltage-gated calcium channel

1 Introduction

Cannabis sativa L. (cannabis) is one of the earliest cultivated plants and is indigenous to central Asia and the Indian subcontinent. The earliest usage dates were reported in China, where archaeological findings indicate that the plant was

cultivated for fibers since 4000 BC (Campos 2012). Furthermore, in western Asia and Egypt, *Cannabis sativa* was used for the cultivation of textile fiber, making it one of the oldest plants to be used as sources of food and fiber. In North America, cannabis was used in the form of hemp and was grown on several plantations for use in rope, cloth, and paper. The seeds of cannabis have been used for animal feed, its fiber for hemp rope, and its oil as a vehicle for paint (Small et al. 2002). In 1851, cannabis found its way into the third edition of Pharmacopeia of the United States, where it was used as a treatment for opioid withdrawal, pain, appetite stimulation, nausea, and vomiting (Pacula and Smart 2017). Growing concerns regarding its usage led to the prohibition of cannabis in several states in the early 1900s. Finally, in 1937, with the passage of the Marijuana Tax Act, the use and sale of the drug were prohibited by federal law. In 1942, Marijuana was removed from the 12th edition of *U.S Pharmacopeia* by American Medical Association (AMA) and was discredited for not having any medical use (Pacula and Smart 2017). In 2014, cannabis was decriminalized by Colorado, followed shortly by six other states that have legalized it for recreational use (Groce 2018).

1.1 Components of Cannabis

More than 100 different compounds have been isolated from cannabis sativa and have been given the term cannabinoids. The three classes of cannabinoids are (a) The plant-based cannabinoids (THC, cannabidiol, cannabinol) (Fig. 1), (b) Endogenous cannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (Fig. 2), and (c) The synthetic cannabinoids (e.g., WIN55212–2, CP-55940, JWH-015) (Fig. 3) (Maroon and Bost 2018). Representative members of each of these classes are shown in Fig. 1–3.

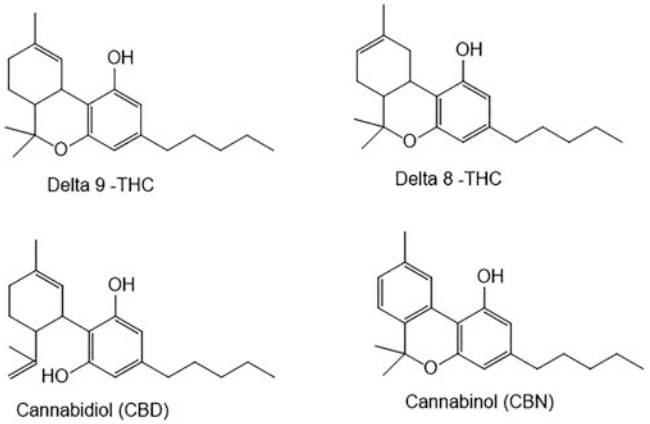

Fig. 1 Plant-based cannabinoids

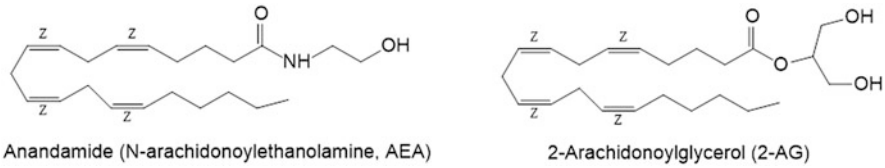

Fig. 2 Endocannabinoids

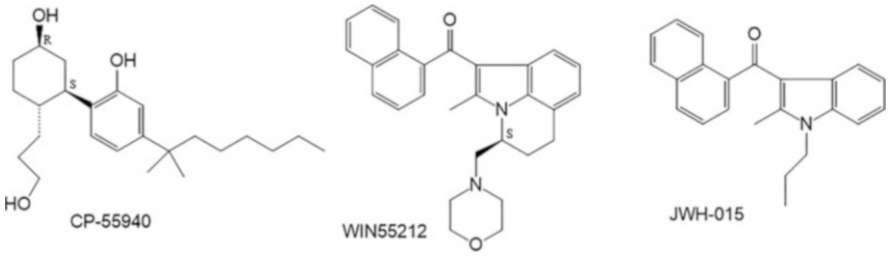

Fig. 3 Synthetic cannabinoids

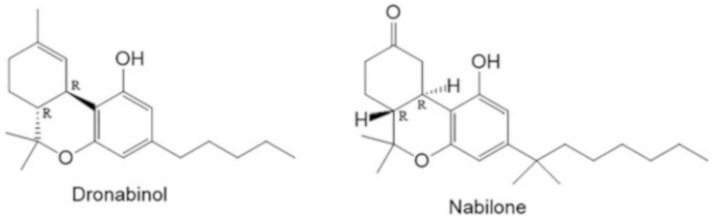

Fig. 4 THC drug derivatives

The most abundant and the primary psychoactive plant-based cannabinoid is tetrahydrocannabinol (THC) or Δ-9-tetrahydrocannabinol (Δ-9–THC). It exerts its effects on the central nervous system (CNS) through partial agonism of G-protein coupled cannabinoid type 1 receptors (CB1) and type 2 receptors (CB2). Other natural cannabinoids include cannabidiol (CBD), a nonintoxicating anti-inflammatory and antianxiety agent, and Δ-8-THC. In 1985, THC derivatives—dronabinol and nabilone (Fig. 4) were approved for therapeutic use (Maroon and Bost 2018). The pharmacological and therapeutic properties of THC, CBD, and other natural cannabinoids are being extensively studied today. Cannabinol (CBN), produced by the oxidation of THC, could be a predictor of cannabis exposure to heat during storage. They possess mild psychoactive effects and have a high affinity for CB2 receptors. CBN is a potential antiemetic, antioxidant, anticonvulsant, and helps in the management of insomnia and possesses analgesic effects like THC (Maroon and Bost 2018).

