ELECTRICAL HIGH; A REVIEW ON THE ELECTRICAL INTERACTION BETWEEN CANNABINOIDS AND THEIR RECEPTORS.

Abstract

Cannabis sativa contains an abundance of poorly understood ingredients, with literature generally focused on decarboxylated cannabinoids and slightly more than a dozen terpene or terpenic alcohols. Humans spread the unique plant across the globe, possibly during the Bronze Age, from a Tibetan Plateau due to its fibrous stalk. But it is the native cannabinoids, consisting of an extra moiety of carboxylic acid, which have liberated our deeper relationship with the cannabis plant throughout history. Embers or cooking produce enough heat to rapidly convert cannabinoid acids, leaving behind their decarboxylated variants alongside CO_2 as byproducts. Earlier work verified that one byproduct, tetrahydrocannabinol (Δ9-THC), binds to special receptors known as CB1 and CB2. CB receptors 1 and 2 are G-protein Coupled Receptors (GPCRs) known to respectively regulate dopamine, and glutamate and GABA. respectively. Tetrahydrocannabinol (THC) isomers contain a carbon side chain that enters pockets within transmembrane three and six of the CB1 receptor, consisting in part of valine and leucine. This biased agonism, importantly, dissociates a Gi/o protein that subsequently downregulates voltage-gated calcium channels and upregulates gated-inward rectifying potassium channels. CB1r agonists combined with allosteric modulators can alternatively bypass G-protein dissociation and instead regulate ERK

1/2 through beta-arrestin activation. Assays covering THC and CBD as CB1 receptor ligands extend from in-silico docking analyses to crystallography mapping. Shortcomings in the literature, unfortunately, exist with interactions across the whole plant. This paper asks why research gaps exist regarding raw acidic cannabinoid binding affinities and molecular dynamics of whole botanical formulations while exploring electrophysiological processes that occur within cannabinoid receptor binding domains.

Keywords: cannabinoids acids, electrical high, electron transfer, cannabinoid receptors

1.0 Introduction

Endocannabinology took form between 1988 and 1995 when researchers discovered receptors that interact with THC [1,2]. Early studies on mice indicate that cannabidiol (CBD) acts as an inverse agonist at the cannabinoid 2 receptor (CB2r) [3]. This was later discovered to not occur in humans [4], with studies showing agonism at the cannabinoid 2 receptor (CB2r) by cannabigerol (CBG) [5,6] and cannabidiol (CBD) in 2019 [7]. Not until 2023, however, was it understood how the polarity of complete cannabis formulations can alter interactions with CB2r [8]. In vitro and in vivo studies on cannabis, therefore, remain limited in their scope [9,10]. Further confusion occurs when comparing pharmacodynamics between pure compounds and preparations that contain a complete ensemble of ingredients extracted from cannabis chemovars.

Amino acids are protein building blocks that combine to form G-protein coupled receptors, including CB1 and CB2. A molecule such as THC manages to find pockets (keys) within the amino acid structure. Some amino acids contain positively or negatively charged molecular pieces, similar to Δ8 or Δ9-THC [11]. Temporary electron bonds can, therefore, occur between cannabinoids and their associated receptors [12]. Previous experiments revealed ionic 'salt' bridges, which include a bond that occurs between LSD and serotonin receptors [13].

Crystallography and cryogenic electron microscopy studies continue to provide new insights into the relationship between cannabis ingredients and human receptors [11,12] Yet, endocannabinology is a new entrant into the public health realm. The preliminary efficacy in successfully treating a variety of diseases using a whole-plant cannabimimetic formulation demands deeper investigations into electrophysical interactions to better understand the matrix of available bioactive botanical compounds which are responsible for such a successful treatment track record. This review examines available literature covering the atomic properties of cannabinoid receptors. It does not, however, expand into complete action potentials, chemoreceptors, or direct interactions with voltage-gated sodium channels.

2.0 The electrical nature of cannabinoids and Cannabinoid receptors

2.1 The cannabinoids

Cannabinoids exist in three primary groups: paleocannabinoids (phytocannabinoids), endocannabinoids, and neocannabinoids (synthetic cannabinoids) [14].

The first group are characteristic of the cannabinoids found in nature without human intervention. They are also known as phytocannabinoids. They represent the first group of cannabinoids isolated as compounds unique to the cannabis plant. The first cannabinoid discovered was oxy-cannabin in 1869 by [15]. They identified a compound produced after exposing a cannabis extract to nitric acid. The first elucidation of a true paleo, or phytocannabinoid, was in 1896. Three scientists identified an ingredient in a red oil which they named cannabinol (CBN) with the chemical formula $C_{21}H_{26}O_2$ [16], although some believe the discovery was rather the misidentification of an impure THC extract [17].

