Phytocannabinoids and endocannabinoids: different in nature

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Abstract
Cannabis is one of the earliest cultivated plants, of which Cannabis sativa and Cannabis indica are the most widespread and best characterized species. Their extracts contain (phyto)cannabinoids (pCBs) of therapeutic interest, such as Δ9-tetrahydrocannabinol and cannabidiol, along with many other compounds, so that there is no “one cannabis” but several mixtures even from the same plant. This complexity is mirrored, or even exceeded, by the complexity of the molecular targets that pCBs find in our body, most of which belong to the so-called “endocannabinoid (eCB) system”. Here, we describe the major pCBs and the main components of the eCB system to appreciate their differences and mutual interactions, as well as the potential of using pCB/eCB-based drugs as novel therapeutics to treat human diseases, both in the central nervous system and at the periphery. Moreover, we address the question of the evolution of pCBs and eCBs, showing that the latter compounds were the first to appear in nature, and that the former substances took a few million years to mimic the three-dimensional structures of the latter, and hence their biological activity in our body.

Graphic abstract
 Keywords  Cannabinoid receptor · Bioactive lipid · Metabolic enzyme · Pharmacophore · Signal transduction · Vanilloid receptor

1 Introduction

Cannabis is one of the earliest cultivated plants. When it is of industrial utility and culinary value, it is generally termed hemp; when it is bred for medical or recreational purposes, it is called marijuana. In both cases, the female plant produces a significant amount of bioactive and psychoactive compounds, but the existence of different species and cultivars of cannabis must be taken into account to evaluate their impact on health. *Cannabis sativa* and *Cannabis indica* are the most widespread and best characterized species of cannabis, and their extracts contain (phyto)cannabinoids (pCBs) of therapeutic interest, such as Δ⁹-tetrahydrocannabinol (Δ⁹-THC) and cannabidiol (CBD), both shown in Table 1. Yet, the effect of cannabis extracts does not depend only on the amount of Δ⁹-THC and CBD, but also on the presence and concentration of > 110 additional pCBs, and > 440 non-phytocannabinoid compounds like terpenoids, flavonoids and sterols (Sohly et al. 2014; Solymosi and Köfalvi 2017). Among the pCBs, the following classes have been clearly detected in cannabis extracts: (1) in abundant amounts Δ⁸-THC and its analogs (including Δ⁸-tetrahydrocannabinol and Δ⁹-tetrahydrocannabinavirin), CBD and its analogs (including the propyl derivative cannabidivarin), cannabinoi and its analogs (including the propyl derivative cannabivarin), cannabigerol and its analogs (2) in less abundant amounts cannabinodiol, cannabichromene, cannabinol, cannabielsoin, cannabinorsiol, cannabinoriol (ElSohly et al. 2017; Morales et al. 2017), as well as others like varinic (short aliphatic chain) and acidic (bearing carboxylic groups) derivatives of the major pCBs. To date, understanding of the pharmacological properties of these pCBs have only scratched the surface (Franco et al. 2020; Russo 2018). Therefore, it should be appreciated that the term “(phyto)cannabinoids” serves to cluster different plant-derived lipophilic compounds, which are clearly distinguishable from other pharmacologically related, but structurally different, natural and synthetic compounds (Ligresti et al. 2016; Pertwee 2014).

It is also remarkable that different cannabis extracts may have a largely different chemical profile (i.e., they may be different “chemovars”), which means that they may contain different components and/or different amounts of the same constituents. In addition, the modes of cultivation, harvest, extraction of active principles, and of their administration routes to subjects, may further affect the final chemical composition, clearly suggesting that there is no “one cannabis” but several mixtures even from the same plant (Friedman et al. 2019). This is the reason why there is still little understanding of the pharmacological efficacy of cannabis extracts, and indeed remaining uncertainties represent a warning for the clinical applications of these natural compounds (Friedman et al. 2019). The pCBs that have been characterized for potential medical applications, and for which cellular targets have been clearly identified, are reported in Table 1 (for more details, see ref. 10).