1.2 Medicinal Uses of Cannabis

The medicinal use of cannabis dates back 5000 years ago when the dried flowers of cannabis, also known as marijuana was used as an important ingredient in holy anointing oil referenced in the original Hebrew version of Exodus. The Egyptians have reportedly used marijuana to treat glaucoma as well as inflammation, and by 100 AD, the Chinese had identified more than 100 medicinal uses for the plant. The roots of the plants were used by the Romans in 70 AD to treat gout, arthritis, and generalized pain and by Arabians in 800–900 AD for migraines, pain, and syphilis. The British discovered several other uses of marijuana, such as for menstrual cramps, convulsions, rheumatism, gout, and joint pain, insomnia, and muscle spasms. Studies have found medical cannabis and cannabinoids to be more effective than standard antiemetics in controlling chemotherapy-induced nausea and vomiting (CINV) although high side effects were equally observed (Tramer et al. 2001). The analgesic properties of cannabis have been clinically proven in conditions like neuropathic pain from multiple sclerosis (MS), human immunodeficiency virus (HIV) infection, acquired immune deficiency syndrome (AIDS), rheumatoid arthritis, cancer, migraine, muscle spasticity, Crohn's disease, and ulcerative colitis (inflammatory bowel disease) (IBD) (Pacula and Smart 2017). In addition, cannabis has been legalized for use for a variety of medical conditions, including Alzheimer's disease, epilepsy, amyotrophic lateral sclerosis, Parkinson's disease, post-traumatic stress disorder, Tourette syndrome, and cachexia. Despite its several uses, decriminalizing cannabis for medicinal purposes is still controversial and is expected to be a major topic of discussion in the forthcoming elections. Similarly, while cannabinoids have demonstrated a significant clinical reduction in symptoms in patients with chronic pain and CINV, further studies are required to determine adverse effects, optimum drug, and dosage choices, long-term effects, the risk–benefit ratio of combinatorial drugs.

CBD is considered the therapeutic champion of cannabinoids. CBD is a 5-HT1A receptor agonist and accounts for neuroprotective and antidepressive effects of the group and also plays a major role in the management of epilepsy, inflammation, and nausea. Furthermore, CBD has shown to stabilize the *N*-methyl-D-aspartate (NMDA) receptor pathway, thus resulting in the reduction of schizophrenia equivalent to amisulpride. The combination of THC with the non-psychotropic CBD (buccal spray, Sativex) was effective in treating neuropathic pain and in reducing sleep disturbances in patients with MS (Bridgeman and Abazia 2017). Furthermore, low doses of THC have been proven to reduce atherosclerosis by its pleiotropic, immunomodulatory effects on myeloid and lymphoid cells (Steffens et al. 2005).

1.3 Adverse Effects of Cannabinoids

Cognitive impairment, such as memory loss, psychosis, and paranoia, are some of the potential short-term adverse effects of cannabinoids (Wilkinson et al. 2014). Long-term adverse effects in adolescents include cognitive impairment, altered brain development, and negative impact on learning. Adverse effects of CBD usage include somnolence, reduced appetite, diarrhea, and fatigue (Wilkinson et al. 2014; Huestis et al. 2019).

2 Endocannabinoid Signaling System

The endocannabinoid signaling system is comprised of the CB receptors, their endogenous ligands or endocannabinoids, synthetic and degradative enzymes that inactivate the endocannabinoids, and the transporters of the endocannabinoids.

2.1 Cannabinoid Receptors in Brain

2.1.1 CB1

One of the most abundant G-protein coupled receptors (GPCRs) found in the brain is the CB1 receptor and is present in high levels in the hippocampus, basal ganglia, cerebellum, and the brain stem, where it may restrict their function to presynaptic and axonal compartments (Marsicano and Kuner 2008). It has attracted considerable attention by exhibiting a variety of brain functions such as execution, emotion, reward, and memory processing by indirect interaction with dopaminergic, glutamatergic, and GABAergic systems. CB1 receptors bind synthetic cannabinoids such as CP55940, JWH-015, WIN55212–2, and endocannabinoids, including arachidonic acid derivatives arachidonylethanolamine (AEA) and 2-AG. Upon activation, CB1 receptors bind to pertussis toxin G_i/o-proteins leading to a decrease in cAMP levels (Kendall and Yudowski 2017). Further, its presynaptic localization and inhibition of adenylate cyclase and voltage-dependent calcium channels suggest an important role of CB1 receptors in neurotransmitter release. The neurotransmitters controlled by the CB1 receptors include GABA, glutamate, glycine, acetylcholine, norepinephrine, dopamine, serotonin, and cholecystokin.CB1 receptors are involved in several neural activities such as appetite, learning, memory, and cognition, as well as several disease states, including anxiety, depression, schizophrenia, stroke, MS, epilepsy, and addiction (Di Marzo et al. 2014). CB1 receptors control appetite from the hypothalamus in the CNS and regulate the energy and food intake from the GI tract. One of the plausible mechanisms by which CB1 mediates neuroprotection against neurological disorders like epilepsy and neurodegenerative

diseases is by inhibiting GABA and glutamate release from the presynaptic terminals of the hippocampal interneurons and the dorsal striatum, respectively (Katona et al. 1999; Di Marzo et al. 2014). CB1 receptors have been indicated in several neurodegenerative diseases such as Huntington's disease, multiple sclerosis, and Alzheimer's disease (Scotter et al. 2010).