Chemical nomenclature follows that paleocannabinoids contain a resorcinyl core, an isoproprenyl residue, and a sidechain. The classic examples are structurally homologous to CBGa or CBGva if not a derivative of a true phytocannabinoid. [18]. In the clinical discipline, however, cannabinoids are active at the endogenous cannabinoid system or the larger endocannabinoidome.

'Endocannabinoid' are eicosanoid compounds produced by animals. They interact with mechanisms directly related to the endocannabinoid system. They include, but are not limited to, 2-Arachidonoylglycerol (2-AG) and *N*-arachidonoylethanolamine (anadamide, AEA.) The ECS includes receptors adapted to accept endocannabinoids, such as CB1r and CB2r [19].

Neocannabinoids include synthetic compounds structurally related to paleocannabinoids or synthetic ligands of the ECS. Beyond the main categories, an unofficial subgroup exists known as the *mycocannabinoids*. For example, a select truffle species produces a CB2 receptor agonist [20], and another produces anandamide [21]. Otherwise, biotechnology

companies can, with limitations, use genetic engineering to imitate paleocannabinoid biosynthesis in yeast and bacterial models.

Phytocannabinoid identified in cannabis are almost entirely lipophilic, whereas *Helichrysum produces* aralkyl cannabinoids [22]. Otherwise, novel hydrophilic neocannabinoids exist at the center of various research projects for their potential in designer drug delivery [23].

The lipophilicity of phytocannabinoids plays a critical role in their activity with receptors and determines their effects [24]. Structural alterations existing between cannabinoids exerts a considerable influence on their lipophilicity. Increasing the length of the side chain in homologous analog, results in an increase in lipophilicity of approximately 3-fold for each CH2 group added. Introducing a hydroxyl group will, however reduce the lipophilicity of the cannabinoid 3- to 40- fold depending on the site of attachment [24].

2.2 The cannabinoids receptors

Cannabinoid receptors 1 and 2 are typical in their structure but unique in their function of accepting lipid-based ligands. CB1 and CB2 are known as G-protein coupled receptors (GPCR), which simply define a protein associated with each receptor [1,2]. Once a ligand like THC binds to the active site, the receptor changes shape before one of the three *G-proteins* dissociates. The cannabinoid receptors are known primarily as Gi ligands. CB1r in skeletal muscle, for example, disassociates Gq and thus engages 2-AG synthesis via phospholipase C. Furthermore, allosteric modulation of CB1r, or disruption by pertussis toxin, induces Gs and upregulates the cAMP pathway [25]. In either case, a chain reaction then occurs involving a physiological effect, yet that process requires more

than a proper fit. Molecules must contain little bits, known as moieties, with the right ionic charge to conform to G-protein coupled receptors like CB1 and CB2 [26].

2.2.1 The binding Pockets

Cannabinoids bind to receptors based on a law of mass and electrical interactions, although the latter is less understood. Ligand binding to CB1 receptors depends on two amino acid toggle switches known as phenylalanine and tyrosine at transmembranes three and six, respectively. They form a cavity that accepts THC, yet [11]found differences between the two cannabinoid receptors at a different amino acid on transmembrane (TM) six. CB1 and CB2 receptors share 44% similarities. The CB1 receptor further depends on a flexible leucine to form a pocket for agonists like THC, unlike CB2r, which contains a more rigid valine at that same position [11].

Polarity further separates CB2 receptor agonists with a lipid bilayer that only receives non-polar ligands, which enter the receptor through a pocket formed by TM1 and TM7. Polar agonists instead use an alternate entry point identified by [8]. Cannabinoid formulations consisting of THC, CBG and CBGa, CBD, or (-)-CBC with increased polarity will, therefore, vary from non-polar extractions in cellular assays dependent on CB2 receptor binding [8]

2.2.2 Binding energies

Published in Chemical Neuroscience by the American Chemical Society, researchers conducted binding free energy calculations on D9-THC and CBD as CB1 ligands and confirmed that neither cannabinoid can fully agonize the receptor [27]. Each primary phytocannabinoid possesses a negative binding energy with a value that suggests an

unstable, temporary docking pose [28]. THC isomers are partial agonists of the CB1 receptor. Molecular docking research has since captured a limited understanding of how D9-THC binds transiently to one of two pockets, causing partial agonism [11]. Similar calculations on phytocannabinoids as potential cannabinoids receptor ligands have, however, not yet been elucidated for acidic and minor cannabinoids, such as tetrahydrocannabiphorol (THCp) and CBGa [12].

2.2.3 How they accept cannabinoids.

While scientists are yet to fully understand how cannabinoid receptors accept cannabinoids, the level of activity between cannabinoids and the receptors are influenced by the differences in the amino acid sequence of the binding pocket. Other factors include signalling mechanisms, tissue distribution and sensitivity of the compounds [25]. The success of their interaction depends on the cannabinoids' marked selectivity for the receptor type and the structure induced activity of the cannabinoids.

