White paper

Science of CBD

Based on literature study
Executed by T. Tamsma for the Free University of Amsterdam, 2021

Background

Dating back more than 1800 years ago, different applications of cannabis have been documented (Clarke & Watson, 2002). All parts of the cannabis plant have been recorded in historical Chinese medical texts, ranging from using the seeds as moistening laxatives, to the more commonly known applications like in western Europe, where cannabis was used as a treatment for conditions resulting in pain and restricted movement (Brand & Zhao, 2017).

Other applications involved processing the leaves and flower tops for treating severe spasm, headaches, insomnia and coughing. This tells us that even hundreds of years ago, people were well aware of the medicinal power cannabis possesses, which parts of the plant to harvest and how they should process these plant parts for consumer use (Zuardi, 2006). Even though the exact substance causing these effects was not chemically understood then, it clearly shows both basic and applied research has been done on cannabis for some time.

Nowadays, research has taught us that the chemicals causing these effects are known as cannabidiol (from now on CBD) and tetrahydrocannabinol (from now on THC). The compounds have the same molecular structure ($C_{21}H_{30}O_2$) but have different effects on the human body due to a slight difference in the way these atoms are arranged (Hložek et al, 2017). CBD can be processed in certain solutions to create what is known as CBD oil.

Cannabinoids

CBD, CBC, CBN, and CBG are known as phytocannabinoids. Phytocannabinoids are cannabinoids derived from the cannabis plant and are physiological ligands for the cannabinoid receptors in the human body (Kinghorn, Falk, Gibbons, & Kobayashi, 2017). The most important receptors are CB_1 and CB_2, both G protein-coupled cannabinoid receptors (Pacher, 2006), but recent discoveries have given strong evidence of other receptors responsible for physiological activity (Begg et al., 2005) or even more receptors being part of the endocannabinoid system. CB_1 receptors are found in our central nerve system (brain and spinal cord), whereas CB_2 receptors are mostly located in the immune system. THC is an agonist for CB_1 and is responsible for the psychoactive properties associated with marijuana. This makes THC an unusable supplement in daily products, which is why THC falls outside of the scope of this white paper. After the first cannabinoid receptor was discovered in 1988 (Devane, Dysarz, Johnson, Melvin, & Howlett), scientists asked themselves why our bodies had receptors for substances that were not found inside our bodies. Extensive research for endogenous ligands led to the discovery of endocannabinoids.

Endocannabinoid system

The endocannabinoid system (ECS) is a signaling system made up out of cannabinoid receptors, endogenous ligands and the enzymes responsible for biosynthesis of ligands and their inactivation. This involves an increasingly large number of pathological conditions as more and more molecules are found that interact with this system. The ECS is an important modulator of the autonomic nervous system, microcirculation and the immune system. As for therapeutic targets, the list is promising:

Diseases of Energy Metabolism
Pain and Inflammation
Sleep cycle
Central Nervous System Disorders
Cardiovascular and Respiratory Disorders
Eye Disorders (Glaucoma and Retinopathy)
Cancer
Gastrointestinal and Liver Disorders
Musculoskeletal Disorders
Endocannabinoids and Reproductive Functions

Even though the research on therapeutic targets done by Pacher et al. (2006) focusses on THC and CB_1, with more and more research being done, it is becoming clear that certain GPCRs, TRPs, nuclear receptors, other ligand-activated channels and even targets such as serotonin receptors, influence endocannabinoid levels (Maurya & Velmurugan, 2018). If phytocannabinoids show affinity towards these receptors, they are surely interesting from a pharmacological perspective.

Pharmacodynamics

CBD

Because of its promising therapeutic effects, cannabidiol is after THC, the most studied cannabinoid today. Despite this, little is still known about the pharmacodynamics due to the complexity of its function. Even though the affinity is low, many studies support the idea that CBD has an auto regulatory function through the CB_2 receptor and acts as a negative allosteric modulator of the CB_1 receptor, explaining some of the in vivo effects (Morales et al., 2017). In vitro studies revealed that CBD displays weak CB_1 and CB_2 antagonistic effects (Pertwee, Ross, Craib, & Thomas, 2002), (Thomas et al., 2007). At the GPR55 and GPR18 receptor, antagonistic properties were also discovered. CBD inhibits FAAH (figure 1) and plays a role in allosteric modulation of μ- and δ-opioid receptors, though this is not a part of the ECS (Noreen, Muhammad, Akhtar, Azam, & Anwar, 2018), (Zagzoog et al., 2020). FAAH is the enzyme that is responsible for breaking down AEA.

Furthermore, outside the endocannabinoid system, cannabidiol is involved in the modulation of different receptors. At the serotonin receptors, CBD acts as a full $5HT_{1A}$ agonist, a $5HT_{2A}$ weak partial agonist, and a non-competitive antagonist of $5HT_{3A}$ (Morales et al., 2017). The ability of cannabidiol to activate the A_{1A} adenosine receptors has also been proposed (Gonca & Darıcı, 2015). Other activity at transient receptor potential (TRP) channels, PPARγ are described in table 2. At the glycine and GABA receptors, CBD's functionality is that of a positive allosteric modulator (Morales, Hurst, & Reggio, 2017).

CBD increases GABA levels, reducing the number of signals running through the central nervous system (Kuffler & Edwards, 1958).

