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Review Article

Neuropharmacology of endogenous, synthetic and phytocannabinoids for pain management

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ABSTRACT

The use of cannabis-derived compounds for medical purposes dates from more than two thousand years. Due to its psychotropic effects and cultural aspects related to the plant of origin, its benefits have been disregarded in several western countries. Nevertheless, the number of studies on Cannabis sativa, especially on clinical applications of cannabinoids, increased significantly in the latest years. Amidst the benefits of cannabis-derived compounds is pain relief. Here we review physiological, pharmacological and chemical aspects of pain management in humans with endocannabinoids, synthetic cannabinoids and phytocannabinoids. The analgesia mechanism can be explained not only through interactions with cannabinoid receptors 1 and 2 but also through direct or indirect interaction with serotonin, glycine, gamma-aminobutyric acid, N-methyl-D-aspartate, adrenergic and opioid receptors, as well as transient receptors potential channels. They can also modify the behavior of molecules such as cytokines, calcitonin gene-related protein and substance P, which largely influence pain-related mechanisms. Exogenous cannabinoids are interesting options to consider when it comes to pain management, especially in complex cases associated to poor response to the currently available drug therapy.

Keywords:
Neuropharmacology
Cannabinoids
Phytocannabinoids
Endocannabinoids
Pain

Introduction

The therapeutic use of parts and extracts of *Cannabis sativa* dates back to 1000 years before Christ, and the first report on its cultivation dates back to 3000 years before Christ, in China (Zuardi, 2006). Different potential uses of this plant in humans have been described, such as management of pain, epilepsy and autism (Baron, 2015). Most of the current investigations on the therapeutic uses of the plant are centered in behavioral and cognitive issues, due to its modulation of neurotransmission (Andre et al., 2016). Despite all legal and social repression due to drug trade, popular and scientific interests on the plant have increased in the latest years. Up to the moment of preparation of this paper, the terms "*Cannabis sativa*" retrieved a total of 3,925 articles in PubMed, with a visible growth since the year of 1990.

At present, over 90 molecules from *C. sativa* have been described as phytocannabinoids. Two of them are

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of special pharmaceutical interest: tetrahydrocannabinol (THC), which has anti-inflammatory, anti-cancer, analgesic, muscle relaxant and anti-spasmodic properties (Andre et al., 2016); and cannabidiol (CBD), which has anxiolytic, anti-nausea, anti-psychotic, anti-inflammatory, immunomodulatory and neuroprotective properties, and modulates the psychoactive effects of THC (Netzahualcoyotzi-Piedra et al., 2009; Carranza, 2012; Andre et al., 2016). Both are structurally and functionally related to endocannabinoids, which are naturally produced by neurons and some cells of the immune system (Bonini et al., 2018). Amidst the varied possibilities of medical use of exogenous cannabinoids (i.e., phytocannabinoids and synthetic cannabinoids), their analgesic potential is of special interest for pain management (Zuardi, 2006; Bonini et al., 2018). Humans and other mammals produce endocannabinoids, which are structurally related to synthetic and phytocannabinoids. These molecules are also relevant for pain and sleep management, and have been investigated for their role in memory, learning and behavioral issues (Grimaldi and Capasso, 2011; Lessa et al., 2016).

The main pharmacological options currently available for pain management include non-steroidal anti-inflammatory drugs, glucocorticoids, opioids, anesthetics, analgesics, antispasmodics and some psychotropic drugs (Barbosa et al., 2021; Silva and Dias-Souza, 2021). The treatment can systemic and topical when necessary. Nevertheless, pain management remains a complex endeavor: genetic variations on drug responses, side effects of the drugs and the complexity of pain mechanisms help to explain the therapeutic failures and slow onset of action often so commonly reported by patients with pain, mainly in cases of chronic pain (Queremel Milani and Davis, 2021). Around 56% of the population experiences different types of pain on a regular basis (GSK 2017), thus, new options for pain management are extremely necessary.

Here we review the neuropharmacology and neurophysiology aspects of pain management by exogenous cannabinoids. We also discuss recent advances on the understanding of how cannabinoids can be used to treat pain in a molecular level.

Neurophysiology of pain: an overview

Pain is a subjective, complex and unpleasant sensory and emotional experience influenced by personal, social and cultural aspects (DeSantana et al., 2020). It is associated to real or potential chemical, mechanical or thermal injuries, and include sensory-discriminative (perception-related), affective-emotional, and cognitive-behavioral dimensions (Raja et al., 2020). Pain can be disabling depending on its intensity and frequency, often precluding patients from performing simple daily tasks. It can have psychological consequences such as anxiety and depression (Baliki and Apkarian, 2015). Susceptibility to pain, as well as its threshold and tolerance, are influenced by sex and can change over time due to changes in lifestyle (Silva and Dias-Souza, 2021). Its manifestations are considered acute when their duration is inferior to three months, and chronic if superior to three months (Anwar, 2016; WHO 2019).

So far, pain was considered a symptom of several diseases. However, the latest version of the international classification of diseases (ICD-11) updated this concept in 2019. Since then, both chronic and acute pain are acknowledged as diseases, and their main mechanisms (Anwar, 2016; Raja et al., 2020) are classified as: Nociceptive: results from the activation of nociceptors due to mechanical, thermal or chemical lesions; Neuropathic: results from nerve damage due to trauma close to or at the site of perception; Nociplastic: when not directly related to real lesions, but rather due to alterations on nociception.

Most of the currently available drug therapy for pain management usually works by interfering in the neuroimmune crosstalk of inflammatory processes underlying these mechanisms. This topic, however, is not on the scope of this review. The reader is referred to recent papers (Barbosa et al., 2021; Silva and Dias-Souza, 2021) to explore more information on this topic. Nociception is often wrongly considered a synonym of pain. Nociception is a process that involves the transmission of a noxious stimuli from an injury to the brain after the activation of free nervous terminations known as nociceptors. In contrast, pain is a subjective unpleasant feeling, which may result (or not) from nociception (Steeds, 2009).