Cannabinoids and their receptors undergo a structure activity relationship (SAR) where the structure of the cannabinoid and the molecules attached to its side chains play a significant role in their activity with receptors. It is pertinent to note that cannabinoid receptors (CB1 and CB2) exhibit 48% similarity in their amino acid sequence. This largely dictates what compounds can interact with which receptor and how.

When observing the SAR between cannabinoids and receptors, some researchers have discovered that a dihydrobenzopyran-type structure with a hydroxyl group at the C-1 aromatic position and an alkyl group on the C-3 aromatic position appears as a major requirement for a successful binding between cannabinoids and CB receptors. Opening the pyran ring will lead to complete loss of activity if both phenolic groups are present

and not substituted. This is why (-)CBD shows less activity for both CB1 and CB2 receptors when compared to Δ^8- or Δ^9-THC [25].

In addition to the pyran ring, the aromatic hydroxyl group must be free or esterified before a significant CB1 activity is observed. Blocking the hydroxyl group as an ether will inactivate the molecule. Esters on the other hand may show little activity since they can undergo hydrolysis to the free phenols in vivo. This is why THC-acetate shows negligible activity in biochemical reactions where Δ^9-THC is active [25].

The length of the chain on C-3 is also very important. An average of 3 carbon atoms are needed to interact with the receptors. D9-THc has a pentyl group thus explaining its high affinity to CB1 receptors. Possessing a heptyl or higher side chain will strongly potentiate the cannabimimetic activity of the compounds that have low activity in the n-pentyl series [25].

2.3 THC & electrons, a unique fit

The idea that receptors work like a 'lock and key' — with the pins in the lock positioned to accept a specific key — began in 1894 by Emil Fisher [29]. Challenging this idea, for example, are varying isomers of THC unique by the position of one electron-bond in their cyclohexene ring. Delta-9 and Delta-8 fit into identical pockets, yet the two THC isomers differ in potency. Literature has not fully assessed how slight polarity shifts between the two isomers might affect ligand entry through the cellular membrane [1,26,30]. Alternatively, agonists bound to a helix in the CB1 receptor at transmembrane 7 depend on the cationic charge of a hydrophobic domain for efficacy [31].

3.0 The classic and the electrophysical perspective

Cannabinoid receptor activation works on a physical principle. A molecule with the right shape binds to a receptor, and the law of mass action forces the associated G-protein to disengage. For example, the side chain of carbon atoms attached to THC forces open structures within the CB1 receptor [11]. THCp contains a seven-carbon tail that locks into the same pocket as tetrahydrocannabivarin (THCv), although the shorter cannabinoid cannot reach a critical toggle switch and instead blocks the respective binding pocket [27]**.** D9-THC further depends on the hydroxyl group attached to its aromatic ring to induce an intoxicating effect. Hydroxyl groups possess a net negative charge unless they borrow electrons from elsewhere [32].

While we now better understand the physical interactions between THC and CB1 receptors due to particular crystallography assays. The second transmembrane of the CB1 consists of a histidine that, for example, must protonate before it forms electrostatic bonds with selective ligands [12]. Research still fails to describe electrical interactions between THCa and either cannabinoid receptor [33]. THCa contains the same net negative moiety as its decarboxylated form. In addition, however, acidic cannabinoids also contain a more evenly charged carboxylic acid (COOH). This means that, in the case of THCa, parts exclusive to the acidic cannabinoid possess a more evenly distributed electrical charge [31]. One study tested molecular interactions between an oxidating cationic compound and either THCa or THC. Results suggest that the decarboxylated cannabinoid possesses more efficient electron transfer and anti-oxidant potential. This is due to the carboxylic acid bound to THCa borrowing a proton from the neighbouring phenolic

(-OH) group. Relative electrical neutrality does not, however, occur in other cannabinoid acids [31,32].

Ionization potentials indicate that THC more liberally donates electrons and is more susceptible to oxidation. The IP value of THC is 138.88 kcal mol^{-1} compared to 142.33 kcal mol^{-1} for CBD. A previous study concluded similar results but with 20 kcal mol^{-1} greater values. The results for THC are similar to butylhydroxytoluene (BHT), which equally prevents chemical oxidation. Whereas CBD has similar antioxidant potential as alpha-tocopherol and hydroxytoluene [32].

