

# CHS and Endocannabinoid Signalling: From Antiemetic to Emetic



**Marieka V. DeVuono, PhD**

Addiction Research Group,  
Schulich School of Medicine & Dentistry,  
Western University

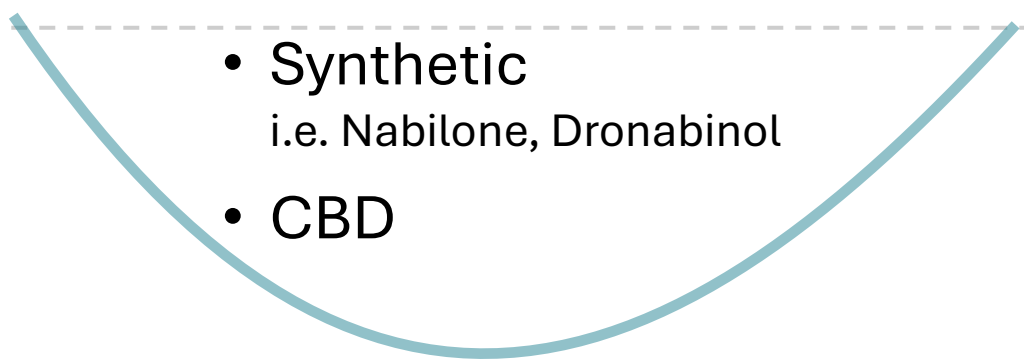
ADAI Symposium | 18 Sept 2026 | Seattle, WA  
No Conflicts of Interest





# The Cannabis Nausea and Vomiting Paradox

## *Anti-Emetic effects:*

- Treatment for chemotherapy induced nausea and vomiting
  - *Low* dose **THC**
  - **CB<sub>1</sub> receptor** activation
- 
- Synthetic  
i.e. Nabilone, Dronabinol
  - CBD
- 



# The Cannabis Nausea and Vomiting Paradox

## **Anti-Emetic effects:**

- Treatment for chemotherapy induced nausea and vomiting
- **Low** dose **THC**
- **CB<sub>1</sub> receptor** activation
- Synthetic  
i.e. Nabilone, Dronabinol
- CBD

## **Pro-Emetic effects:**

- *High doses* produce nausea and vomiting
  - i.e. Shrews, Rats, Cats, Dogs, Non-human primates, Humans
- (Johal et al. 2020; Amissah et al. 2022; Cluny et al. 2008; Ford et al., 2017)
- **Cannabinoid Hyperemesis Syndrome**

Dose: 



