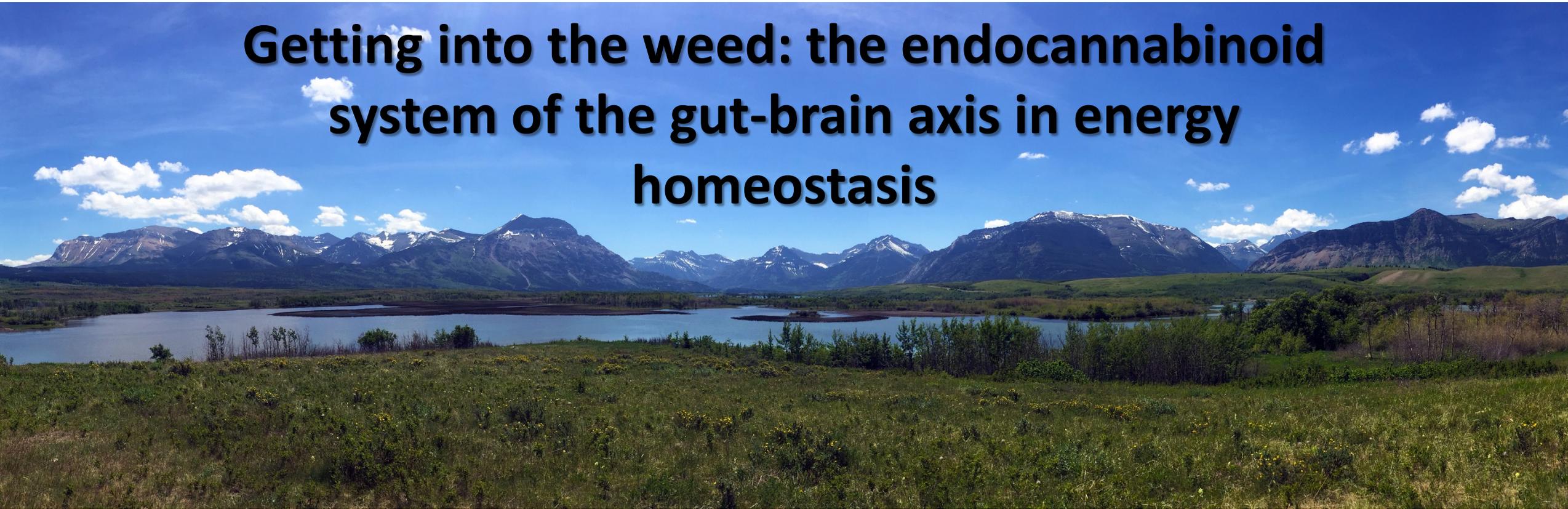


Getting into the weed: the endocannabinoid system of the gut-brain axis in energy homeostasis



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(over the past 24 months)

No relevant financial relationships with any
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Cannabis and food intake – the two go hand in hand!



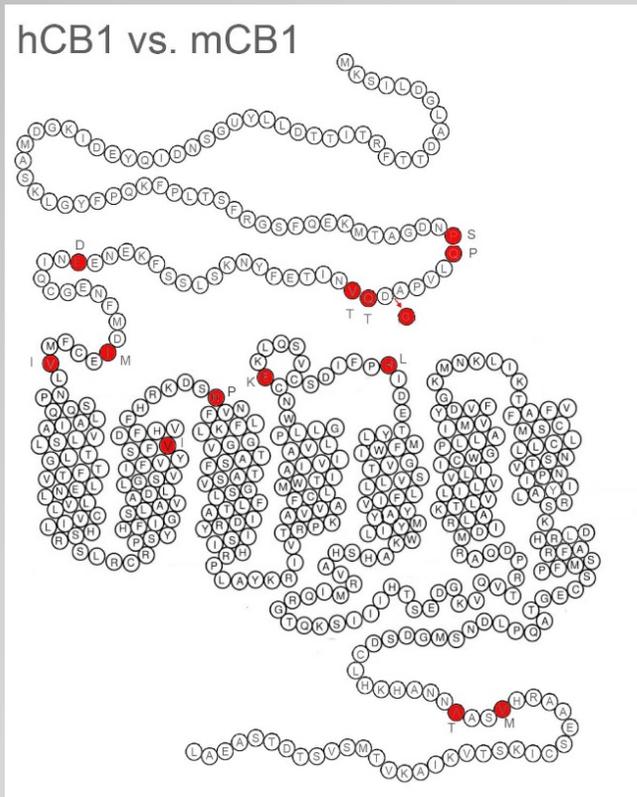
<http://metro.co.uk/2016/03/07/7-really-surprising-health-benefits-from-smoking-cannabis-5738619/>



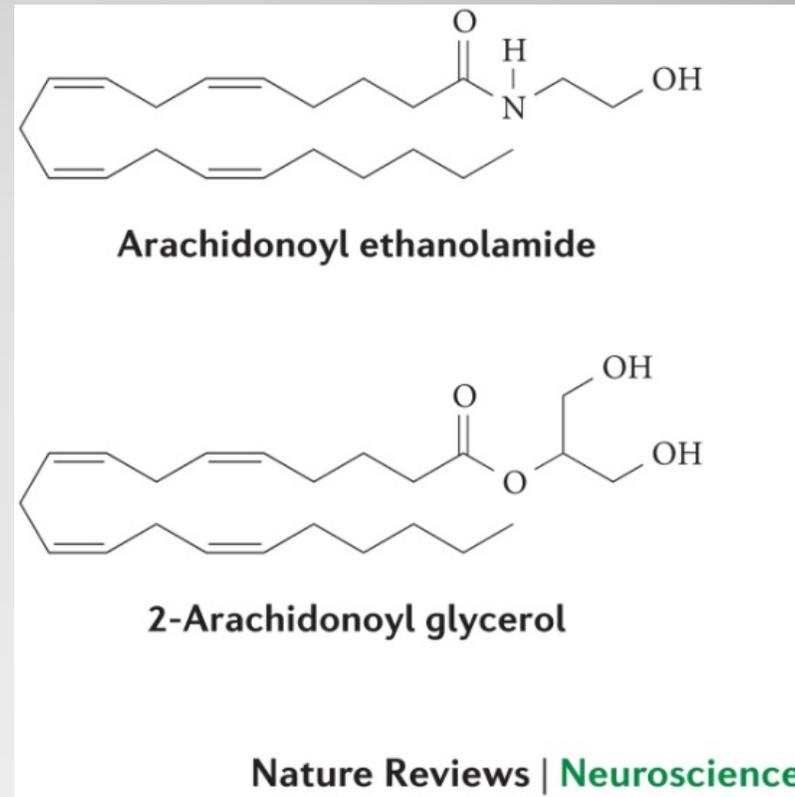
<http://movesmart.org/author/joy-nalywalko/>

Endocannabinoid system: ligands and receptors

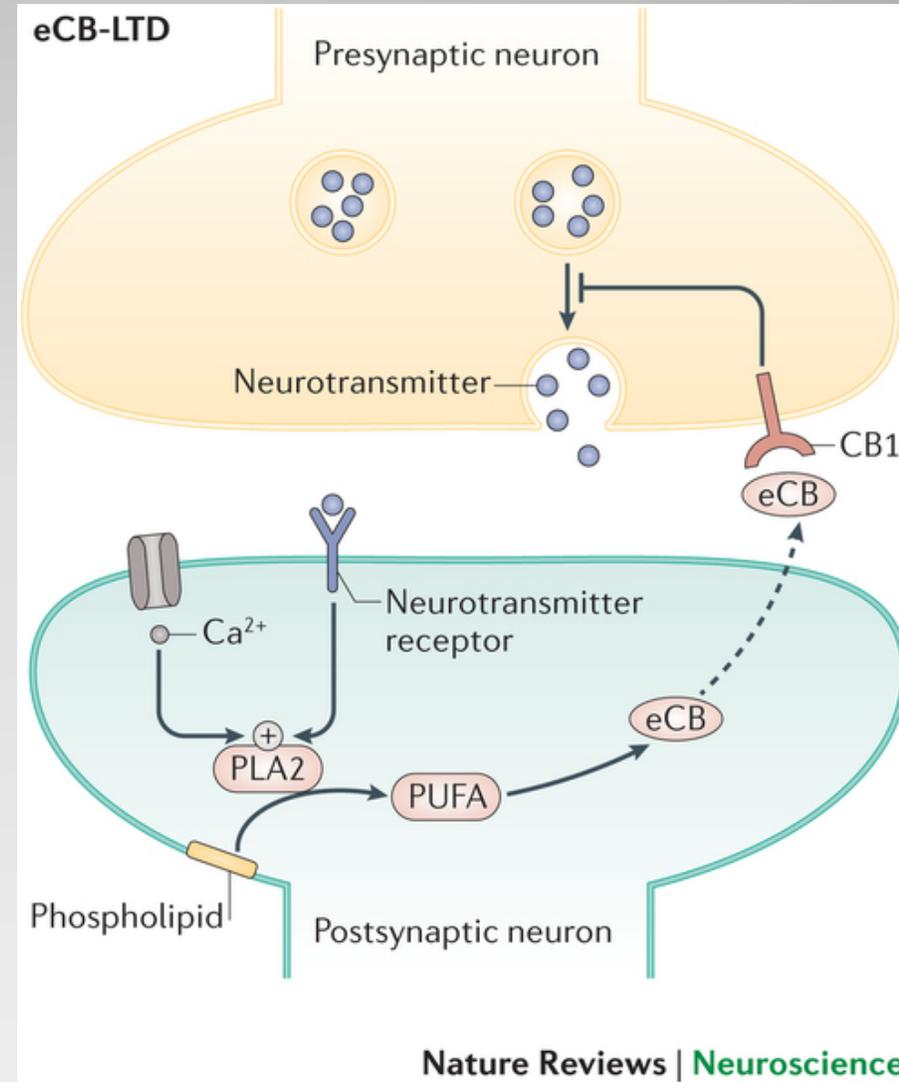
CB₁ receptor



Endocannabinoids

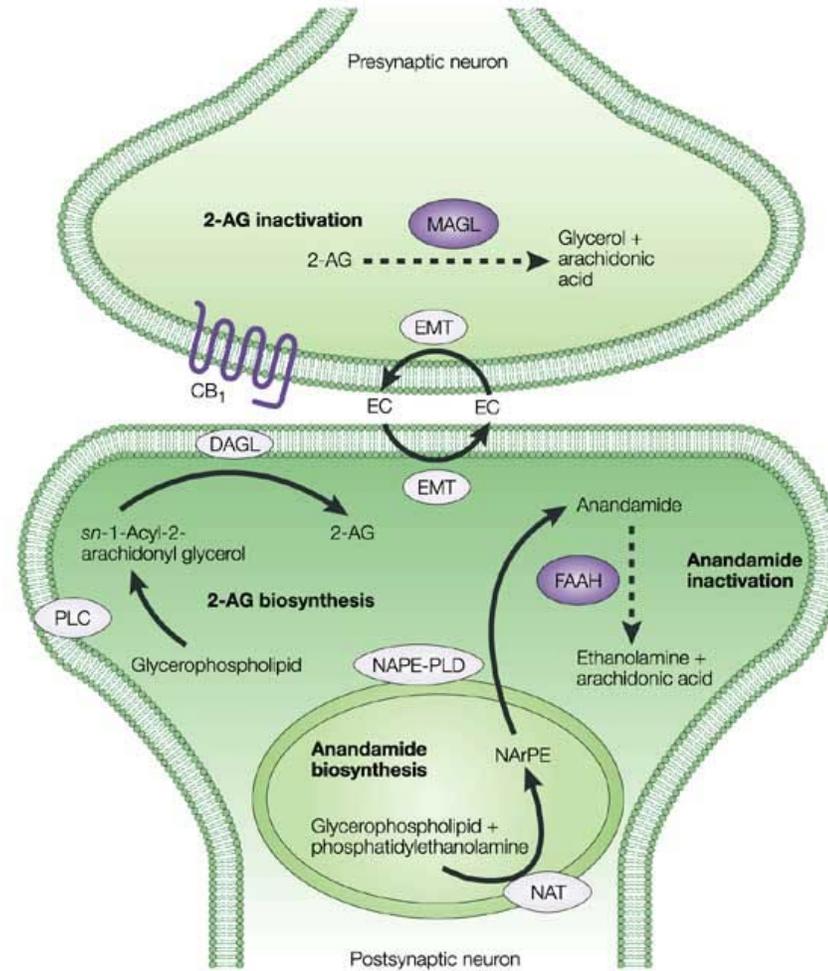


Endocannabinoids in the nervous system function as retrograde transmitters



Bazinet and Layé, Nature Reviews Neuroscience 15, 771–785 (2014)

