

Cannabis and Health

Module 1

Lecture 5: More on Cannabinoids in the Brain

Cannabinoid Pharmacology

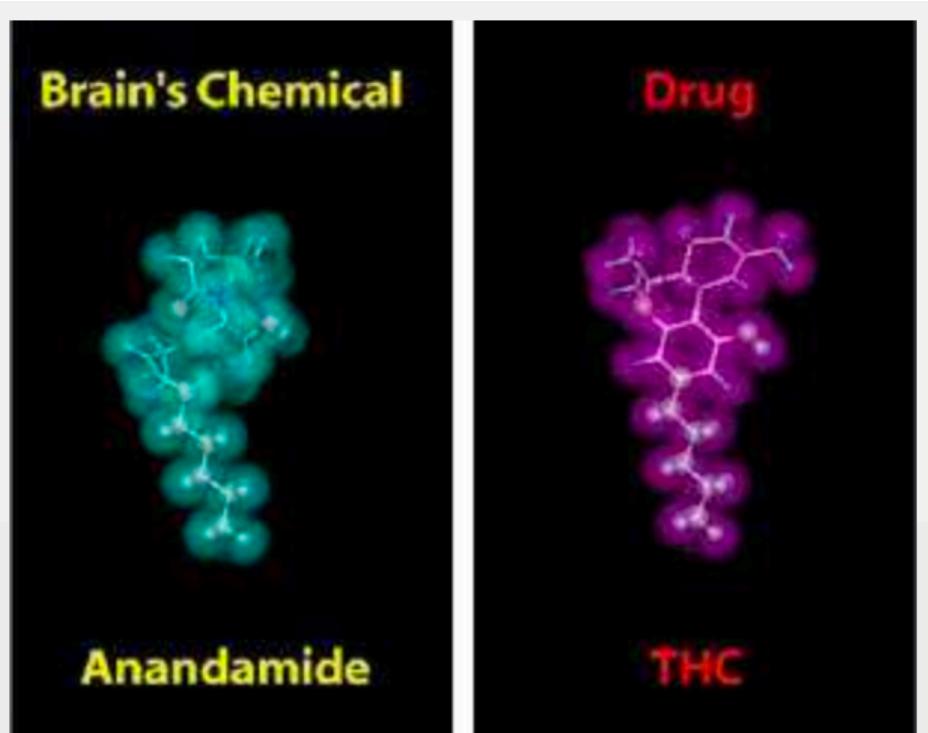
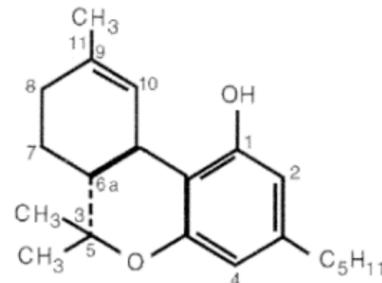
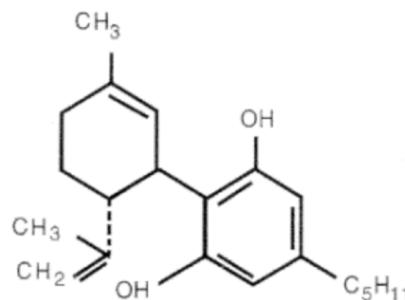


Image by the NIDA

THC's chemical structure is similar to the brain chemical anandamide. Similarity in structure allows drugs to be recognized by the body and to alter normal brain communication.



Δ^9 -Tetrahydrocannabinol (Δ^9 -THC)



Cannabidiol (CBD)

The Endocannabinoid System (ECS)

- To understand the pharmacology of cannabinoids, we need to understand the ECS
- There are two endocannabinoids, 2-archidonoylglycerol (2-AG) and anandamide
- 2-AG and anandamide can act via CB₁ and CB₂ receptors to exert a range of biological effects in central and peripheral cells
- Anandamide is broken down by FAAH; Inhibitors of FAAH lead to increased anandamide (therapeutic potential)