# Cannabinoid Hyperemesis Syndrome (CHS)

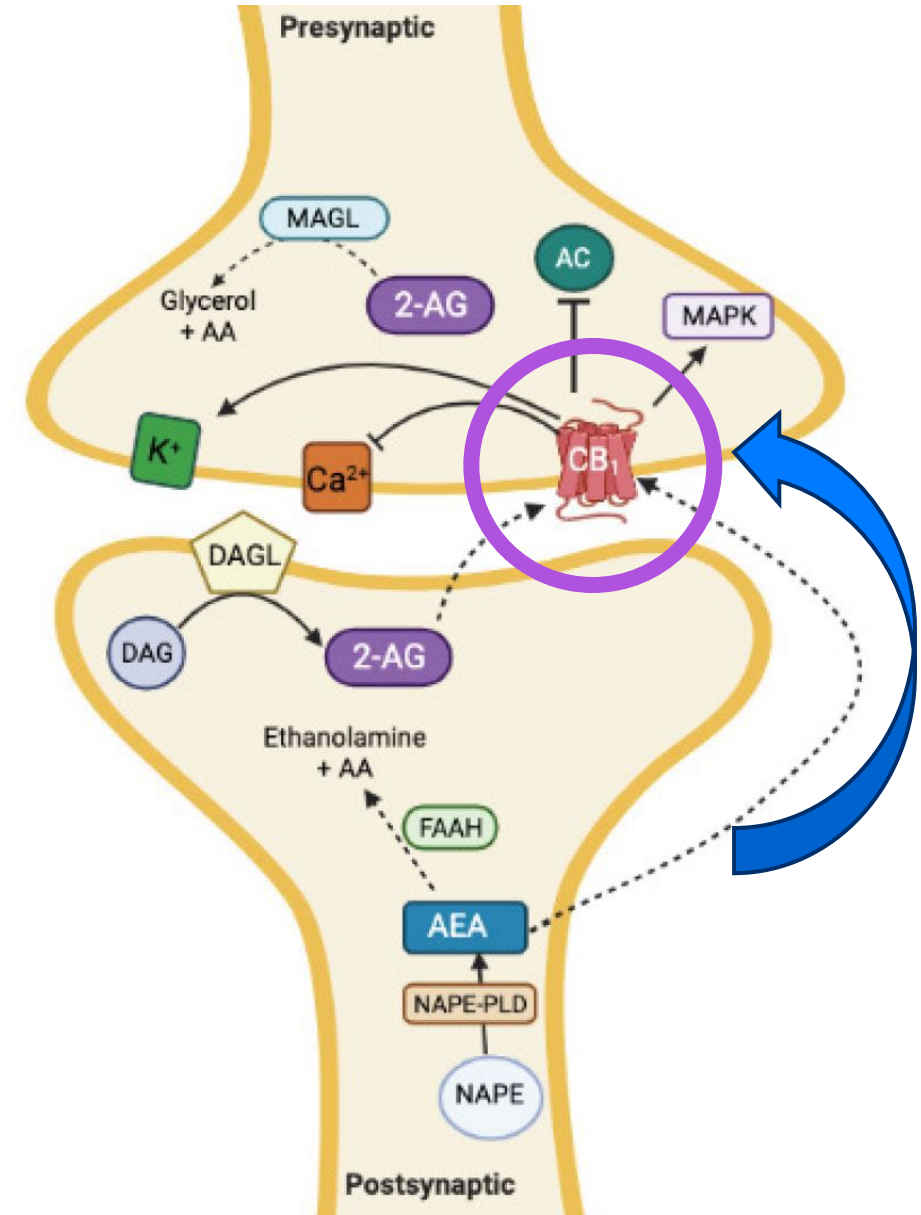
---

- Cyclical episodes of severe **nausea**, **vomiting** and abdominal **pain**, in long-term heavy cannabis users
- *What do we know?*
  - Resistant to typical antiemetics (i.e. ondansetron)
  - Anxiolytic or antipsychotic medication (i.e. lorazepam, haloperidol)