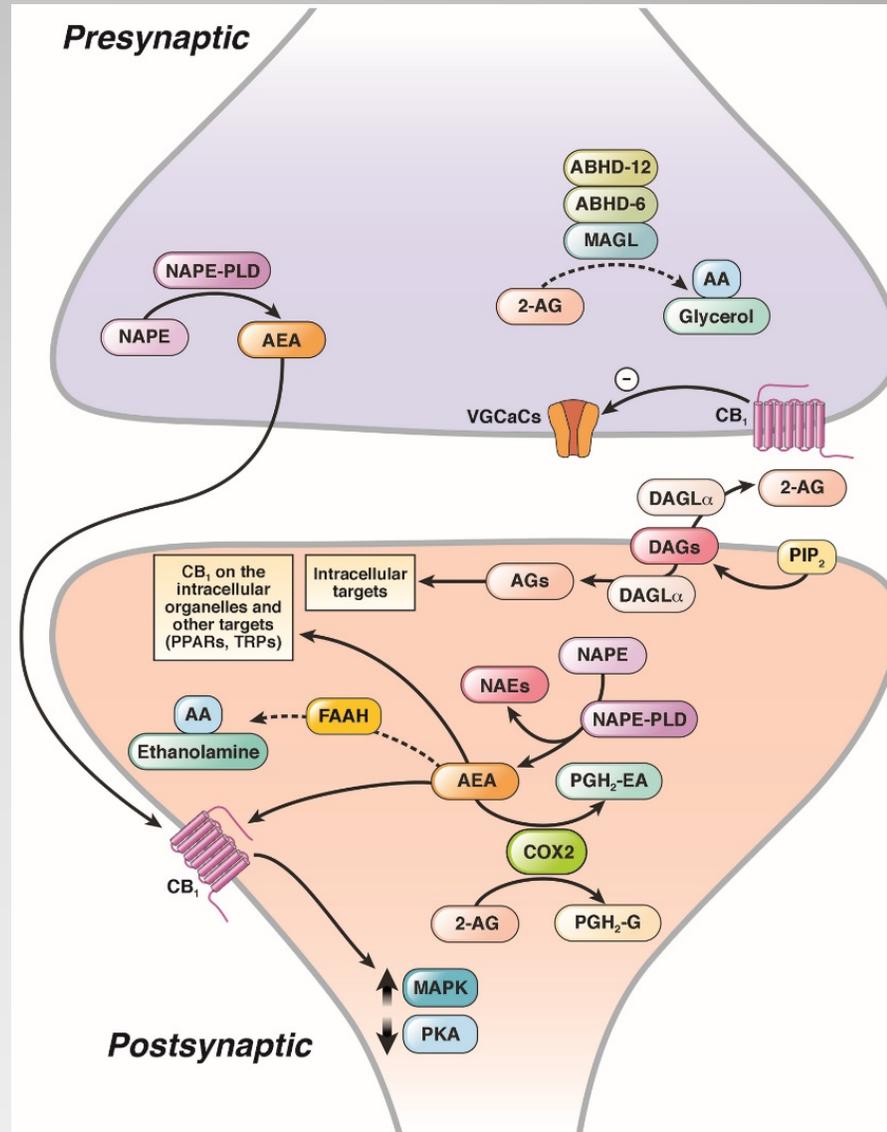
Endocannabinoid system: mechanisms of synthesis and degradation



Nature Reviews | Drug Discovery

Endocannabinoid system: novel mechanism of synthesis, degradation & metabolism and new targets

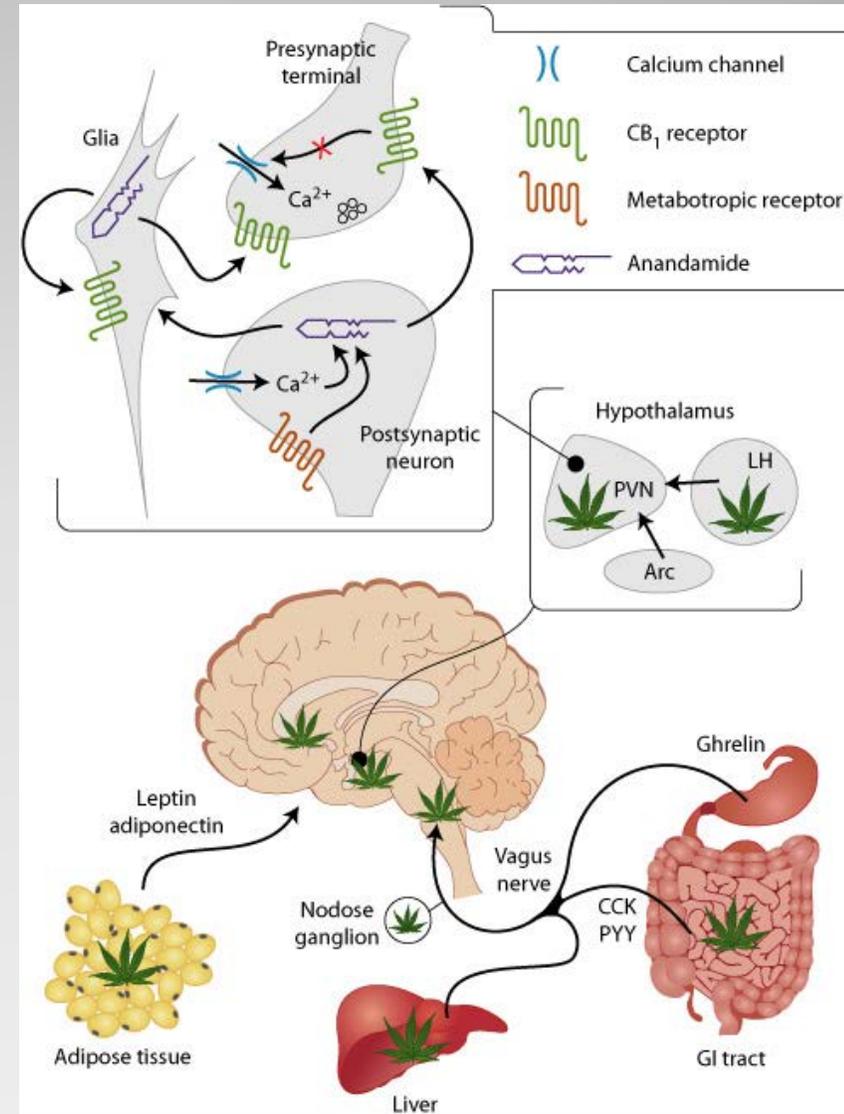
2-AG – 2-arachidonoylglycerol
 AEA - Anandamide



The endocannabinoid system

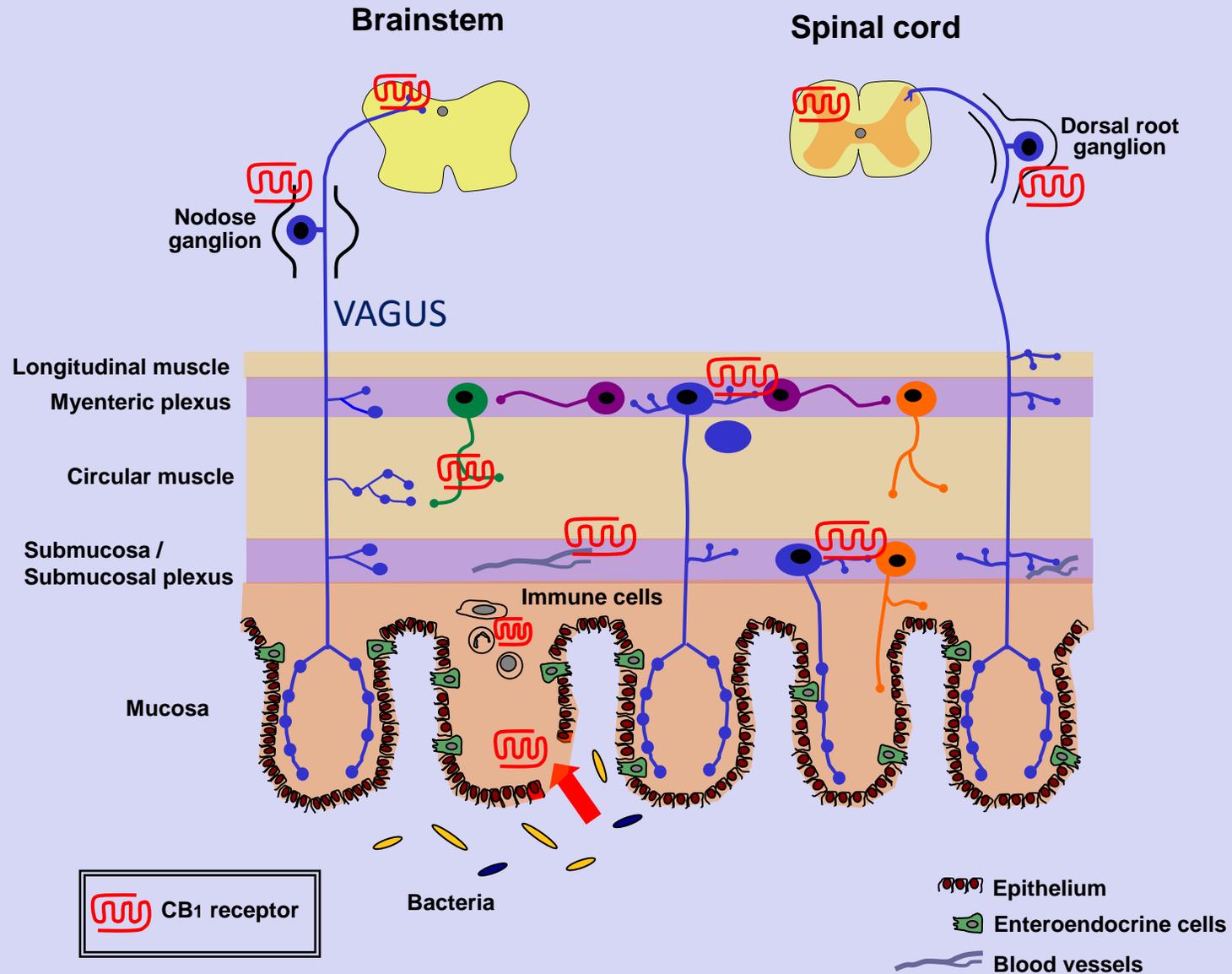
- Cannabinoid receptors –CB₁ and CB₂
- Endogenous ligands – novel lipid mediators
- Specific mechanisms of biosynthesis and degradation
- Produced "on demand"
- Unique mechanism of action in the brain

Endocannabinoid system is present throughout the body

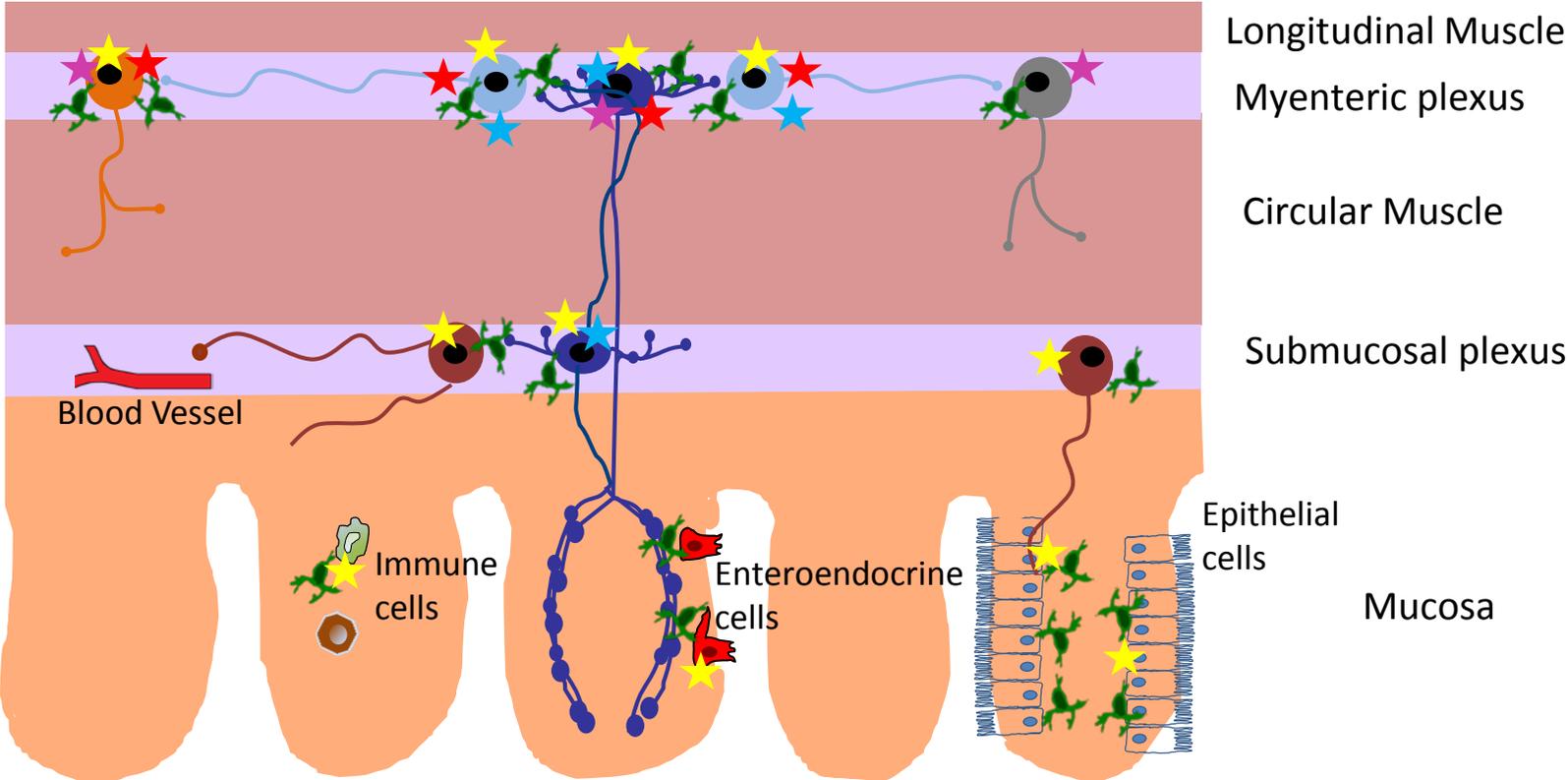


Sharkey and Pittman, Science STKE 277, pe15 (2005)

