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

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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

Endocannabinoid system: mechanisms of synthesis and degradation

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

2-AG – 2-arachidonoylglycerol
AEA - Anandamide

Sharkey and Wiley, Gastroenterology 151, 252-266 (2016)
The endocannabinoid system

- Cannabinoid receptors – $\text{CB}_1$ and $\text{CB}_2$
- 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

CB₁ receptors in the gut-brain axis

- Brainstem
- Spinal cord
- Nodose ganglion
- Dorsal root ganglion
- VAGUS
- Longitudinal muscle
- Myenteric plexus
- Circular muscle
- Submucosa / Submucosal plexus
- Immune cells
- Mucosa
- Epithelium
- Enteroendocrine cells
- Blood vessels
- Bacteria
Endocannabinoid system in the GI tract

- Longitudinal Muscle
- Myenteric plexus
- Circular Muscle
- Submucosal plexus
- Blood Vessel
- Epithelial cells
- Enteric neurons
- Enteric glia
- Enteroendocrine cells
- Immune cells
- CB₁
- DAGL
- FAAH
- MAGL
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

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.

Yoshida et al., PNAS 107, 935-939 (2010)
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.

DiPatrizio et al., PNAS 108, 12904-12908 (2011)
Sham feeding increases jejunal endocannabinoid levels: blocking this with CB₁ antagonists reduces food intake

DiPatrizio et al., PNAS 108, 12904-12908 (2011)
Fasting increases jejunal endocannabinoid levels: blocking this with CB$_1$ 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

Moss et al., Diabetologia 55, 3094-3103 (2012)
How do these peripheral endocannabinoid signals mediate their orexigenic effects?

- Vagal afferents (cell bodies in the nodose ganglia)

Cluny et al., Autonomic Neuroscience 179, 122-130 (2013)
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.

Gómez et al., J Neuroscience 22, 9612-9617 (2002)
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

Sticht, Hill and Sharkey, unpublished observations
ICV FAAH inhibition reduces stress-induced anorexia: mediated by CB₁ receptors

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

Cani et al., Nature Rev Endocrinol 12, 133-143 (2016)
Endocannabinoids regulate the expression of tight junction proteins

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

<table>
<thead>
<tr>
<th>Frequency of Cannabis Use</th>
<th>Obesity rate</th>
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</thead>
<tbody>
<tr>
<td>No use in the past year</td>
<td>22-25 %</td>
</tr>
<tr>
<td>≥ 3 Days per week</td>
<td>16-17 %</td>
</tr>
</tbody>
</table>

>50,000 respondents across 2 nationally representative US studies

Obesity and the endocannabinoid system

Mazier et al., Trends Endocrinol Metab. 26, 524-537 (2015)
Cannabis and obesity: a hypothesis

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

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.
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