  - Hot showers/baths → temporary relief
  - Cessation of cannabis → long-term relief

# Endocannabinoid System

---

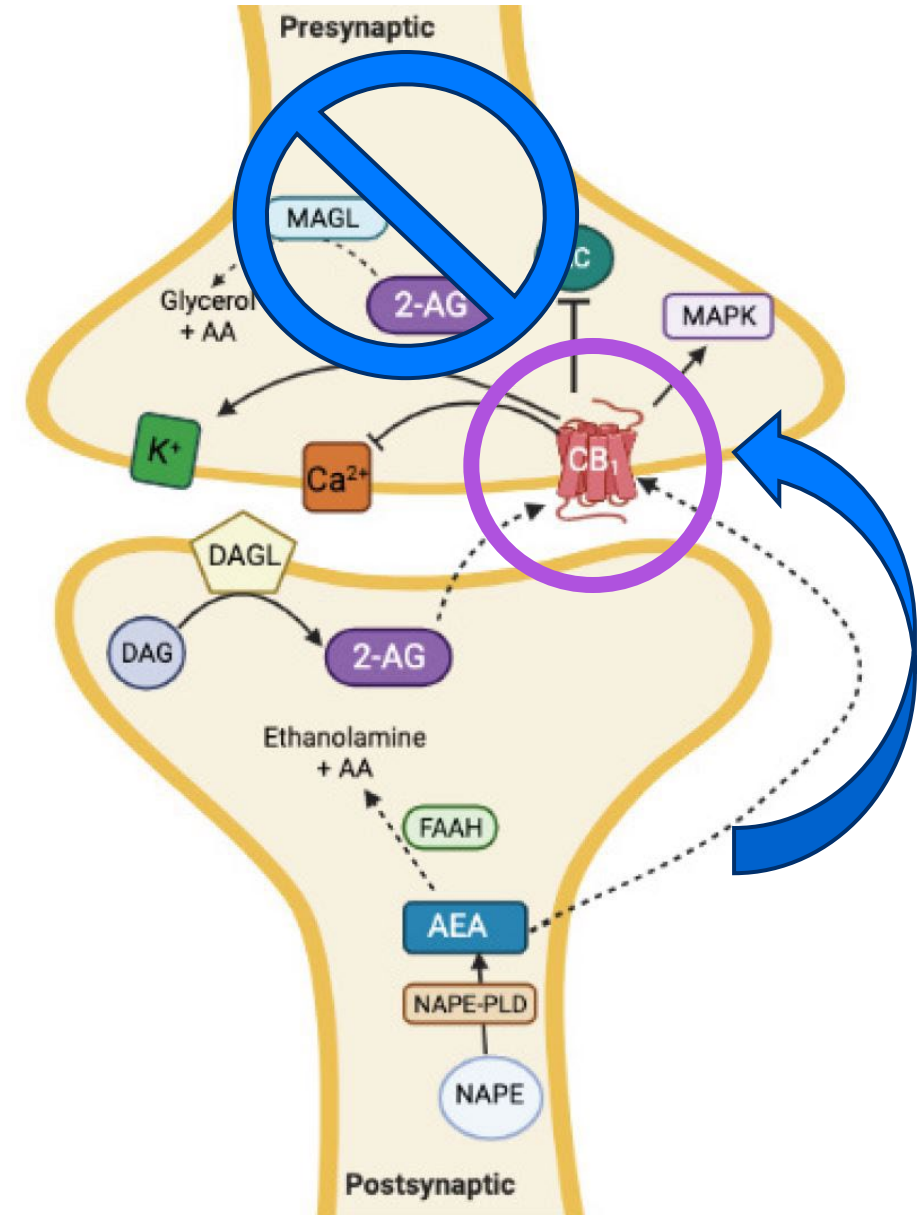
- Endogenous + Cannabinoid
- **THC** = activates the cannabinoid 1 (**CB1**) receptor
- Endogenous Ligands:
  - Anandamide and 2-AG
- Retrograde signalling - **Inhibitory**