CB₁ receptors in the gut-brain axis



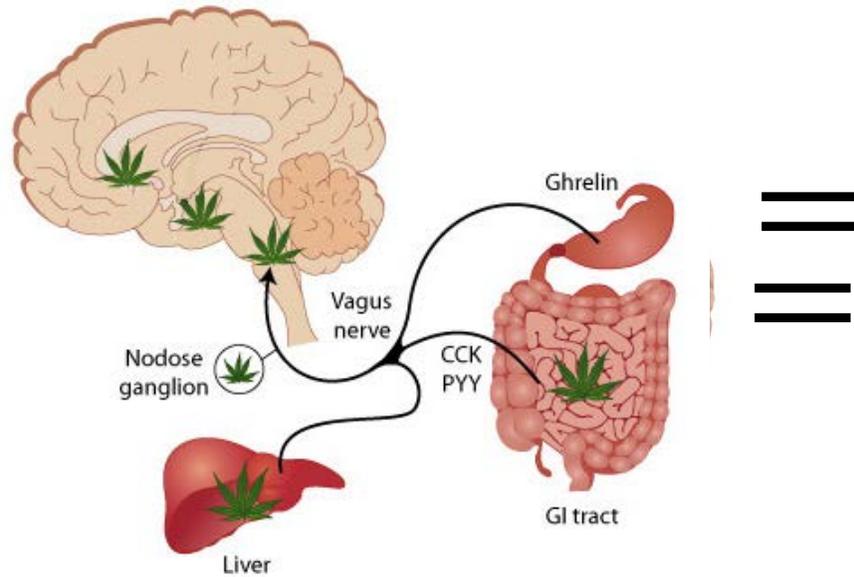
Endocannabinoid system in the GI tract



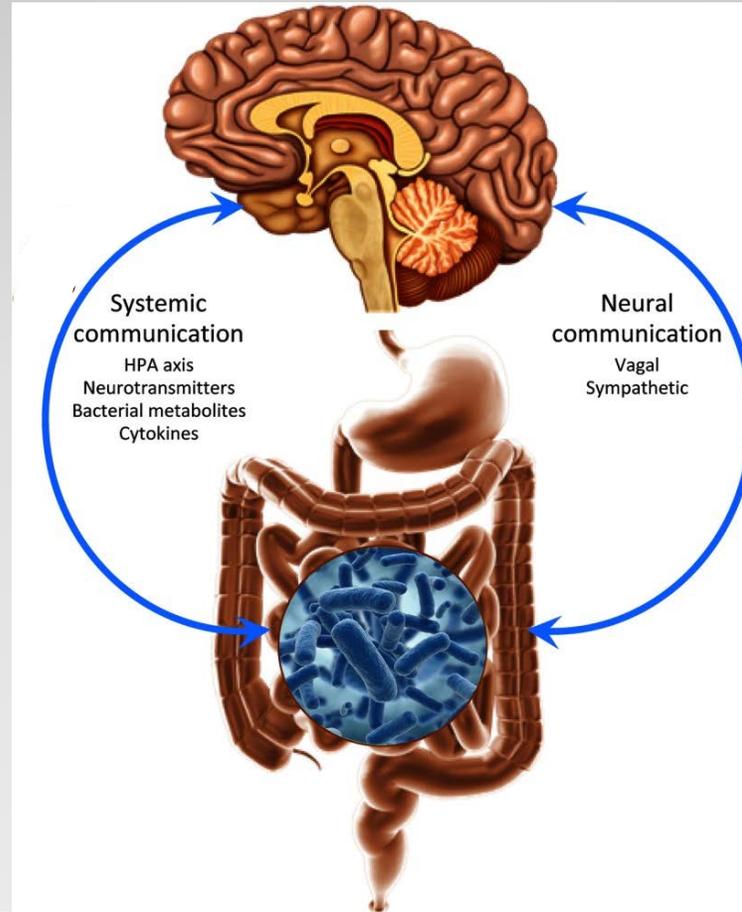
The endocannabinoid system

- Present throughout the body
- An important signaling system in the gut-brain axis
- Role in energy homeostasis.
Endocannabinoid system adjusts behaviour and metabolism to food availability

Endocannabinoid system of the gut-brain axis: the orchestra of food intake and metabolism

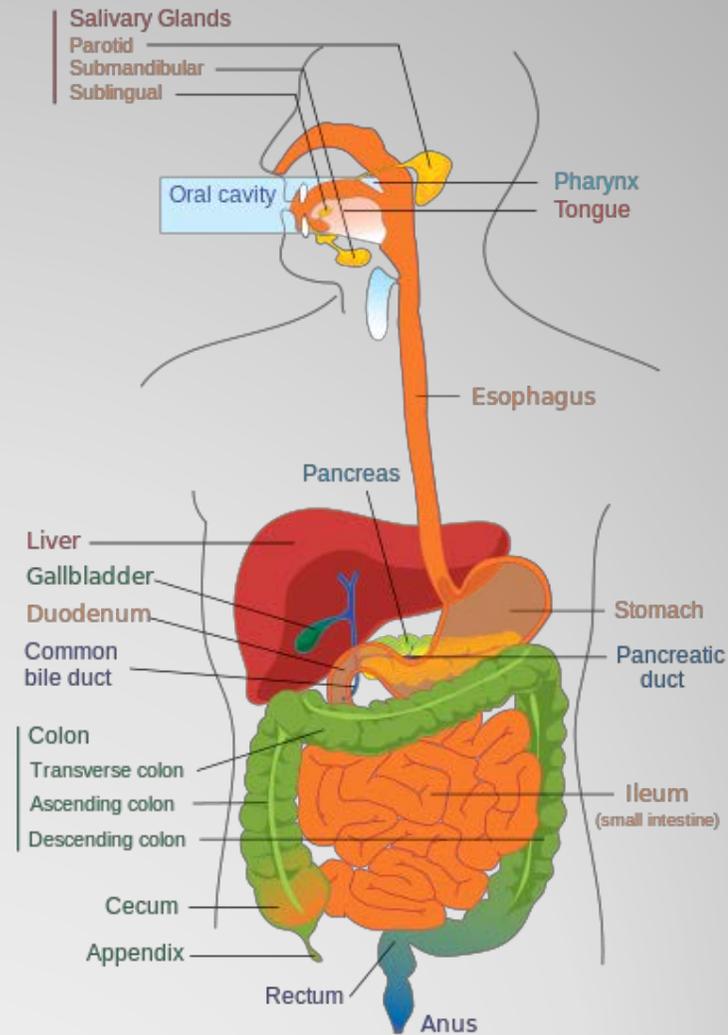


The gut-brain axis – is now – gut-brain-microbiota axis

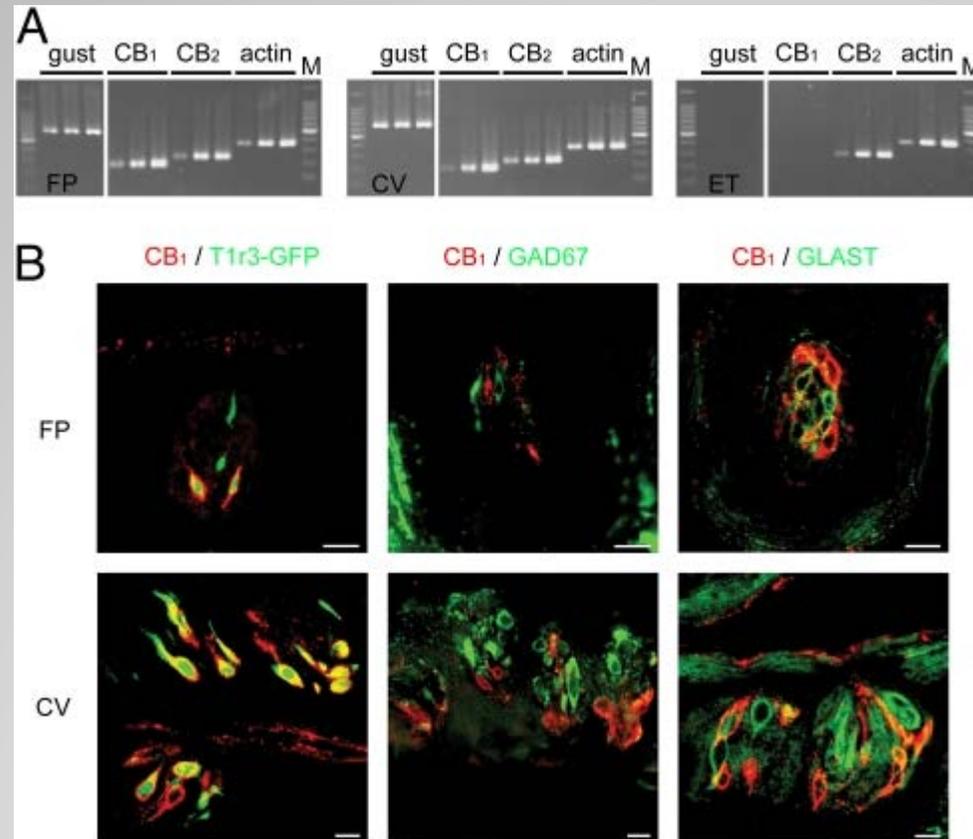


Mayer et al, J. Neuroscience 34, 15490-15496 (2014)

Endocannabinoids regulate taste and taste (of fat) stimulates the production of endocannabinoids in the gut

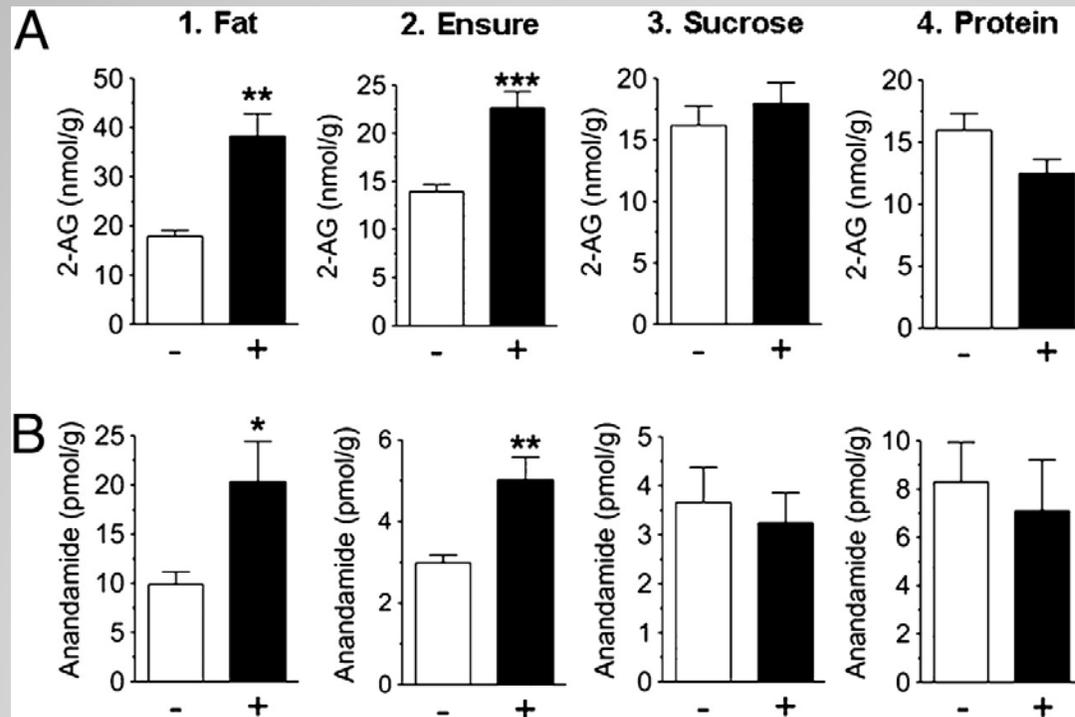


Endocannabinoids enhance sweet taste



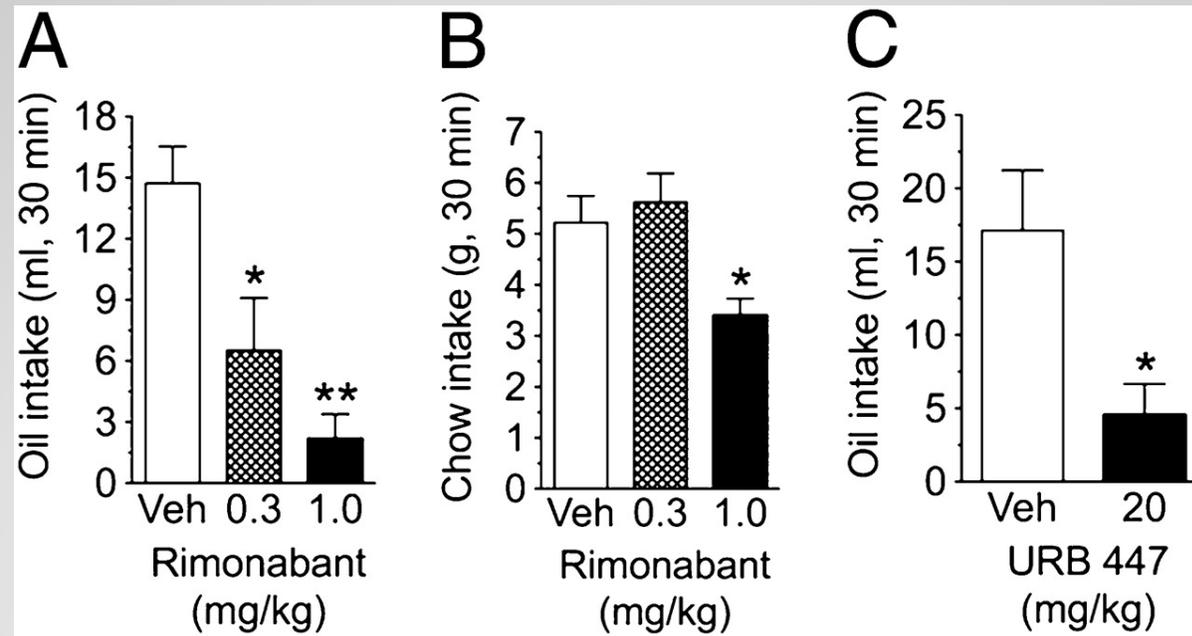
- CB receptors are present in taste buds.
- Selectively enhance sweet taste by stimulating gustatory nerve activity.