Given that pain is an experience with potential psychological consequences, psychogenic pain can not be disregarded. It is not related to physical damages, but results from neuropsychological disorders such as depression, anxiety and personality disorders (Danilov et al., 2018). Thus, it is not surprising that psychotropic

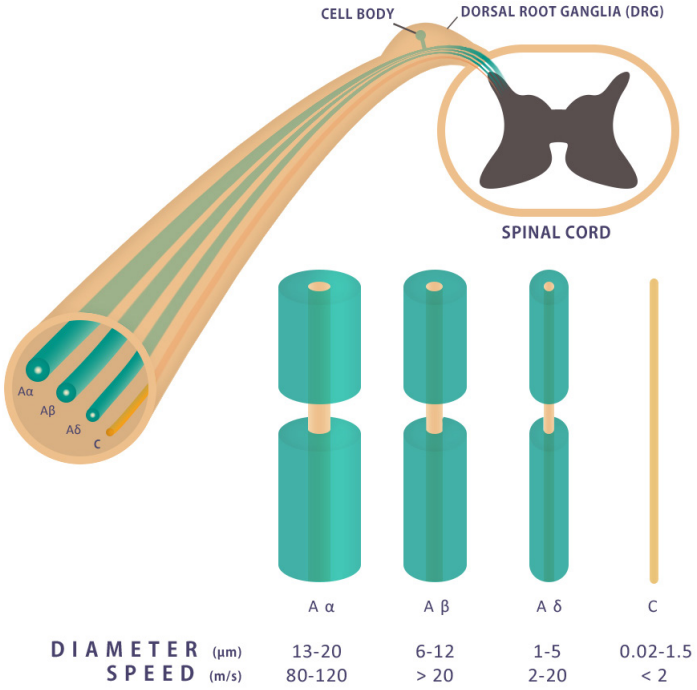

FIGURE 1. Myelination, transmission speed and diameter of primary nerve fibers. Created by the authors based on information from (Bourne et al., 2014; Lee and Neumeister, 2020; Sneddon, 2018).

drugs are used to treat pain (Dunne et al., 2018; Silva and Dias-Souza, 2021). Psychogenic pain can affect both children and adults, and although its exact mechanisms are not fully known, they are clearly not related to nociceptive, neuropathic or nociplastic mechanisms (Russu and Russu, 2008; Danilov et al., 2018; Dunne et al., 2018).

It is important to mention that, regardless of the mechanism, pain can deeply interfere on sleep quality and memory. Different studies provided evidence that pain, sleep and memory share neural circuitry and brain regions where the information is processed (Mansour et al., 2014; McCarberg and Peppin, 2019; Haack et al., 2020). Pain impairs memory retrieval (especially short-term working memory) and impairs sleep, which in turn, decreases the threshold of pain perception and tolerance (Haack et al., 2020).

There are four types of nerve fibers involved in the transmission of nerve impulses: Aα, Aβ, Aδ and C (Figure 1). Those with higher myelin content provide faster inputs and outputs transmission (Sneddon, 2018). The Aδ fibers make a faster and more precise transmission of stimuli and are related to "first (or quick) pain", which is referred as a localized sharp pain. Notwithstanding, transmission by type C fibers is slower and associated to a diffuse perception of pain, often described as an aching/burning sensation (Lee and Neumeister, 2020). The neural circuitry of pain comprises afferent and efferent pathways involving the spinothalamic tract (Figure 2). This pathway is divided into neospinothalamic and paleo-spinothalamic tracts. The neospinothalamic tract is associated to the cognitive aspects of pain, including conscious response to acute pain, definition of its localization, intensity and duration (Almeida et al., 2004; Marchand, 2008; Lee and Neumeister, 2020). The paleo-spinothalamic tract is associated to affective and emotional aspects of pain, as the noxious stimuli reach the limbic system and different areas at the cortex, where they are integrated and expected to be controlled (Almeida et al., 2004).

Afferent signaling pathway conducts peripheral stimuli to the cortex, where it can be interpreted as pain. Mechanical, chemical, and/or thermal stimuli received at nociceptors (free nerve endings of a first order neuron) and are converted into electric impulses, which are then conducted throughout the dorsal root ganglion to the dorsal horn of the spinal cord (Bell, 2018). The Aδ fibers synapse to second order neurons on Rexed's lamina I (posteromarginal nucleus, involved in processing rapid acute pain-related stimuli) and V (also related to

TABLE 1: Important brain regions and the way they are related to pain

Acute pain	Chronic pain
Insula	*Periaqueductal gray matter*
Pain perception, connects the limbic system to somatic sensory areas of the cortex, and rates the intensity of pain. It also associates tastes, smells and sounds to emotions and feelings.	Efferent pain control with dopaminergic and opioidergic neurotransmission.
Thalamus	*Locus coeruleus*
Attention and consciousness, connects the cortex with motor neurons.	Regulates wakefulness and pain perception with noradrenergic neurotransmission.
Base nuclei	*Amygdala*
Connects the cortex to the limbic system, and integrates emotions to focused attention processing.	Negative memories and emotions, pain anticipation, and reactions to threats in general.
Cingulum gyrus	*Prefrontal gyrus*
Integrates emotional, attentional and visceral information, projects conflicting information concerning affection/motivation to decision making.	Active in anxiety, processes information regarding negative consequences of pain.

