

# Endocannabinoid System 101

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Medical Cannabis Research Advocacy Alliance  
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# Conflicts of Interest

I have equity in the following companies:

- Verdient Science
- Altus Labs
- EndoCanna Health
- iNDi TruDose
- Agri-Genesis

# The Endocannabinoid System (ECS)

## Part I:

### Components of ECS

- Ligands
- Enzymes
- Receptors

## Part II:

### Functions of the ECS

- Metabolism
- Stress
- Pain

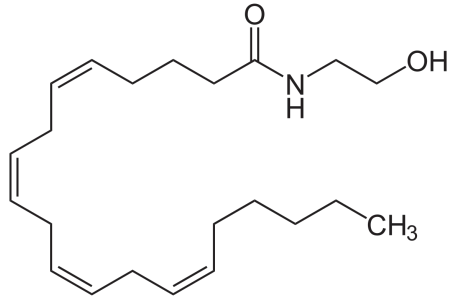
# Endocannabinoids



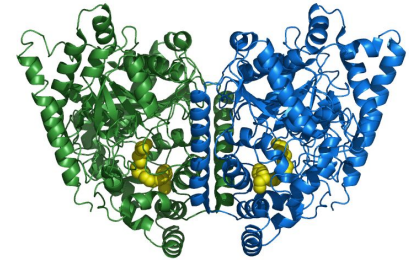
Synthesizing  
enzymes



**Anandamide (AEA)**



Degrading  
enzymes



**FAAH**

# Anandamide

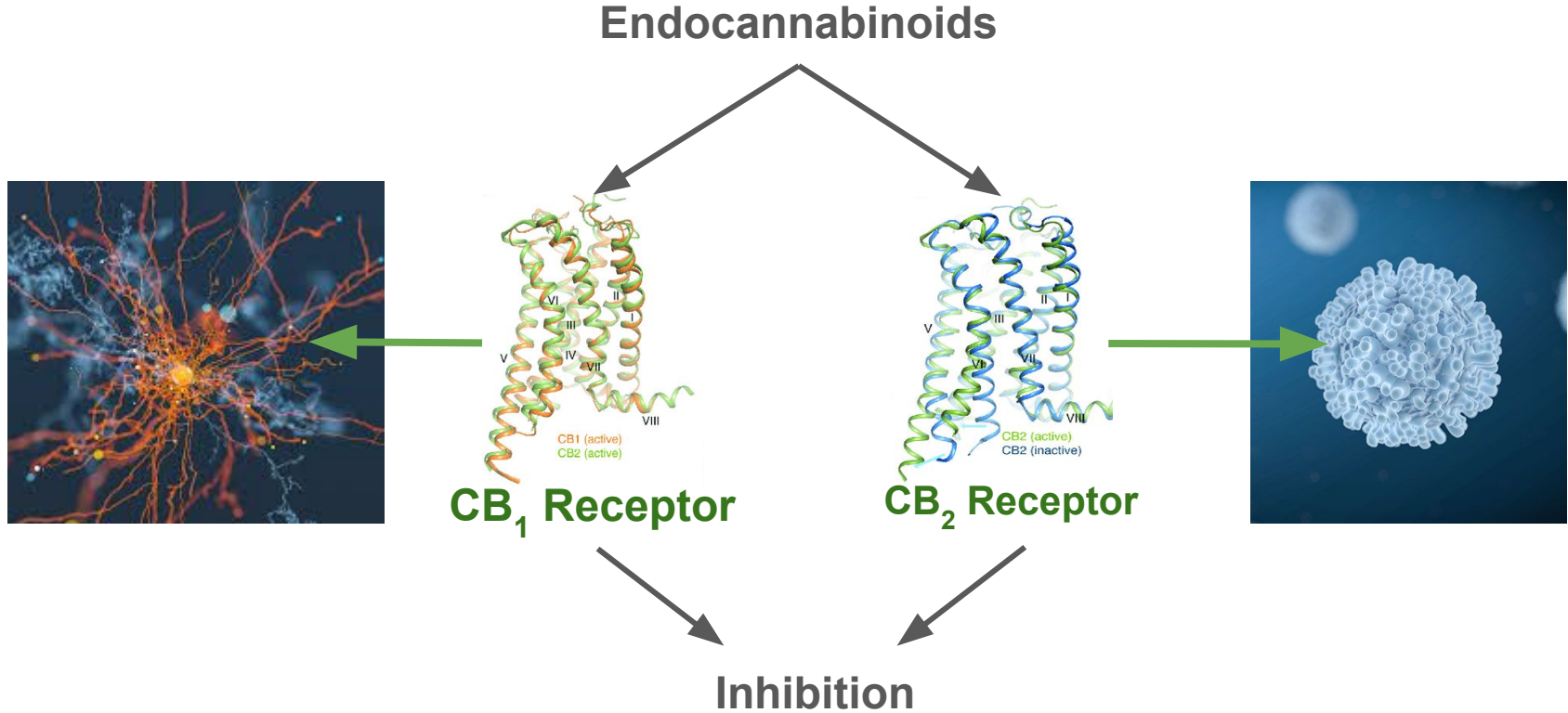
## Found in virtually every tissue:

- Blood
- Brain
- Fat
- Skin
- Intestines
- Spleen
- Bone
- Liver
- Kidneys
- etc...

## Levels may vary by:

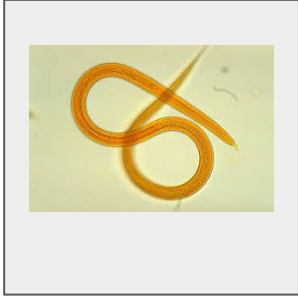
- Tissue
- Eating
- Exercise
- Stress
- Body fat
- Various diseases
- Drugs
- FAAH genetics
- etc...

# Cannabinoid Receptors

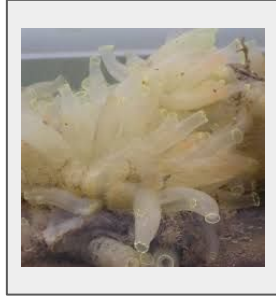


# The ECS - Who's Got One?

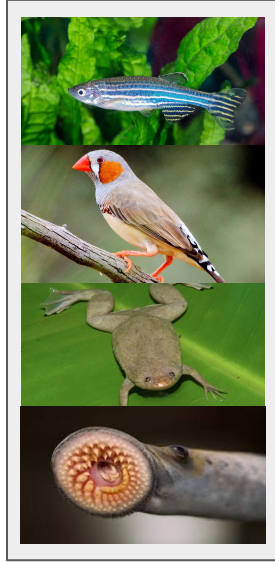
Non-chordate  
Animals



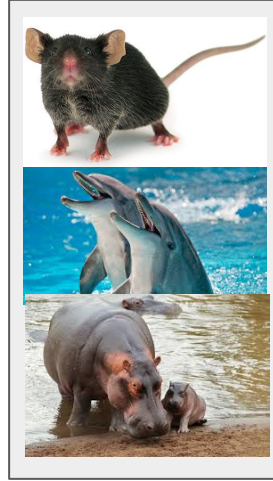
Chordates



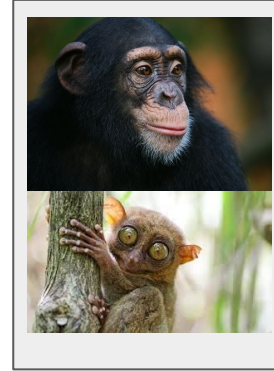
Vertebrates



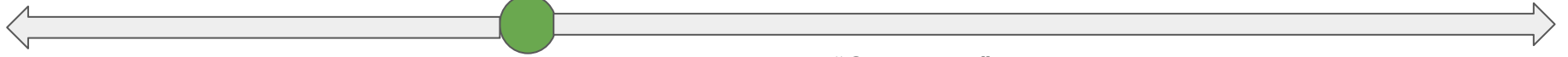
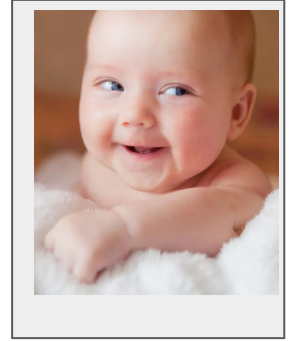
Mammals