Sham feeding increases jejunal endocannabinoid levels

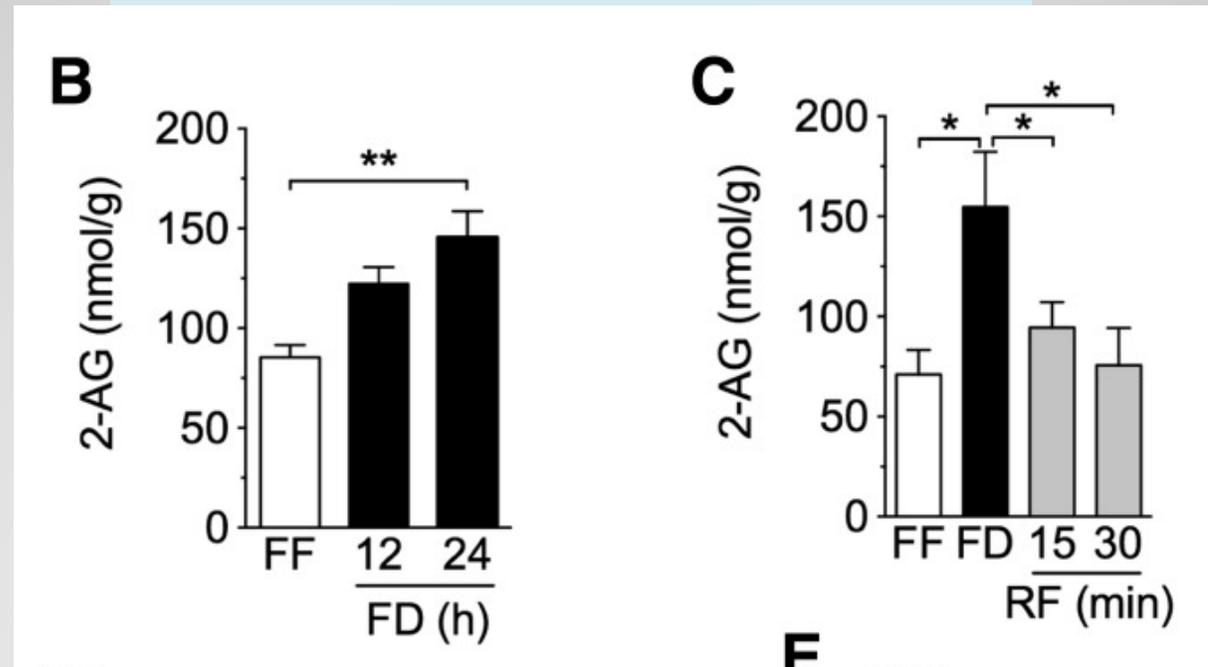


- Blocked by vagotomy.
- Increases are due to an reduction in endocannabinoid degradation.
- Significant increases are caused by 18:2, vs 18:0 or 18:3 fatty acids.

Sham feeding increases jejunal endocannabinoid levels: blocking this with CB₁ antagonists reduces food intake

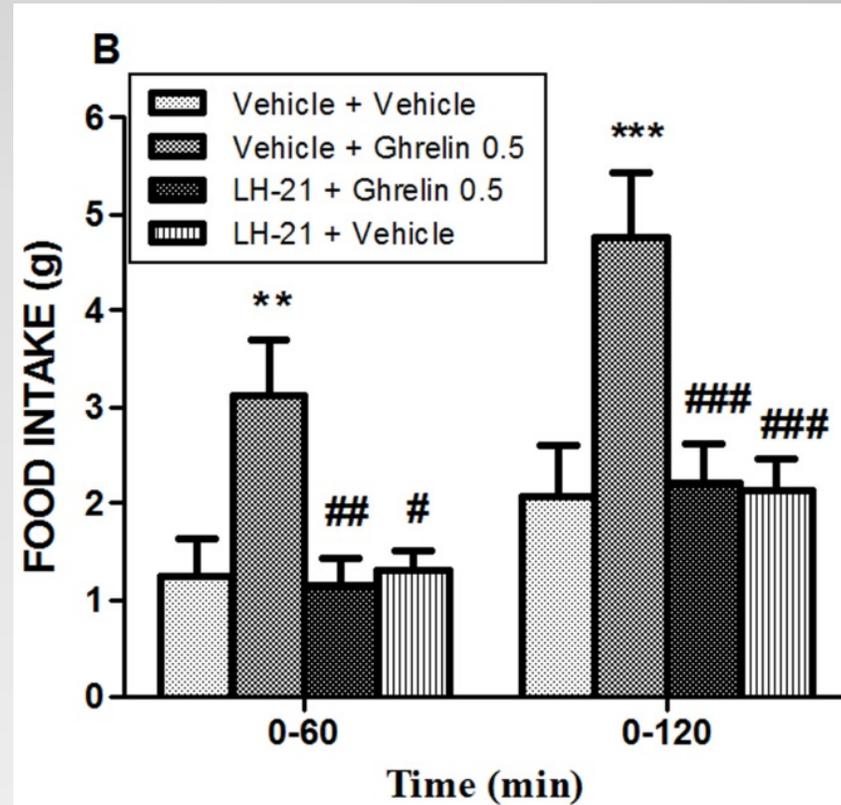


Fasting increases jejunal endocannabinoid levels: blocking this with CB₁ or muscarinic M3 antagonists reduces food intake



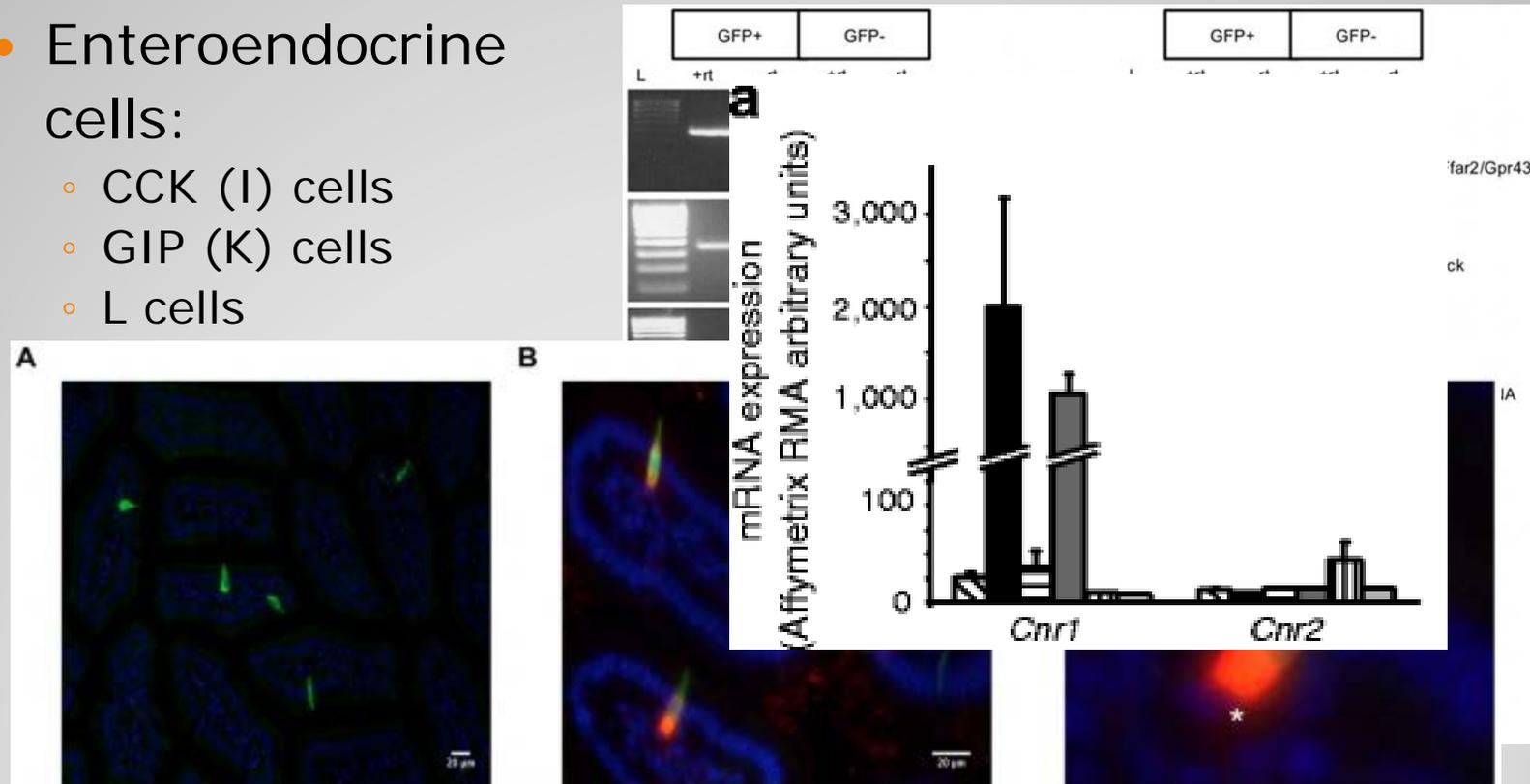
How do these peripheral endocannabinoid signals mediate their orexigenic effects?

- Inhibiting the action of ghrelin – released from the stomach



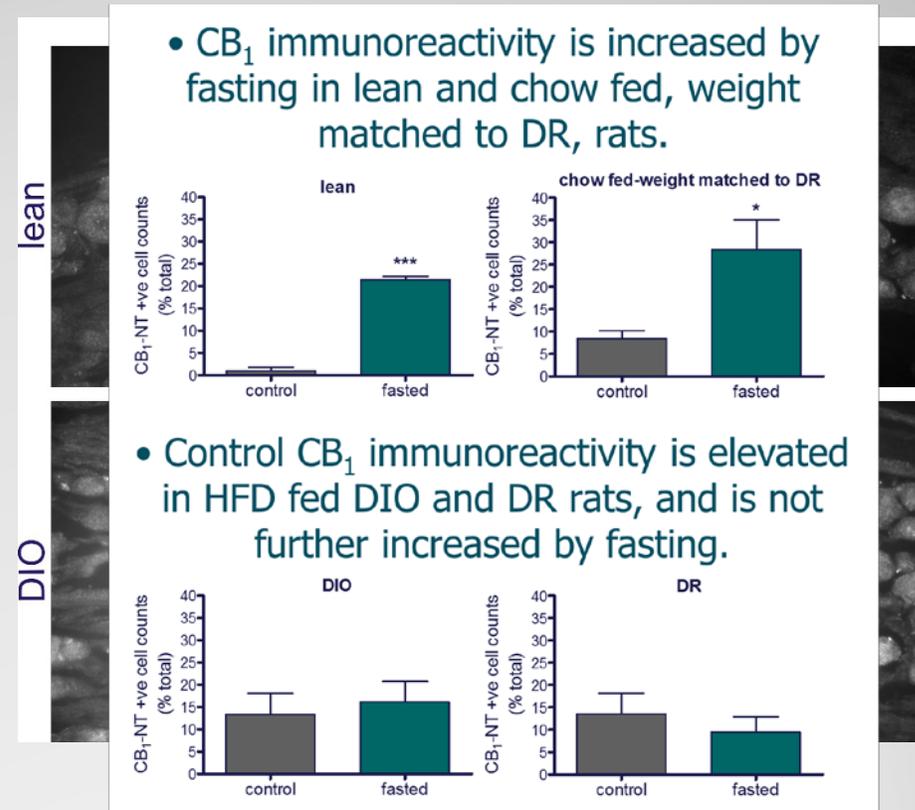
How do these peripheral endocannabinoid signals mediate their orexigenic effects?

