Cannabis

Introduction

Cannabis, a plant with a rich history of medicinal and recreational use, exerts its effects primarily through its interaction with the endocannabinoid system (EC). Understanding how cannabis, particularly its active component THC, affects the EC system provides insights into both its therapeutic potential and its risks.

The Endocannabinoid System (EC) and its function

The endocannabinoid system is a complex retrograde signalling system that plays a crucial role in regulating various physiological processes. **The EC system consists of endogenous cannabinoids (endocannabinoids) like anandamide (AEA) and 2-arachidonic glycerol (2-AG)**, their receptors (primarily CB1 and CB2 receptors), and the enzymes responsible for their synthesis and degradation. Endocannabinoids are lipid-based molecules synthesized on demand and rapidly degraded, by enzymes **like fatty acid amide hydrolase (FAAH)** allowing for tight spatial and temporal control of their effects.

The endocannabinoid system's dynamic nature allows it to tune neuronal activity and maintain homeostasis finely. **Endocannabinoids like 2-AG act as retrograde messengers**, released from postsynaptic neurons in response to increased **intracellular calcium levels**. They **travel back across** the synapse to bind to **presynaptic CB1 receptors**, **modulating** the release of neurotransmitters. This process, known as **depolarization-induced suppression of inhibition (DSI)** or excitation (DSE), **DSI occurs in hippocampal pyramidal cells** and plays a vital role in **synaptic plasticity**, learning, and memory

MAGL terminate 2-AG

The endocannabinoid system also plays a crucial role in neurodevelopment, particularly during synaptogenesis, where it guides synaptic connections. Termination of 2-AG signalling induces synaptogenesis, but THC exposure disrupts this process, leading to long-lasting changes in brain wiring. Prenatal THC exposure has detrimental cognitive and behavioural effects throughout life, as EC signalling is essential for neurodevelopment, especially during late adolescence when significant myelination and synaptic changes occur. This disruption in EC signalling due to THC can lead to lifelong impacts on brain function, particularly concerning given the widespread cannabis use during adolescence.

CB1 and CB2 Receptors

CB1 receptors are the most abundant **G-protein coupled receptors (GPCRs)** in the brain and are widely distributed in regions associated with **reward, emotion, motor function, pain processing, and cognition**. They are densely located in the **basal ganglia, cerebellum, hippocampus, cortex**, and **pain-associated regions** like the **periaqueductal grey (PAG)** and **spinal cord dorsal horn**. CB1 receptors are primarily **expressed on presynaptic terminals,** where they modulate neurotransmitter release Cannabinoid receptors are not limited to the brain; they are **also found in peripheral tissues.** For example, **CB1 receptors are present in endothelial cells**, adipocytes, and **peripheral nerves**. Activation of these receptors promotes lipogenesis and **influences body weight**, which could contribute to the **increased appetite** often observed in cannabis users. CB2 receptors, primarily located on **immune cells**, mediate the **anti-inflammatory and neuroprotective effects** of cannabinoids. They are found in the **spleen, tonsils, thymus, and various circulating immune cells.** The presence of CB2 receptors in immune cells suggests that cannabinoids can modulate

immune function, providing therapeutic potential for inflammatory and autoimmune diseases (Chiurchiu et al., 2014).

THC Mechanism and Effects

THC (Δ9-tetrahydrocannabinol), the primary psychoactive component of cannabis, exerts its effects by binding to **CB1 receptors in the brain**. This interaction initiates a cascade of intracellular events leading to the **inhibition of adenylate cyclase**, reduction of cAMP levels, and modulation of ion channels. Consequently, **THC reduces neurotransmitter release** from presynaptic neurons, affecting various neurotransmitter systems, including **GABAergic and glutamatergic pathways.** THC's binding to CB1 receptors also activates G protein-sensitive inwardly rectifying potassium (GIRK) channels, causing membrane hyperpolarization and further inhibiting neurotransmitter release (Pertwee, 2015).
The biphasic effects of THC arise from its action on CB1 receptors at different concentrations. At low doses, **THC can activate CB1 receptors** on **GABAergic** interneurons, **reducing GABA** release and thereby **disinhibiting dopaminergic neurons.** This disinhibition leads to **increased dopamine** release in reward-related areas such as the nucleus accumbens, **contributing to the euphoria and pleasure** associated with cannabis use. However, at higher doses, **THC can also activate CB1 receptors on glutamatergic neurons**, leading to a **decrease in glutamate release**. This action can result in **hyperlocomotion, hypothermia, and catalepsy**, as observed in rodent studies (Rubino et al., 2012).