Primates



Humans



Earlier "incomplete" versions  
~hundreds of Ms of years

"Complete" cannabinoid system  
~500 million years

# Munchies

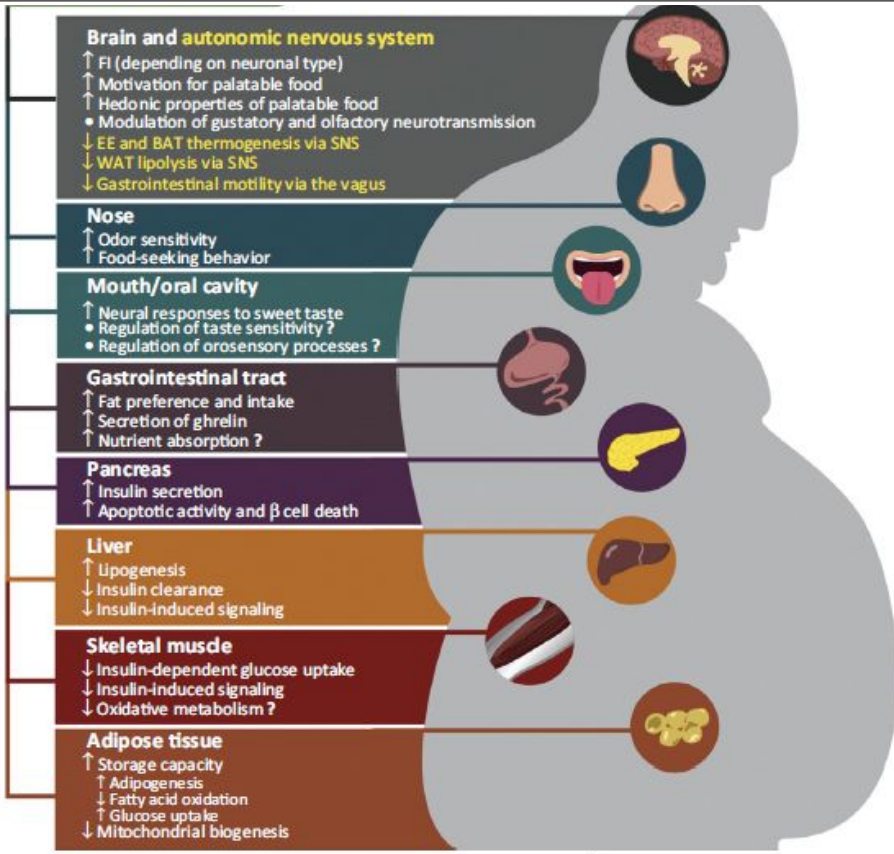


THC increases appetite

The  $CB_1$  receptor is highly expressed in the hypothalamus and regulates how hungry you feel