2.1.2 CB2

Unlike CB1, CB2 has been referred to as the "peripheral cannabinoid receptor" because it is predominantly found in the cells and tissues of the immune system and is responsible for the anti-inflammatory effects of cannabis (Buckley et al. 2000). The receptor is localized to microglia, and this is of great relevance since microglial cells play a significant role in Alzheimer's disease (Roche and Finn 2010). However, contradicting studies by Benito et al. have recently identified functional CB2 throughout the CNS (Benito et al. 2003). CB2 expression can be induced in the brain, suggesting its potential role in neurological diseases. While CB1 is expressed in the presynaptic terminals, CB2 is expressed in postsynaptic areas (somatodendritic), thus, suggesting contrasting roles neuronal firing and neurotransmitter release (Roche and Finn 2010). Thus, CB2 equally plays an important role in neuroprotection, and targeting CB2 offers a novel therapeutic approach in treating neurological diseases.

2.2 Endocannabinoid-Mediated Synaptic Transmission—Mechanism of Signaling

For nearly a decade, neurophysiologists were looking for candidate molecules that mediated retrograde synapsis until when in 2001; cannabinoids were discovered to produce such an effect in the central synapse (Ohno-Shosaku et al. 2001; Maejima et al. 2001). The endocannabinoids serve as retrograde messengers that mediate feedback inhibition modulating synaptic plasticity (Katona and Freund 2012). Endocannabinoids are released from postsynaptic neurons due to receptor activation and/or postsynaptic depolarization. The released endocannabinoids activate CB1 receptors at the presynaptic terminal. The activation of the CB1 receptor leads to activation of inwardly rectifying K+ channel, inhibition in N-type, and P/Q-type voltage-dependent Ca^{2+} channel and endocannabinoid production (Mackie et al. 1995; Twitchell et al. 1997). This leads to suppression of inhibitory neurotransmitter GABA (a.k.a depolarization-induced suppression of inhibition or DSI) or excitatory neurotransmitter glutamate (a.k.a depolarization-induced suppression of excitation or DSE) or long-term depression or potentiation (LTD/LTP) during synaptic plasticity. Also, the presence of CB1 receptors at the mitochondrial membrane reduces mitochondrial respiration and contributes to DSI. The DSI and DSE have been

characterized in the cerebellum and hippocampus parts of the brain (Heifets and Castillo 2009).

2.3 Endocannabinoid Mediated Long-Term Plasticity

The involvement of endocannabinoids in long-term plasticity or long-term depression was observed in 2002 at excitatory synapses in the dorsal striatum and has since been observed in the accumbens, amygdala, hippocampus, visual cortex, somatosensory cortex, prefrontal cortex, cerebellum, ventral tegmental area, and brain stem. The induction of LTD begins with the activation of postsynaptic metabotropic glutamate receptors, following presynaptic glutamate activation. The receptors are coupled to Phospholipase C-β (PCLβ) and $G\alpha_{q11}$ leading to diacylglycerol formation, which is converted to 2-AG by diacylglycerol lipase (DGL). 2-AG is released from postsynaptic by endocannabinoid membrane transporters and binds the CB1 receptors in the excitatory terminal. In some cases, Ca^{2+} in the postsynaptic terminal also contributes to the endocannabinoid mobilization in a PLC dependent (activating it) or independent manner. In others, LTD occurs independently of Ca^{2+} release. The CB1 receptors at the presynaptic terminal inhibit adenylate cyclase and protein kinase A via $G\alpha_{q11,}$ suppressing the release of neurotransmitters. Reduced protein kinase A (PKA) activity, together with Ca^{2+}-sensitive phosphatase calcineurin, shifts the phosphorylation/kinase balance leading to dephosphorylation of a presynaptic target that is involved in the reduction of neurotransmitter release. Other players include active zone protein RIM1α, and vesicle-associated rab3b is required for PKA-dependent inhibitory LTP (Heifets and Castillo 2009; Castillo et al. 2012).

2.4 Endocannabinoid-Mediated Short-Term Plasticity

The release of endocannabinoids characterized by DSI or DSE triggers Ca^{2+} influx into postsynaptic neurons. Alternatively, other methods of endocannabinoid release from hippocampal cells have been proposed, which include activation of metabotropic postsynaptic glutamate receptors or muscarinic acetylcholine receptors (mAChRs). Activation of metabotropic glutamate receptors contributes to the endocannabinoid mobilization by triggering PLC. Furthermore, DGL promotes the synthesis and release of 2-AG release, targeting presynaptic CB1 receptors. The beta and gamma subunits couple with the presynaptic voltage-gated calcium channel (VGCC) to reduce neurotransmitter release (Castillo et al. 2012; Diana and Marty 2004).

2.5 Endocannabinoid Signaling in Astrocytes

Growing evidence supports the endocannabinoid signaling in astrocyte–neuron communication and synaptic transmission in hippocampal and cortical astrocytes. CB1 receptor activation by endocannabinoids in hippocampal astrocytes has been reported, resulting in increased intracellular Ca^{2+} levels. The increase in Ca^{2+} levels from pyramidal neurons activated by endocannabinoids stimulates glutamate release from astrocytes. This evokes the release of slow inward currents in an adjacent CA1 pyramidal neuron, thus indicating that endocannabinoids play a major role in the communication between neurons and astrocytes via eCB glutamate signaling (Navarrete et al. 2014).

2.6 Endocannabinoid-Mediated Non-Retrograde Signaling

There is considerable evidence that endocannabinoids function to regulate the neural system and synaptic transmission in a non-retrograde or autocrine fashion using transient receptor potential vanilloid 1 (TRVP1) (expressed predominantly in the afferent sensory neurons and activates synaptic transmission associated with pain) and the postsynaptic CB1 receptors. The AEA-LTD is observed in nucleus accumbens, dentate granule cells, bed nucleus of stria terminalis, and induces LTD at the postsynaptic terminal. Activation of metabotropic glutamate receptors, via PLC activation of intracellular Ca^{2+} release, leads to the synthesis of AEA, which in turn activates TRPV1. Ca^{2+} release triggers α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) endocytosis and LTD via calcineurin/dynamin. In another signaling mechanism proposed by Bacci et al., neocortical GABA-containing interneurons induce CB1-dependent postsynaptic hyperpolarization reducing its excitability (Bacci et al. 2004). The self-induced inhibition is activated by intracellular Ca^{2+} endocannabinoid mobilization and CB1 receptor activation leading to activation of inwardly rectifying K^+ channel (Castillo et al. 2012).