Unsurprisingly, marijuana is surrounded by controversies, debates and misconceptions related to its medical potential, legalization and long-term health consequences. To date, marijuana is the most widely used recreational drug in Western countries, and is consumed by ~ 3% of the world population (~ 185 million individuals) (United Nations Office on Drugs and Crime 2017). The advent of legalized cannabis in multiple regions of the United States, and elsewhere around the world, have raised additional and urgent concerns about its potential hazard to health. Nevertheless, research on the therapeutic potential of cannabis extract-based drugs suggests them to be clinically useful in a wide range of pathological conditions, including neurological (Friedman et al. 2019; Cristino et al. 2020) and psychiatric disorders (Cohen et al. 2019). Conversely, repeated cannabis use has been associated with short-term and long-term side effects, including cognitive alterations, psychosis, schizophrenia and mood disorders (Cohen et al. 2019), as well as with respiratory and cardiovascular diseases (Maccarrone et al. 2015).

2 Metabolism of phytocannabinoids

Phytocannabinoids are synthesized via metabolic pathways that start from farnesyl diphosphate to produce geranyl diphosphate, that is then condensed with olivetolic acid in a reaction catalysed by cannabigerolic synthase. From the cannabigerolic acid product, a number of pCBs are generated (Solymosi and Köfalvi 2017; Schafroth and Carreira 2017), as depicted in Fig. 1a.

It is very important that pCBs cannot be degraded by our body. Yet, biotransformation of Δ⁹-THC may occur primarily within the liver by hydroxylation and oxidation reactions catalyzed the cytochrome P450 subfamily 2C9 (CYP2C9) enzymes, which play a major role in rodents and humans (Watanabe et al. 1993, 2007). Such a “phase I metabolism” involves hydroxylation of Δ⁹-THC to its primary metabolite 11-hydroxy-Δ⁹-tetrahydrocannabinol (11OH-THC), that in turn undergoes further oxidation by other liver enzymes to the inactive secondary metabolite 11-nor-9-carboxy-Δ⁹-tetrahydrocannabinol (11-COOH-THC, or THC-COOH), as shown in Fig. 2b. The latter substance is then biotransformed further during “phase II
metabolism” by UDP-glucuronosyltransferase (UGTase)-dependent glucuronidation, producing a water-soluble glucuronide which can be more easily excreted by the body. Much in the same way, Δ⁹-THC degradation product cannabinol (CBN) can be converted by CYP2C9 into 11OH-CBN (Fig. 1b).

As mentioned above, pCBs are endowed with many pharmacological properties, due to their ability to hit and modulate (as agonists, inverse agonists, antagonists, or even positive or negative allosteric modulators) different cellular targets (Morales et al. 2017; Turner et al. 2017; Friedman et al. 2019; Cristino et al. 2020; Hanuš et al. 2016). Indeed, it should be appreciated that the complexity of cannabis extracts is mirrored, and possibly even exceeded, by the complexity of the molecular targets that they find in our body, most of which belong to the so-called “endocannabinoid system” described in the following section.

3 Metabolism of endocannabinoids

It is well-established that Δ⁹-THC binds to and activates specific G protein-coupled receptors, known as type-1 (CB₁) and type-2 (CB₂) cannabinoid receptors, which endogenously are triggered by ligands that were identified in the ‘90 s as anandamide (N-arachidonylethanolamine, AEA) (Devane et al. 1992) and 2-arachidonoylglycerol (2-AG) (Mechoulam et al. 1995; Sugiura et al. 1995). These two compounds, respectively, an amide and an ester of the ω-6 arachidonic acid (Table 1), are the most active and best studied endocannabinoids (eCBs). Additional members of this family are ω-3 fatty acid derivatives like N-eicosapentaenoylethanolamine and N-docosahexaenoylethanolamine (Table 1); or the eCB-like compounds N-palmitoylethanolamine and N-oleoylethanolamine (also shown in Table 1) that do not bind to CB₁ nor to CB₂, but inhibit eCB degradation thus prolonging their biological activity with an “entourage effect” (Maccarrone et al. 2015,2014). AEA and 2-AG are metabolized by a complex array of biosynthetic enzymes and hydrolases, and are transported through the plasma membrane and intracellularly by distinct carriers. Altogether receptors, enzymes and transporters of eCBs form the “eCB system”, that has been recently discussed in comprehensive reviews (Friedman et al. 2019; Cristino et al. 2020; Sugiura et al. 1995; Maccarrone et al. 2014; Baggelaar et al. 2018; Maccarrone 2020; Iannotti et al. 2016). The main components of the eCB system are shown in Fig. 2, and support and control the manifold actions of eCBs, both in the central nervous system (Cristino et al. 2020; Maccarrone 2020; Iannotti et al. 2016) and at the periphery (Maccarrone et al. 2015).