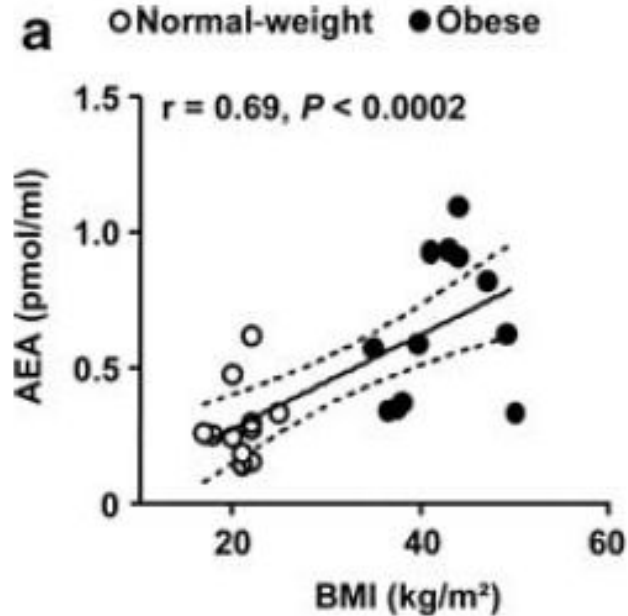


# The ECS & Energy Balance



- The ECS regulates energy balance in nearly every relevant tissue.
- For example, the ECS can regulate insulin release and sensitivity

# The ECS & Obesity



People with higher anandamide (due to their genetics) have slightly higher risk for obesity, insulin resistance, and high triglycerides

(Gatta-Cherifi, 2012, Int J Obesity)

# Blocking CB<sub>1</sub> Receptors Reduces Body Weight



- Rimonabant is a **CB<sub>1</sub> receptor antagonist / inverse agonist**
- Obese/overweight subjects taking rimonabant lost 14 pounds compared to 3.5 lb for those on placebo
- Rimonabant improved HbA1c (a measure of average blood sugar level) in diabetic subjects

(Acomplia product label)

# Blocking CB<sub>1</sub> Receptor Increases Anxiety & Depression

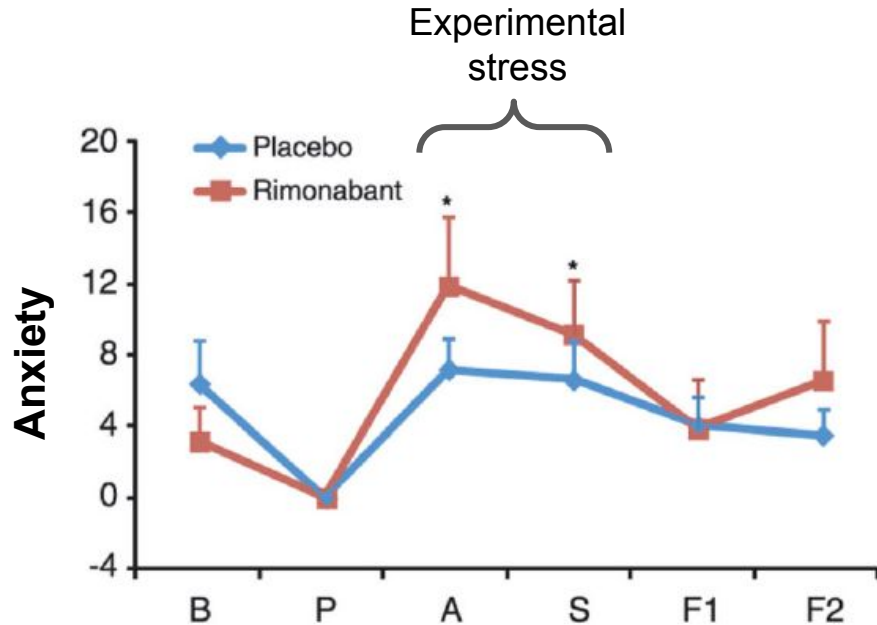


Compared to the placebo arm, subjects randomized to receive rimonabant were:

- **3-fold** more likely to drop out due to anxiety symptoms
- **2.5-fold** more likely to drop out due to depressive symptoms

(Christensen, 2007, Lancet)

# Blocking CB<sub>1</sub> Receptor Increases Effects of Stress



(Bergamaschi, 2013, Hum Psychopharmacol)

The increase in anxiety from being placed in a stressful situation was ~50% higher after a single dose of rimonabant

