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A Beginners Guide to Marijuana: Vernacular Taxonomy and Pharmacology

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Abstract

Despite being used by humans both for medical and recreational use for thousands of years marijuana has not been properly investigated for its pharmacological potential. This was principally due to it's recreational use and the associated bad press. Thankfully, due to a shift in public perception and an appreciation of the medical uses of marijuana, appropriate research is now being performed and funded. This is resulting in an increased knowledge of the endocannabinoid system which is the target of the principal active components found in the secreted resin of marijuana plants. Legalization of marijuana use for medical treatments in the US has also allowed the patient to select a specific strain of plant to match their medical needs and this mini review attempts to bring some clarity to the vernacular taxonomy as well as an introduction to cannabinoid pharmacology.

Keywords: *Marijuana; Cannabidiol; Δ9-Tetrahydrocannabinol; Endocannabinoid System; N-Arachidonoylethanolamine; 2-Arachidonoylglycerol*

Abbreviations

CBD: Cannabidiol; THX: Δ9-Tetrahydrocannabinol; FDA: Food And Drug Administration; AIDS: Acquired Immunodeficiency Syndrome; GPCR: G-Protein Coupled Receptor; CBR: Cannabinoid Receptor; CNS: Central Nervous System; GI: Gastrointestinal Tract; AEA: N-Arachidonoylethanolamine; 2-AG: 2-Arachidonoylglycerol; MS: Multiple Sclerosis; NAPE: N-Arachidonoyl Phosphatidyl-Ethanol; FAAH: Fatty Acid Amino Hydrolase; Cox: Cyclooxygenase; MGL: Monoacylglycerol Lipase; GABA: Gamma-Amino Butyric Acid; GIRK: G-Protein Coupled Inwardly-Rectifying Potassium Channel; MAPK: Mitogen-Activated Protein Kinase; ERK: Extracellular Signal-Related Kinase; JNK: C-Jun N-Terminal Kinase; PI3K: Phosphoinositide 3-Kinase; AKT: Protein Kinase B; cAMP: Cyclic Adenosine Monophosphate

Introduction

Despite being used by humans for thousands of years only recently has the cannabis genus (which includes the species *Cannabis sativa, Cannabis indica* and *Cannabis ruderalis*) been investigated properly for its pharmacological potential. The first recorded medical use was to treat pain, inflammation, seizures and nausea in China 5,000 years ago [1,2]. But it was also used recreationally and it was this use which resulted in its bad reputation especially in the West over the last 60 years. Cannabis is an annual flowering plant which is dioecious and wind pollinated. It has small glands called trichomes which produce a sticky resin containing pharmacologically active ingredients; these are particularly concentrated in the female flowers [3] and include cannabidiol (CBD; Figure 1) and Δ9-tetrahydrocannabinol (THC; Figure 1) which will be discussed later. THC was identified as the component that produced the psychoactive effect (the "high") which was responsible for its recreational use [4]. Interestingly there is still no clear consensus on the function of this secreted resin. The vast

majority of cannabis users, both medically and recreationally, ingest the whole plant in some form and are therefore exposed to the whole spectrum of active ingredients found in cannabis. It might therefore be useful if this review first attempted to clarify the vernacular taxonomy of cannabis; this is discussed in depth in McPartland's excellent 2018 review which I summarize below [5]. It should be stated however that for any new drug regime, especially those with chronic conditions and/or the elderly on long-term medications, the patient should still discuss marijuana use with their doctor to avoid any potential drug interactions; it may be that certain strains may have the potential for such interactions and therefor another can be sampled [6,7].