Adapted from (Marchand, 2008; Lee and Neumeister, 2020)

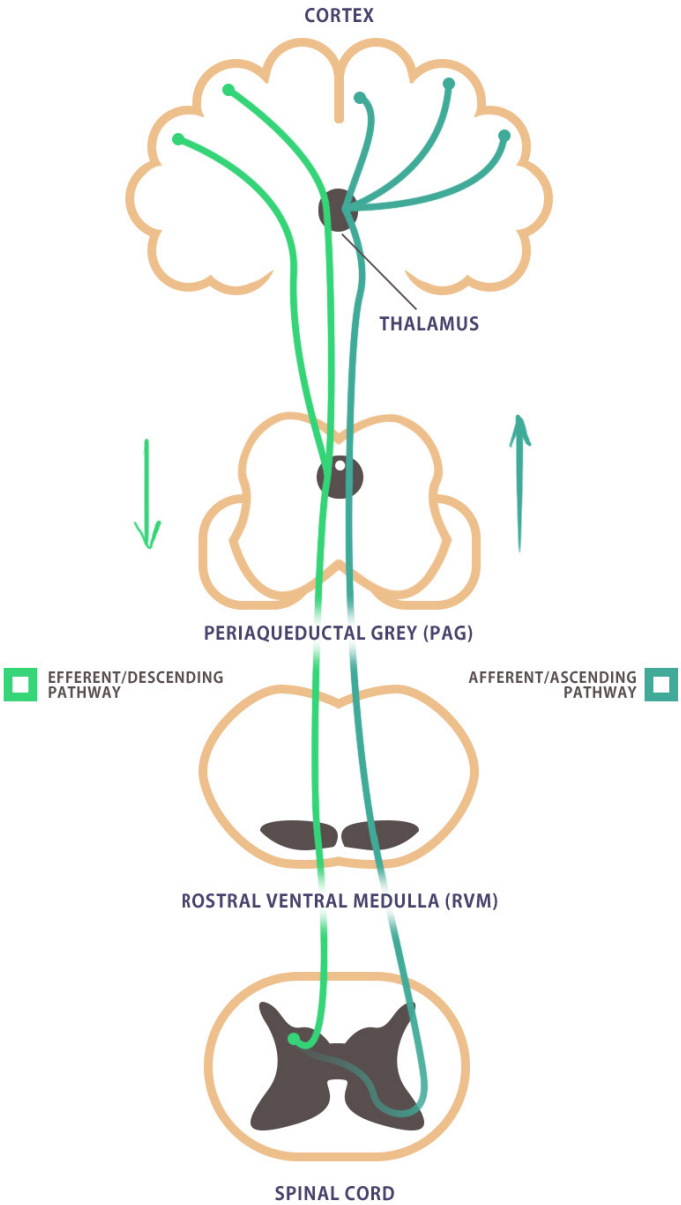

FIGURE 2. Afferent/ascending (dark green, displayed on the right side) and efferent/descending (light green, displayed on the left side) pain pathways. Created by the authors based on information from (Bourne et al., 2014; Sneddon, 2018; Khan et al., 2019; Lee and Neumeister, 2020).