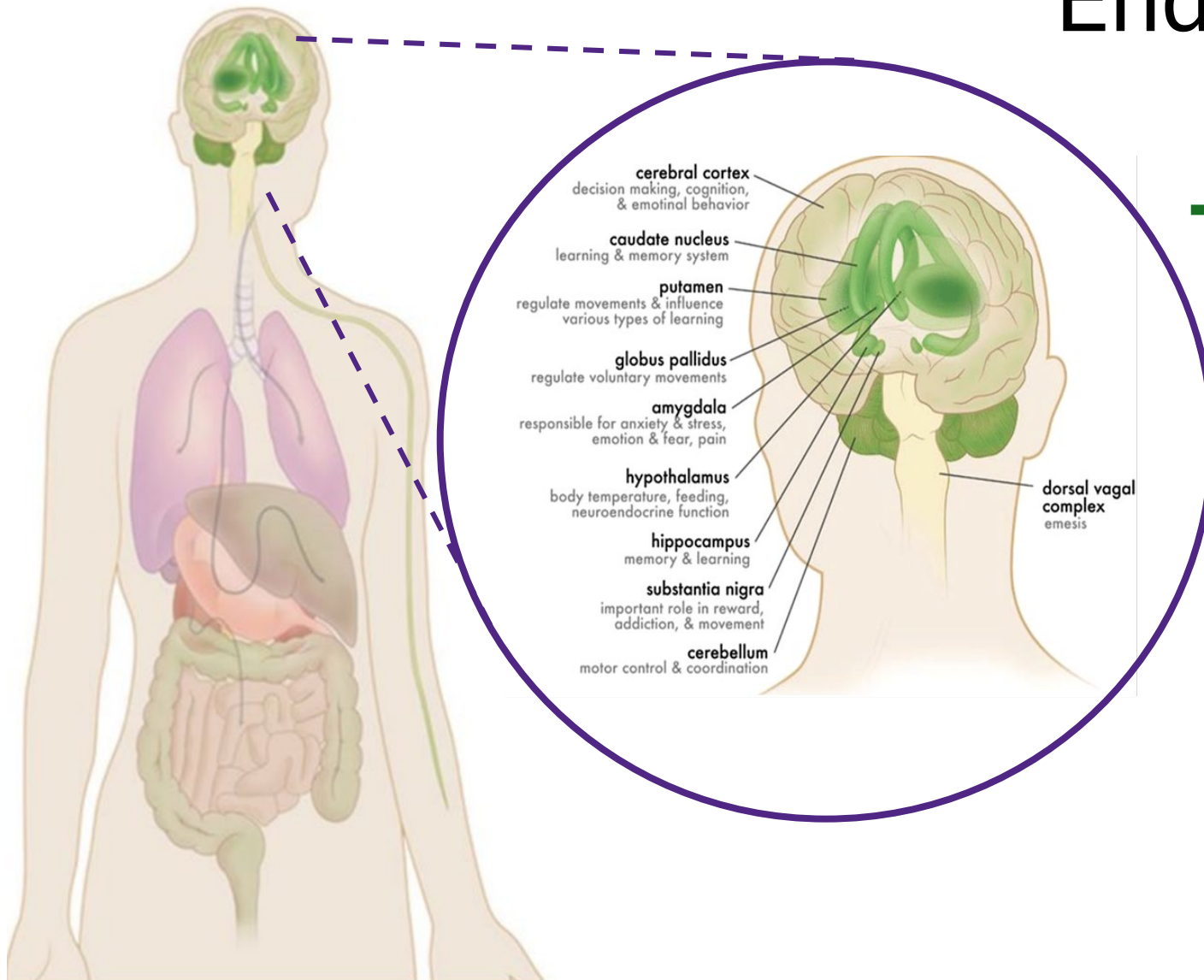
# Endocannabinoid System

---

- Endogenous + Cannabinoid
- **THC** = activates the cannabinoid 1 (**CB1**) receptor
- Endogenous Ligands:
  - Anandamide and 2-AG
- Retrograde signalling - **Inhibitory**
- CB1 is a brake
  - Nausea, gut function and the stress response



# Endocannabinoid System Distribution



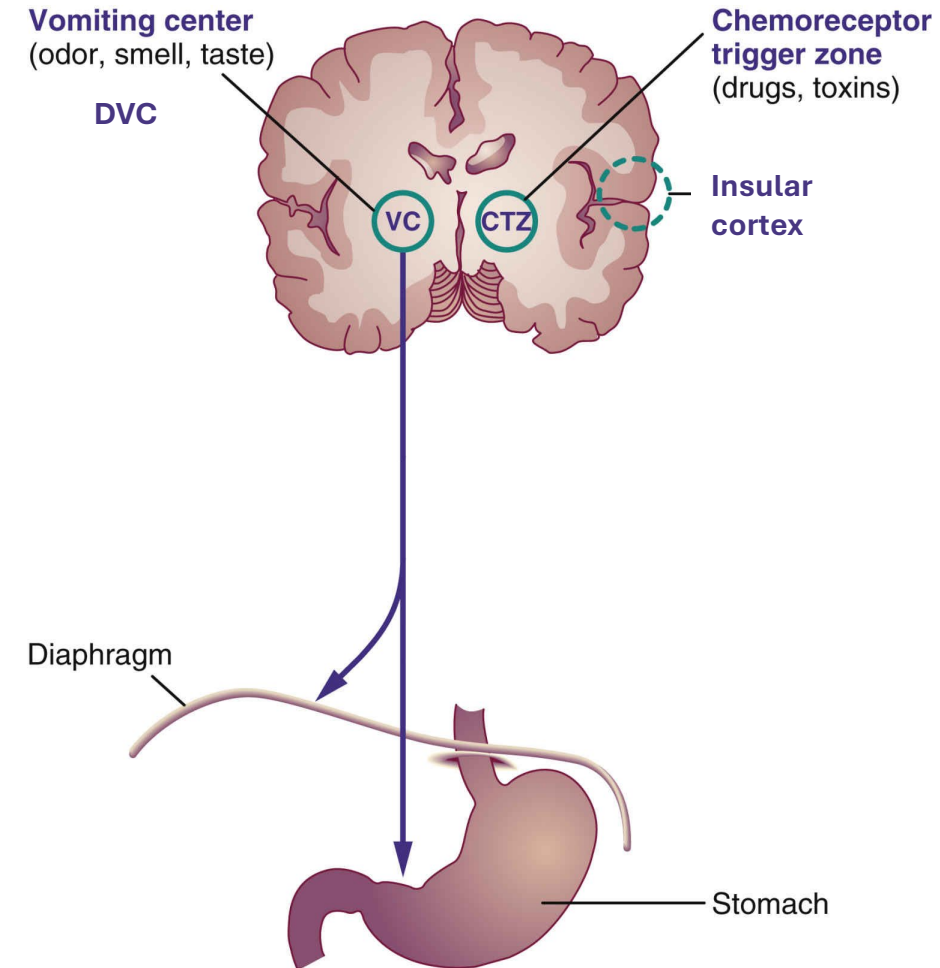
- Gastrointestinal (GI) Track
- Liver
- Central Nervous System
  - Brainstem **Dorsal Vagal Complex (DVC)**