- Enteroendocrine cells:
 - CCK (I) cells
 - GIP (K) cells
 - L cells

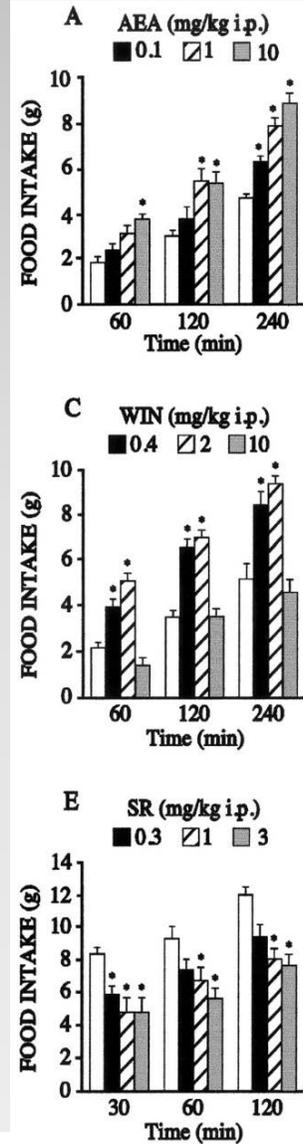


How do these peripheral endocannabinoid signals mediate their orexigenic effects?

- Vagal afferents (cell bodies in the nodose ganglia)

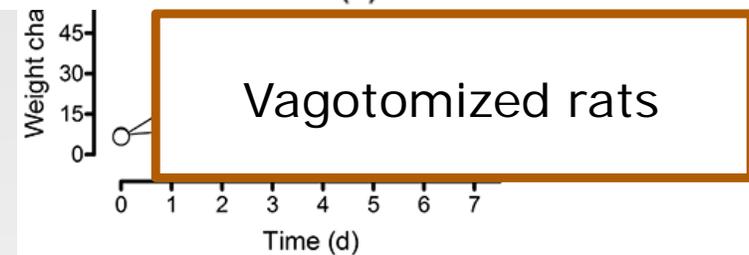
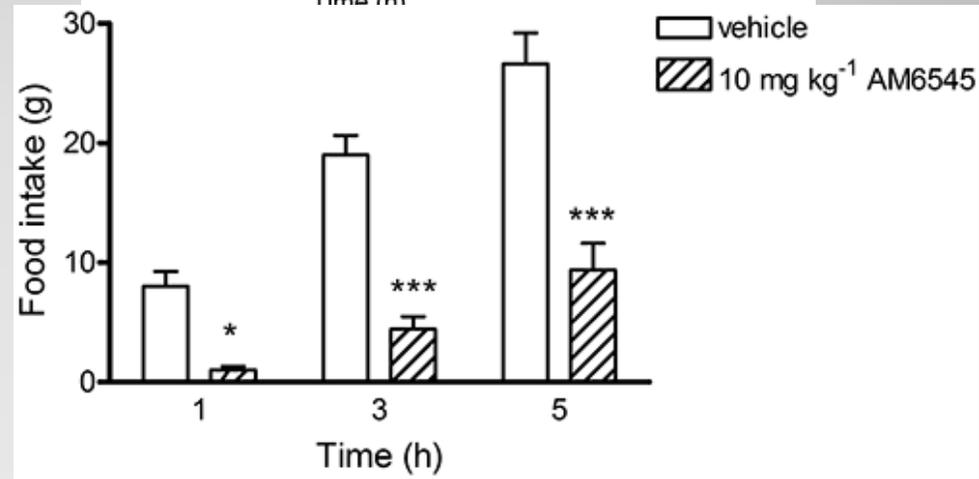
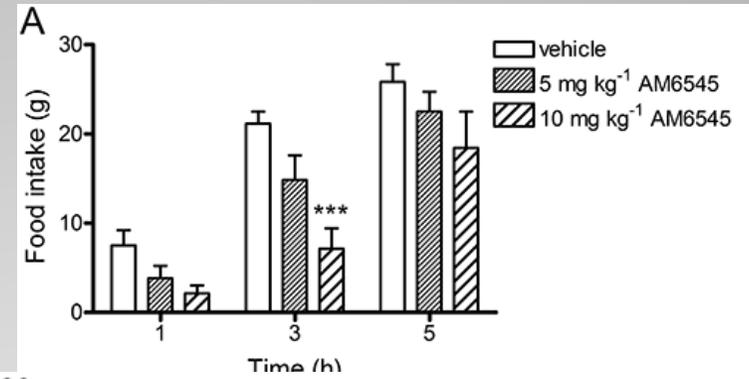


Vagal pathways are required for the orexigenic effects of CB₁ agonists and antagonists

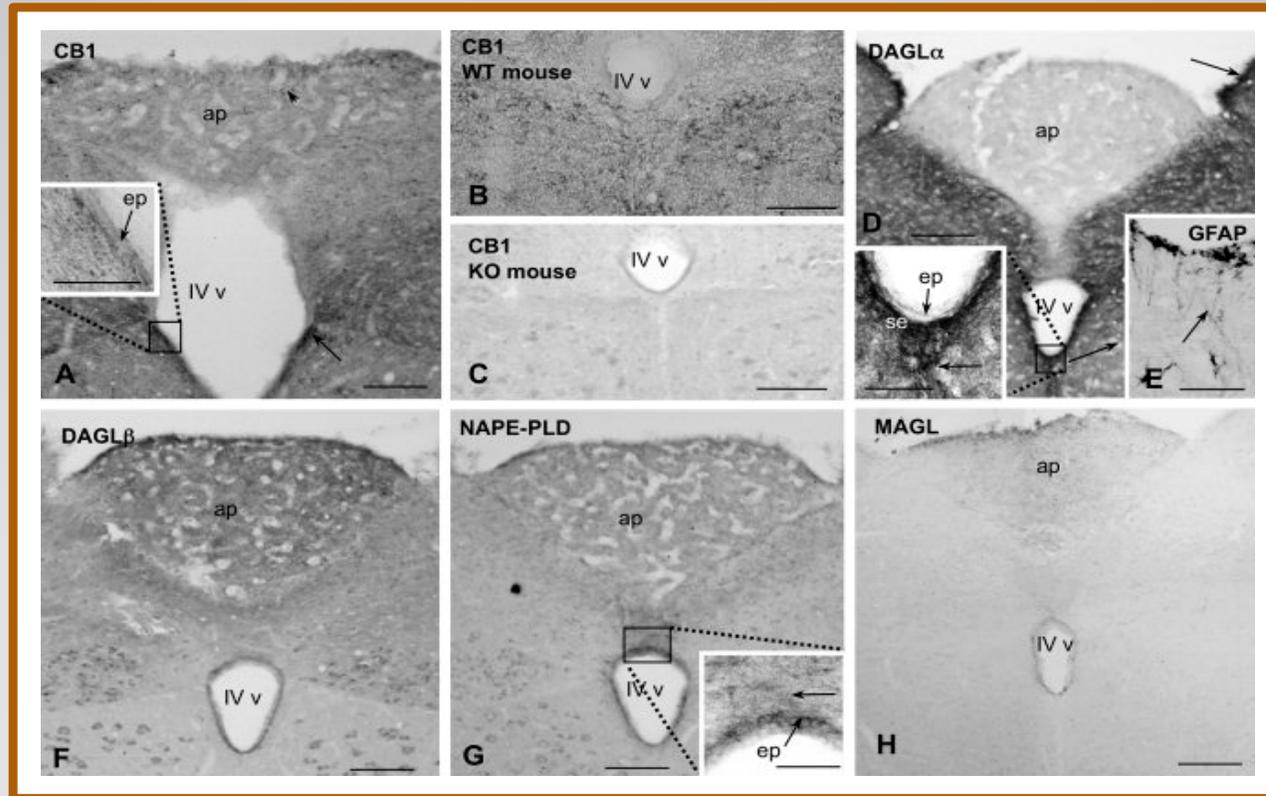


- Vagal afferents mediate these effects – they are blocked by vagal capsaicin treatment.

Vagal pathways are not always required for the orexigenic effects of CB₁ agonists and antagonists



Endocannabinoid system is expressed in circumventricular organs



Suárez et al., J Comp Neurol 518, 3065-3085 (2010)

The endocannabinoid system in the gut brain axis

- Endocannabinoids in the gut are elevated after fasting and stimulated by oral fats.
- They enhance food intake – sweet and fatty foods!
- Mediated by:
 - Enteroendocrine peptides
 - Vagal afferent nerves
 - Circumventricular organs (?)

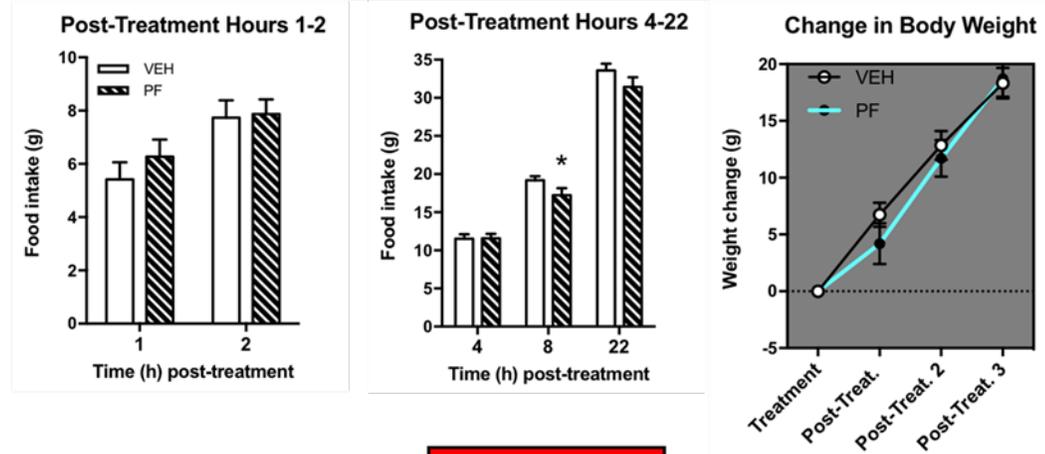
The endocannabinoid system in stress

- Stress impacts metabolic homeostasis:
 - in decreased food intake (i.e. stress-induced anorexia)
 - increased consumption of palatable substances (non-homeostatic eating).
- The stress response and feeding behaviour are regulated by the endocannabinoid system, but
 - Is stress-induced anorexia mediated by the endocannabinoid system?
 - If so, is this a peripheral or central effect?
- Given that fatty acid amide hydrolase (FAAH) inhibition is known to attenuate a variety of stress effects (via increases in anandamide), we investigated whether a FAAH inhibitor would attenuate stress-induced anorexia.

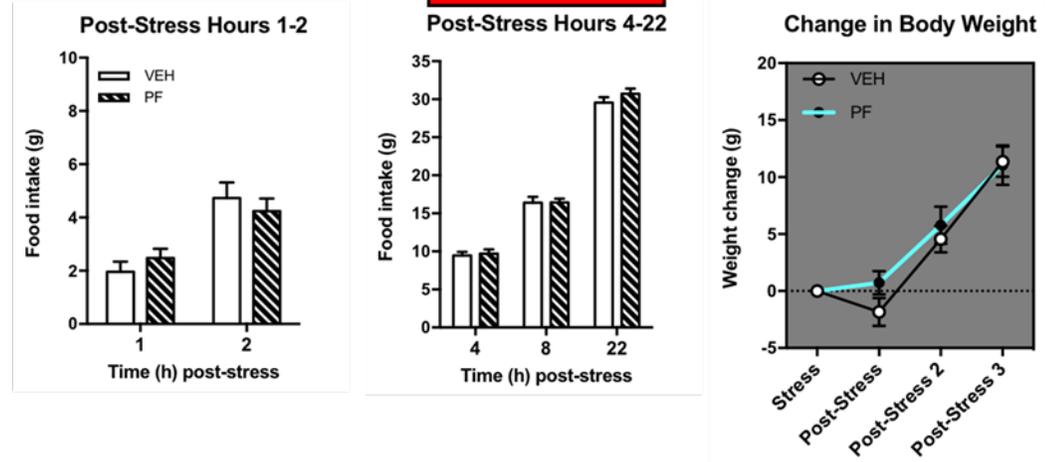
Systemic
FAAH
 inhibition
 does not
 reduce
 stress-
 induced
 anorexia



Home-Cage (2hr Food Deprivation)