In particular, the number of receptors activated by eCBs in the same cell, both on the plasma membrane and in the

| Table 1 Major plant-derived and endogenous cannabinoids |
|---------------------------------|---------------------------------|
| **Name (abbreviation)** | **Chemical structure** |
| **Phytocannabinoids** | |
| Δ⁹-Tetrahydrocannabinol (Δ⁹-THC) | |
| Cannabidiol (CBD) | |
| Cannabidivarin (CBDV) | |
| Cannabigerol (CBG) | |
| Δ⁹-Tetrahydrocannabivarin (THCV) | |
| **ω-6 Endocannabinoids** | |
| N-Arachidonylethanolamine (Anandamide, AEA) | |
| 2-Arachidonoylglycerol (2-AG) | |
| **ω-3 Endocannabinoids** | |
| N-Eicosapentaenoylethanolamine (EPEA) | |
| N-Docosahexaenoylethanolamine (DHEA) | |
| **Endocannabinoid-like compounds** | |
| N-Palmitoylethanolamine (PEA) | |
| N-Oleoylethanolamine (OEA) | |
nucleus, appears striking. Indeed, these receptors include: (1) CB₁ and CB₂, as well as the G protein-coupled orphan receptor (GPR) 55 (all on the plasma membrane and with an extracellular binding site); (2) transient receptor potential vanilloid 1 (TRPV1) and additional transient receptor potential (TRP) channels (all on the plasma membrane, but with an intracellular binding site); and (3) nuclear peroxisome proliferator-activated receptors (PPARs) α, γ and δ, that are all transcription factors able to regulate gene expression (Maccarrone 2020). It is of paramount importance that receptor-mediated activities of eCBs are subjected to a stringent “metabolic control”, which means that their cellular concentration (and hence biological activity) depends on a balance between synthesis and degradation by different biosynthetic and hydrolytic enzymes (Friedman et al. 2019; Cristino et al. 2020; Maccarrone 2020). Among the latter, N-acyltransferase (NAT), N-acylphosphatidylethanolamines-specific phospholipase D (NAPE-PLD), along with phospholipase A₂ (PLA₂) and α/β hydrolase domain 4 (ABHD4), catalyze parallel routes for the release of AEA from phospholipid precursors; then, fatty acid amide hydrolase (FAAH) and N-acylethanolamine acid amidase (NAAA) cleave AEA to ethanolamine and arachidonic acid (AA), terminating its signalling (Maccarrone 2020) (Fig. 2). Much alike AEA, a phosphohydrolase (PH) transformation of pCBs in our body by cytochrome P450 subfamily 2C9 (CYP2C9), liver enzymes and UDP-glucuronosyltransferase (UGTase).
4 Cross-talk between pCBs and eCBs