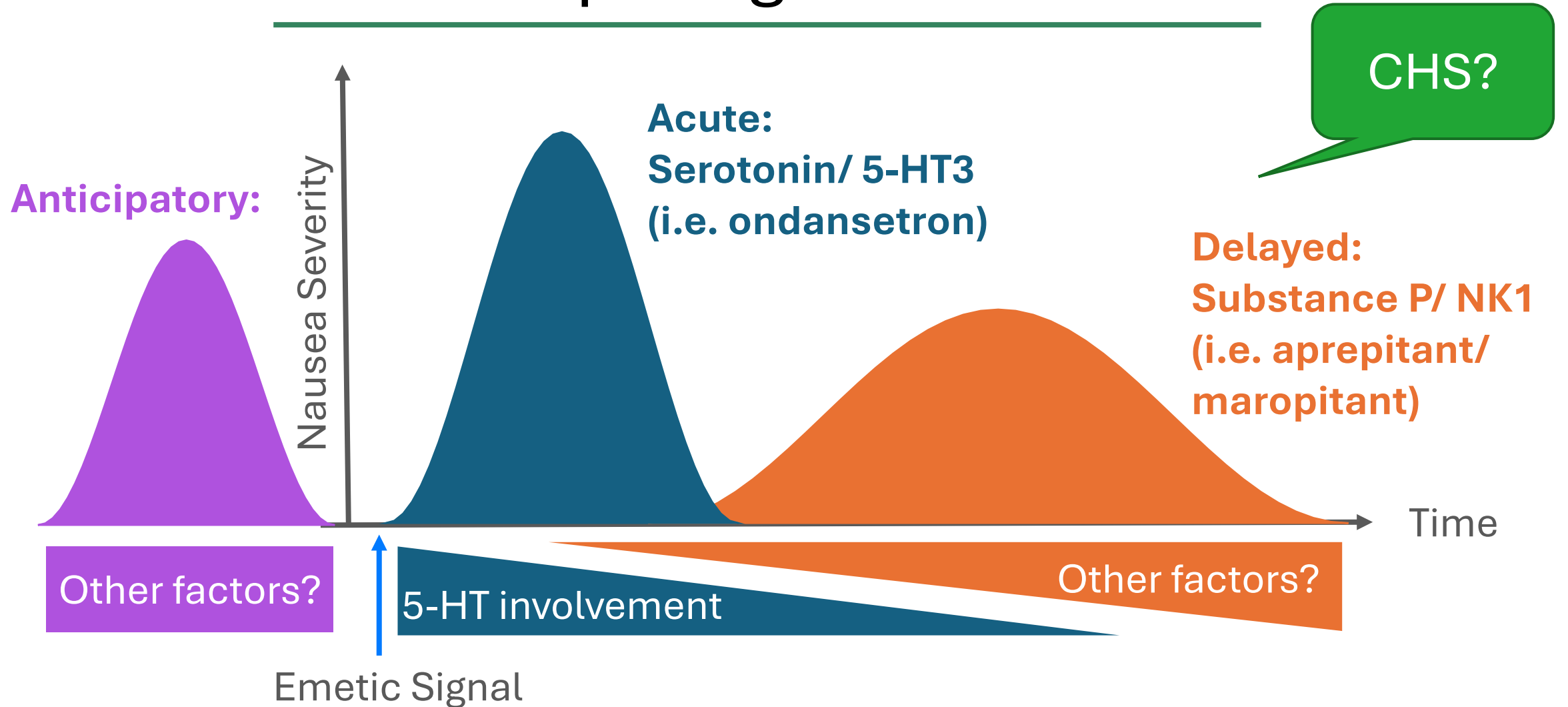
# Nausea and Vomiting

- Many causes, and often a side effect of treatment:
  - Infections, Reflux, Diabetes, Gastroparesis, Anxiety, Motion sickness, Pregnancy, Migraines, Cyclic Vomiting Syndrome, Chemotherapy, Radiation
- **Distinct** experiences and mechanisms
  - **Vomiting:** Reflex, Brainstem - Dorsal Vagal Complex (**DVC**)
  - **Nausea:** Adverse subjective experience, Interoceptive Insular Cortex (**IIC**)