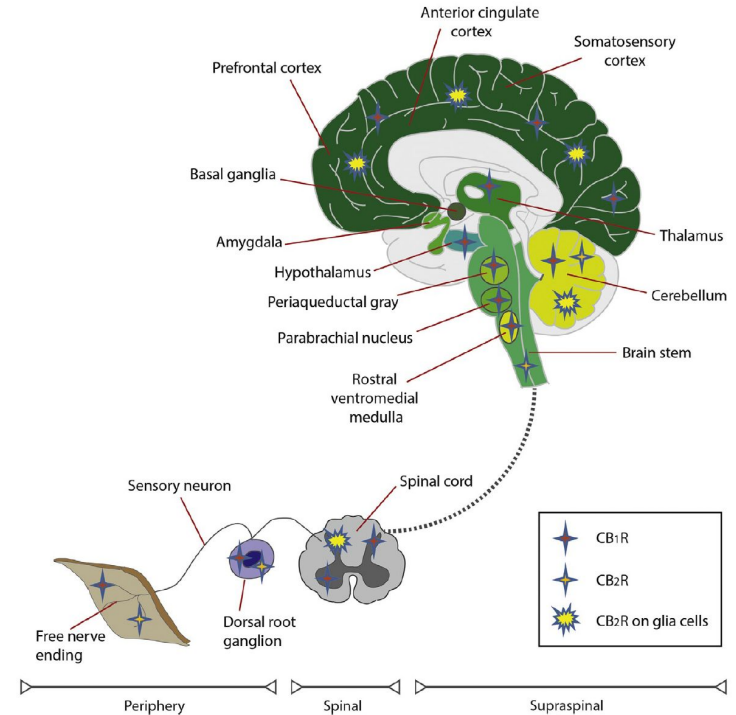
The opposite also occurs - augmenting CB<sub>1</sub> receptor activation decreases anxiety levels in a stressful situation

(THC: Childs, 2017, Drug Alcohol Depend ;  
FAAH inhibitor: Mayo, 2020, Biol Psychiatry)

# The ECS & Pain

- The CB<sub>1</sub> receptor is expressed in virtually every tissue involved in nociception and pain processing

(Sexton, 2016, Cannabis Cannabinoid Res)



(Starowicz, 2017, Adv Pharmacol)

# The ECS & Pain

Case of a 66 year old Scottish woman:

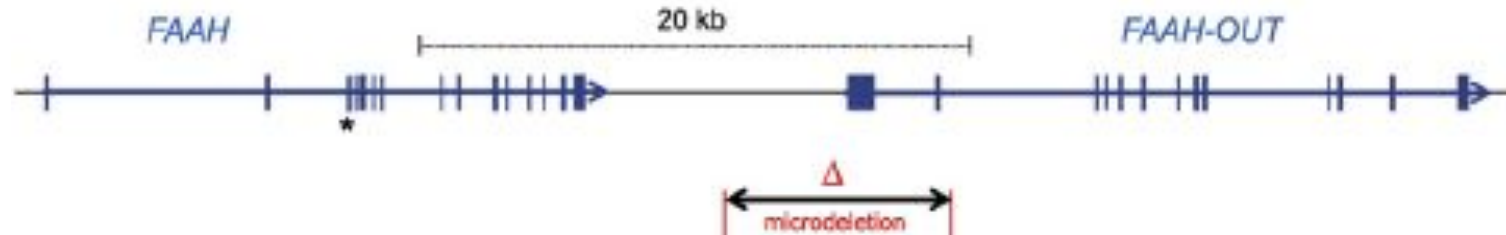
- Underwent a normally painful orthopedic surgery of her hand due to osteoarthritis
- Reported virtually no pain, despite minimal use of postoperative analgesics
- Genetic sequencing did not reveal any of the variants known to cause congenital insensitivity to pain



(Habib, 2019, Br J Anaesth)

# The ECS & Pain

- Patient had a deletion of a segment of DNA in a region adjacent to the FAAH gene, now called “FAAH-OUT”



- The mechanism remains unknown, but FAAH-OUT may regulate expression of FAAH in tissues such as dorsal root ganglion (DRG)
- The physiology of nociception and pain is extremely complex - the role of the ECS is still not fully understood.



