The history, mechanism of action and social impacts of cannabis

History

Cannabis, a class B drug, acts as a relaxant, enhances perception, and delivers a euphoric effect to its user. The drug is extracted from the plant Cannabis sativa L which originates from Central Asia (Andre et al., 2016); this plant has 400 chemical entities, 60 of which are cannabinoid compounds (Atakan, 2012). Colloquially, known as weed, grass, and marijuana, Cannabis dates back to 2700 BCE, written in the Shennong Ben Cao Jing. The Shennong Ben Cao Jing is a Chinese book on agriculture and medicinal plants, where Shennong wrote about the hallucinatory effects, appetite stimulation, tonic, and anti-senility effects of Cannabis (Russo, 2014). The first compound to be extracted from the plant was cannabinol, which was thought to have a psychoactive effect. However, it was later discovered that this was incorrect. Then in 1963, Mechoulam and Shvo extracted a second compound from it called cannabidiol, also known as CBD. This discovery led to the isolation of delta-9-tetrahydrocannabinol (d-9-THC) the following year by Gaoni and Mechoulam, the primary psychoactive compound (Atakan, 2012) [Index *figure 1*].

In 1968 clinical investigation started to recognise the clinical applications of Cannabis. Between then and 1985, the discovery of its various properties, such as; using it as an anticonvulsant and antiemetic to decrease anxiety and intraocular pressure. However, the mechanism by which this drug acted was still unclear until 1988, when the cannabinoid receptor CB_1 was discovered. A year later, it was understood that this receptor was a G-protein coupled receptor, and following this, in 1993, the CB_2 receptor was identified (Russo, 2014).

Throughout the discovery of Cannabis, the understanding of its effects, and the innovation in medical uses, it underwent some legal scrutiny. In the UK, in 1928, the use of Cannabis was prohibited under the 1925 Opium Convention, classifying Cannabis under the Dangerous Drugs Act 1920 (Manning, 2013) (Porter, 2016). Around this time, many other countries also made the use of Cannabis illegal and criminalised it. Regardless, some countries still allow medicinal and personal use of it. It was not until 1996 in the USA, California, that the jurisdiction changed, and Cannabis was legalised for medicinal use (Bartos et al., 2019). Promptly, in 2004 the UK decided to strip Cannabis of its class B title and move it down to class C, as its class was disproportionate to its inherent toxicity and other substance within its class (Home Office, 2002). However, this quickly pivoted in 2009 when Cannabis was given its class B classification based on concern surrounding a link between high-strength Cannabis and schizophrenia (Hamilton et al., 2014). Since then, it has stayed as a class B drug in the UK, landing individuals 5 years in prison for possession and up to 14 years for supply or production.

Mechanism of Action

Cannabis contains multiple compounds, thereby triggering a bodily response by multiple mechanisms of action. The 2 main compounds within Cannabis are CBD and THC, more formally known as cannabidiol and delta-9-tetrahydrocannabinol, respectively. Endogenous cannabinoids, such as Cannabis, are taken for relaxation, enhancement of perception, and euphoria. THC is a low-efficacy, partial cannabinoid agonist that acts on G protein-coupled CB_1 and CB_2 receptors (Paronis et al., 2012). CB_1 receptors are found in neurons, and CB_2 receptors are found in the periphery. CB_1 interactions cause CNS effects via coupling to G_i, subsequently inhibiting adenylate cyclase, activating ion channels, such as K^+, and inhibiting Ca^{2+} channels (Page & Pitchford, 2020). THC has a similar structure to anandamide, an endogenous cannabinoid that functions as a neurotransmitter [Index *figure 2*]. They both contain a fatty acid chain making them lipophilic molecules, allowing them to pass the blood-brain barrier, causing CNS effects. Anandamide is derived from phosphatidylethanolamine. The precursor to anandamide is NAPE which is hydrolysed by multiple enzymes to convert to anandamide [Index *figure 3*]. Anandamide modulates the brain's reward system by indirectly interacting with the dopamine system. This is why THC exerts a euphoric effect when smoked or consumed, it causes an increased extracellular level of dopamine. This effect is via the CB_1 receptor, as CB_1 antagonist Rimonabant blocks this effect indicating a link between extracellular levels of dopamine and CB_1 (Scherma et al., 2018). THC also exerts other effects, such as; increased appetite, inhibition of nausea and

vomiting, and modulation of muscle contraction. CB_1 receptors are highly concentrated in the hippocampus, cerebellum, and hypothalamus. Therefore, Cannabis user experience memory loss effects, loss of coordination, and change in appetite and body temperature control, as these portions of the brain are responsible for these functions (Rang et al., 2012).

