Endocannabinoids & Feeding

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What is the ECS?

• Endocannabinoid system!
• Important in the modulation of appetite and food intake.
• Feeding status and dietary patterns influence the ECS.
• Important molecules: (endo)cannabinoids & phytocannabinoids
• Why should we focus on the ECS?
Endocannabinoid Receptors & Enzymes

• What are endocannabinoids?
• Endocannabinoid receptors?
• Important ligands:
  • AEA
  • NADA
• Important receptors:
  • CB1
  • CB2

https://thegoodearth.global/glossary/endocannabiniiods/
Fig. 1. Chemical structure of some endocannabinoids: anandamide, 2-arachidonoylglycerol, N-arachidonoyldopamine (NADA), noladin ether and virodhamine.

Fig. 2. Examples of some ‘phytocannabinoids’ from Cannabis and other plants. (a) (−)-Trans-Δ⁹-tetrahydrocannabinol (Δ⁹-THC), main psychoactive compound present in Cannabis. (b) Δ⁹-Tetrahydrocannabinol (Δ⁹-THC), cannabinoid (CB₁) antagonist present in Cannabis. (c) Cannabidiol, non-psychoactive compound from Cannabis with diverse pharmacological spectrum, low affinity for CB₁ and CB₂ receptors, antagonist for G-protein coupled receptor (GPR) 55, agonist for GPR18 and PPAR-γ, etc. (d) (E)-β-caryophyllene, CB₂ agonist, widespread in plants. (e) Falcarniol, selective CB₁ inverse agonist, covalently binding. Present in different plants, including carrots, celery and Panax ginseng. (f) Yangonin, selective CB₁ ligand (over CB₂) present in Kava (Piper methysticum). See text for further details and references.
ECS & the Human Body

• Highly pleiotropic
• Energy homeostasis, eating behavior, reproduction, growth, development, learning, memory, anxiety, immune function, etc.

• Homeostatic functions:
• Controls metabolic function [energy balance, food intake]
• Acts on the peripheral tissues [adipocytes, hepatocytes, GI tract]
Endocannabinoid System

• Not as distinct as we once thought?
• Discovered to be part of a larger class of structurally similar amides, esters, ethers of fatty acids.
• Widens the spectrum of physiological engagement.
• Pathways have been discovered with synthesis, hydrolysis/ oxygenation, showing crossroads with other bioactive lipids.
The Role of Endocannabinoids in Normal Feeding

- THC acts via CB₁ receptors in hypothalamic nuclei to directly increase appetite
  - And endocannabinoid levels are seen to be inversely correlated with the amount of leptin in the blood

- Mice without leptin - massively obese; express abnormally high levels of hypothalamic endocannabinoids
- Vs. mice with inverse agonists (eg. rimonabant) - food intake is reduced
- Vs. mice with CB₁ receptors knocked out - leaner and less hungry than wild-types

https://www.nature.com/articles/35071088
A Focus on Animal Studies

- A breakdown of feeding:
  - Appetitive phase - associated with the approach to food
    - Motivational and emotional factors
  - Consummatory phase - components regarding actual ingestion
    - Palatability and reward
The Appetitive Phase

- **Use of progressive ratio paradigm**: experimental animals work progressively harder to obtain successive food rewards
  - CB₁ agonists - increased animal’s effort to obtain food reward
  - CB₁ inverse agonists - attenuated instrumental responses to rewarding food
- Thornton-Jones et al. tested the effect of a CB₁ antagonist (rimonabant) on the motivational state and palatability in rats; involved:
  - Consumption of highly palatable fat emulsion vs. 10% sucrose solution
  - Antagonist effects vs. behavioral manipulation
    - Eg. pre-feeding (reduce motivation to feed), adding bitter quinine (reduce palatability)
  - Saw a greater effect of rimonabant on the ingestion of the fat solution
    - Suggests an interaction between CB₁ modulation and macronutrient/taste/texture takes place

The Consummatory Phase

- Grill & Norgren - **Taste Reactivity** (TR) test: measures palatability of a flavoured solution by monitoring the mimetic responses of an animal
  - A solution is directly infused into the animals’ oral cavity
    - Allows the measure of strictly consummatory responses, minus the appetitive behavior
  - Palatable solutions - elicit characteristic responses
    - Ie. tongue protrusions, licking of the mouth/lips
  - Aversive solutions - elicit rejection responses
    - Ie. gaping, chin rubbing, paw threading
Using the TR test,

- Saw that low THC doses enhanced the palatability of sucrose solutions, regardless of their concentrations
  - Results were reversed by a pre-treatment of rimonabant
    - Shows the effect is mediated by CB$_1$ receptors
  - Also showed that THC ligands not only enhance positive properties of taste, but also reduce rejection of unpalatable foods
    - THC - reduced rejection of unpalatable quinine solution
    - Vs. pre-treatment of CB$_1$ antagonists - increased rejection
Central & Peripheral Connections

- A lot of focus on the CNS
  - Ex. nucleus accumbens shell: an endocannabinoid “hotspot” for sensory pleasure
    - With injection of 2-AG in the shell - induced eating in rats
- Emerging evidence of the modulation of taste function at peripheral levels
  - Sweet-sensitive taste receptors present in peripheral gustatory system - which also express CB and leptin receptors
    - So, sensitivity can be altered by orexigenic (CB) and anorexigenic (leptin) factors

Overall, the ECS regulates food appetite and intake by the modulation of palatability!