# Thank You!

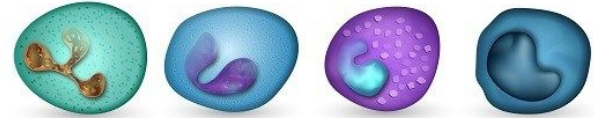
I'm happy to receive questions or comments:

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# Cannabinoid CB<sub>2</sub> Receptor

The CB<sub>2</sub> receptor is not highly expressed in the brain under normal conditions

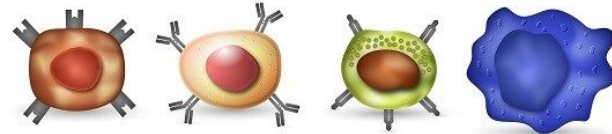


**Neutrophil**

**Eosinophil**

**Basophil**

**Monocyte**



**T Cell**

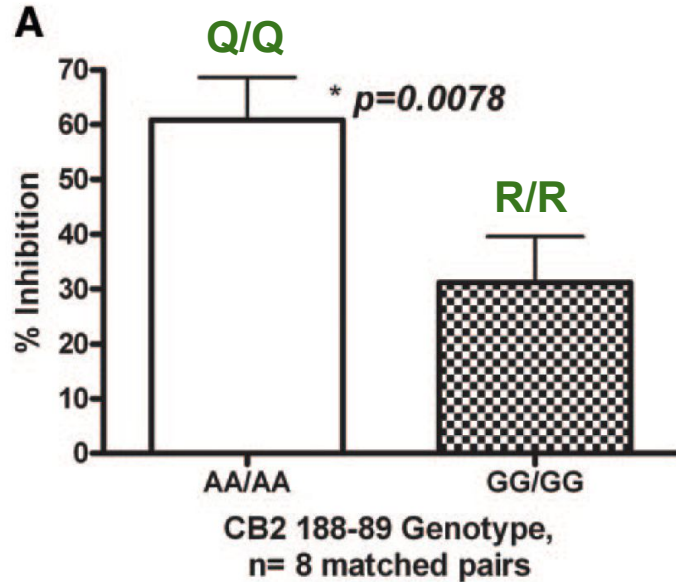
**B Cell**

**Natural killer**

**Macrophage**

CB<sub>2</sub> receptor is expressed in almost every type of immune cell:

# Q63R Variant Determines CB<sub>2</sub> Receptor Signaling



- **Q version:** typical receptor signaling
- **R version:** 50% lower receptor signaling

(Sipe, 2005, J Leukocyt Biol)

# CB<sub>2</sub> Receptor Signaling & Immune Diseases

	<b>Disease</b>	<b>Odds ratio</b>	<b>References</b>
<b>Joints</b>	Rheumatoid arthritis	10.8 (RR vs QQ)	Ismail, 2018, Clin Rheumatol
	Juvenile idiopathic arthritis	2.5 (RR vs QQ)	Bellini, 2015, Scand J Rheumatol
<b>GI</b>	Celiac disease	6.1 (RR vs QQ)	Rossi, 2012, Pharmacol Res
	Pediatric inflammatory bowel disease	1.8 (RR vs QQ)	Strisciuglio, 2018, J Clin Gastroenterol
<b>Liver</b>	NASH in obese children with NAFLD	5.3 (RR/QR vs QQ)	Rossi, 2012, PLoS One
	Severe inflammatory damage in viral hepatitis	4-5 (RR/QR vs QQ)	Sagnelli, 2017, PLoS One; Coppola, 2014, Clin Gastroenterol Hepatol
<b>Immune</b>	Chronic immune thrombocytopenic purpura	2.3-2.9 (RR vs QQ)	Ezzat, 2017, Egypt J Immunol; Mahmoud, 2013, Blood Coag; Rossi, 2011, Haematologica
<b>Brain</b>	Multiple sclerosis	2.70 (RR/QR vs QQ)	Tahamtan, 2020, J Mol Neurosci; Sipe, 2005, J Leukocyt Biol

Low CB<sub>2</sub> receptor signaling = higher risk of autoimmune / inflammatory disease