3 Endogenous Ligands, Natural and Synthetic Compounds Acting on Cb Receptors

3.1 Endogenous Ligands that Act upon Endocannabinoids

3.1.1 Arachidonoylethanolamine (Anandamide, Aea) and 2-AG

Cannabinoids receptors have neutral and lipophilic ligands that are derived from arachidonic fatty acids. The most common types are AEA and 2-AG. AEA was first

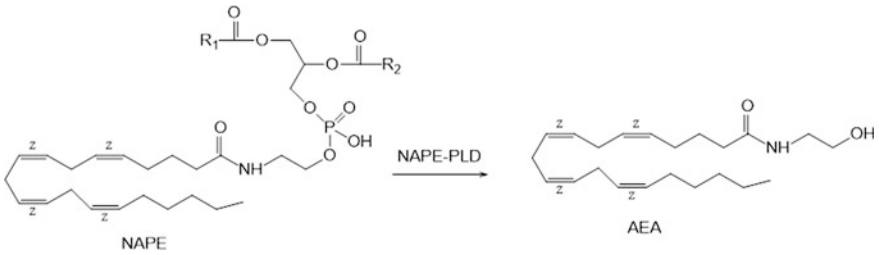

Fig. 5 Formation of AEA

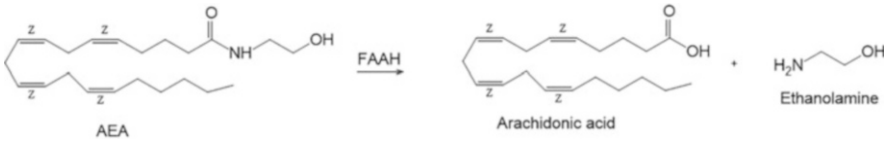

Fig. 6 Metabolism of AEA

isolated from the porcine brain (Devane et al. 1992). AEA has high affinity and serves as a partial agonist for the CB1 receptor and has a low affinity for CB2 receptors. 2-AG has a moderate-to-low affinity and serves as a full agonist at both CB1 and CB2 receptors (Di Marzo and De Petrocellis 2012). Nyilas et al. have demonstrated that N–acyl phosphatidylethanolamine hydrolyzing phospholipase D (NAPE-PLD), an enzyme involved in the formation of AEA, is present at the hippocampal excitatory presynaptic terminal and is associated with intracellular Ca^{2+} reserves (Nyilas et al. 2008), leading to the belief that unlike 2-AG, AEA has a presynaptic origin (Fig. 5). Following CB1 receptor activation, AEA is taken up by postsynaptic cells by transport proteins on both neurons and glia. Furthermore, inside the postsynaptic cell, AEA is metabolized to arachidonic acid and ethanolamine by an enzyme called fatty-acid amide hydrolase (FAAH) that is located within the endoplasmic reticulum (Ahn et al. 2009) (Fig. 6). A study by Pertwee has shown that AEA, along with other CB1/CB2 receptor agonists such as Δ-9–THC, HU-210, and WIN55,212, induces signs of antinociception in mouse, rat, and monkey models of acute thermal, inflammatory, and neuropathic pain (Pertwee 2012).

Other endogenous endocannabinoids identified are 2-eicosa-5′,8′,H′,14′-tetraenylglycerol (2-AG ether, noladin ether), and virodhamine and *N*-arachidonoyl-dopamine (NADA) (Fig. 7). Virodhamine is arachidonic acid, and ethanolamine conjugated by ester and has antagonistic properties against the CB1 receptor. NADA is a "capsaicin" like substance observed in mammalian nervous tissue and activates CB1 receptors and is an agonist for vanilloid receptors (Console-Bram et al. 2012). Activation of CB1 modulates adenylate cyclase to inhibit 3′,5′-cyclic adenosine monophosphate (cAMP) accumulation, VGCC, K+ channels, and 6 release. The basal levels of 2-AG have been found to be 1000 times higher than AEA in the brain. 2-AG also has been shown to play a significant role in

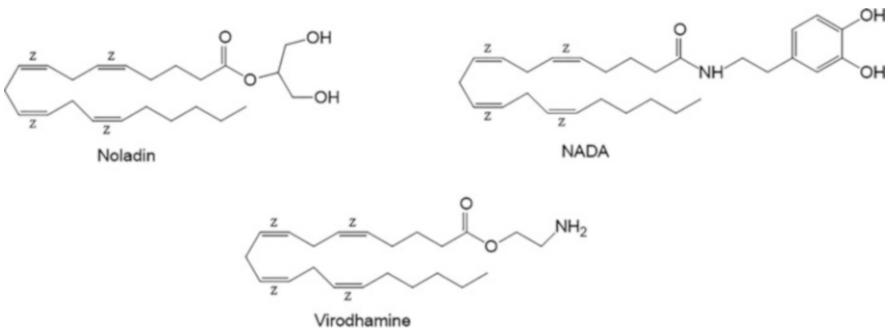

Fig. 7 Other endogenous cannabinoids

retrograde signaling. In light of all these findings, it is established that 2-AG is the primary endogenous ligand for CB receptors in the CNS (Zou and Kumar 2018).

3.2 Natural and Synthetic Cannabinoids and their Therapeutic Applications

3.2.1 Synthetic Cannabinoids

Synthetic compounds involved in stimulating the cannabinoid receptors mimic the psychoactive effects of cannabis variably. Research on these natural compounds, especially THC, has led to several modifications in basic molecular structures, chemistry, and pharmacology. A number of synthetic cannabinoids have been tested for their clinical effects. Three cannabinoids that are currently being used in the clinic are Cesamet (nabilone), Marinol (dronabinol), and Sativex (cannabidiol)—all three activate CB1/CB2 receptors.