Based on the observation that activities of pCBs and eCBs overlap to some extent, at the level of target receptors and/or metabolic enzymes, it remains challenging to design effective drugs based on these substances (Marzo and Piscitelli 2015; Jacobson et al. 2019). As yet, it appears that pCBs like Δ⁹-THC and CBD modulate CB₁ and CB₂ (and CBD does the same also at the level of TRPV₁, PPARs and FAAH), whereas other pCBs like cannabidivarin and CBD acid can modulate DAGLs and COX-2 (Marzo and Piscitelli 2015). In line with this, it is well-established that chronic or recent cannabis exposure leads to down-regulation of CB₁ (Jacobson et al. 2019). Unfortunately, the structural and functional properties of only a few elements of the eCB system have been thoroughly investigated (Maccarrone 2020), and this gap of knowledge must be filled to really appreciate how pCBs can interact with the eCB system, and how novel pCB/eCB-based therapeutics can be designed against human disorders. In this context, one may wonder how two so markedly different compounds like Δ⁹-THC (a terpeno-phenol) and AEA (an N-arachidonoyl ethanolamine) can share common cellular targets. This apparently striking feature is due to the unanticipated similarity of their 3D structures, that indeed present three different “pharmacophores” (i.e., spatial arrangements of atoms that are essential to interact with a specific receptor target) at the same positions (Van der Stelt et al. 2002). Stereoviews of these 3D structures are shown in Fig. 3, and clearly explain why pCBs can mimic eCB biological activity.

Another interesting question arises as to whether pCBs appeared in nature before eCBs, or viceversa. This issue has recently found an answer, because mature black truffles (Tuber melanosporum Vittad.) were reported to contain AEA and its metabolic enzymes (Pacioni et al. 2015). It should be recalled that the botanical family of truffles (Tuberaceae) evolved during or after the first major radiation of Angiosperms in the Jurassic period (140–180 million years ago, Mya) (Solitis; 2020).
et al. 2008). Instead Cannabis diverged from Humulus, both genera of the family Cannabaceae, at the end of Paleogene (28 Mya) (McPartland 2018). In keeping with these data, the phylogenetic analysis of cytochrome c oxidase subunit 1 clearly showed that T. melanosporum is more ancestral than C. sativa (Pacioni et al. 2015). Furthermore, a recent study on the historical biogeography of the genus Tuber has estimated its molecular dating at the end of the Jurassic period, that is 156 Mya (Bonito et al. 2013); instead, in the order Rosales, that includes the family Cannabaceae and the genus Cannabis, dates 76–107 Mya (Wikström et al. 2001; Wang et al. 2009). Incidentally, it seems interesting that many animals involved in truffle spore dispersal (e.g., nematodes, arthropoda, mammalia) possess cannabinoid receptors (Trappe and Claridge 2010; Elphick 2012), supporting the concept that AEA has an ancient role in attracting truffle eaters. In this context, it should be recalled that eCBs, unlike other eCB-like molecules devoid of activity at cannabinoid receptors, contain in their structure arachidonic acid, which has been reported in little amounts only in a few higher terrestrial plants (Shanab et al. 2018). Thus, the biosynthesis of arachidonate-containing AEA in Tuber melanosporum remains to be further investigated. Moreover, AEA and 2-AG have been described in very simple invertebrates, such as Hydra vulgaris, which evolved earlier (> 500 Mya) than cannabis plant (Petrocelli et al. 1999). Finally, AEA and other N-acyylethanolamines have also been identified in a unicellular eukaryote, such as Tetrahymena, which evolved even earlier (Karava et al. 2005; Anagnostopoulou et al. 2010).

Taken together, available evidence clearly supports the view that eCBs are “older” than pCBs, and that the plant-derived compounds took quite a few million years to mimic the biological and pharmacological activity of our endogenous counterparts.

5 Conclusions

Plant-derived and endogenous cannabinoids represent two different but equally complex systems, so that the terms “(phyto) cannabinoids” and “endocannabinoids” are actually used to identify rather heterogeneous groups of lipophilic substances. It is striking how some of these molecules happened to share 3D structures, allowing exogenous pCBs to play so many biological activities in our body. The additional layer of complexity brought about by these structural similarities makes extremely challenging the use of pCBs as potential therapeutics to combat human diseases, and requires deeper knowledge of the structural and functional details of their potential targets in the cell. Overall, understanding these fine molecular clues will allow to turn pCBs from threats to treasure trove for human health.

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