CBG

CBG differs from CBD at a pharmacological level in a variety of ways. It functions more like THC at CB_1/CB_2 but with much lower affinity as seen in table 1 (Nachnani, Raup-Konsavage, &Vrana, 2021). Granja et al. (2012) argues that the affinity is so low that it does not fulfill any function here at all, but more in vivo research is needed to understand the CBG - cannabinoid receptor activity completely. At the six transient receptor potential cation channels, table 2 tells us that CBG differs little from CBD (Nachnani et al., 2021), giving CBD more potential as its effects are better studied. The GPR55 binding is not known from this research, though others (Morales et al., 2017) have stated CBG has a very weak effect on GPR55 as an inhibitor of lysophosphatidylinositol, an endogenous neurotransmitter ligand. CBG proved to be a very potent agonist at the a_2-adrenoceptor (with nanomolar to sub-nanomolar affinity), activating this receptor into inhibiting the release of noradrenaline and adrenaline through negative feedback (Levick, 2013). There is also a clear distinction in function between CBD and CBG with respect to the 5-HT_{1A} receptor. The former is reported to be an antagonist, meanwhile the latter acts as an indirect agonist (Nachnani et al., 2021). An important note is that these results have been obtained through experiment set ups involving animals, whole cells or subcellular preparations.

TABLE 1

Pharmacodynamic properties of Δ9-THC, CBD, and CBG at cannabinoid receptors

Binding affinities for Δ9-THC, CBD, and CBG at the two canonical cannabinoid receptors (CB1 and CB2), as well as a third receptor, GPR55 (commonly referred to as CB3). Δ9-THC acts as an agonist at all three receptors, whereas CBD acts as an antagonist; CBG acts as a weak or partial agonist at CB1 and CB2, and its function at GPR55 is currently unknown.

	Δ9-THC		CBD		CBG	
Receptor	Affinity	Function	Affinity	Function	Affinity	Function
	nM		*nM*		*nM*	
CB1	5.1–80.3 (Ki)*a,b*	Partial agonist	1458.5–4900 (Ki)*a,b*	Inverse agonist/antagonist	440–1045 (Ki)*b,c,d,e*	Weak agonist
CB2	3.1–75.3 (Ki)*a,b*	Agonist	372.4–4200 (Ki)*a,b*	Inverse agonist	153.4–1225 (Ki)*b,c,d,e*	Partial agonist
GPR55	8 (EC_{50})*f*	Agonist	445 (IC_{50})*f*	Antagonist	N.T.	Unknown

(Nachnani et al., 2021)

Table 2 gives deeper insights of the physiological activities at non-cannabinoid receptors and show that CBG tends towards GPCR mediated inhibition, autoregulatory activity through the endocannabinoid system and calcium based signaling.

TABLE 2

Pharmacodynamic properties of Δ9-THC, CBD, and CBG at noncannabinoid receptors

Binding affinities for Δ9-THC, CBD, and CBG at TRP ion channels, α-2 adrenoceptors, the serotonin receptor 5-HT_{1A}, and PPARγ are presented. Values are all EC_{50} for agonists and IC_{50} for antagonists.

	Δ9-THC		CBD		CBG	
Receptor	Affinity	Function	Affinity	Function	Affinity	Function
	nM		*nM*		*nM*	
TRPA1	230*a,b*	Agonist	110*a,b*	Agonist	700*a,b,c*	Agonist
TRPV1	N.D.*a,b*	Unknown	1000*a,b*	Agonist	1300*a,b,c*	Agonist
TRPV2	650*a,b*	Agonist	1250*a,b*	Agonist	1720*a,b,c*	Agonist
TRPV3	9500*b,d*	Agonist	3700*b,d*	Agonist	1000*b,d*	Agonist
TRPV4	850*b,d*	Agonist	800*b,d*	Agonist	5100*b,d*	Agonist
TRPM8	160*a,b*	Antagonist	140*a,b*	Antagonist	160*a,b,c*	Antagonist
α-2 adrenoceptor	N.T.	Unknown	N.T.	Unknown	0.2–72.8*e*	Agonist
5-HT_{1A}	N.T.	Unknown	N.D.*f,g*	Indirect agonist	51.9*d,e*	Antagonist
PPARγ	2120*h*	Agonist	2010*h*	Agonist	1270*h*	Agonist

(Nachnani et al., 2021)

CBN

Cannabinol (CBN) acts at both CB_1 and CB_2 receptors but with higher affinity for CB_2. In vivo, CBN has been shown to be a CB1 receptor agonist. This is why CBN has mild psychoactive properties, but in lower concentrations like CBD oil, this should not be a problem for day-to-day use. Although the activity at receptor CB_2 is unknown according to Turner at al. (2017) other speak of agonist behavior (Petitet, Jeantaud, Reibaud, Imperato, & Dubroeucq, 1998). Cannabinol also acts at targets outside of the endocannabinoid system. It is a potent agonist of TRPA1 cation channels, potently blocks TRPM8 cation channels, and also desensitizes TRPA1 cation channels to activation by the agonist allyl isothiocyanate. (Turner, Williams, Iversen, & Whalley, 2017).

CBC

Similar to CBG, cannabichromene (CBC) was a partial agonist of both CB_1- and CB_2-receptor dependent signaling, with great selectivity and potency at CB_2 relative to CB_1 in the assays utilized here (Udoh, Santiago, Devenish, McGregor, & Connor, 2019). At the TRP channels, CBN is a potent agonist of TRPA1 and can also desensitize the channel. This is its most important function as non-covalent modulator. It also functions as antagonist at TRPM8. CBC can normalize excessive sebaceous lipid production and at micromolar concentration and it increases the endocannabinoid level by inhibiting the cellular uptake of AEA and the enzymatic downfall of 2-AG (Pollastro et al., 2018). This small, but statistically significant antinociceptive effect of CBC in the tail withdrawal assay in mice was measured independently of cannabinoid receptors so the mechanism could also be due to the interaction with adenosine or $TRPA_1$ receptors (Zagzoog et al., 2020), (Pollastro et al., 2018).

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