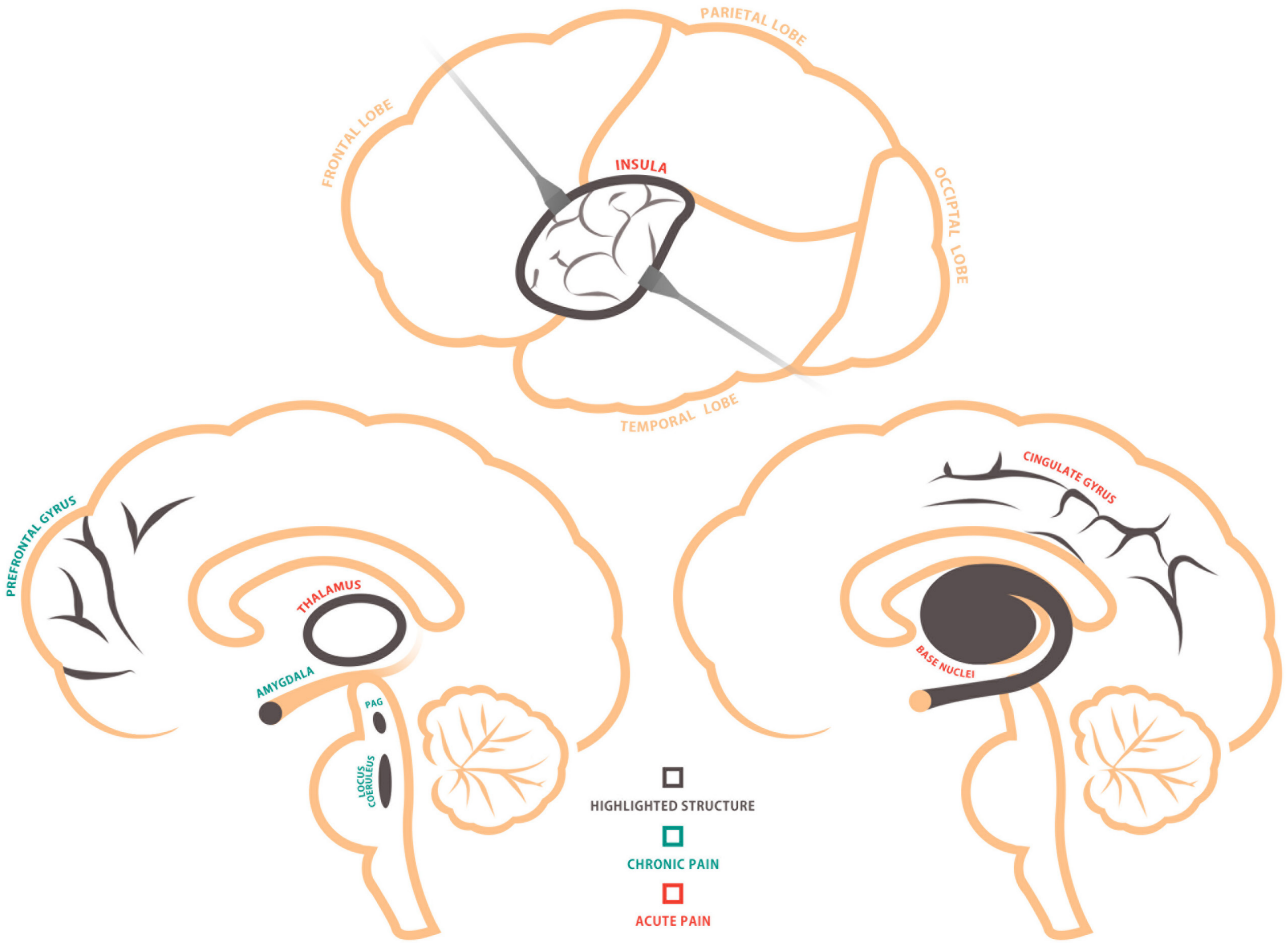

FIGURE 3. Central nervous system (CNS) affected areas during chronic and acute pain.

processing rapid noxious stimuli); following, type C fibers synapse to second order neurons on lamina I and II (substantia gelatinosa, involved in processing slow chronic pain-related stimuli) (Marchand, 2008; Bell, 2018; Lee and Neumeister, 2020). Finally, the stimuli reach the brain, where they are processed and integrated to other sensorial information. Some of the main areas activated by - and involved in processing pain-related stimuli are summarized in Table 1 and Figure 3.

Pro-nociceptive biochemical messengers such as potassium, bradykinin, prostaglandins, histamine, serotonin, adenosine triphosphate, cytokines and transcription factors are very relevant to pain mechanisms (Bell, 2018; Dinakar and Stillman, 2016). Their levels and intensity of signaling fluctuate due to neuroimmune interactions generated in response to noxious stimuli such as lesions, inflammatory processes, and even depression (Dinakar and Stillman, 2016). Such messengers are also involved with hyperalgesia and allodynia. Hyperalgesia is the decrease in the activation threshold of nociceptors by pro-nociceptive molecules, resulting in increased pain intensity following a noxious stimulus; allodynia refers to the individual's ability to feel pain from non-noxious stimuli, due to a critical decrease in activation and tolerance thresholds (Sandkuhler, 2009).

Biomolecules involved in increasing pain perception include glutamate, substance P and calcitonin gene related protein (Sluka and Clauw, 2016). The posterior medullary horns are rich in NMDA receptors, which are part of the pathway used by sensory nerve fibers. The agonism of NMDA receptors by glutamate results in removal of Mg^{2+} from within the receptor, leading to increased calcium influx and increased and prolonged intensity of the noxious stimuli (Fantegrossi et al., 2018; Ji et al., 2019; Jewett and Thapa, 2022). Conversely, gamma aminobutyric acid (GABA), serotonin (5-HT) and norepinephrine can decrease pain perception (Marchand, 2008; Zhou et al., 2010), although extra

TABLE 2: Distribution of cannabinoid receptors throughout the human body

Organ/System	Cannabinoid Receptor
Brain	CB1
Gastrointestinal Tract (GIT)	CB1
Genitals	CB1
Heart	CB1
Liver	CB1
Lungs	CB1
Muscles	CB1
Vascular System	CB1
Bone Marrow	CB1, CB2
Immune System	CB1, CB2
Pancreas	CB1, CB2
Spinal Cord	CB1, CB2
Integumentary System	CB2
Spleen	CB2

Adapted from (Howlett and Abood, 2017; Tudurí et al., 2017; Bonini et al., 2018; Amin and Ali, 2019; Argenziano et al., 2019; dos Santos et al., 2019; Gregus and Buczynski, 2020; Mecha et al., 2020; Salami et al., 2020).

neuronal 5-HT may have a pro-nociceptive effect as it excites nociceptors (Dinakar and Stillman, 2016; Hill et al., 2017). Nociception may be modulated by the glia cells at the spinal cord, such as astrocytes, in an efferent pain control pathway (Ji et al., 2019).

The efferent pain control pathway consists of modulatory mechanisms that are activated to avoid or suppress pain-related stimuli that involves areas at the CNS such as periaqueductal gray matter (PAG), locus coeruleus, the spinal cord and limbic system. The process is mediated mostly by serotoninergic and noradrenergic neurotransmission along the dorsal horn of the spinal cord, following the information received from the limbic system, resulting in inhibition of pain perception (Chen and Heinricher, 2019; Lee and Neumeister, 2020). The opioidergic neurotransmission also mediates pain perception: opioid receptors (μ, δ, κ) are spread throughout the CNS, being more concentrated at PAG, locus coeruleus and substantia gelatinosa (Rexed's lamina II) (Pathan and Williams, 2012; Ferdousi and Finn, 2018). Endogenous opioids (enkephalins, endorphins and dynorphins) inhibit noxious stimuli with indirect effects on efferent pathways (Pathan and Williams, 2012; Bagley and Ingram, 2020).

General aspects of cannabinoid receptors

Up to the moment of preparation of this manuscript, only two endocannabinoid receptors have been officially described: cannabinoid receptor 1 (CB1) and CB2, both being G protein-coupled receptors (GPCRs) (Amin and Ali, 2019; Joshi and Onaivi, 2019; Lessa et al., 2016). The GPR55, which is also a GPCR for cannabinoid molecules, is often named as CB3, but this is still in discussion (Ryberg et al., 2007; Lauckner et al., 2008; Yang et al., 2016; Shi et al., 2017; Tudurí et al., 2017). It is important to mention that phytocannabinoids and most of the known synthetic cannabinoids have low affinity to CB1, CB2 and CB3 (Yang et al., 2016; Amin and Ali, 2019; Joshi and Onaivi, 2019). Thus, only endocannabinoids are expected to effectively modulate pain by interacting with CB1, CB2 or CB3.

