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A brief introduction to cannabinoid pharmacology

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Abstract

This paper serves as an introduction to the basic pharmacology of the major components of Cannabis sativa L., Δ^9-tetrahydrocannabinol and cannabidiol. We consider the molecular targets of these compounds in the form of the endocannabinoid system and reflect on studies exploring therapeutic benefit.

Key words: Cannabis, cannabinoid, THC, CBD

Introduction

Cannabis sativa L. (C. sativa) is considered one of the oldest cultivated plants with evidence for its origin and domestication found primarily in Central and South East Asia at several Neolithic sites with later use across Africa (Smet, 1998; Bonini et al., 2018). In addition to its cultivation for cordage and textile manufacture, the psychotropic effects of C. sativa have been associated with religious rituals and moreover, with medical applications, recorded as early as 5000 years ago in ancient Chinese texts (Smet, 1998; Bonini et al., 2018). The use of C. sativa by indigenous communities for a variety of diseases, remains prevalent to date (Smet, 1998; Bonini et al., 2018). Research into the pharmacological profile of C. sativa began as early as the 19th C but was hampered by an inability to isolate the active compounds. With advancements in the field of chemistry, in the 1940's Lord Todd and Roger Adams were able to independently isolate cannabinol (CBN) and cannabidiol (CBD), (Mechoulam, Fride and Di Marzo, 1998). However, it was only in 1964 that the main psychoactive component, 9-tetrahydrocannabinol (THC) was isolated and its structure determined by Raphael Mechoulam and Yehiel Gaoni (Mechoulam, Fride and Di Marzo, 1998). This discovery provided an impetus into identifying firstly, the molecular targets of THC which in turn led to the discovery of the endocannabinoid system in humans and animals; and secondly, other compounds including terpenes, fatty acids, flavonoids and additional cannabinoids in C. sativa that hold potential pharmacological benefit.

The endocannabinoid system

We now know that the endocannabinoid system consist of receptors and their ligands using common intracellular machinery; moreover, this system is evolutionarily conserved (Malfitano et al., 2014). Initially, the mechanism of action of THC was considered to be non-specific; however, in the late 1980's Allyn Howlett and colleagues, using a cannabinoid analogue, discovered that specific receptors are indeed involved (Maccarrone et al., 2015; Alves et al., 2020). First identified was the cannabinoid receptor 1 (CB1), with the cannabinoid receptor 2 (CB2) later identified due to its sequence homology (Maccarrone et al., 2015; Alves et al., 2020). CB1 and CB2 receptors are serpentine (7-pass) transmembrane proteins that are part of the G-protein coupled receptor (GPCR) family (Alves et al., 2020).

Engagement of these receptors and the associated Gi/o-protein, inhibits the activity of the enzyme, adenylate cyclase, thereby reducing the production of the secondary messenger cyclic-adenosine monophosphate (cAMP) and thus modulating the activity of multiple downstream kinases and selected ion channels, having a profound effect on physiological processes (Mechoulam, Fride and Di Marzo, 1998; Maccarrone et al., 2015; Maayah et al., 2020).

Following the identification of these classical cannabinoid receptors, CB1 and CB2, researchers set out to determine what the endogenous ligands for these receptors could be – and thus discovered what is now termed *endocannabinoids*. The first endocannabinoid isolated was anandamide (N-arachidonoylethanolamine, AEA)

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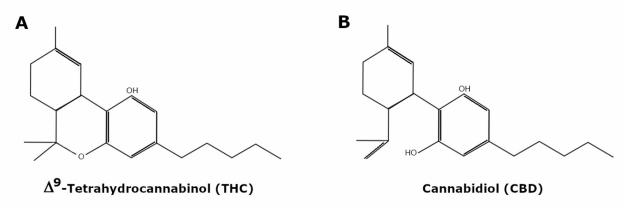

Figure 1. Chemical structure of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

in 1992 followed by 2-arachydonoylglycerol (2-AG) in 1995 (Alves et al., 2020; Maayah et al., 2020). These endocannabinoids are synthesised from membrane phospholipids via enzymatic action; specifically, AEA is synthesised from N-arachidonoyl phosphatidylethanolamine by phosphodiesterase phospholipase D enzyme, and 2-AG from inositol-1,2-diacylglycerol by phospholipase C (Alves et al., 2020; Maayah et al., 2020). Following binding to CB receptors and the subsequent induction of intracellular signal transduction pathways, these endocannabinoids undergo hydrolysis. The endocannabinoid system thus comprises the canonical cannabidiol receptors, the endocannabinoids and the enzymes involved in their synthesis and metabolism. Today, we are becoming aware of the role of the endocannabinoid system in modulation of a number of physiological pathways including pain, circadian rhythm, inflammation, stress, reproduction and appetite (Alves et al., 2020). Unravelling these pathways is, however, an intricate process that is far from linear and requires thorough analysis at multiple levels to understand the intersection of phytocannabinoids with this system and to identify therapeutic targets.