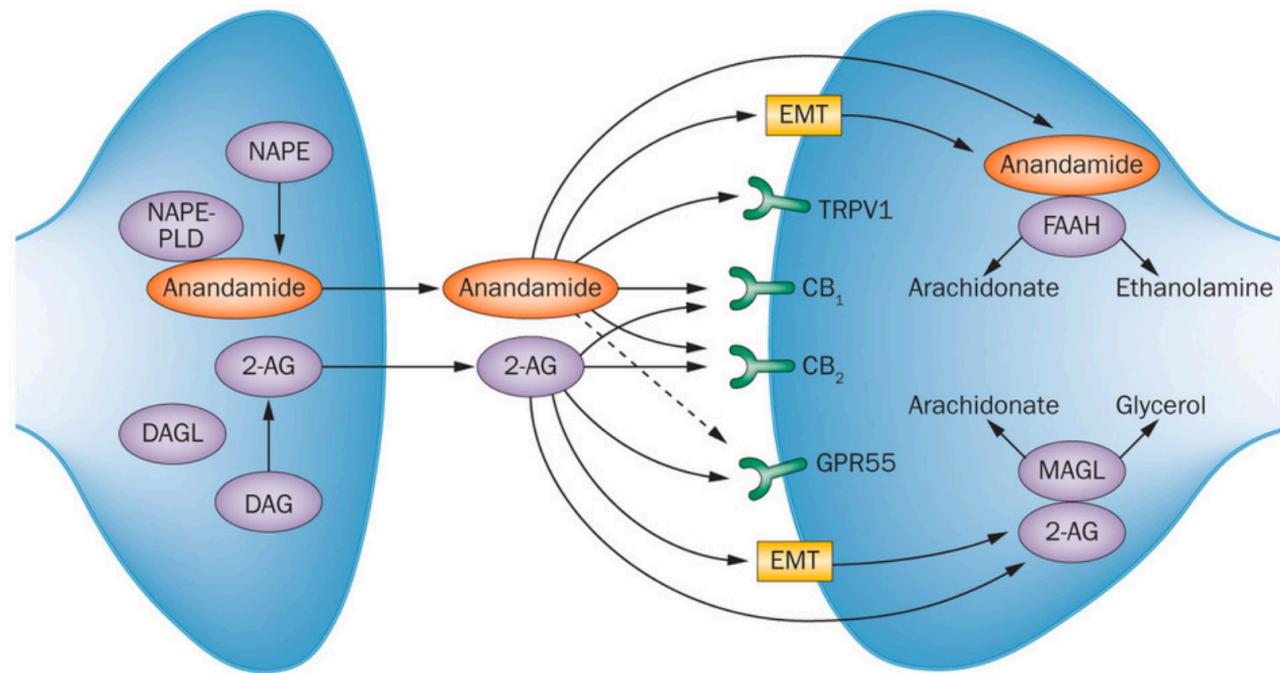
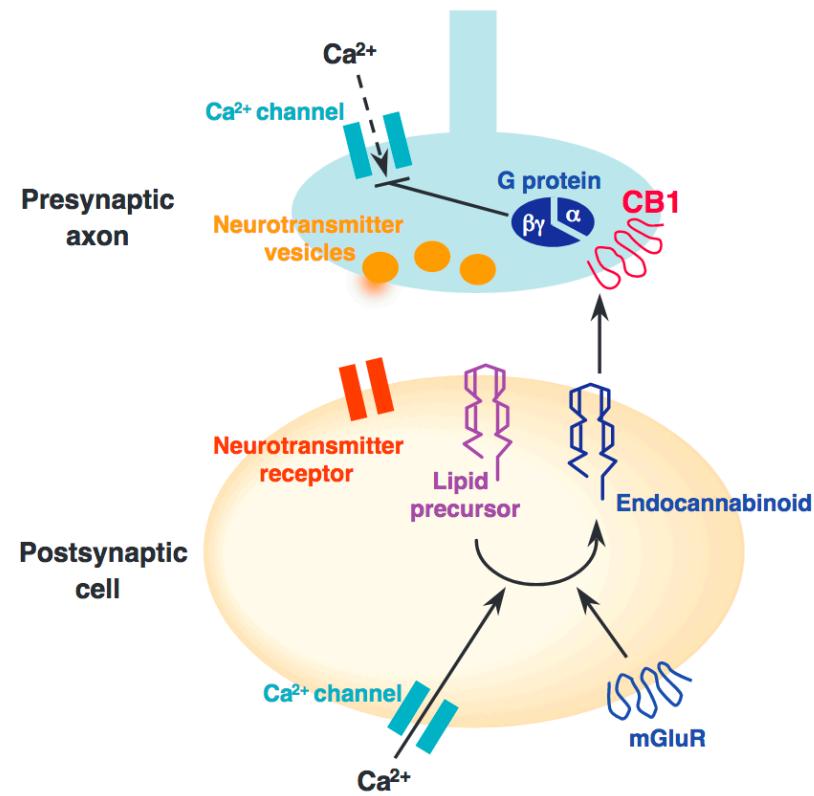