CB1 receptor is found mainly on neurons in the basal ganglia, cerebellum, hippocampus, cortex and, to a lesser extent, spinal cord and peripheral nerves, what helps to explain the psychotropic and motor effects of endocannabinoids (Lessa et al., 2016; Howlett and Abood, 2017). The CB1 is also expressed to a lesser extent in macrophages, mast cells, keratinocytes, adrenal glands, heart, lungs, prostate, liver, uterus, ovaries, testis, bone marrow, thymus, tonsils and in an even smaller extent in astrocytes (Hill et al., 2017; Howlett and Abood, 2017; Lessa et al., 2016). The CB1 agonism results in retrograde inhibition of neurotransmitters release, control of neuronal excitability and regulation of synaptic plastici-

FIGURE 4. Structure of *N*-arachidonoylethanolamine (Anandamide).

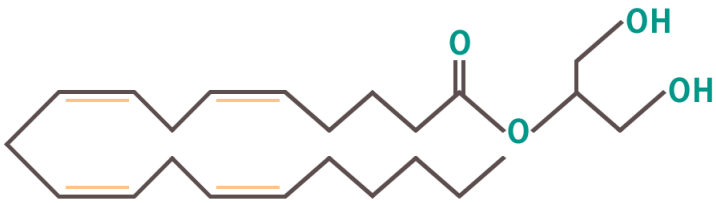

FIGURE 5. Structure of 2-Aquidonyl glycerol (2-AG).

ty (Lessa et al., 2016; Howlett and Abood, 2017). These are possible explanations for the effectiveness of cannabinoids in epilepsy treatment, especially for patients that are refractory to conventional treatments, although the exact mechanism is not fully understood (Lessa et al., 2016; Howlett and Abood, 2017; Rapino et al., 2018; Amin and Ali, 2019; Mecha et al., 2020; Singh and Neary, 2020). The agonism of CB1 receptors is also associated to increased food intake, reduced intestinal motility and increased lipogenesis (Tudurí et al., 2017). It was described that acetaminophen-mediated antinociception was lost in CB1 receptor and fatty acid amide hydrolase (FAAH) knock-out mice (Klinger-Gratz et al., 2018).

The CB2 receptor is found at the peripheral nervous system (mostly spinal cord and dorsal root ganglion), in the brain - to a lesser extent than CB1 (Hill et al., 2017; Howlett and Abood, 2017; Joshi and Onaivi, 2019), B lymphocytes, NK cells, monocytes, neutrophils and CD4/CD8 lymphocytes (Argenziano et al., 2019; Rossi et al., 2020). The CB2 is an important modulator of neuroimmune interactions in hyperalgesia and analgesia, inducing apoptosis, expression of regulatory T cells, suppressing cell proliferation and production of pro-inflammatory cytokines (Rossi et al., 2020). The CB2 expression is increased under pathological conditions and/or nerve injury and inflammation (Hill et al., 2017; Howlett and Abood, 2017; Joshi and Onaivi, 2019), and CB2-mediated analgesia only seems to be relevant if combined to other therapeutic options such as CB1 agonists or reduced opioid doses (Morales et al., 2016). The CB receptor agonists, mostly at PAG zone, may suppress nociception especially through a CB1 opioid-independent stress-induced pathway (Hohmann et al., 2005). In addition, activation of CB1 and CB2 in the spinal cord has been shown to suppress allodynia induced by vincristine, a widely used antitumoral drug (Russo, 2008).

Synthesis, metabolism and activity of endocannabinoids

Most of the known endocannabinoids are derived from long-chain polyunsaturated fatty acids such as arachidonic acid. *N*-arachidonyl ethanolamine (anadamide) and 2-aquidonyl glycerol (2-AG) are the two main endocannabinoids found in humans and other mammals. They are synthesized on demand and are related to neurological events such as relaxation, eating, sleeping, memory impairment, emotional displays, cognition, motor skills, proprioception and pain regulation (Fraguas-Sanchez and Torres-Suarez, 2018; Mücke et al., 2018). Both molecules are agonists of CB1 and CB2 receptors (CBR1 and CBR2) (Grimaldi and Capasso, 2011; Lessa et al., 2016). Anandamide (Figure 4) was the first endocannabinoid described. It is an effective CB1 agonist, but is less effective as a CB2 agonist (Di Marzo and Piscitelli, 2015; Lessa et al., 2016). It is synthesized by *N*-acyl-phosphatidylethanolamide selective

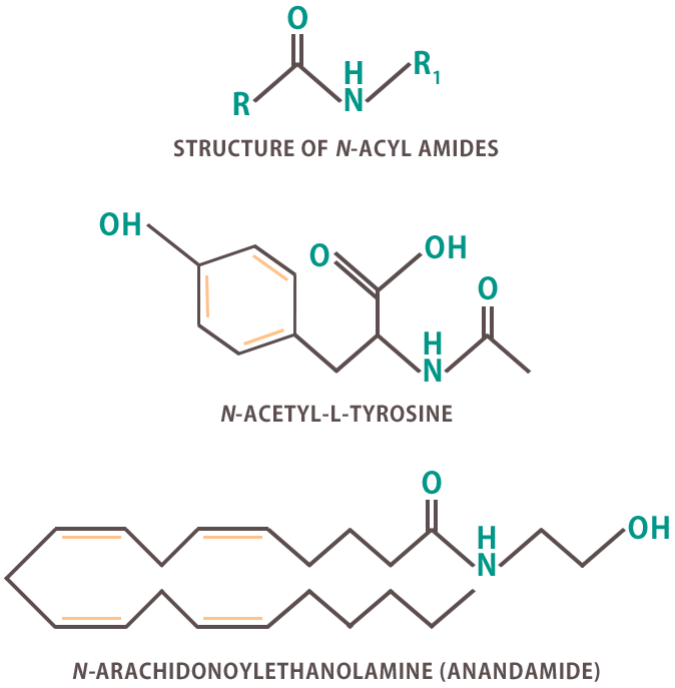

FIGURE 6. Structural formulas of N-acyl amides, N-Acetyl-L-Tyrosine and N-arachidonoylethalonamine (anandamide)