3.2.2 Natural Cannabinoids

CBN is one of the nonpsychoactive cannabinoids present in the cannabis plant at low levels and occurs as a degradant of THC. CBN is produced in trace amounts when THC is exposed to air, light, and heat, and when the plant dies. With potential anti-inflammatory and immunosuppressive effects, CBN has a low affinity for CB1 but binds the CB2 receptor, triggers apoptosis, and inhibits the production of cytokines. CBN has also been proposed as an antiemetic, anticonvulsant, and in the management of insomnia (Holt 2016).

CBD is a nonpsychoactive phytocannabinoid derived from cannabis and has shown promise with anti-inflammatory, analgesic, anticonvulsant, muscle relaxant, neuroprotective, antioxidant, and antineoplastic properties. CBD is known to act as a negative allosteric modulator of the CB1 receptor. In addition to its effects on CB1

Table 1 A selective list of medications composed of natural and synthetic cannabinoids (Hruba and McMahon 2014)

Medications	Comments
Dronabinol	• THC that is used to treat anorexia in HIV patients and CINV
Nabilone	• Synthetic cannabinoid and analog of Marinol • Approved for CINV
Sativex	• Contains THC, CBD, and other cannabinoids • Licensed in Canada in 2005 for relief of neuropathic pain and spasticity in MS • Approved as an analgesic for patients with cancer
Rimonabant	• Trade name: Acomplia and Zimulti • CB1 receptor inverse agonist • Approved in the EU market for use as an anorectic anti-obesity drug and withdrawn in 2008 due to causation of depression and suicide
JWH-018	• A synthetic cannabinoid agonist included in herbal incense mixtures • Named "spice," "K2" • Increasingly sold in "legal" smoke blends that are illegal
CP55,940	• A synthetic cannabinoid that mimics THC but has been identified to be more potent than THC
HU-210	• Synthetic cannabinoid • At least 100 times more potent than THC
HU-331	• Anticarcinogenic drug synthesized from CBD • Inhibits DNA topoisomerase II

and CB2 receptors, it is known to activate 5-HT1A/2A/3A serotonergic and TRPV1–2 vanilloid receptors and antagonizes alpha-1 adrenergic receptors and μ-opioid receptors. It is also reported to trigger the synaptosomal uptake inhibition of noradrenaline, dopamine, serotonin, and gamma-aminobutyric acid (GABA). CBD acts on mitochondrial Ca^{2+} stores, blocks T-type Ca^{2+} channel, and stimulates inhibitory glycine and FAAH. Nabiximol contains CBD and THC in equal proportions. Epidiolex, an oral CBD solution, has been approved for the treatment of refractory epilepsy due to Lennox–Gastaut syndrome and Dravet syndrome. THC and CBD account for 95% of marijuana's active ingredient.

Cannabigerol (CBG)—Both THC and CBD are produced from precursor CBG, which is subject to enzymatic conversion to CBD, THC, and other cannabinoids. Studies have suggested that CBG is nonpsychoactive and has anti-inflammatory and antioxidant effects and has been used for treatment in IBD. CBG also possesses COX-2 inhibitor properties. CBG has been investigated for use in prostate cancer. Other natural cannabinoids, such as cannabidivarin, are being investigated for epilepsy. The cannabinoid tetrahydrocannabivarin is currently being investigated for its role in diabetes mellitus and metabolic syndrome (Jadoon et al. 2016).

A selective list of medications composed of natural and synthetic cannabinoids has been given in Table 1 and the chemical structures are shown in Fig. 8.

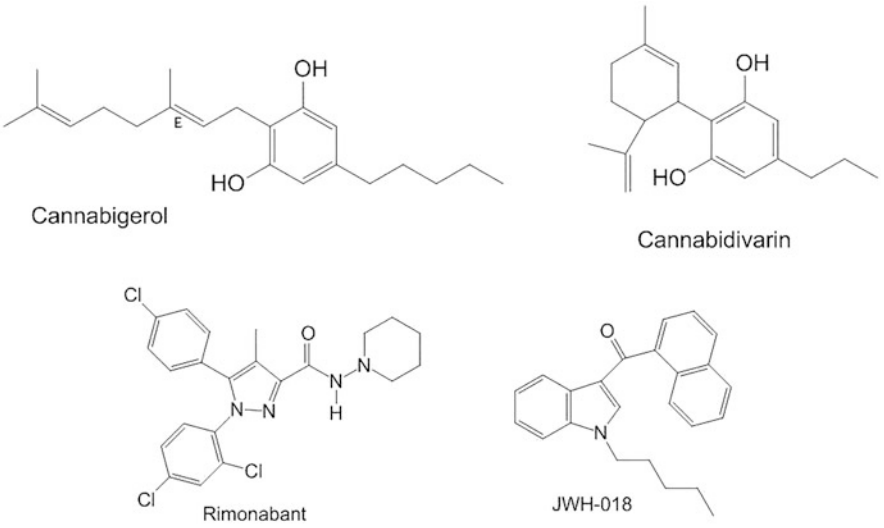

Fig. 8 Other natural and synthetic cannabinoids

4 Neuroprotective Effects of Cannabis

In 2600 BC, the Chinese emperor Huang Ti prescribed taking cannabis for the relief of cramps in rheumatic and menstrual pain. THC has been used to improve symptoms of neurodegeneration in multiple sclerosis (MS), adrenoleukodystrophy (ALD), Huntington disease (HD), amyotrophic lateral sclerosis (ALS), and Alzheimer's disease (AD). Furthermore, THC offers neuroprotection on neuronal and nonneuronal elements in the brain via modulation of excitatory and glutamatergic and synaptic transmission, immune modulation, and release of anti-inflammatory mediators (Maroon and Bost 2018).

