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The Endocannabinoid System: A Primer



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Module Overview

- Two most known ECS receptors: CB1 + CB2
- Two primary endogenous cannabinoid neurotransmitters: anandamide + 2-AG
 - Enzymes that break down these neurotransmitters: FAAH + MAGL





CB1 Receptor Variability

- Receptor patterns + locations (cortex, hippocampus, hypothalamus, cerebellum, basal ganglia) in the brain are unique to individuals
- Helps to explain the diverse and broad effects of cannabis
- Receptors on spinal cord explains pain modulation + the pain signal to the brain





Cannabis Is Safe

- Nontoxic but not innocuous
- Does not depress the respiratory system or the heart, as do opioids
- Cannot overdose or die from cannabis, but can create an unpleasant experience





CB1 Drives Energy Production

- Receptors are located inside cells + neurons, not on membrane wall
- Helps to explain why CB1 regulates the mitochondria





Cannabis + Memory Therapy

- CB1 is useful for the extinction of memory
- Valuable for PTSD + sexual abuse victims





Cannabis Tolerance

- Some motor impairment with cannabis, but not as severe as alcohol
- Continued cannabis use enhances the body's tolerance
- Beginning use of cannabis should be low and slow





CB1 + Glutamate Regulation

- CB1 helps regulate glutamate, a brain neurotransmitter
- Glutamate is excitatory, giving the brain a green light for neurotransmission
- Process may help explain why cannabis can help with MS





Cannabis + Cellular Health

- CB1 located inside lysosomes + endosomes, helping to remove cell waste products (misfolded proteins)
- Process may help to explain why cannabis can help with neurodegenerative disease





Broad Implications for CB1

- Knockout mice bred with no CB1 receptors enable valuable research
- No CB1 indicates propensity for addictive behavior, anxiety + depression
- CB1 locations on brain glial cells act as a protective system for neurons, helping to explain why cannabis tames inflammation in central nervous system





Cannabis as Personalized Medicine

- Brings the body into balance (homeostasis) to lessen inflammation, activate immune system
- Response can vary greatly among individuals, requiring significant patient involvement to help determine best strains + method of ingestion





The Tale of Cannabis + Opium

- Cannabis + opium share a long history as medicine
- Morphine molecule from opium revolutionized pain treatment
- THC was first isolated by Raphael Mechoulam in 1964
 - Discovery of CB1 receptor 20 years later → helped clarify how THC works





The Discovery of Anandamide

- Anandamide: the neurotransmitter of balance
- Endogenous compound can be therapeutically activated by upregulating the ECS system via cannabis





The Mystery of Anandamide

- Unclear exactly which pathway in the brain produces anandamide
- Levels are highest in uterus which may infer importance in pregnancy + implantation
- Quick-acting, fast-response molecule that dissipates quickly versus THC, which lingers in the body





CB2 Receptor Landscape

- CB2 most present in immune cells of the blood + every organ of the body
- CB2 appears to create a psych-neuro-hormonal communication, connecting the body to the brain
- Significant activation of CB2 receptors occurs during brain injury + inflammatory repair





CB2 Lowers Inflammation

- CB2 lowers inflammation across a wide range of diseases
- Beta caryophyllene (terpene) activates + binds to CB2
 - Cultivars (commonly called strains) with high levels of this terpene seem to do well for pain management
- Terpenes + cannabinoids combine for the entourage effects, maximizing therapeutic outcomes





More on CB2

- Many cannabinoids, terpenes, flavonoids contribute to CB2 activation, making it difficult to segment how cannabis influences the ECS
- Highest levels of CB2 found on T-cells (the immune system's killer cells), helping to explain how cannabis can combat disease
- CB2 is present on organs throughout the body, resulting in widespread therapeutic results across many health conditions





CBD for Multiple Use

- All cannabinoids influence bone health + hormonal balance, but especially CBD (cannabidiol)
- CBD as a protective measure for women over 55 may be indicated
- The activation of CB2 by using CBD may help with cardiovascular disease, GI issues, liver inflammation, kidney disorders + more





2-AG: An Endogenous Cannabinoid

- Neuroprotective after brain injury
- Works on the vagus nerve axis + is present in higher levels than anandamide
- Metabolized by Cox-2 enzyme, enabling various versions of the molecule to be present
- High levels found in breast milk, influences placenta proliferation + apoptosis





The Intricacy of 2-AG

- Difficult to know the exact mechanism + how to harness the power of 2-AG
- In some cases, controlling/reducing 2-AG may provide therapeutic response
- Pharmaceutical companies researching the hydrolysis of these compounds





FAAH – Fatty Acid Amide Hydrolase

- Enzyme which breaks down anandamide to regulate the ECS
- FAAH may balance anandamide + 2-AG to maximize the ECS





FAAH + MAGL

- Variations of FAAH molecule among individuals help explain different responses to pain + anxiety
- Enzyme MAGL is responsible for 2-AG breakdown
- Inhibiting MAGL allows for more 2-AG, which facilitates brain injury repair
- Balancing act of moderation may be the key to activating both these enzymes





Wrap-Up

- Key components of the ECS include
 - CB1 + CB2 receptors
 - anandamide + 2-AG
 - accompanying control systems – FAAH + MAGL
- Variability among individuals (different ECSs + cannabinoid response) = personalized lifestyle approach to cannabinoid medicine