Phytocannabinoids

Over 500 compounds including terpenes, fatty acids and flavonoids, as well as over 100 cannabinoids have been identified in C. sativa (Bonini et al., 2018). The botanical cannabinoids are distinguished as phytocannabinoids (including cannabidivarin, cannabigerol and cannabichromene amongst others), as opposed to the endocannabinoids, AEA and 2-AG, found in humans and animals. In addition to THC, the main psychoactive component, cannabidiol (CBD) which conversely shows no psychoactivity, is one of the more abundant and more studied phytocannabinoids (Bonini et al., 2018). Within the C. sativa plant, THC and CBD are derived via decarboxylation from their acidic precursors Δ 9-tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA) (Alves et al., 2020; Maayah et al., 2020); however, the variety of strains cultivated today have resulted in considerable variation in concentration of THC and CBD (A. M. Freeman et al., 2019; T. P. Freeman et al., 2019). The majority of basic science and translational studies have tested the effects of isolated compounds; however, evidence suggests that the spectrum of the cannabis extract may hold more pharmacological benefit (Bonini et al., 2018), in that other compounds including terpenes which are responsible for the distinctive aroma of C. sativa, notwithstanding the other phytocannabinoids, may have therapeutic capacity and may further enhance the effects of THC – known as the 'entourage effect' or mitigate the negative effects of THC (Blasco-Benito et al., 2018; Byars, Theisen and Bolton, 2019).

Cannabinoids and the Endocannabinoid system

THC is structurally analogous to the endocannabinoid AEA, and exerts its agonist effects through high affinity binding to CB1 (primarily) and CB2 receptors (Maayah et al., 2020). THC and CBD also present a similar structure (Figure 1); however, CBD is rather regarded as a low affinity, negative allosteric (THC binds to the orthosteric site) regulator (Ibeas Bih et al., 2015; Laprairie et al., 2015; Bonini et al., 2018). Thus, instead of activating the CB receptors, CBD is rather able to modulate their function. This may also speak to the role of CBD in mitigating some of the adverse effects of THC and enhancing its therapeutic potential (Laprairie et al., 2015; A. M. Freeman et al., 2019). CBD is also able to act independently of the CB receptors; specifically, as an agonist for the transient potential vanilloid receptor type-1 (TPVR-1), serotonin receptors (5-HT), peroxisome proliferator-activated receptor (PPAR), and as an antagonist for the receptor GPR55 and the nicotinic acetylcholine receptor, notwithstanding its association with enzymes (including members of the CYP450 family) involved in xenobiotic metabolism (Ibeas Bih et al., 2015; Pisanti et al., 2017).

The CB1 expression is the most abundant in the central nervous system (CNS), but it is also found in the autonomous nervous system (ANS) (Puhl, 2019; Maayah et al., 2020). These receptors are primarily expressed on the pre-synaptic terminals of glutamatergic and gamma-aminobutyric acid (GABA)-ergic neurons where they function in preventing the release of neurotransmitters into the synaptic cleft, thereby preventing post-synaptic activation (Puhl, 2019; Maayah et al., 2020). Based on the regions of the CNS in which CB1 receptors are primarily concentrated, by regulating the balance between excitatory and inhibitory neurotransmitter release, they are implicated in modulation of nociceptive functions and neuropathic functions speaking to their role in pain management - one of their better known functions (Byars, Theisen and Bolton, 2019; Maayah et al., 2020). CB2, which has limited expression in the CNS, is nevertheless associated with pain regulation, primarily in the periphery (Maayah et al., 2020), and commonly associated with inflammatory conditions including arthritis and colitis (Byars, Theisen and Bolton, 2019). Notably, THC activation of CB1 is associated with the psychoactive effects of cannabis; however, by engaging CB2 neuroprotective, anti-spasmodic and anti-inflammatory effects are also initiated, illustrating the dual and contrasting effects of these receptors (Byars, Theisen and Bolton, 2019; Alves et al., 2020). CB1 is also distributed across a range of tissues including adipose tissue; skeletal muscle; the gastrointestinal tract and associated organs, the liver and pancreas; and the reproductive system (Rajesh et al., 2012; Maccarrone et al., 2015; Bonini et al., 2018; Maayah et al., 2020), highlighting the role of the cannabinoids in multiple physiological pathways.