4.1 Alzheimer's Disease

Alzheimer's disease (AD) is characterized by enhanced deposition of β-amyloid peptide A (βA) and glial activation in senile plaques, neuronal loss, and cognitive impairment. Cannabinoids have been found to be neuroprotective against excitotoxicity and brain damage. In AD patients, studies on senile plaques have demonstrated expressions of CB1 and CB2 receptors as well as markers of microglial activation. CB1-positive neurons were high in controls compared to areas of microglial activation. Furthermore, AD brains have decreased GP-receptor coupling and CB1 receptor expression. Cannabinoids HU-210, WIN55,212–2, and JWH-133 have blocked β-amyloid-induced activation of microglial cells, and

administration of WIN55,212–2 to rats have known to prevent βA-induced microglial activation and cognitive impairment (Ramirez et al. 2005).

4.2 Parkinson's Disease (PD)

PD is the second common neurodegenerative disorder characterized by the degeneration of "dopaminergic" neurons in substantia nigra. The center for disease control and prevention (CDC) has rated the complications from PD as the 14th leading cause of death in the United States. CBD acts via antioxidant properties independent of cannabinoid receptors and has been found to be neuroprotective in an experimental model of Parkinsonism and is effective in attenuating PD-related dystonic movements (Maroon and Bost 2018). CBD was found to upregulate the mRNA levels of Cu/Zn-superoxide dismutase, a key enzyme involved in the defense mechanism against oxidative stress, indicating its neuroprotection against the degeneration of nigrostriatal dopaminergic neurons in PD. Activation of CB2 and not CB1 has also been implicated in the contribution of cannabinoids in PD (Milano and Capasso 2018).

4.3 Amyotrophic Lateral Sclerosis (ALS)

ALS is a progressive neurodegenerative disease affecting the motor neurons in the brain and spinal cord, leading to their destruction. Areas of degeneration are usually characterized by the presence of cytokines, immune cells like T-cells, microglia, and astrocytes. Currently, no effective pharmacological treatments have been established for this debilitating disease; however, cannabinoids have been found to reduce the progression of ALS through interactions with CB1 and CB2 receptors, delaying the progression of the disease (Milano and Capasso 2018). In an animal model of ALS, endogenous cannabinoids were found to be elevated in the spinal cords of mice, and treatment with nonselective cannabinoids delayed disease progression and prolonged survival (Raman et al. 2009). Furthermore, CB2 receptors, which primarily exist in the periphery, are upregulated in the inflamed neural tissues in ALS models. The administration of selective CB2 agonist AM-1241 increased the survival interval by 56%, suggesting that CB2 agonists may slow mortar degeneration and preserve mortar function, and may represent a novel therapeutic target for the treatment of ALS (Shoemaker et al. 2007). A phase 2 trial in Italy called the CANALS, or Safety and efficacy of nabiximols on spasticity symptoms in patients with motor neuron disease, studied the safety, efficacy, and tolerability of Sativex in ALS patients demonstrated that Sativex was well tolerated with no serious side effects (Riva et al. 2019). An ongoing phase 3 study, Efficacy of Cannabinoids in ALS or Motor Neuron Disease, is currently evaluating the effects of CBD oil capsules on slowing disease progression in ALS (Urbi et al. 2019). Another large

observational study, OMNI-CAN (Outcomes Mandate National Integration With Cannabis as Medicine), which included people with several disease conditions, used an anonymous online questionnaire to determine the potential benefits and side effects of cannabis.

4.4 Huntington Disease (HD)

Despite its clinical utility in many neurodegenerative diseases, cannabis has not received a lot of attention from the HD scientific community. It is significant to note that, in cases like HD and MS, the clinical effects of CBD reported to date are observed only when combined with THC in a ratio of 1:1 (Sativex). In patients who were administered Sativex and THC in a ratio of 1:1, there was attenuated GABA deficiency, decreased loss of Nissl-stained neurons, downregulation of CB1 receptors, i*nsulin-like growth factor 1* (*IGF-1*) expression, and upregulation of calpain expression, and reversed superoxide dismutase expression (Sagredo et al. 2011). Preclinical and postmortem studies in HD patients suggested an inverse relationship between CB1 receptor decrease and CB2 receptor increase in glial elements, astrocytes, and reactive microglial cells (Milano and Capasso 2018). Another study confirmed that CB1 receptor reduction in basal ganglia is linked to increases in chances of Huntington-like symptoms and associated lower levels of brain-derived neurotrophic factor (BDNF) with a lack of CB1 receptors, thereby leading to the development of HD (Blázquez et al. 2011).

4.5 Multiple Sclerosis (MS)

MS is a chronic illness where the immune system attacks the myelin sheath causing demyelination of neurons, compromised oligodendrocytes, and aberrant neuronal firing leading to spasticity and neuropathic pain. The pathological changes in MS include inflammation, excitotoxicity, neurodegeneration including AD, and cerebral ischemia. The use of cannabis in the treatment of MS has a long history. It is reported that healers in Greece, Rome, China, and India have used cannabis to treat muscle cramps, spasms, and pain related to MS. In an experimental model consisting of encephalomyelitis rats, treatment with THC reduced neuroinflammation and improved neurological outcomes. A combination of Δ-8-tetrahydrocannabinol (a more stable analog of THC) and non-psychotropic Dexanabinol was found to reduce the neurological deficits, thereby suggesting a tonic control in muscle tone by the endocannabinoid signaling system. In another murine model of MS, treatment with cannabinoids reduced the progression of symptoms, leading to downregulation of delayed-type hypersensitivity, interferon production, and inhibited proinflammatory cytokine production. In experimental models of MS, activation of CB1 and CB2 receptors appears to be beneficial against inflammation, thus

Table 2 Effects of medical marijuana on select neurological diseases

Condition	Effects
Spasticity in MS	Oral *cannabis* extract (OCE) is effective. Nabiximol (Sativex) and THC were probably effective for objective measures and patient-related symptoms
Central pain and painful spasms in MS	OCE is effective THC or nabiximol may be effective
Urinary dysfunction in MS	Nabiximol is probably effective for reducing the bladder voids after 10 weeks THC and OCE are ineffective
Tremor in MS	THC and OCE are probably ineffective. Nabiximol is probably ineffective
Other neurological conditions	OCE is ineffective in treating levodopa-induced dyskinesia in Parkinson's disease

suggesting a reduction in frequency in relapses in patients with MS when smoking marijuana. In another multicenter study in the United States and United Kingdom, treatment with Marinol (synthetically produced dronabinol) or cannador (plant extract, consisting of THC and CBD in the ratio of 2:1), significant improvement was observed in spasticity, pain, sleep quality, and reduction in admissions for relapse (Milano and Capasso 2018).