Vernacular taxonomy

Medical professionals and patients might feel overwhelmed by the huge number of so-called cannabis strains currently available (>700) [8] but botanists have been struggling to correctly categorize these plants phylogenetically since the 16th century [5]. Recently, cannabis has found a home in the family *Cannabaceae* but this does not clarify the status of the 3 so-called subspecies *sativa, indica* and *ruderalis*. Small and Cronquist compared gene sequences of *sativa* and *indica* plants (the so-called "barcode gap" method) and have been finally able to justify them as 2 distinct subspecies; *C. sativa* subspecies *sativa* and *C. sativa* subspecies *indica* [9]. *C. ruderalis* may be a separate subspecies for plants exhibiting three characteristics, namely CBD content approximately equal to THC content, it's morphology and the ability to "autoflower." Normally cannabis plants start to flower when the day length decreases in the fall but *ruderalis* flowers independently with respect to day length. *Ruderalis* typically has low levels of CBD and THC but has been utilized to produce autoflowering crosses [3,10,11]. For medical marijuana users this may help in selecting a suitable plant for home cultivation as allowed legally. The vernacular taxonomy is based on generalizations and is utilized by breeders to name and promote the huge array of strains available. *Sativa* dominant strains/hybrids/cultivars were typically described as having a higher THC content than *indica* and a so-called terpenoid profile resulting in a sweet odor. *Sativa* dominant strains typically grow 5 to 18' with few branches and have been used for the treatment of depression, headaches, nausea and loss of appetite. *Indica* dominant strains have a higher CBD content than THC and express a different terpenoid profile resulting in a "skunky" odor. They are typically much shorter and compact, growing only 2 to 4' with many branches and are recommended for insomnia, pain, inflammation, muscle spasms, epilepsy, glaucoma and sedation [5,8,12-14]. The extensive interbreeding and hybridization have really made categorizing as either *sativa* or *indica*-dominant meaningless. A good example of this is the strain known as *AK47* which has won awards both as a *sativa* and *indica*-dominant strain [15]. The principal selected characteristic for breeding was often the THC content. In the Netherlands for example, the average THC content (dry weight) has increased from 8 to 20% from 2000 to 2004 [16]. ElSohly., *et al*. in 2006 published a study showing a 3 to 12% increase in THC content in confiscated cannabis from 1980 to 2012 [17]. Another fairly recent improvement for the medical marijuana grower is the availability of feminized seeds. Normally one would have to wait until the plants were ready to or induced to flower before the sex of the plants was known. Unless seeds were required, the male plants would then be culled so the females produced more flowers and therefore more resin but the culling would reduce the total number of plants and hence the potential yield. If you treat female plants with foliar sprays of silver thiosulphate for example, it induces them to produce male flowers with female (XX) sperm. These can then be used to cross with normal females which can then only produce female seeds [18,19]. Although the vast majority of medical marijuana users utilize the whole plant in some form or other, there are concentrated preparations such as CBD oil that are freely available. In the United States the FDA permits the sale of such preparations as long as the THC content is equal or less than 0.3% [20]. In addition, there are several pharmaceutical preparations derived from plants with known THC and CBD content that can be prescribed. These include Sativex (Nabiximol) [21-23] which is an oral spray containing both THC and CBD in roughly equal amounts and which is indicated for the treatment of MS-related spasticity, neuropathic pain and bladder complaints [24-26]. Another example is Epidiolex which contains purified CBD and is used for the treatment of severe forms of pediatric epilepsy [27,28]. Finally, there are preparations containing synthetic THC analogs. These include Cesamet (Nabilone) used to address nausea and vomiting associated with chemotherapy when not treated adequately by traditional antiemetics [29,30]. Marinol (Dronabinol) is also a synthetic THC analog indicated for the treatment of anorexia-associated weight loss in patients suffering from the AIDS virus and nausea and vomiting associated with chemotherapy [31,32].