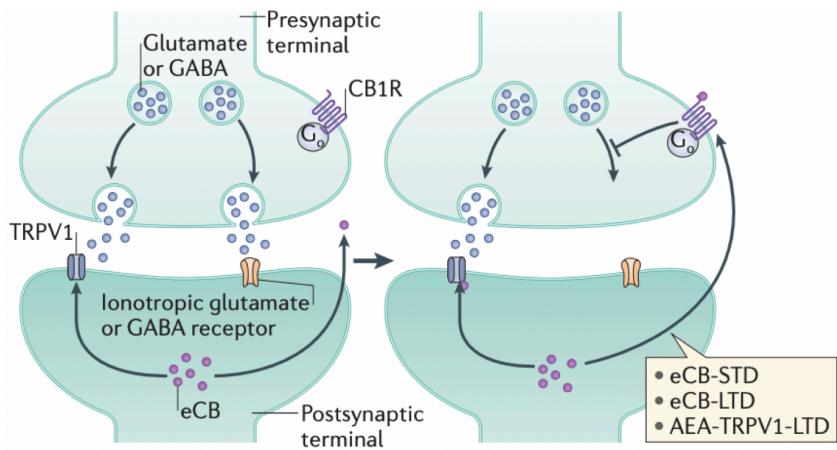
Image: <https://cannabiswikipedia.com/research/what-is-the-endocannabinoid-system/>

Unique Features of Endocannabinoid Signaling in the CNS

- Endocannabinoid signaling occurs in a retrograde direction
 - i.e., the signaling is initiated in postsynaptic neurons and acts upon presynaptic terminals
- In contrast to classical neurotransmitters, endocannabinoids are not produced and stored in vesicles pending release
 - They are produced “on demand” upon stimulation of postsynaptic cells through a variety of signals.



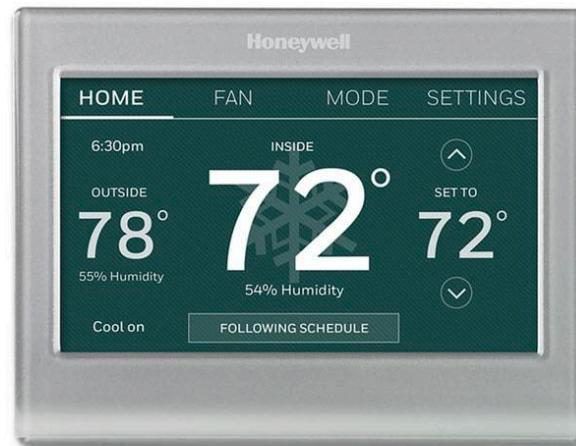
From Wilson & Nicoll, 2002, *Science*



The endocannabinoid system in guarding against fear, anxiety and stress

Beat Lutz, Giovanni Marsicano, Rafael Maldonado & Cecilia J. Hillard

[Nature Reviews Neuroscience 16, 705–718 \(2015\)](#) | [Download Citation](#)

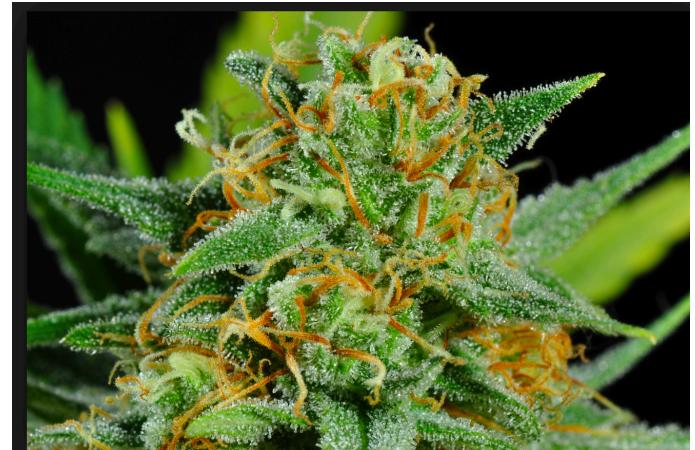


A “thermostat” function for the ECS?