In 2014, the American Academy of Neurology (AAN) published a systematic review of the effects of medical marijuana on select neurological diseases. Conclusions from the study are summarized in Table 2.

4.6 Post-Traumatic Stress Disorder

Treatment with CBD has been reported to reduce the symptoms such as chronic anxiety associated with p*ost-traumatic stress disorder* (PTSD). Also, treatment with cannabis resin containing CBD reduced the depression and anxiety in patients with PTSD. In rodent models reexposed to stressful situations, CBD treatment led to fear of memory extinction by causing a significant decrease in freezing time and attenuated fearful memories associated with past experiences. CBD has also demonstrated a decrease in the production of inflammatory cytokines, activation of glial cells, and brain leukocyte infiltration (Maroon and Bost 2018; Mecha et al. 2012). CBD has been involved in the modulation of receptors outside the endocannabinoid signaling system as well. Adenosine receptor activation by CBD leads to the enhancement of adenosine signaling activation and mediates anti-inflammatory and immunosuppressive effects. Furthermore, CBD is known to improve hippocampal neurogenesis. Animal studies have indicated that treatment with CBD improves AEA, which reduces short-term brain damage, improving the brain's metabolic activity and causing a reduction in the cerebral hemodynamic impairment brain edema and seizure. In addition to helping reducing seizures, CBD is also proven to

produce anti-epileptiform and anticonvulsant effects in vitro and in vivo models (Maroon and Bost 2018).

In conclusion, there exists a strong link between neurodegenerative diseases and cannabinoids. Furthermore, CB1 receptors play a significant role in the neuroprotective role of cannabis and thus appear to be a promising therapeutic target. Increased research on cannabis and cannabinoid signaling systems may lead to novel therapies to delay the progression and onset of these diseases and their symptoms.

5 Neurotoxic Effects of Cannabis

Evidence of cannabis associated neurotoxicity suggests long-term changes in the human brain such as (a) reduced orbitofrontal cortex gray matter volume (enriched in CB1 receptors, implicated in addictive behavior under the possible mechanism neuronal loss, changes in cell size, and reduction in CBI density), (b) increased structural and functional connectivity, and (c) changes in neural architecture impacted by the age of onset of disease and its duration. Several studies have demonstrated poorer cognitive performance upon early-onset chronic cannabis exposure (Filbey et al. 2014). A study by Rocchetti et al. also concluded a significant reduction in brain volume, and that the frequency of use significantly impacted hippocampus functioning (Rocchetti et al. 2013). At a neurophysiological level, the effect of cannabinoids in the hippocampus was envisaged by neurocognitive impairments. Prolonged use of cannabis (almost daily use) leads to the greatest risk of adverse health outcomes. Thus, chronic administration of cannabis has been determined to decrease hippocampal volume causing memory dysfunction (Rocchetti et al. 2013). Impaired coding, storage, manipulation, and retrieval mechanisms have been observed in long-term and/or heavy cannabis users (Solowij and Battisti 2008). In cultured neurons, THC induced shrinkage of neuronal cell bodies, nuclei, and genomic DNA strands, which includes hallmarks of apoptosis (Chan et al. 1998).

The effects of cannabinoids are characterized by several responses, including a reduction in memory, antinociception, hypothermia, catalepsy, and diminished motion. Lesions in the hippocampus reduce the acquisition and storage of new information or reduce the capacity to recover previous knowledge. Further cannabinoids within the intrahippocampal impair spatial memory, suggesting the primary role of cannabinoid receptors in meditating memory deficits with the gradual development in alteration of brain function. The activation of cannabinoid receptors induces the expression of early genes Krox24, Krox20, and Jun B increases NF-Kb (*nuclear factor* kappa-light-chain-enhancer of activated B cells) activity, which further activates the expression of tumor necrosis factor- α (TNF-α), which induces apoptosis. Furthermore, activation of these pathways with the release of arachidonic acid and ROS may be possible in neurotoxicity. Therefore, it can be concluded that THC mediates a transcription-mediated cell death on hippocampal neurons. Cannabinoids mediate cell death in certain populations of neurons in response to the release