Pharmacology and the endocannabinoid system

Just over 50 years ago THC was isolated along with over 70 phytocannabinoids from cannabis plants [33,34]; this directly led to the identification and cloning of the first endogenous cannabinoid receptor CB1R which is a G-protein coupled receptor (GPCR) [35,36]. Soon after a second receptor CB2R, also a GPCR, was identified and cloned [37,38]. The CB1R is encoded by the CNR1 gene which results in a 472 amino acid protein in humans. The receptor's crystal structure complete with both agonist and antagonist binding have been resolved [35,36,39-41]. Three different isoforms have now been characterized with differential expression in the CNS and many other tissues [42]. CB1R is in fact the most widely expressed receptor of all the GPCR family with its highest levels found in the olfactory bulb, hippocampus, basal ganglia and cerebellum in the CNS [43,44]. Outside the CNS it is expressed in sympathetic nerve terminals, trigeminal ganglion, dorsal root ganglion and 1° sensory neuron processes thought to be involved in nociception [45-48]. CB1R is also expressed in the GI tract where it may affect motility, secretion and permeability [49]. It is also thought to be involved in cardiac dysfunction and is expressed in certain cancerous cells [50,51]. The CB2R is encoded by the CNR2 gene whose product is a 360 amino acid protein in humans with apparently 2 isoforms differentially expressed in the CNS and other tissues [52]. CB2R was first identified in macrophages and subsequently throughout the immune system and in various tissues including the cardiovascular and reproductive systems, GI tract, liver, adipose tissue and bone [37,53]. Expression in the CNS is lower than CB1R but still thought to be significant and may affect nociception, addiction, neuroinflammation and cortical excitation [54-57]. THC is a partial agonist of both cannabinoid receptors and its psychoactive and nociceptive actions are via CB1R activation. CBD appears to have little direct effect on either receptor and may even antagonize THC binding. It is thought that CBD can interact with other receptors apart from CB1R and CB2R [58,59]. The endogenous ligands for these receptors are the arachidonic acid derivatives N-arachidonoylethanolamine (AEA/anandamide; Figure 1) and 2-arachidonoylglycerol (2-AG; Figure 1); these endocannabinoids and associated receptors define the neuromodulatory endocannabinoid system [34,60-62]. In the CNS the endocannabinoid system is known to affect appetite, learning and memory, anxiety, depression, schizophrenia, stroke, MS, neurodegeneration, epilepsy and addiction [34,43,63,64]. In the peripheral nervous system and other tissues the endocannabinoid system is known to affect nociception, metabolism, cardiovascular and reproductive function, inflammation, glaucoma, cancer, liver and musculoskeletal disorders [50,65]. Virtually all research on the endocannabinoid system has been performed using these agonists. AEA is a high affinity partial agonist of CB1R but almost inactive on CB2R [66]; 2-AG exhibits moderate to low affinity for both cannabinoid receptors [38]. In the CNS 2-AG is found at significantly higher levels than AEA and it is thought 2-AG is probably the principal endogenous ligand for cannabinoid receptors in the CNS [66-68]. AEA and 2-AG are both produced on demand due to increasing intracellular calcium or activation of the heterotrimeric G-protein $G_{q/11}$ [43,67,69,70]. Most AEA is produced from N-arachidonoyl phosphatidyl ethanol (NAPE) while 2-AG is derived from arachidonoyl-containing membrane phospholipids [34]. There are multiple pathways thought to produce AEA including the activation of dopamine D1 receptors in the striatum. NAPE can be acted on by a variety of phospholipases (B, C and D) to produce AEA [71-75]. Pathways that activate phospholipase C can produce a diacyl glycerol that is subsequently hydrolyzed by a lipase to produce 2-AG. These pathways include glutamate metabotropic receptors, M1 and M3 muscarinic receptors and orexin A [68,76,77]. In the CNS AEA is thought to be degraded primarily by fatty acid amino hydrolase (FAAH) or N-acyl ethanolamine amino hydrolase. Cyclooxygenase-2 (Cox-2) is also thought to convert AEA to the prostaglandin prostamide E_2 [78-80]. 2-AG is degraded primarily by 3 hydrolytic enzymes, namely monoacylglycerol lipase (MGL), and the α/β domain hydrolases 6 and 12 (ABHD6 and 12). Additionally, 2-AG can be oxidized by Cox-2 and FAAH [81-83]. MGL is expressed widely in the adult CNS and is often localized in synaptic terminals while ABHD6 is primarily expressed on dendrites of cortical neurons [84].