...but what about cannabinoid effects in humans?
Marijuana and Taste in Humans

- Increased appetite for *sweet* food
  - Is this due to changes in senses -> increased palatability of sweets?
  - *Matts, Shaw, and Engelman (1994)*:
    - Effects of marijuana on sweet, sour, bitter, salty stimuli responses
    - No significant changes in taste responses found
    - May be due to change to cognitive processes (such as memory) instead of senses
    - More studies needed...
Marijuana and Weight

- *Foltin et. Al (1988)* on Marijuana and weight
  - 3 days of Marijuana alternated by 3 days of placebo for 2 weeks
  - Avg 3 kg+ during marijuana period, 3 kg- during placebo period.
  - Cannot be explained due to increased energy intake
  - Could it be due to less physical activity, increased fluid retention, increased sleep time, and decreased rest metabolism from hypothermia?

BUT...
Obesity prevalence much lower in cannabis users compared with non-users!

- Acute THC use more likely to create hyperphagic effects and weight gain
  - But it is not so with chronic users!
  - Possible Explanations:
    - THC acts as a partial agonist for CB1, but may be an antagonist of other endocannabinoids (2-AG, AEA) -> reduction of endogenous ECS tone
    - Down-regulation/desensitization of CB1 receptors -> down-regulated ECS signaling
**Drawbacks in Human Cannabinoid Research**

- Reported data relies on many factors such as
  - Social: being alone/in groups
  - Different methods of administration -> differing plasma drug levels/being “high”
  - Energy status: being full/hungry for how long

- Leads to highly variable findings

- Pariah status
  - Lack of good experiment designs
  - Only a few compounds that can be used in humans
    - Compounds may also vary in quality (variable composition/irregular bioavailability of present compounds)
What influences endocannabinoid levels?

- Development of obesity co-occurs with increased endocannabinoid levels and CB1 receptor expression.
- ECS is deregulated in eating disorders, which is not solely linked to homeostatic control, but also in the rewarding aspects of eating behaviors.
- Abnormal eating behaviors like self starvation and binge eating become rewarding because of endocannabinoid deregulation.
- The ECS is well known to be involved in the regulation of appetite, food intake, and energy metabolism

- An excessive food supply and an overactivation of CB1 can lead to overeating and a susceptibility of metabolism to favor energy storage and obesity

- The physiology of endocannabinoids and other central and peripheral appetite modulators like leptin and ghrelin in patients with eating disorders, goes beyond the homeostatic control of food intake
Dietary modulation

- Levels of individual endocannabinoids are higher in plasma of obese compared to lean individuals.

- Since endocannabinoids are released on demand and rapidly metabolised in tissues, plasma levels will probably not directly reflect dynamic changes in discrete areas in the brain and other tissues.
Dysfunction of ECS & therapeutic application

❖ ECS:

➢ Therapeutic target in treatment for overeating
➢ Unintentional weight loss in elderly
➢ Treatment of disease-related loss of appetite
Disease-related anorexia

- Advance stages of Cancer and AIDS
  - Wasting Syndrome (Cachexia)
  - Anhedonia
  - Loss of appetite

https://www.pinterest.com/pin/56717276534163944/?lp=true
CB Agonists: appetite stimulants

❖ Dronabinol
  ➢ Synthetic THC
  ➢ Marinol

❖ Nabilone
  ➢ THC analogue
  ➢ Cesamet

In 1999, the DEA rescheduled Marinol (synthetic marijuana).
SCHEDULE III.
(A) The drug or other substance has a potential for abuse less than the drugs or other substances in schedules I and II.
(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

Meanwhile, the DEA refuses to change marijuana’s schedule I status.
Conclusion

- ECS modulate food reward:
  - ECS $\rightarrow$ neurochemical signal $\rightarrow$ Receptor + Ligands
  - Endocannabinoids $\rightarrow$ stimulate appetite by:
    - Increase palatability [sweet & fatty tastes]
    - Promote the storage of energy as fat
DON’T BE AFRAID OF CANNABINOID

CB₁ RECEPTORS
Located in the brain and the central nervous system.

CB₂ RECEPTORS
Found on cells throughout the body’s immune system.

https://www.pinterest.com/pin/56717276534163944/?lp=true