- The ECS regulates neurotransmission
 - Too “hot” and the ECS cools it off
 - But important to know type of neuron!
- Glutamate neurons are excitatory
 - By slowing down glutamate neurons, the ECS is also suppressing downstream excitatory activity
- GABA interneurons are inhibitory
 - By slowing down the firing of GABA neurons, the ECS is INCREASING downstream activity (e.g., by suppressing GABA interneurons, the ECS may be increasing activity of dopamine neurons that synapse with GABA neurons)
- Dysregulation of the ECS can lead to disorders
- Cannabinoids in cannabis may impact this system for better or for worse

Cannabinoid Pharmacology

- More than 104 cannabinoids have been identified as part of the cannabis plant
- Other compounds identified in cannabis include terpenoids, flavonoids, nitrogenous compounds, and more common plant molecules



Pharmacology of THC

- THC is a partial agonist at CB₁ and CB₂ receptors
- Both CB1 and CB2 signal through transducing G proteins
- Activation of these G-proteins by THC or other agonists causes:
 - inhibition of adenylyl cyclase activity
 - closing of voltage-gated calcium channels
 - opening of inwardly rectifying potassium channels
 - stimulation of mitogen-activated protein kinases such as extracellular signal-regulated kinases (ERKs) and focal adhesion kinases (FAKs)

References:

National Academies Report, 2017

Mackie, 2006, *Annual Review of Pharmacology*

Pharmacology of CBD

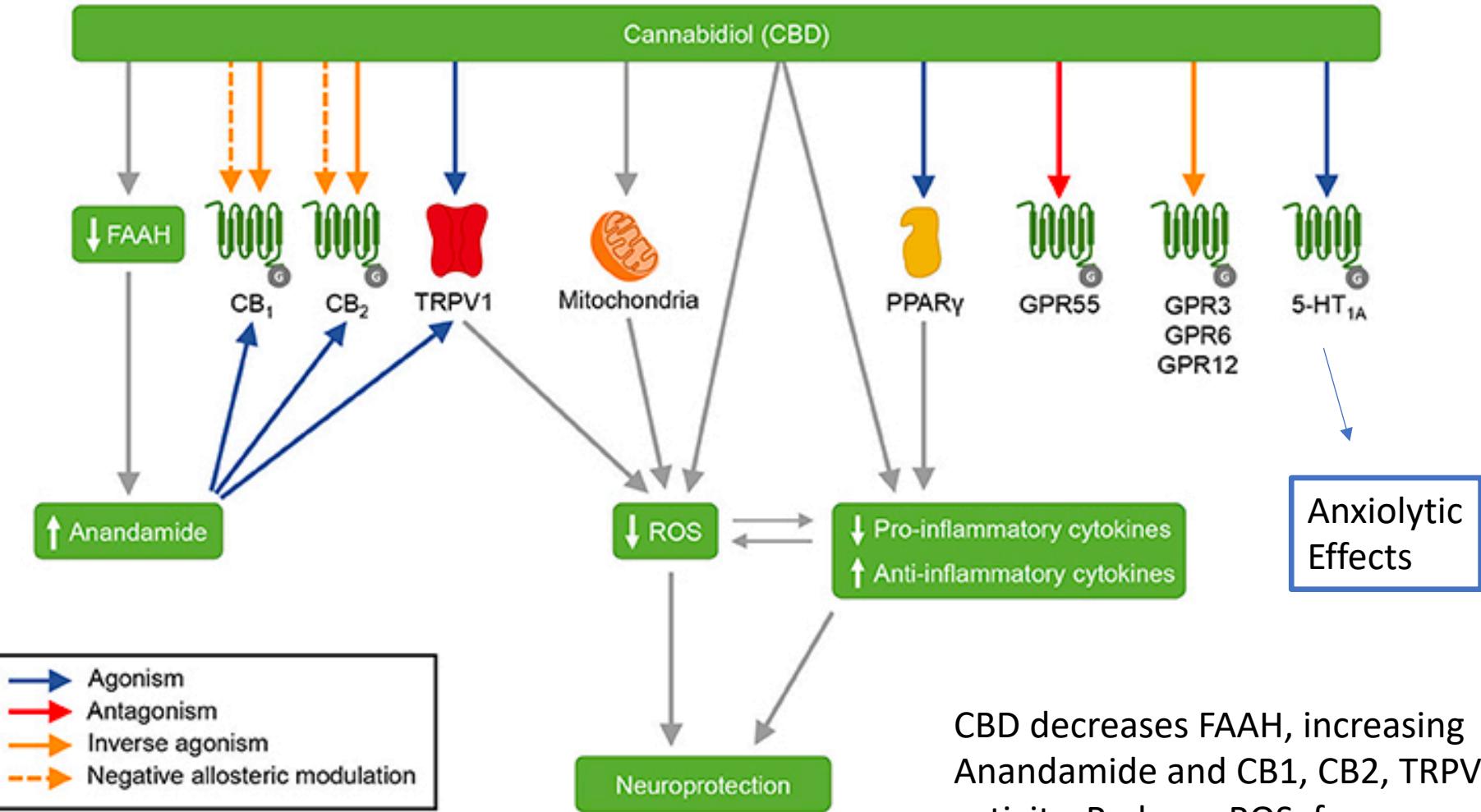
- CBD displays low affinity for CB₁ and CB₂ receptors
- CBD is a known agonist of serotonin 5-HT1A receptors and transient receptor potential vanilloid type 1 (TRPV1) receptors
- CBD can enhance adenosine receptor signaling by inhibiting adenosine inactivation
 - potential therapeutic role in pain and inflammation