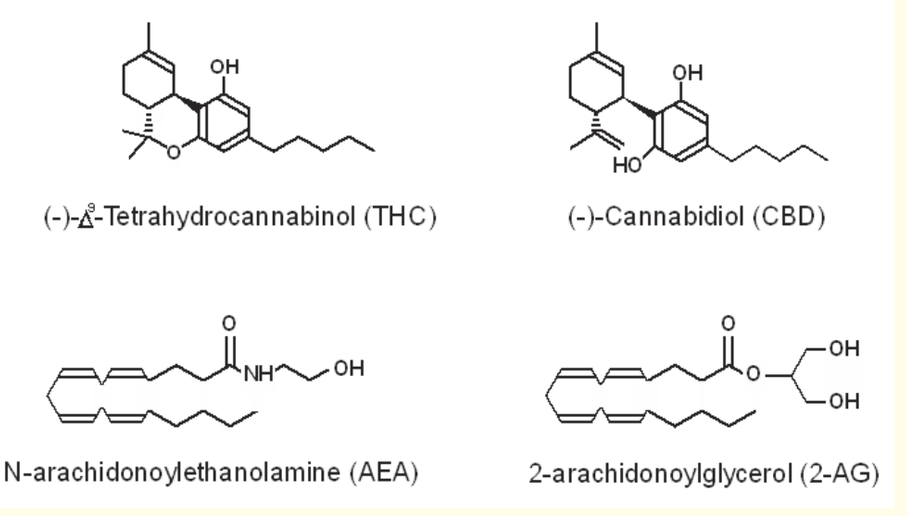

Figure 1: *Representations of the 2 principal active cannabinoids in marijuana Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) and principal endocannabinoids N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG).*

Signal transduction and effectors

Both CB1R and CB2R are members of the GPCR family and act predominantly via the heterotrimeric G-protein $G_{i/o}$ to inhibit adenylate cyclase and reduce cAMP levels [53]. CB1R may also interact with other G-proteins depending on the cell type and ligand involved; the activated by heterodimer can stimulate certain adenylate cyclase isoforms directly [85,86]. In mouse hippocampal slices CB1R is expressed in astrocytes coupled to Gq/11 which causes an increase in intracellular calcium causing the release of glutamate [87]. CB1R is known to interact with multiple ion channels. CB1R inhibits N-type Ca^{2+} channels in a variety of rodent preparations; if presynaptically located this can lead to a decrease in GABA release [88-92]. This receptor can also inhibit P/Q-type and R-type calcium channels in various model systems and activate G-protein coupled inwardly-rectifying potassium channels (GIRKs) [88,91,93-96]. CB1R G-protein signaling recruits β-arrestins 1 and 2 which affect receptor internalization and signaling [97,98]. Arrestin binding together with G-protein-coupled receptor kinases can activate mitogen-activated protein kinase (MAPK) [99-102] pathways including the extracellular signal-related kinase 1/2 (ERK1/2) [103], c-Jun N-terminal kinase (JNK) and p38 affecting proliferation, cell-cycle and cell death [85,104-108]. CB1R activates the PI3K/AKT pathway in various preparations including human astrocytes giving protective effects and increased cell survival [109-111]. CB2R in addition to inhibiting adenylate cyclase and decreasing cAMP levels, also appears to activate MAPK and affect gene expression [112,113]. It promotes neuronal survival by activating PI3K/AKT and JNK pathways [114]. Similarly, CB2R activation can result in β-arrestin 1 and 2 recruitment and MAPK activation [115,116]. Brain CB2R activation can affect neuronal excitability. For example CB2R agonists can inhibit ventral tegmental area dopaminergic neurons and can also activate GIRKs in cortical neurons [117-119].

Summary

It is very encouraging to finally see the full pharmacological potential of cannabis being explored and the resulting availability of cannabinoids in various forms to treat many ailments. As we discover more about the function and involvement of the endocannabinoid system in various pathologies, the more useful will these potential medications become. The development of better pharmacological tools for the cannabinoid receptors along with the ability to manipulate synthesis and degradation will also allow improvements in the treatment of these pathologies and an increased understanding of the endocannabinoid system. Hopefully this mini review will help non-experts appreciate the pharmacology of the cannabinoids but additionally help navigate the huge range of different cannabis strains available to the medical marijuana patient. This aspect makes medical marijuana fairly unique in that patients will be able to select their own particular strain and cultivate it themselves for personal use.

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Conflicts of Interest

None.

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