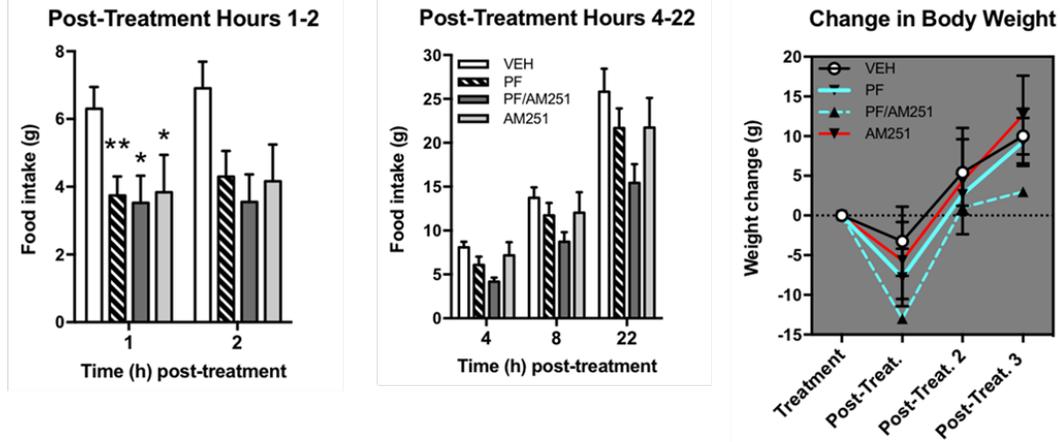
2hr Restraint Stress



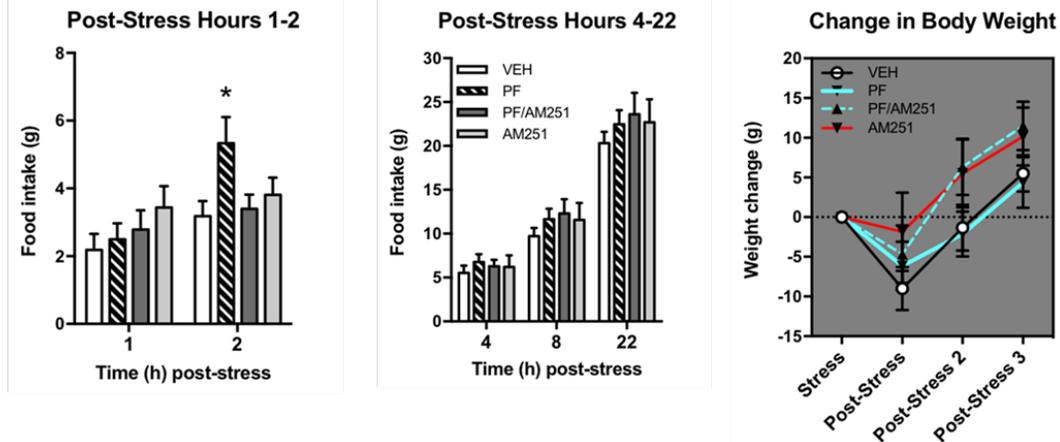
Sticht, Hill and Sharkey, unpublished observations

[ICV FAAH inhibition reduces stress-induced anorexia: mediated by CB₁ receptors

Home-Cage (2hr Food Deprivation)



2hr Restraint Stress

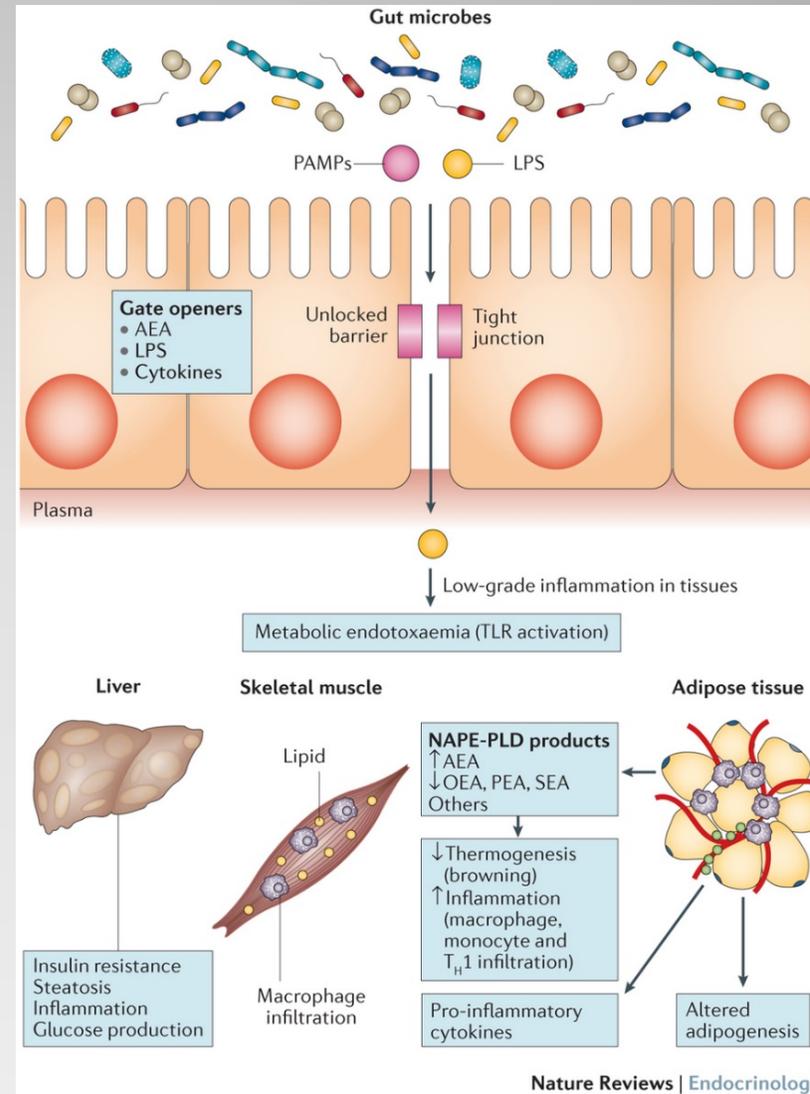


Sticht, Hill and Sharkey, unpublished observations

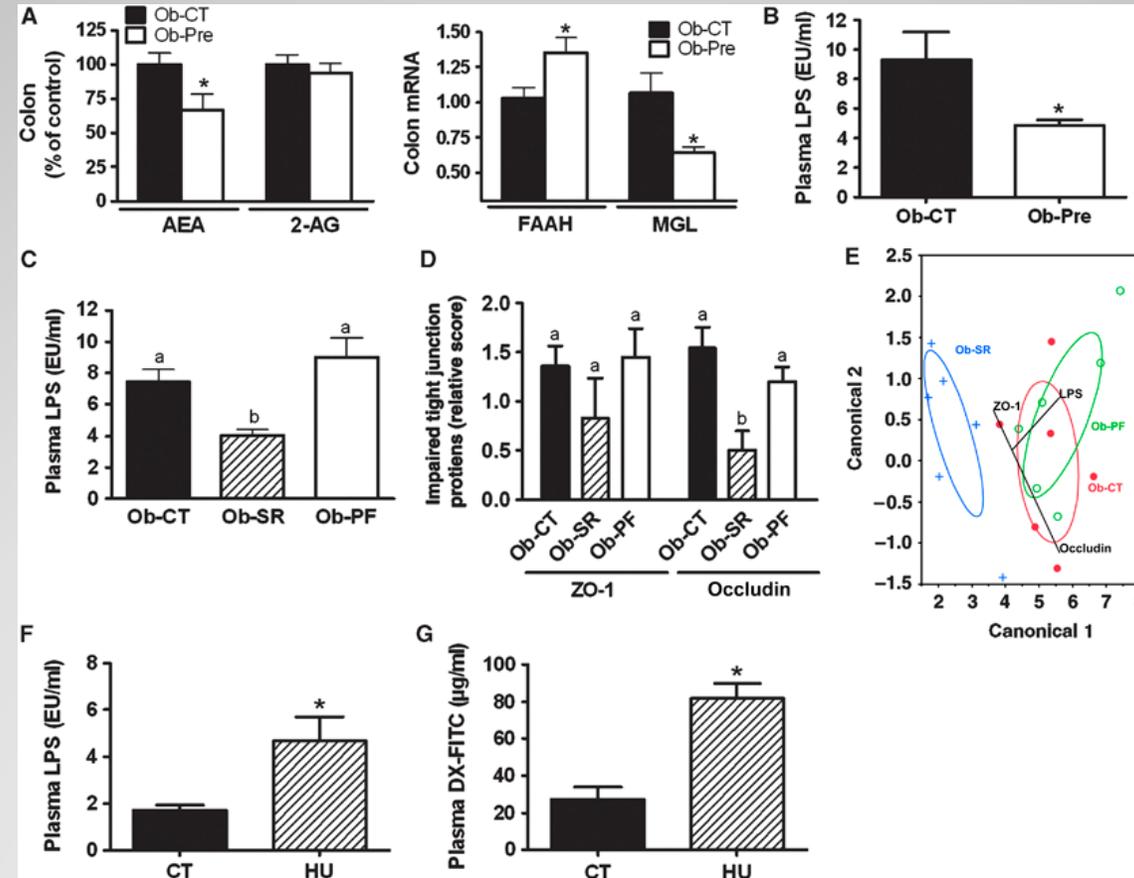
Endocannabinoids contribute to the development of obesity by regulating intestinal permeability

- LPS release from the gut lumen induces a state of metabolic endotoxemia leading to obesity.

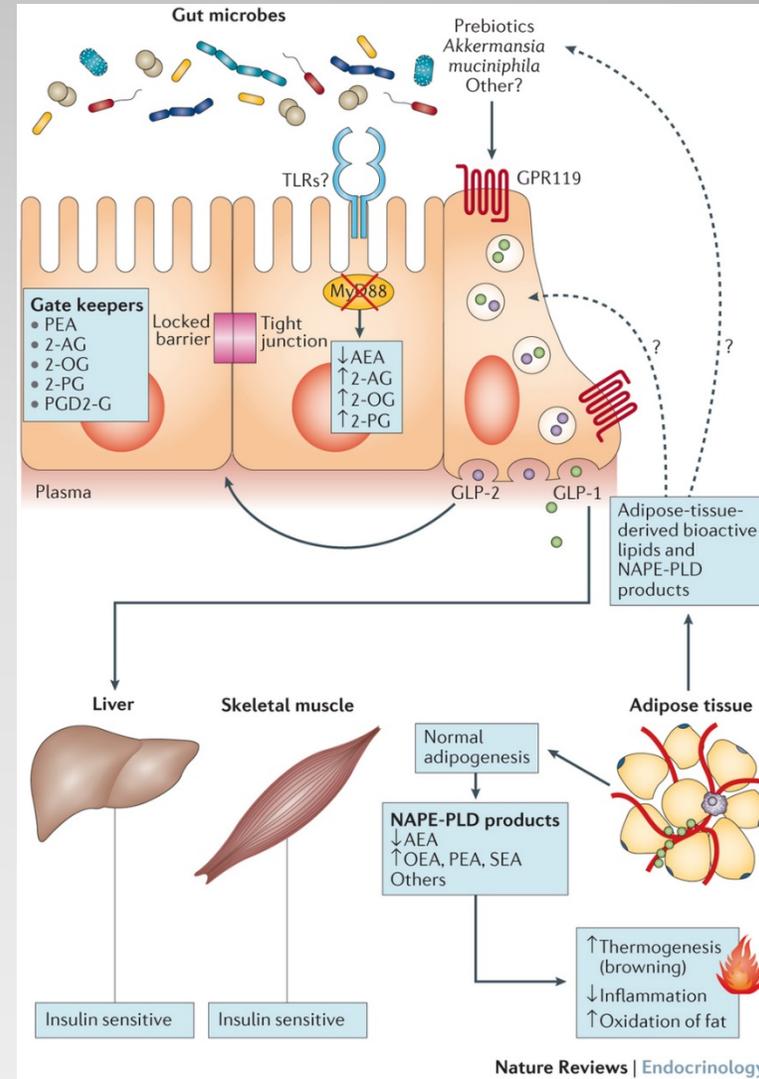
Endocannabinoids (anandamide) negatively regulates the expression of tight junction proteins



Endocannabinoids regulate the expression of tight junction proteins



Endocannabinoids (2-AG) and probiotic bacteria positively regulate the expression of tight junction proteins



Cani et al., Nature Rev Endocrinol 12, 133-143 (2016)

The endocannabinoid system in the gut-brain axis

- Endocannabinoids regulate stress induced anorexia centrally – not at the level of the gut-brain axis.
- Endocannabinoids regulate intestinal epithelial permeability and this potentially contributes to the development of obesity through metabolic endotoxemia.

Cannabis and food intake – the two go hand in hand!