CB_2 receptors are located in the periphery, and when activated, have inhibitor effects on immune cells such as macrophages and T cells. When CB_2 receptors are activated alone, they do not have psychotropic effects (Dhopeshwarkar & Mackie, 2014). CB_2 has a lot of downstream effects, which can result in the gene expression of various genes that inhibit inflammatory and pain responses [Index *figure 4*]. Alongside this, it is recognised that CB_2 stimulation can have a protective effect over an anti-tumoral signature in B-cell acute lymphoblastic leukemia, helping to reduce the development and maintenance of these tumours (Punzo et al., 2022).

The other primary compound in Cannabis is CBD; however, CBD has a low affinity for CB_1 and CB_2 receptors, thus not causing a euphoric effect. CBD interacts with the multiple receptors in the body, but mainly the 5-HT_{1A} receptor delivering an anti-anxiety effect [Index *figure 5*]. Cannabis displays a full agonist effect on the 5-HT_{1A} serotonin receptor, with which serotonin endogenously interacts (MOHAMMAD-ZADEH et al., 2008). Serotonin is a neurotransmitter that has a variety of mechanisms within the body and is known for its role in mood and gastrointestinal motility. It interacts with the family of receptors known as the 5-HTP. The 5-HT_{1A} receptors are predominately located in the CNS, regulating sleep, feeding, thermoregulation, and anxiety. This receptor is a GPCR (G_i/G_o), which reduces intracellular cAMP and may also modulate Ca^{2+} channels. CBD can interact with this receptor, causing these effects, but also other agonists such as; Buspirone, 5-CT, and 8-OH-DPAT can modulate these effects too (Rang et al., 2012).

Social Impacts

Alongside the variety of effects Cannabis has on the body, it profoundly affected society, even dating back to 2700 BCE when it was used for Chinese medicine (Russo, 2014). Politically, there have been many stances on the substance with its changing class due to its apparent relation to Cannabis causing schizophrenia. Reviews covering Cannabis use and the development of schizophrenia highlight that Cannabis use roughly doubles the risk of becoming schizophrenic (Smit et al., 2004). Research has mainly looked into the development of schizophrenia in adolescence that use it frequently. This raises the question of whether it could be legalised with an age restriction, like, alcohol and cigarettes that causes other diseases such as alcoholic hepatitis, lung cancer, and fibrosis. Adding an age restriction would allow the consumer to understand the adverse effects and make more informed decisions when using it. Furthermore, this would allow for education around the subject in school curriculums and in house holds, as it would be more socially acceptable. This could influence people to use Cannabis in moderation and a more sensible manor. Potentially, this could also reduce the development of schizophrenia; however, there is insufficient knowledge on Cannabis' effects on large-scale populations and if it plays a role in psychosis development in larger populations like this. There are states in the US that have now legalised the use of Cannabis, and research could be done on populations like this to give us a broader understanding of how the population could be affected (Hamilton & Monaghan, 2019). The illegal drug market for Cannabis is large, and a significant problem we would have if we made Cannabis legal is drug dealers selling to the younger population. This would be due to adults no longer being targeted by drug dealer, as they would be able to buy Cannabis legally. Consequently, this could potentially increase the prevalence of schizophrenia in the long term due to more adolescents buying and consuming Cannabis. Also, current research in 2021 has looked into Cannabis causing psychosis in genetically predisposed people. It was discovered that people who carry the specific variant of the AKT1 gene, coding for an enzyme that affects dopamine signalling in the striatum, are more at risk. It was revealed that people that smoked weed daily with this variant were seven times more likely to develop psychosis (Is there a link between marijuana use and psychiatric disorders? 2021) [Index *figure 6*].