of anandamide. Several processes during neurogenesis and neuroplasticity and dysregulation of the endocannabinoid system interact to cause neuroanatomical interactions. Chronic cannabis exposure leads to profound morphological changes in hippocamps. Three months of exposure decreases the volume of neurons, nuclei, synaptic density, and the dendritic length of CA3 pyramidal neurons. Cannabinoids and marijuana have been said to exert deleterious effects on the immune system (Chan et al. 1998). According to Baldwin et al. alveolar macrophages were unable to phagocytose *Staphylococcus aureus* and were unable to kill bacteria and tumor cells. Furthermore, these alveolar macrophages produced fewer amounts of TNF-α, granulocyte–macrophage colony-stimulating factor (*GM-CSF), and interleukin*-6 (*IL*-6) upon lipopolysaccharide stimulation (activator of macrophage) (Baldwin et al. 1997). Further THC reduced the TNF-α production when exposed to large granulocyte lymphocyte and cytolytic activity against K562 leukemia cells (Kusher et al. 1994). An anecdotal report by Juel-Jensen indicated that marijuana exposure altered resistance to infections in humans (Juel-Jensen 1972). Marijuana smokers with herpes simplex virus had an increased recurrence of lesions. Studies by Nadia Solowij determined the neuropsychiatric and psychobiological aspects of taking cannabis. Acute intoxication of cannabis exposure is said to lead to mild hallucinations, perpetual distortions, and delusions (Parrott et al. 2016). There has also been a considerable amount of evidence suggesting a causal relationship between usage of cannabis during adolescence and the development of depression, anxiety, and schizophrenia. Besides, the neurobiological effects of cannabis can lead to psychosis and/or may affect a preexisting condition to cause psychosis. Cannabis is known to exacerbate symptoms of schizophrenia by complex interactions between dopaminergic, serotonergic, and glutamatergic, GABAergic, cholinergic, opioid, and endogenous cannabinoid systems. Chronic cannabis exposure has been found to increase cannabinoids leading to schizophrenia-like neurotransmitter conditions in the prefrontal cortex with the desynchronized cortex, resulting in cognitive dysfunction (Parrott et al. 2016). Another study demonstrated that chronic cannabis exposure was associated with diminished neuronal integrity in the dorsolateral prefrontal cortex (Jacobus and Tapert 2014). In addition, THC, Δ-8-THC, tetrahydrocannabivarin, and cannabinol that are known to have different effects still have undefined roles.

Several studies have investigated the potential causes of neurotoxicity. According to Shamarka et al. the neurotoxicity of THC was a result of the prostanoid synthesis pathway and generation of free radicals by cyclooxygenase. EI-Shamarka et al. observed that coadministration of cannabis in adolescent rats potentiated the neurotoxic effects of nandrolone decanoate, a commonly used anabolic–androgenic steroid, by mediating oxidative stress and inflammation, intrinsic and extrinsic apoptosis in the hippocampus and prefrontal cortex of rats (El-Shamarka et al. 2020). Studies by Chan et al. suggested that THC-mediated apoptosis was attributed to the activation of phospholipase A_2—cyclooxygenase pathway (Chan et al. 1998).

While researchers do not fully understand the long-term risks and effects associated with cannabis use, research is currently ongoing. However, it can be said with confidence that long-term exposure to cannabis increases the risk of substance abuse,

thereby leading to memory and concentration deficits. Currently, the *National Institutes of Health (*NIH), USA, has enrolled more than 11,000 children between ages 9 and 10 for the ongoing "Adolescent Brain Cognitive Development" (ABCD) study. Researchers plan to utilize functional and structural neuroimaging tools to track them into late adulthood.

6 Current Treatments and Future of Cannabis Pharmacology

The use of medical cannabis in the legal system faces a few challenges. Effective delivery systems are quintessential and are being developed. Since the cannabinoids are volatile and vaporize at a low temperature, when the heated air is drawn through marijuana, the active compounds can be vaporized into a mist, which is then dosed and inhaled without the generation of smoke. Patient individuality, including the severity of the condition, lung capacity, inhalation and exhalation habits, GI absorption, greatly varies. Other concerns with the use of medical cannabis include the constant need for monitoring and prevention of addiction. The future is likely to see extensive research that digs into the therapeutic effects of cannabinoid receptor agonists and determine its side effects. Despite good therapeutic efficacy, the production of potent medications can be hindered by the fact that these natural compounds in cannabis work at its best only when all the natural cannabinoids are allowed to work concurrently. This "orchestration" of effects can be seen best in the combination of THC and CBD, which is known to produce anxiolytic effects (Bridgeman and Abazia 2017). Refinement of cannabinoids is expected to facilitate cleaner and highly efficacious drugs; however, this may also lead to dire consequences. For example, in patients with ALS, dronabinol has been found to be too sedating and less effective compared to natural cannabis (Group AL 2012). The legalization of cannabis for medicinal use of cannabis warrants a lot of research into the pharmacokinetics and pharmacodynamics of cannabis. Oral THCs nabiximol and nabilone have been shown to improve cannabis withdrawal symptoms. The effectiveness of nabilone in preventing relapse has yet to be tested in a clinical setting. In contrast, nabiximol, although, has been approved by 15 countries, requires further studies to determine its longitudinal effects (Copeland and Pokorski 2016). Despite the therapeutic effects of THC and CBD, a lack of well-controlled, double-blind, randomized, clinical trial fails to establish its long-term and short-term efficacy. In addition, safety issues impede their use in the clinic. THC and CBD can have undesirable effects on the CNS, and dose optimization may not be an option before the onset of side effects. However, CBD receptor agonists that modulate the endocannabinoid system are promising agents in the treatment of unmanageable disorders. Further research is required to completely understand the endocannabinoid system in antinociception/pain and antispasticity. Improved methodologies, a larger study population, standard formulations are required to establish

the use of medical cannabis. Although medical cannabis has been approved for muscle spasms and pain, especially when standard therapy failed, the adverse events involving CNS and gastrointestinal (GI) system may preclude its usage. Extreme caution is advised in patients with a history of cardiovascular or mental disorders.

Cannabis can be regarded as neither a miracle drug nor be regarded as being responsible for people's illness. Several aspects must be considered in the risk to benefit ratio. The United States has spent a tremendous amount of money on curbing the illicit use of cannabis with limited success. Regarding medical use, laws must consider scientific research and logic during policy-making decisions rather than political views that debate over the harmful effects of the illicit use of recreational marijuana. Clinicians and students must be encouraged to improve their knowledge base and educate themselves in the science of cannabis pharmacology and medicine. Although nabilone and dronabinol are well-regulated drugs that have demonstrated safety and efficacy, there is a dearth of evidence of medical use of cannabis, which requires the drugs to be used with the greatest caution.

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