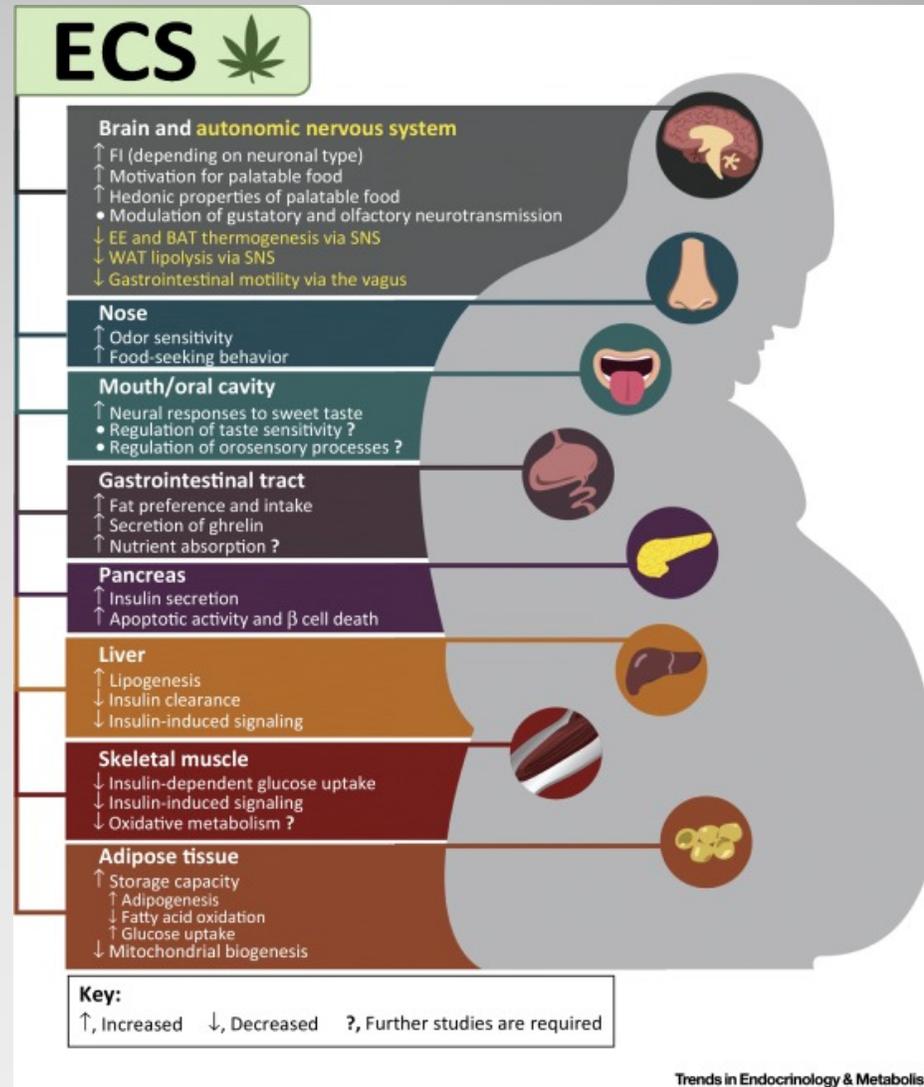
Are cannabis users obese?

Obesity rates are lower in frequent cannabis users!

Frequency of Cannabis Use	Obesity rate
No use in the past year	22-25 %
≥ 3 Days per week	16-17 %

>50,000 respondents across 2 nationally representative US studies

Obesity and the endocannabinoid system



Cannabis and obesity: a hypothesis

Medical Hypotheses 80 (2013) 564–567



Contents lists available at SciVerse ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy



Cannabis and Δ^9 -tetrahydrocannabinol (THC) for weight loss?

Bernard Le Foll^{a,b,c,*}, Jose M. Trigo^a, Keith A. Sharkey^d, Yann Le Strat^{a,e,f,g}

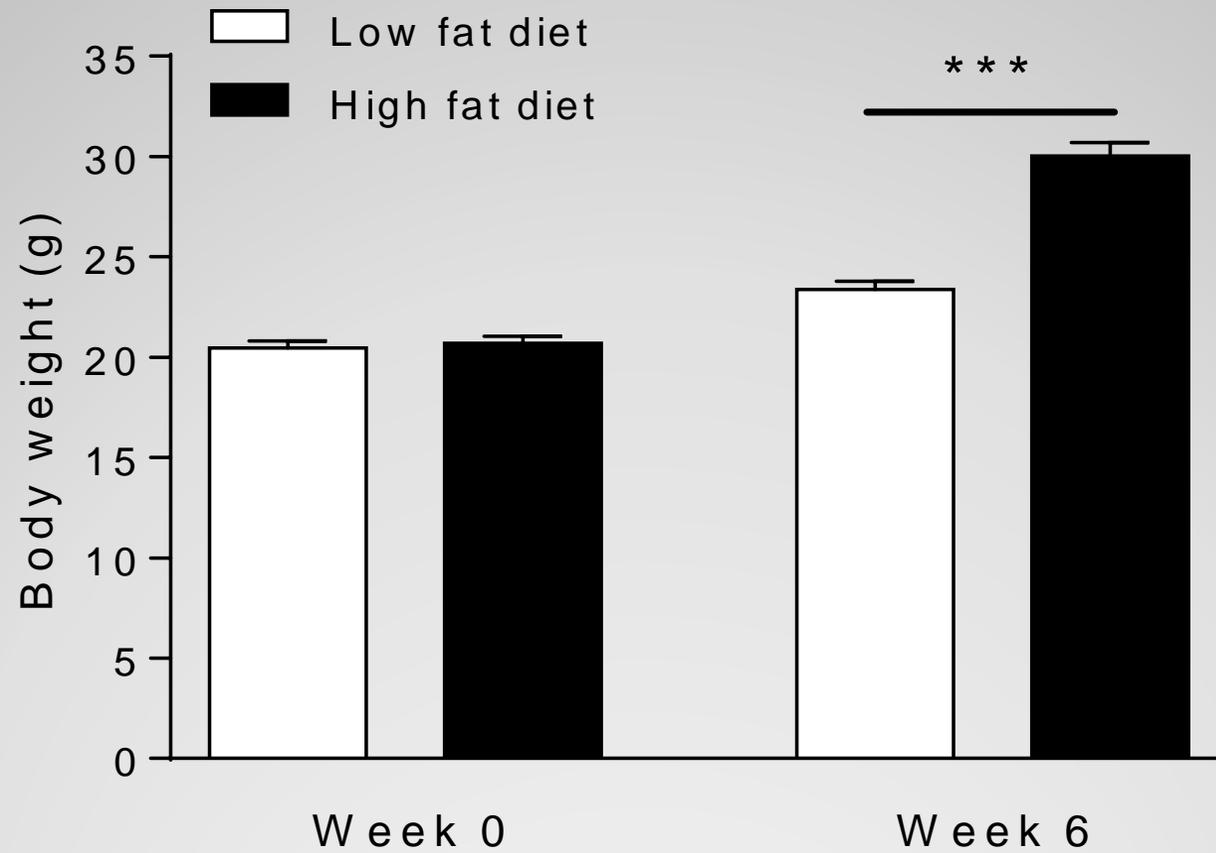
THC blocks endogenous agonists from binding to cannabinoid
CB₁ receptors during high fat food-induced high
endocannabinoid tone

Le Foll et al., Medical Hypotheses 80, 564-567 (2013)

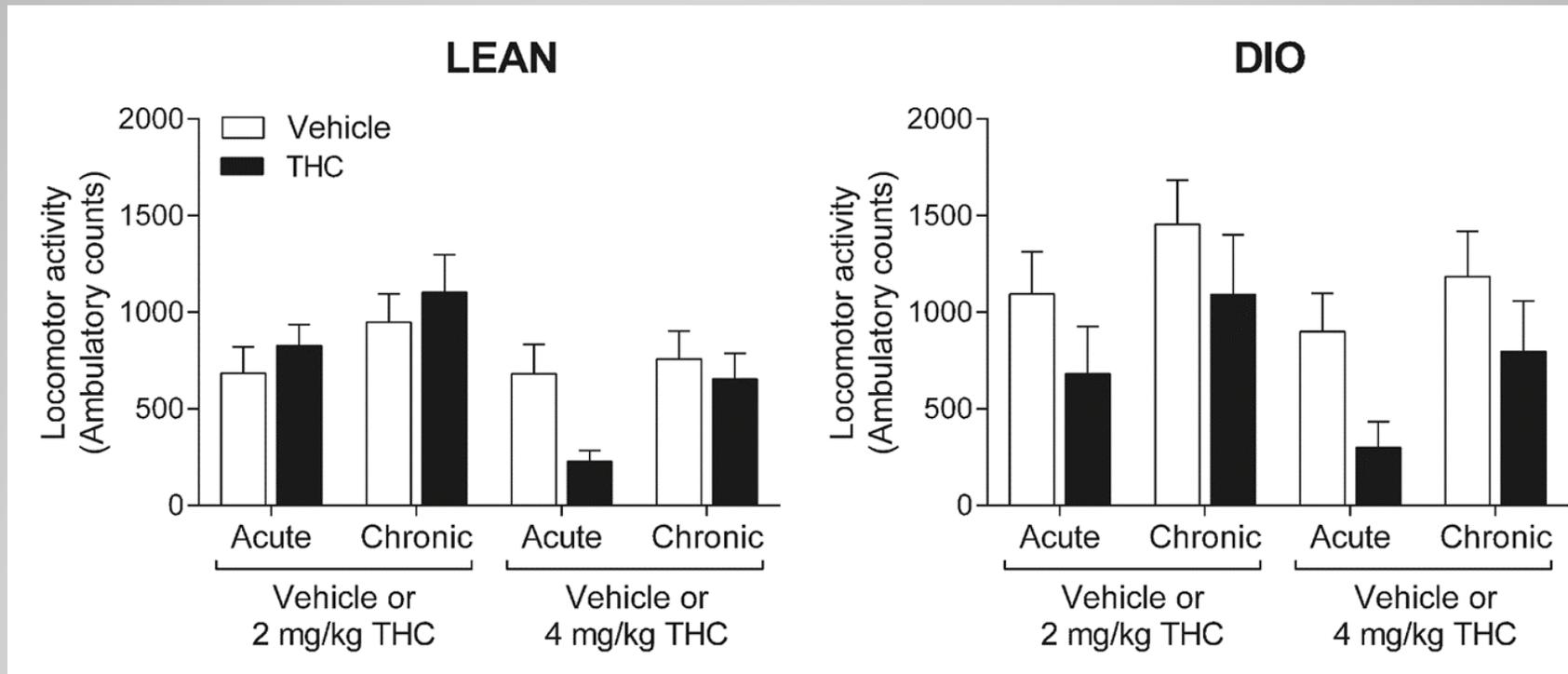
What are the effects of chronic THC in mice?

- Male mice
- High-fat diet (45% calories from fat) or mouse chow (13% calories from fat) for 6 weeks
 - Lean or Diet-induced obese (DIO)
- Daily treatment with THC – 2mg/kg for 3 weeks or 4mg/kg for 1 week.
- Measure locomotion, GI transit, food intake, body weight and cecal microbiota