In the cardiovascular system, hyperactivation of CB1 and the production of endocannabinoids, has been linked to the development of cardiac disease including cardiomyopathy and atherosclerosis; however, engagement of CB2 has been shown to mitigate these effects, rather being cardioprotective (Rajesh et al., 2012; Maccarrone et al., 2015; Chanda, Neumann and Glatz, 2019). Complicating these cardiovascular effects, is that CB1 also induces pro-inflammatory effects whereas, CB2 which is primarily expressed on immune cells, elicits an anti-inflammatory response – this indicates a fine balance in the endocannabinoid system in regulating cardiometabolic function (Malfitano et al., 2014; Maccarrone et al., 2015; Puhl, 2019). In the gastrointestinal tract, THC is shown, via engagement of the CB1 receptor (Maayah et al., 2020), to inhibit the release of the neurotransmitter, acetylcholine, from

enteric nerve terminals (Maccarrone et al., 2015; Puhl, 2019). Control of gastric motility, appetite and energy expenditure was ultimately highlighted as being under the control of the endocannabinoid system (Maccarrone et al., 2015). Phytocannabinoids and synthetic cannabinoids have also been shown to have value in treating gastrointestinal disorders, with consideration of the role of the CB receptors in inflammation; and in treating psychological disorders (anorexia and bulimia) associated with impairment of the interoceptive awareness, eating behaviours and reward systems (Bonini et al., 2018).

In this regard the pharmacological benefit of cannabinoids has been exploited in drug development. For example, nabiximols (Sativex®), a 1:1 ratio of THC and CBD, is used for relief of muscle stiffness and neuropathic pain associated with multiple sclerosis; and dronabinol (Marinol®) and nabilone (Cesamet®), synthetic analogues of THC, alleviate vomiting and nausea associated with chemotherapy in cancer patients; however, these drugs are not available globally (Alves et al., 2020). Given the distribution of the endocannabinoid system in tissues, it is not unexpected that such drugs have evidenced effectiveness in multiple applications, including nabilone in addressing sleep disorders and chronic pain conditions and dronabinol in appetite stimulation in HIV/AIDS patients (Whiting et al., 2015; Alves et al., 2020).

The route of administration of cannabinoids, as well as the dosage, for which there remains no standard guideline, must be considered in developing therapeutic interventions (Puhl, 2019). For example, THC/CBD therapy for cancer-associated pain and neuropathic pain is suggested to be most efficacious delivered via an oro-mucosal route, notwithstanding that the effectiveness of different doses of THC/CBD may be associated with the specific type of pain experienced (MacCallum and Russo, 2018; Rabgay et al., 2020). Since cannabinoids can have biphasic properties, dose-dependent effects as well as the duration of treatment must be taken into consideration with respect to management of any disease. Cannabinoids can also alleviate multiple symptoms, but similarly, could also result in adverse effects without the aforementioned reflections and consideration of contraindications (MacCallum and Russo, 2018; Byars, Theisen and Bolton, 2019).

Conclusion

The effects of the endocannabinoids and phytocannabinoids are associated with not only the particular receptors they may bind to, but also with the tissues in which those receptors may be expressed, ligand concentration and receptor distribution - these factors ultimately influence the resulting physiological processes; notwithstanding the dose, duration of treatment and route of administration would impact the effectiveness of treatment as well as any adverse effects that may be elicited (Whiting et al., 2015; MacCallum and Russo, 2018; Byars, Theisen and Bolton, 2019). Additionally,, while the full spectrum compounds in C. sativa extract may enhance the positive effects of THC, the cultivation of strains that have altered the concentrations of these components (T. P. Freeman et al., 2019), and thus may elicit a variance of effects that may not recapitulate previous studies (Bonini et al., 2018). Following significant changes in the global perception of C. sativa, we now have opportunity to address the gaps in our knowledge and determine what other therapeutic benefits we may gain from this plant.

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