THC's Disruption of EC System

THC's interaction with the EC system can disrupt this delicate balance. Chronic exposure to high doses of THC can lead to **downregulation and desensitization of CB1 receptors,** resulting in tolerance. This means that over time, higher doses of cannabis are required to achieve the same effects, as the receptors become less responsive. Additionally, prolonged THC exposure can alter the expression and activity of enzymes involved in endocannabinoid synthesis and degradation, further **affecting EC signalling** (Pertwee, 2015).

CBD Mechanism and Effects

Cannabidiol (CBD), another major component of cannabis, **lacks the psychoactive properties of THC** but can **exhibit anticonvulsant activity**. CBD lacks the affinity for CB1 and CB2 receptors. It mainly modulates the **endocannabinoid system by inhibiting FAAH**, an enzyme necessary to metabolize 2-AG, which increases the concentration of 2-AG and enhances endocannabinoid signalling. One important aspect of the relationship between THC and CBD is their **complementary and sometimes opposing effects**. So CBD has been shown to **ameliorate some of the effects of THC**, providing a potential therapeutic balance. For instance, while THC induces euphoria and potential anxiety at high doses, CBD can counteract these effects, making cannabis-based medications **more tolerable for patients.** This is possibly due to **CBD binding to 5-HT1A receptors**. Science agonist of 5-HT1A is a treatment for anxiety. High levels of THC can lead to a reduction in CBD content in cannabis strains due to selective breeding practices, creating a cycle where the protective effects of CBD are diminished, leading to more pronounced adverse effects from THC.

Therapeutic Potential and Risks

The therapeutic potential of cannabis lies in its ability to modulate the EC system. For example, THC and other cannabinoids have shown promise in **managing chronic pain**, as CB1 receptors are abundantly expressed in pain pathways. By modulating neurotransmitter release in these pathways, cannabinoids can **reduce pain signalling and provide analgesia.** Similarly, cannabinoids' **anti-inflammatory and neuroprotective properties**, mediated **through CB2 receptors on immune cells,** offer potential benefits for conditions like multiple sclerosis and neurodegenerative diseases. However, the therapeutic use of cannabis is **not without risks**. Chronic cannabis use has been linked to adverse effects such as **cognitive deficits, anxiety, and the potential for addiction.** The biphasic nature of **THC's effects means that while low doses might offer therapeutic benefits, higher doses can lead to negative outcomes**. For instance, while low-dose THC may reduce anxiety, higher doses can induce anxiety and panic attacks. Additionally, as disscuss before, the developing brain, particularly **during adolescence**, **is highly susceptible to the disruptive effects of THC**, which can interfere with neurodevelopmental processes and lead to **long-term cognitive impairments**

Conclusion treatment for PD AD

In conclusion, cannabis exerts its effects primarily through its interaction with the endocannabinoid system, a critical regulator of neuronal activity and homeostasis. THC, the main psychoactive component of cannabis, modulates neurotransmitter release by binding to CB1 receptors, resulting in both therapeutic and adverse effects. The biphasic nature of THC's action and the dynamic adaptability of the EC system highlight the complexity of cannabis' impact on the brain. While there is significant potential for the therapeutic use of cannabinoids, careful consideration of dosage and long-term effects is essential to maximize benefits and minimize risks. Further research is necessary to fully understand the mechanisms underlying cannabis' effects and to **develop targeted therapies** that harness the positive aspects of the endocannabinoid system while mitigating its negative consequences.