phospholipase D from *N*-arachidonoyl-phosphatidylethanolamines produced from phospholipid modulation by *N*-acyl-transferases, and can behave as autocrine or paracrine messenger (Lu and Mackie, 2016; Hill et al., 2017; Guerrero-Alba et al., 2019; Shahbazi et al., 2020).

The 2-AG (Figure 5) is a highly effective CB1 and CB2 agonist synthesized mostly by *sn*-1-diacylglycerol lipase from sn-2-araquidonate-containing diacylglycerols (Di Marzo and Piscitelli, 2015). It can also be produced from *sn*-1-lyso-phospholipids through sequential action of phospholipase A_1, lysophospholipase C, or dephosphorylation of lysophosphatidic acid (Lessa et al., 2016; Lu and Mackie, 2016).

As exposed, anandamide and 2-AG are produced on phospholipid-dependent pathways and are not stored in synaptic vesicles and released like neurotransmitters. After being released, they are rapidly metabolized into inactive compounds by FAAH, a postsynaptic enzyme that regulates anandamide levels near the sites of synthesis, and by monoacyl glycerol lipase, a presynaptic enzyme that controls 2-AG levels after its action (Lessa et al., 2016; Guerrero-Alba et al., 2019). Anandamide and 2-AG may also be metabolized by cyclooxygenase (COX) II and cytochrome P450 enzymes (Martínez et al., 2020). Anandamide and 2-AG can be transported into pre- or post-synaptic neurons by the endocannabinoid membrane transporter: as the molecules reach the cells, 2-AG is hydrolyzed, and anandamide binds to PPARγ or is hydrolyzed (Martínez et al., 2020). Anandamide and 2-AG are produced in the CNS and injured tissues in specific cases such as pain modulation, and that they have been reported to reduce hyperalgesia, allodynia, peripheral pain and inflammatory processes (Lessa et al., 2016; Hill et al., 2017). Increased levels of endocannabinoids are associated to pathological conditions that include Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, colitis, anorexia, binge eating disorders, obesity, malignant neoplasia such as glioblastoma, meningioma, and colon, prostate, and pituitary adenomas (Grimaldi and Capasso, 2011; Ramer et al., 2019; Navarrete et al., 2020).

Transient receptors potential channels (TRPs)

TRPs are a superfamily of transmembrane ionotropic receptors found in the membrane of neurons, which regulate the influx of different ions. They are involved in physiological processes such as nociception, scratching, perception of cold/heat, and also in cancer and genetic disorders (Muller et al., 2019; Tsagareli and Nozadze, 2020). Currently there are 28 known channels divided into six subfamilies: canonical (TRPC), vanilloid (TRPV), polycyline (TRPP), mucolipine (TRPML),

ankyline (TRPA) and melastatin (TRPM) receptors (Muller et al., 2019; Tsagareli and Nozadze, 2020). Here we will discuss the physiological roles of vanilloid TRPV1-4, ankyline TRPA1 and melastin TRPM8 receptors, as they are related to pain control when interacting with cannabinoids.

TRPV1 is found at the cerebellum, basal ganglia, hippocampus, diencephalon, dorsal root ganglion (DRG) neurons, trigeminal ganglion, skin, pancreas, spinal and peripheral nerve endings (Nilius and Owsianik, 2011; Csekő et al., 2019). Cannabinoids that bind to TRPV1 include 2-AG, anandamide, *N*-aquidonyl dopamine, *N*-oleoyl dopamine, palmitoylethanolamide, tetrahydrocannabivarin, cannabidivarin and CBD (Nilius and Owsianik, 2011; Amin and Ali, 2019; Csekő et al., 2019; Muller et al., 2019; Di Marzo, 2020). TRPV1 is involved in pain perception, thermoregulation and neuroplasticity (Benítez-Angeles et al., 2020).

TRPV2 is found at the DRG, CNS, trigeminal ganglion, gastrointestinal tract, spleen, mast cells, as well as in cardiac, striated and smooth muscle cells (Nilius and Owsianik, 2011; Shibasaki, 2016). It is related to inflammatory process and chronic pain, temperature, axon growth in spinal motor neurons and phagocytosis in macrophages (Huang et al., 2018; Lévêque et al., 2018). The TRPV2 is mainly activated by THC, its analogues (with the exception of 11-OH-THC) and CBD (Muller et al., 2019). Synthetic and endocannabinoids, however, trigger discrete or no response of it (Amin and Ali, 2019; Muller et al., 2019; Nilius and Owsianik, 2011).

The TRPV3 is found at the DRG, trigeminal ganglion, neurons, brain, keratinocytes, tongue, and testicles (Singh et al., 2018). It is involved in thermal sensation, nociception, skin integrity, wound healing, hair growth and sebaceous gland function (Nilius et al., 2014; Singh et al., 2018). Tetrahydrocannabivarin, tetrahydrocannabivarin, cannabigerovarin, cannabinogerolic acid and CBD bind to TRPV3 (Muller et al., 2019). The *N*-acyl amides (Figure 6), a family of endogenous lipids structurally related to anandamide, present different molecules that may bind to TRPs (Raboune et al., 2014).