Although marijuana socially can lead to many legal implications, the medicinal use of Cannabis is an ongoing blossoming field. Cannabis is legally allowed in medicine now in the UK and the US for a specific diagnosis criterion; multiple sclerosis, adults with nausea and vomiting during chemotherapy, Lennox-Gastaut syndrome, and glaucoma. During chemotherapy, many patients

experience nausea due to chemotherapy being a toxin that is entering the body. Thus natural selection causes the body to have a vomit response to extract the toxin from the body. Alongside this, in the brain is the chemoreceptor trigger zone which senses damage or toxicity from the blood. During chemotherapy, serotonin in released in the gut and goes to the CTZ, binds the $5HT_3$ receptor in the vomiting centre, causing patients to feel nauseous and vomit. Cannabis compound CBD has inhibitory effects on the $5HT_3$ causing suppression and alleviating these symptoms during treatment. Furthermore, cannabinoids can inhibit norepinephrine release via activation of the CB_1 receptor; this indirectly inhibits the release of aqueous humour, thus making Cannabis an excellent method to combat glaucoma symptoms.

To conclude, Cannabis has been around for an extended period, and over this time, the negatives have been brought to light, but also the benefits in which it can advance medicine. Greater research into its mechanism in disease treatment and its interaction with specific genetic factors needs to be broadened. Alongside this, understanding its effects on large-scale populations needs to be studied to utilise it to its full potential. However, this natural plant that propagates in sunny climates may have more potential uses in therapeutics, like aiding anxiety disorders and sleep disorders, but also as an antiemetic or analgesia.

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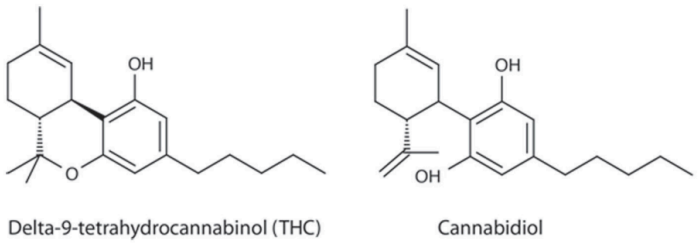

Figure 1. Chemical structure of THC and CBD (Russo & Guy, 2006)

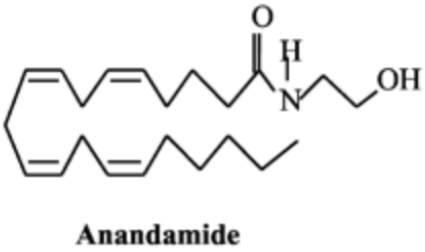

Figure 2. Anandamide structures (Baskfield et al., 2004)

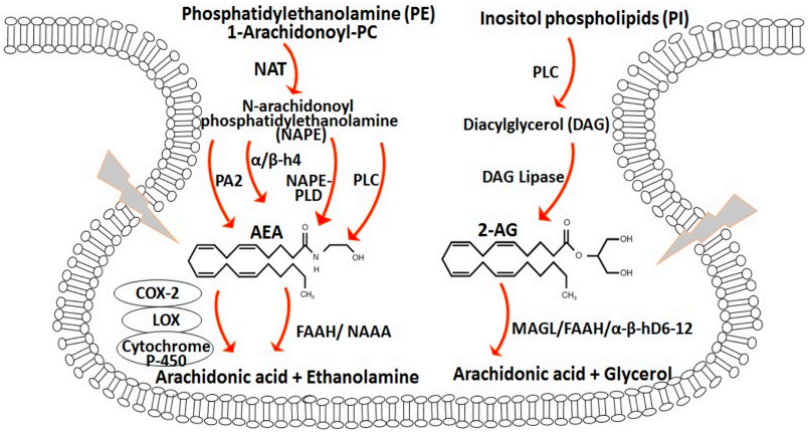

Figure 3. The biosynthesis and degradation of anandamide (Scherma et al., 2018)