References:

Russo et al., 2005, *Neurochemical Research*

Bisogno et al., 2001, *British Journal of Pharmacology*

Carrier et al., 2006 , *Proceedings of the National Academy of Sciences*



Peres et al., 2018, Front. Pharmacol

<https://www.frontiersin.org/articles/10.3389/fphar.2018.00482/full>

Table 5

Most plausible molecular targets of cannabidiol (CBD) warranting further investigation in specific disease stated

Disease or disease group	Most plausible molecular targets of CBD
Epilepsy	VDAC1, CaV3.x, 5-HT _{1A} , GlyR, GPR55, adenosine modulation (ENT1)
Movement disorders	CaV3.x, 5-HT _{1A} , VDAC1
Neurodegenerative diseases	VDAC1, FABP, GPR55, NRF2, ENT1
Pain	TRPV1, TRPA1, TRPM8
Psychosis and anxiety	5-HT _{1A} , adenosine modulation (ENT1)
Addiction	CYP2D6, opioid receptors, ABCG2

VDAC1 = voltage-dependent anion channel 1; 5-HT = serotonin; GlyR = glycine receptor; GPR55 = G protein-coupled receptor 55; ENT1 = equilibrative nucleoside transporter 1; FABP = fatty acid binding protein; NRF2 = Nuclear factor erythroid 2-related factor 2; TRPV1 = transient receptor potential vanilloid-type 1; TRPA1 = transient receptor potential ankyrin type 1; TRPM8 = transient receptor potential subfamily M; CYP = cytochrome P

CBD Pharmacology – Take Home Points

- CBD is a messy drug with a number of molecular targets and putative mechanisms
- This is compounded by the fact that hemp derived CBD (unlike the purified or synthetic forms) comes with a number of other cannabinoids/terpenes
- Nobody really knows it works
- Best guess is that the overall effect stems from the combination of smaller effects across a number of targets (mentioned above)