The TRPV4 is found at CNS large neurons, trigeminal ganglion, heart, liver, kidneys, keratinocytes, osteoblasts, endothelium, bladder and testicles (Nilius and Owsianik, 2011; Plant and Strotmann, 2007). The TRPV4 is related to the regulation of osmotic pressure in the brain, perception of heat/cold, pain and nociception, modulation of cell migration, endothelial vasomotor control, control of skin adherens junctions, osteogenesis and osteoclast function (Nilius and Owsianik, 2011; Muller et al., 2019). Cannabinoids that bind to TRPV4 include *N*-aquidonyl dopamine, *N*-oleoyl dopamine, THC, tetrahydrocannabivarin, cannabidivarin, cannabigerolic acid, cannabigerovarin, cannabinol, anandamide and 2-AG metabolites produced by cytochrome P450 (Nilius and Owsianik, 2011; De Petrocellis et al., 2012; Muller et al., 2019).

The TRPA1 is found at hair follicles, DRG, trigeminal ganglion and fibroblasts, being extensively co-localized with TRPV1 in sensory neurons (Nilius and Owsianik, 2011). The TRPA1 is involved with processes of cold/heat and pain perception, olfaction, cold-induced contraction of colon and bladder, and its activation alongside TRPV1 results in analgesia (Araujo et al., 2020). Exogenous cannabinoids that bind to this receptor include anandamide, CBD, cannabidiolic acid, THC, cannabichromene, cannabigerol, cannabidivarin and tetrahydrocannabinolic acid (Amin and Ali, 2019; Di Marzo, 2020; Muller et al., 2019; Nilius and Owsianik, 2011).

The TRPM8 is found in DRG, trigeminal ganglion, upper viscera nerves, vascular smooth muscle, liver, prostate, breast, colon, lung and skin tumors (Iftinca and Altier, 2020). This receptor is involved in cold/heat perception, sperm motility and acrosome reaction (Muller et al., 2019). Unlike other TRP receptors, cannabinoids are antagonists of TRPM8 receptors, being *N*-Arachidonoyl dopamine, anandamide, THC, tetrahydrocannabivarin, CBD, cannabidiolic acid, cannabidivarin, cannabinogerol, cannabinogerolic acid, cannabinogerovarin and cannabinol are some of the main antagonists (Muller et al., 2019; Nilius and Owsianik, 2011).

G protein-coupled receptors (GPCRs) 18 and 55

Data concerning GPR18 is still controversial, despite its first description a long time ago (Neumann et al., 2020). It is expressed at testis, spleen, peripheral blood leukocytes and lymph nodes, suggesting its potential immunomodulatory effect (Neumann et al., 2020). The *N*-araquidonylglycine, an anandamide derivative, was proposed as one of the endocannabinoids agonists of this receptor, resulting in apoptosis of leukocytes during inflammation (Guerrero-Alba et al., 2019; Neumann et al., 2020). Phytocannabinoids can be ligands of GPR18 as well, which include THC (agonist) and CBD (antago-

nist) (Morales et al., 2017; Senn et al., 2020).

GPR55 is expressed at the hypothalamus, nucleus accumbens, caudate nucleus, corpus striatum, cerebellum, thalamus, hippocampus, frontal cortex, stomach, intestine, pancreatic alpha and beta cells, as well as in adipose tissue (Tudurí et al., 2017). Lysophosphatidylinositol is generally accepted as the endogenous ligand for this receptor, but after the discovery of the GPR55 (CB3) agonism by cannabinoids (Ryberg et al., 2007; Lauckner et al., 2008; Yang et al., 2016; Shi et al., 2017; Tudurí et al., 2017). Anandamide, 2-AG, THC, CBD, JWH-015, rimonabant and AM251 are some of the GPR55 agonists, but the resulting effects remain poorly understood (Amin and Ali, 2019; Neumann et al., 2020; Saliba et al., 2018; Tudurí et al., 2017; Wróbel et al., 2020). CBD is a reverse agonist of GPR3, GPR6 and GPR12, and it has been suggested that this mechanism is effective to treat Alzheimer's, Parkinson's, cancer and infertility cases (Atalay et al., 2020).

Opioid receptors

Opioid receptors are part of the GPCR superfamily, being expressed mainly in the CNS and to a lesser extent in knee joints, gastrointestinal tract, heart and immune system cells (Pathan and Williams, 2012). They are classic effective targets in the control of acute pain, in spite of the significant side effects caused by opioid drugs such as sedation, nausea/emesis and respiratory depression (Guerrero-Alba et al., 2019). In addition, cannabinoid and opioid receptors are co-expressed at important sites in the CNS involved in pain modulation, especially in PAG, an area that receives noxious stimuli from the spinal cord and modulates pain signaling (Datta et al., 2020).

THC and CBD have been shown to be positive allosteric modulators of μ-opioid receptors, and CBD has also been shown to be able to modulate δ receptors (Morales et al., 2017; Rodríguez-Muñoz et al., 2018). The combined use of opioids in phytocannabioids makes it possible to keep analgesia with lower doses and decreased side effects (Kathmann et al., 2006; Morales et al., 2017).