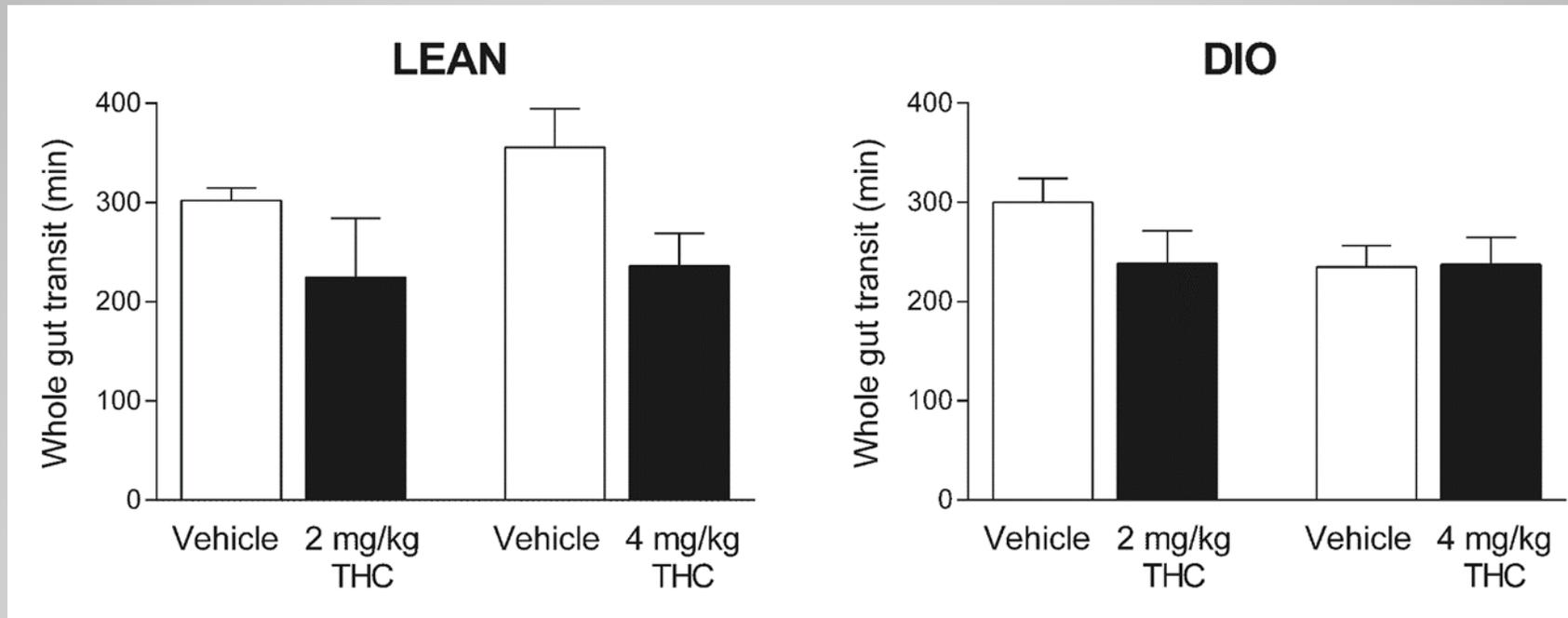
Development of obesity



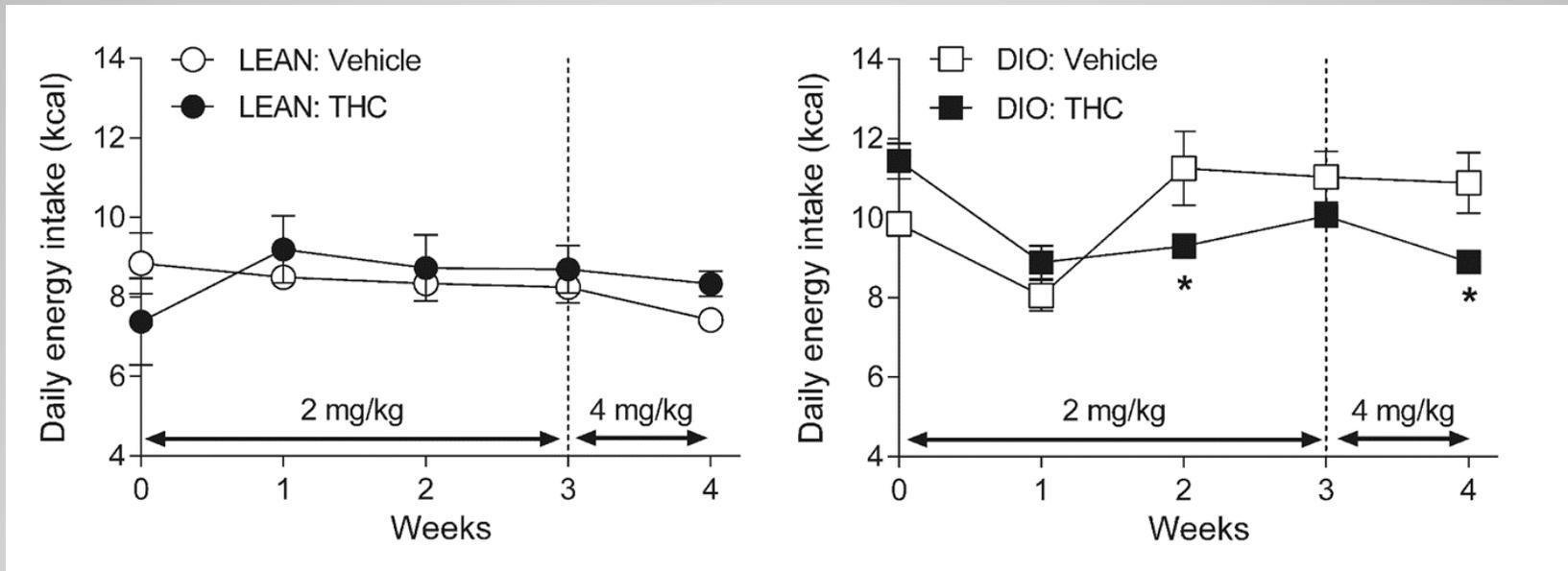
Chronic THC does not induce sedation



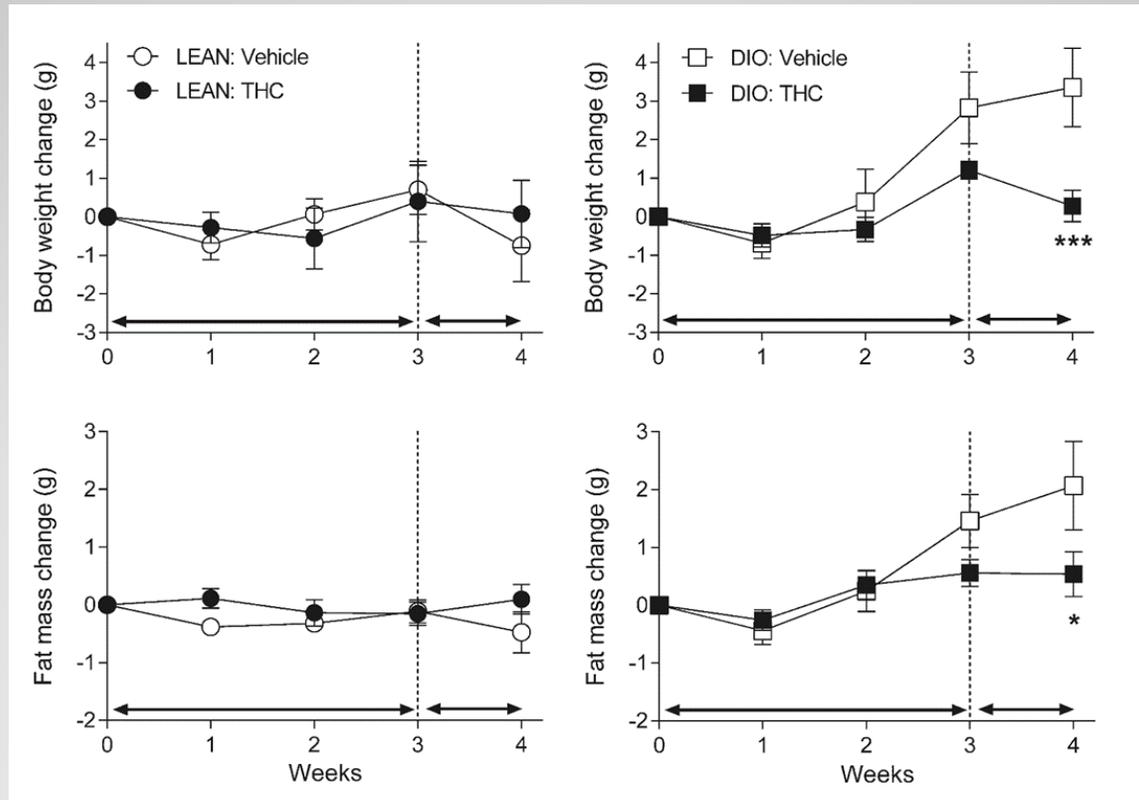
Chronic THC does not alter gastrointestinal transit



Chronic THC reduces food intake in obese, but not lean mice

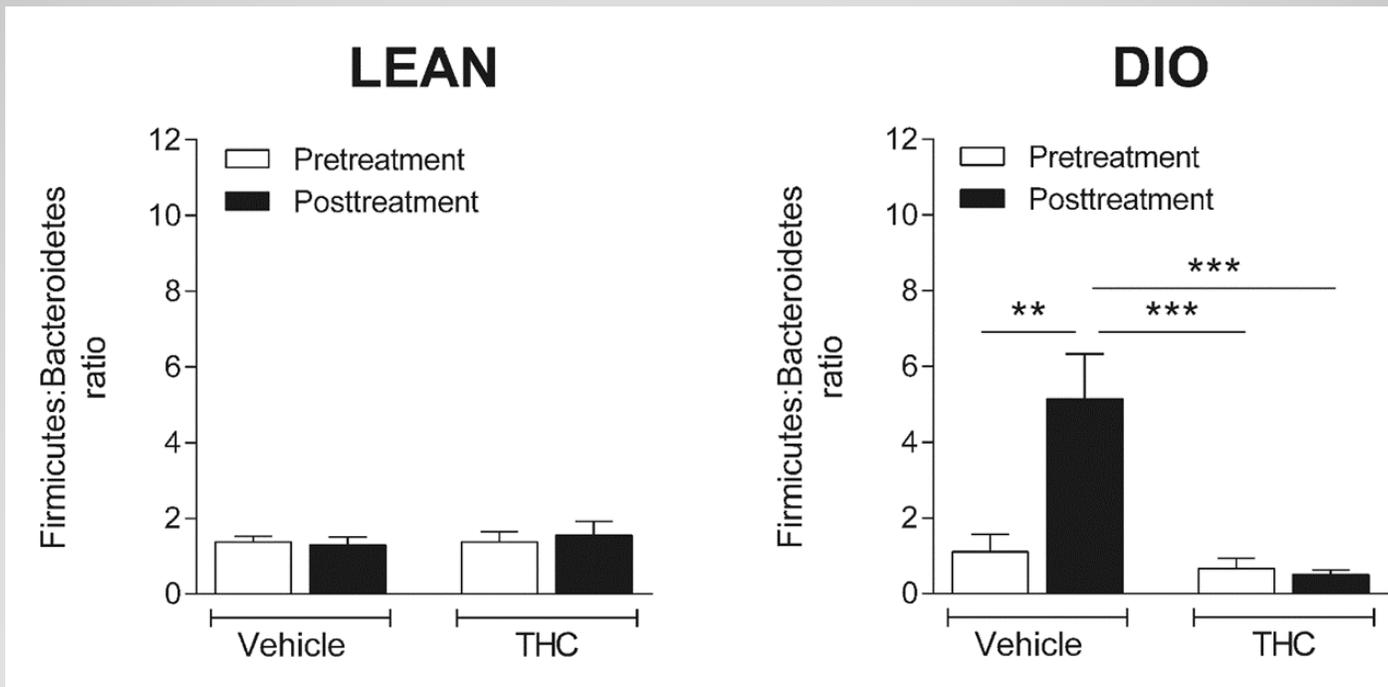


Chronic THC prevents weight gain and fat accumulation in obese, but not lean mice

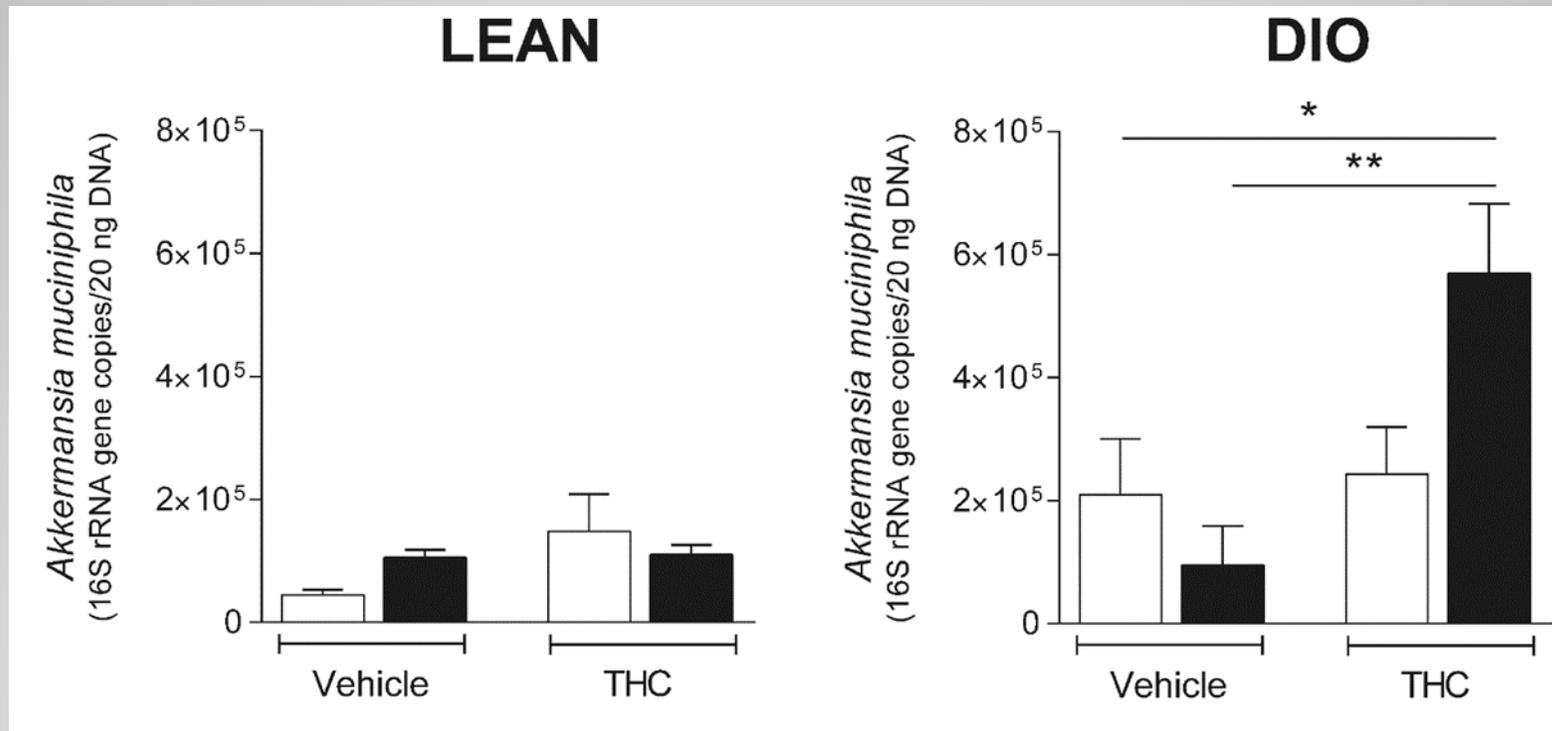


Cluny et. al., PLoS One, 10, e0144270 (2015)

Chronic THC prevents high fat diet-induced changes in gut microbiota in obese, but not lean mice



Chronic THC increases weight loss-promoting "beneficial" gut bacteria



Summary

- Chronic THC treatment inhibits food intake and prevents high fat diet-induced weight gain and adiposity
- The effects of chronic THC treatment are not due to sedation or altered GI transit
- Potentially due to changes in gut microbiota, with increases in “beneficial” bacteria

Endocannabinoid system of the gut-brain axis

- The endocannabinoid system is important for the regulation of energy homeostasis.
- The endocannabinoid system adjusts behaviour and metabolism to food availability, in particular promoting the intake of fatty and sweet foods.
- It contributes to the development of obesity.
- But cannabis may also be part of the solution!!
By shedding new light on gut-microbial interactions that potential promote healthy metabolism.

Acknowledgements

Dr. Martin Sticht

Dr. Nina Cluny

Winnie Ho and **Cathy MacNaughton** contribute to all aspects of the research from my lab.