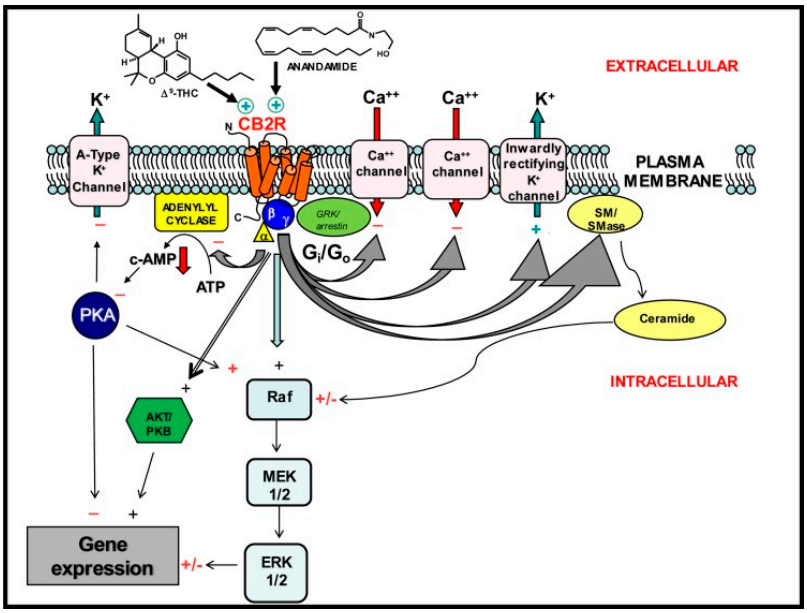

Figure 4. Downstream cascade due to activation of the CB_2 receptor (Dhopeshwarkar & Mackie, 2014).

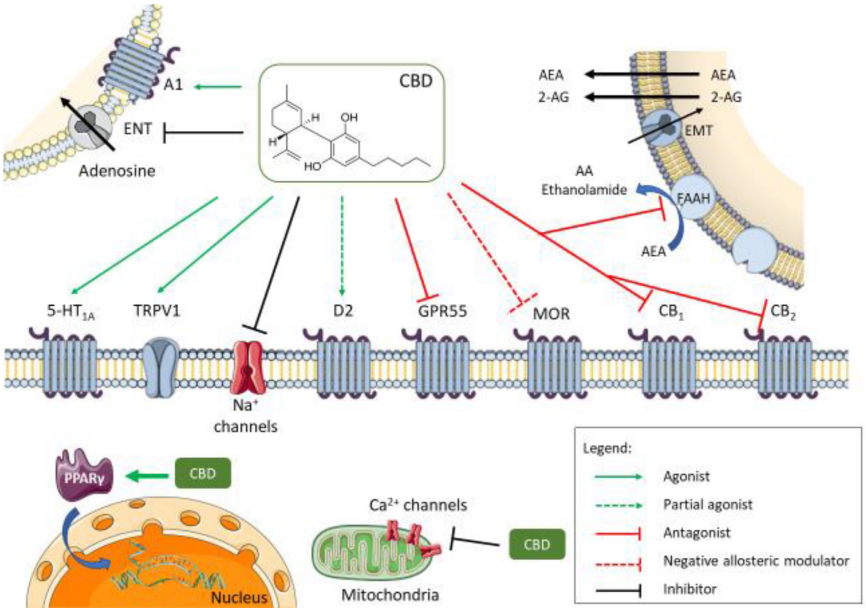

Figure 5. CBD receptor interactions within the body (Almeida & Devi, 2020)

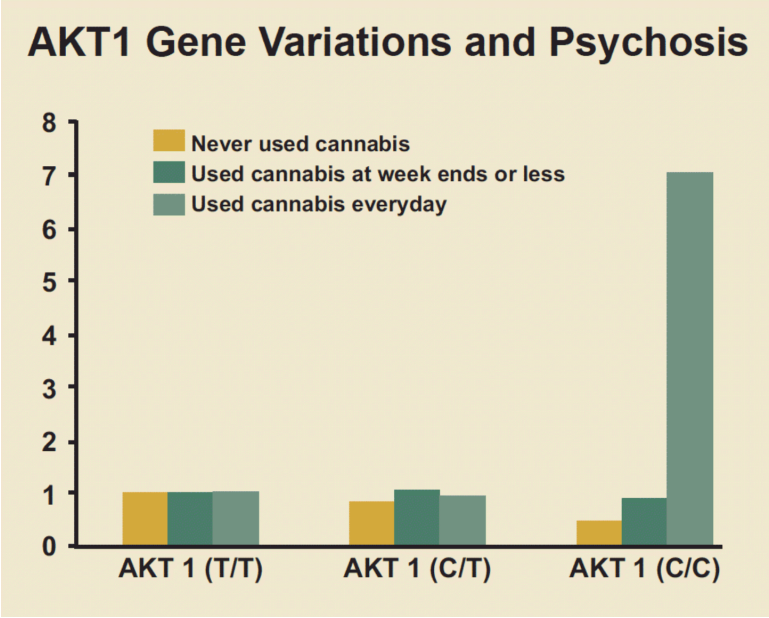

Figure 6. Development of psychosis when smoking Cannabis in the population with AKT1 genes (Is there a link between marijuana use and psychiatric disorders? 2021)

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