Serotonin receptors

Serotonin (5-HT) receptors are GPCRs expressed in the CNS, gastrointestinal tract and platelets, being a widely explored as drug targets for depression (Gresch, 2013). Cannabinoids are related to 5-HT receptors due to interactions of CBD and 5-HT_{1A}, what results in attenuated diabetic neuropathy in animal models (Jesus et al., 2019). CBD is a partial agonist of $5HT_{2A}$ and antagonist of $5HT_{3A}$ receptors (Fernández-Ruiz et al., 2013; Soares and Campos, 2017; Meissner and Cascella, 2022;). The potential benefits of these interactions to pain management, however, are still unclear. THC and tetrahydrocannabivarin are antagonists of 5-HT_{3A} and 5-HT_{1A}, respectively, and such interactions have been associated to inflammation control and decreased pain perception (Hanuš et al., 2016; Morales et al., 2017; Guerrero-Alba et al., 2019). Cannabigerol is an antagonist of 5-HT_{1A}, and this interaction results in antidepressant effect and control of inflammatory intestinal diseases (Atalay et al., 2020).

GABAergic and glutamatergic receptors

GABA and glutamate are the main inhibitory and excitatory neurotransmitters, respectively, and are influenced by the endocannabinoid system. Some of the resulting effects of decreased GABA release include fear suppression and memory impairment, whilst decreased glutamate release decreases pain perception (Lessa et al., 2016; Lötsch et al., 2018). The synthetic cannabinoid rimonabant has also shown the ability to be able to potentiate $GABA_A$ currents (Baur et al., 2012). It has also been observed that CB1 agonism activation by anandamide, THC or synthetic cannabinoids suppresses glutamatergic neurotransmission via inhibitory modulation of NMDA receptors (Baron, 2015). Agonism of CB1 receptors decreases GABA and glutamate release (Petroff, 2002). The CBD is also a positive allosteric modulator of $GABA_A$ receptor (Morales et al., 2017) and THC is also an agonist of benzodiazepine site of GABA receptors (Netzahualcoyotzi-Piedra et al., 2009).

Adrenergic receptors

Adrenergic receptors also belong to the GPCR superfamily (Hieble, 2009). It is known that α_2 receptors are expressed in peripheral nerves, spinal cord and supraspinal pain modulating centers; when activated, they mediate analgesic effects, being useful to the management of neuropathic and acute postoperative pain (Bantel et al., 2007). Cannabigerol and CBD activate α_2 receptors (Hanuš et al., 2016; Muller et al., 2019). There is evidence of functional desensitization of adrenergic α_2 re-

ceptors due to agonism of co-localized CB1 receptors at the medial prefrontal cortex, an important brain region associated to control of pain sensations (Cathel et al., 2014).

Glycine receptors

Glycine receptors (α_1-GlyR, α_2-GlyR, α_3-GlyR, α_4-GlyR and β-GlyR) are expressed throughout the CNS at pre-synaptic (modulating glutamatergic and glycinergic neurotransmission) and post-synaptic neurons (mediating inhibition of neurotransmission in the spinal cord, brainstem, and retina) (Lynch et al., 2017). These receptors are involved in neurological disorders such as temporal lobe epilepsy, autism, respiratory disorders and chronic inflammatory pain (Lynch et al., 2017; Zou et al., 2020). The THC and CBD are known to potentiate GlyR-mediated anti-inflammatory and anti-nociceptive effects as agonists of α1-GlyR and α3-GlyR (Xiong et al., 2012; Lynch et al., 2017; Morales et al., 2017).

Peroxisome proliferator-activated receptors (PPAR)

There are three known isoforms of PPARs: PPARγ, PPARα and PPARδ, which are expressed at the heart, pancreas, liver, skeletal muscles, kidneys, immune cells and adipose tissue (Janani and Kumari, 2015; Marion-Letellier et al., 2016). Agonism of PPARα and PPARγ by cannabinoids results in neuroprotective, anti-nociceptive, antiproliferative, anti-stress, anxiolytic and anti-inflammatory effects, and increased metabolism rate (Di Marzo, 2020; Morales et al., 2017). Cannabigerol is an agonist of PPARγ, with higher affinity than THC and CBD (Nachnani et al., 2021). This results in modulation of COX-2, TNF-α, IL-1β, IL- 6 and NFκB expression (Atalay et al., 2020). The synthetic cannabinoid WIN55,212-2 mediates analgesia through agonism on PPARγ and PPARα receptors (Tamba et al., 2020). Curiously, antagonism of PPARα by phytocannabinoids resulted in antinociceptive effects in animal models (O'Sullivan, 2016; Morales et al., 2017).

Adenosine receptors

Adenosine receptors comprise four subtypes of GPCRs expressed at the CNS (regulating sleep), macrophages, thymocytes, liver, lung, choroid plexus, kidneys and intestines. They are involved in modulation of neurotransmission, synaptic plasticity and neuroprotection against ischemia, hypoxia and oxidative stress (Atalay et al., 2020; Sheth et al., 2014). The CBD is agonist of $A2_A$ receptors, resulting in anti-inflammatory and immunosuppressive effects, and decreased expression of TNF-α and VCAM-1 (Atalay et al., 2020).

Conclusion

Exogenous cannabinoids can modulate pain and nociception by different pathways other than the cannabinoid system, which is properly activated by endogenous cannabinoids. Different pharmacological properties can be observed with their use, such as antitumoral effects and neuromodulation with cognitive effects. As cannabinoids can interact directly or indirectly with multiple sites such as CB1, CB2, Opioid, 5-HT, GABA, adrenergic, glycine, PPARs and adenosine receptors, combined therapy might be more effective than single molecules to provide proper pain management, especially in chronic conditions. Thus, studies on potential synergism of cannabinoids are of interest, especially regarding synthetic and endocannabinoids, as phytocannabinoids are effective options for pain management. Futhermore, studies concerning pharmacokinetics and toxicology of cannabinoids are necessary to establish optimal conditions for clinical treatments regarding each pain condition.

Conflict of interest

The authors have no conflicts of interest to declare.

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