Cannabinoid Receptor Distribution in the Brain

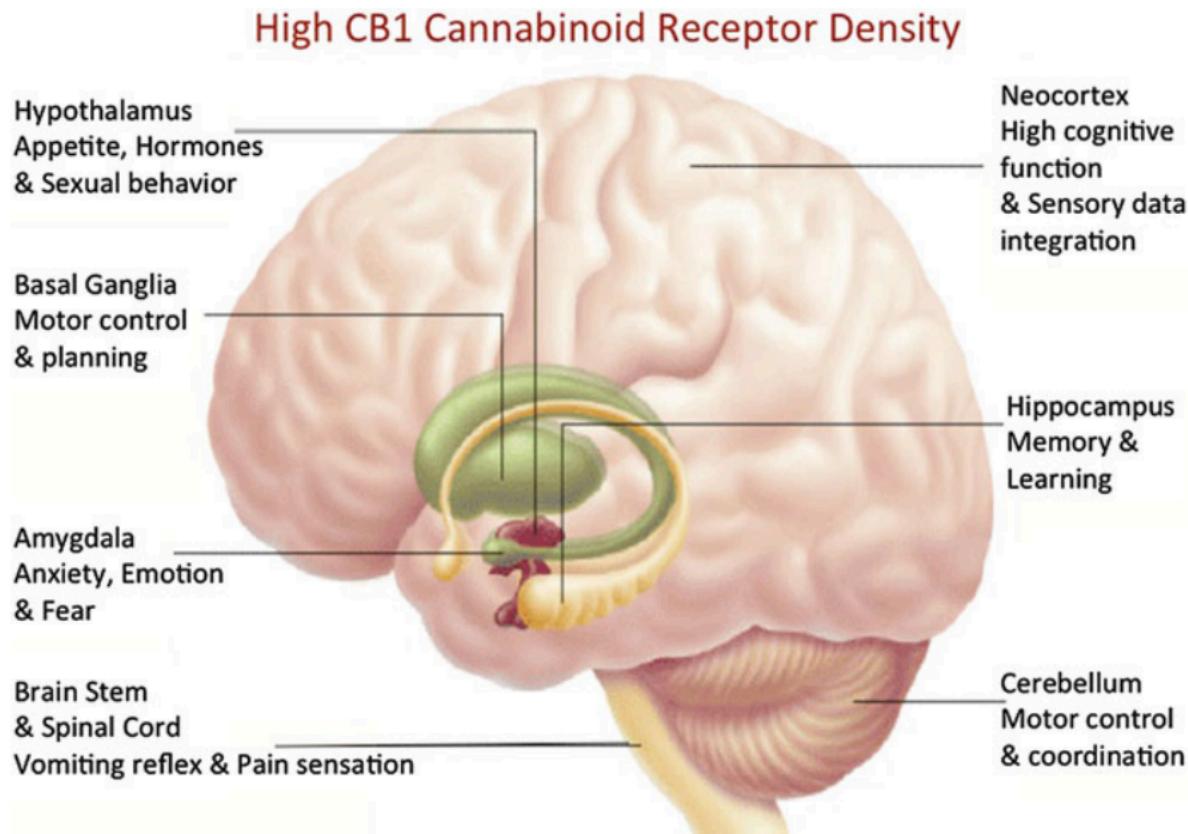
- The expression pattern of CB₁ receptors in brain structures correlates with the psychoactive effects of cannabis
- In mammals, high concentrations of CB₁ are found in brain areas that regulate appetite, memory, fear extinction, motor responses, and posture such as the hippocampus, basal ganglia, basolateral amygdala, hypothalamus, and cerebellum
- The brain also contains a small number of CB₂ receptors
 - mainly expressed in macrophages and macrophage-derived cells such as microglia, osteoclasts, and osteoblasts

References:

National Academies Report, 2017

Mackie, 2006, *Annual Review of Pharmacology*

Effects of Cannabis on the Brain

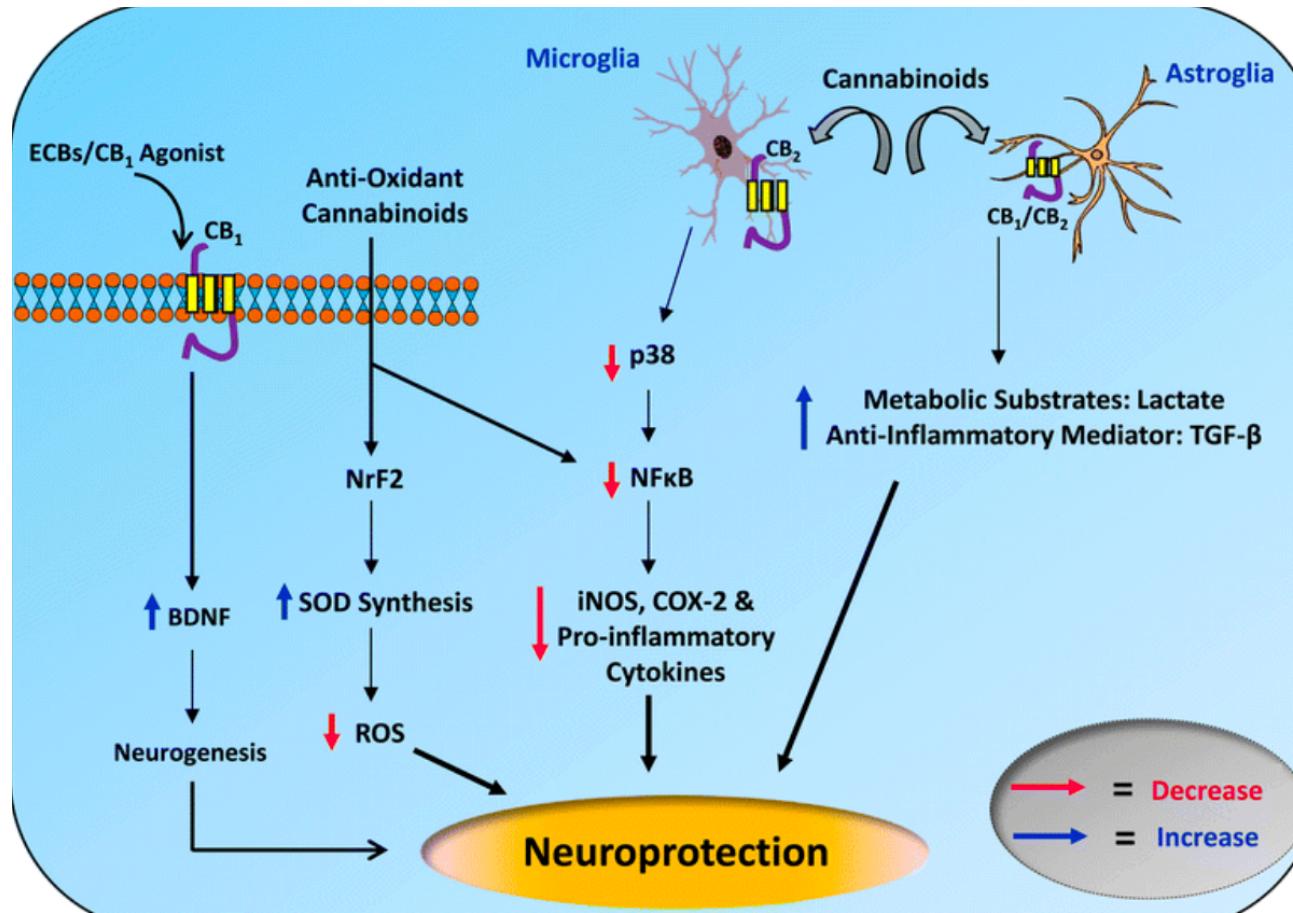


Neuroimmune Effects of Cannabis

From National Academies Cannabis and Heath Report:

- Studies using animals or cells suggest that cannabinoids modulate the functions of many types of immune cells
- **However, in humans:**
 - There is limited evidence of a statistical association between cannabis smoking and a decrease in the production of several inflammatory cytokines in healthy individuals
 - There is insufficient evidence to support or refute a statistical association between cannabis smoking and other adverse immune cell responses in healthy individuals
- Considerable additional human research is needed

Positive Neuroimmune Effects: Proposed Mechanisms



From More & Choi, 2015, *Molecular Neurodegeneration*

Cannabis and Genetics

- Candidate genes for cannabis use disorders (may influence acute effects of cannabis)
 - genes posited to have specific influences on cannabis effects include *CNR1*, *CB2*, *FAAH*, *MGL*, *TRPV1* and *GPR55*
- Challenges:
 - biological complexity underlying effects of cannabis
 - gene-gene and gene-environment interaction

Summary

- Two endocannabinoids, 2-AG and anandamide, have important biological effects in the brain and body
- In the brain, endocannabinoids have a homeostatic function (like a thermostat) and can inhibit or excite neurotransmission via retrograde signalling
- THC is a partial agonist at CB₁ and CB₂ receptors
 - The expression pattern of CB₁ receptors in brain structures correlates with the psychoactive effects of cannabis
- CBD has numerous molecular targets and putative mechanisms
- Cannabinoids have diverse immune and neuroimmune effects
 - Implications for various psychiatric and immune disorders