3.1 – Ions and their voltage gates down the CBr stream

Downregulation of voltage-gated calcium current and upregulation of gated-inward rectifying potassium channels (GIRKs) occurs following biased activation of either cannabinoid receptor. Selective CB1 agonists bind to Gai to regulate Ca+ and K+ and to inhibit cAMP activity. Biased CB2 receptor agonists must dissociate the ϐ/y subunits of the Gai protein to activate GIRKs and turn down calcium current [34]. Phytocannabinoids, however, display further interactions with ion channels via [35–37] GPR55 dependent on lysophosphatidylinositol (LPI) expression [38,39] and transient receptor potential channels.

Cannabimimetics following GPCR and the kinetic interactions they depend on are well explored. Deeper electrical and atomic involvement in ligand-receptor binding is less

explored due to limitations in analytical techniques. Electrophysiological studies detailing likewise investigations into the latter exist for a select few hydrophilic GPCRs, including voltage membrane-dependent $GABA_A$ receptors [40]. Studies on cannabis formulations and electron transfer also exist regarding moderation of mitochondria and a few endogenous and phytocannabinoids [41–43].

3.2 Oxidative stress down an electron transport chain

Before the discovery of cannabinoid receptors, researchers investigated how THC affects mitochondria as early as 1972. Rat livers expressed mitochondria that responded to doses of Δ9-THC, according to an 8-anilinonaphthalene-1-sulfonic acid (ANS) flouresence probe [42]. Living organisms consist of cells that, during normal function, burn energy produced as adenosine triphosphate (ATP). Mitochondria are known as anaerobic organelles, which exist and produce ATP within aerobic cells. ATP synthase demands a polarized environment, which occurs following electron delivery to the inner mitochrondria. Limitations remain in the literature, although evidence suggests that cannabinoid receptors also regulate the electron transport chain (mETC) [43,44].

The mETC is a system that involves cationic and anionic mineral nutrients and two molecules that transport electrons through mitochondrial membranes. Nicotinamide adenine dinucleotide (NADH), an electron donor, is a molecule at the start of the mETC. An experiment conducted by researchers from McGill University, published in The Journal of Biological Chemistry 1976, discovered how Δ9-THC interacts with NADH [44]. Earlier results concluded that liphophillic cannabinoids interact with membranes. Since

then, however, experiments revealed those findings depended on Gai protein dissociation post cannabinoid receptor activation. Bénard et al. (2012) employed receptor knockout mice to verify that CB1 agonists regulate energy production within mitochondria.

2-AG levels were detected in measurable levels in brain mitochondria. Researchers, therefore, blocked endocannabinoid degradation in normal mice and mice bred without CB1 receptors. Brain respiration only changed in mice with CB1 receptors, showing that the brain contains cannabinoid receptor-expressing mitochondria and a respective ligand. Typical cAMP and protein kinase A involvement occurs in cellular respiration, although results also displayed dependence on electron complex 1 [42]. This gives plausibility for whole cannabis formulations to interact with the mETCS through receptor agonism via decarboxylated THC isomers but also by the preservation of an endogenous ligand in an aggressive environment via CBGa > THCa > CBG [27,44].

4.0 Allosteric influence of whole plant formulations at CB receptors

The ensemble of effects between cannabinoids and terpenes remains poorly understood. Earlier evidence revealed that CBD must follow an agonist into CB1r to moderate the receptor from an allosteric position [3,7]. Whole cannabis formulations still displayed unique properties relative to pure isolated compounds with little explanation in the literature [10,26]. Recent experiments do, however, explain how amino acid conformations cause less acute CB2 receptor plasticity relative to domains within the CB1r [11]. The electrical uniformity of a cannabis formulation might affect its medical value by modifying access to the CB2 receptor [8]. Whole cannabis formulations can induce CB2

receptors with various selective binding potentials from several individual ingredients. Current analytical methods to understand activity at either cannabinoid receptor poorly capture a complete schematic of cannabis pharmacology.

Carrier oils are typically understood as containing a neutral pharmacodynamic profile adjacent to cannabis preparations. Interactions between cannabinoid receptor binding and ingredients comprised of electron/proton donors or acceptors are often constrained to pharmacokinetics while investigating the entourage effect of cannabis chemovars. In addition, protein displacement following GPCR activation is a small caveat of cannabis therapy. Cannabis formulations interact with several types of receptors, including tyrosine kinase receptors and ion channels. Endocannabinologists must appreciate the multiplex of systems that define an organism to understand cannabis's intricate properties.

5.0 Conclusion

Anecdotal reports suggest that the ensemble of ingredients in a cannabis chemovar will induce a unique therapeutic profile for each patient. Extractions that preserve native components in a given chemovar will further generate a greater sum of medical efficacy across whole botanical formulations relative to degenerative processing methods. Cannabis induces a set of therapeutic mechanisms that appear further dependent on polarity and electrical distribution across the totality of each preparation. Careful extraction and formulation methodologies combined with dose delivery operations that do not drastically alter a prepared chemovar can, therefore, grant patients greater efficacy during selective treatment regimens.

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