**Nausea is more *common* and *debilitating*, and far less controlled**

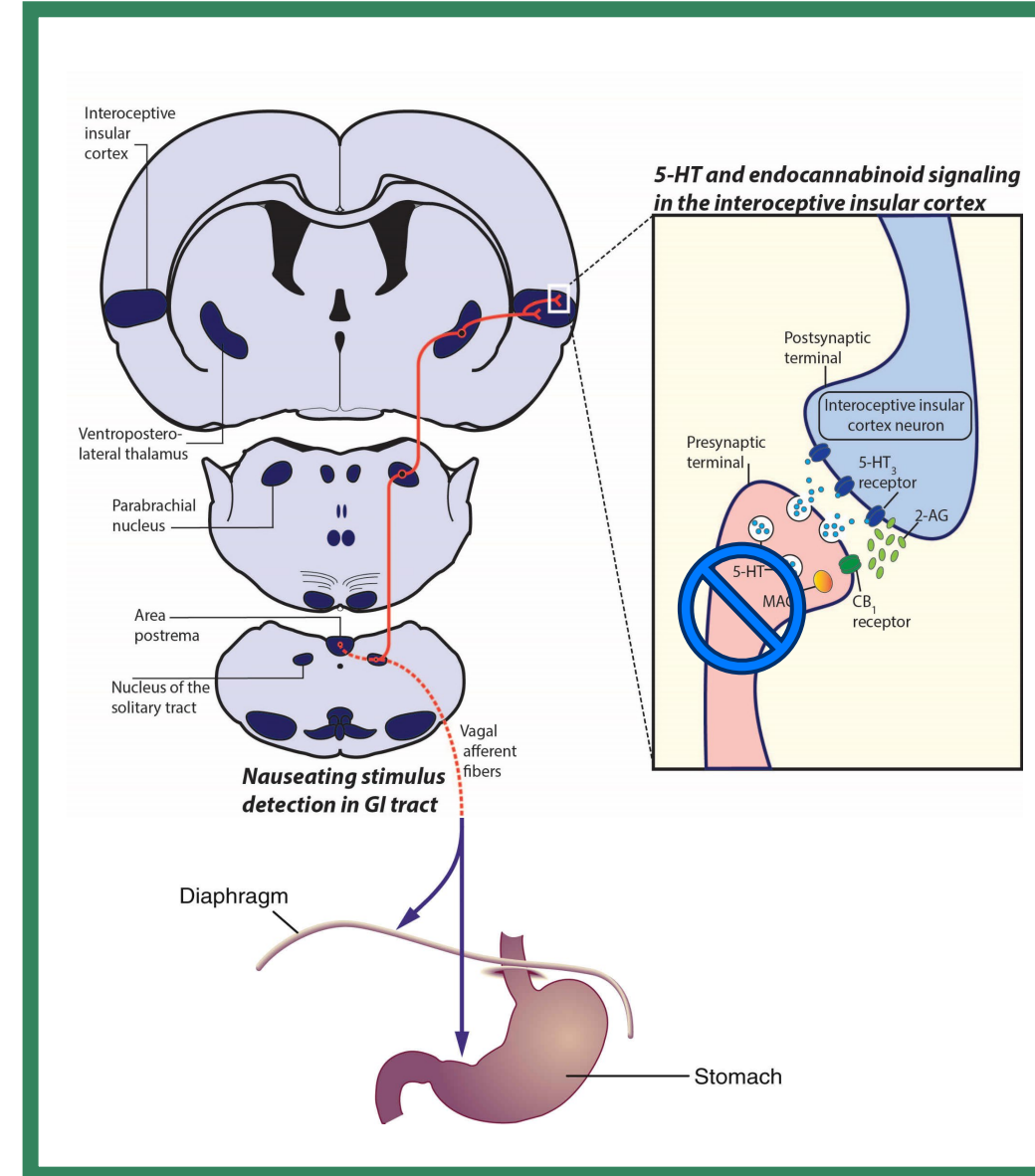


# The Multiple Signals of Nausea



# The Endocannabinoid Brake

- CB1 receptors in brainstem (**DVC**) and the insular cortex (**IIC**)
  - Activation reduce 5-HT release in both brain regions
  - And in the gut
- CB1 activation blocks Substance P/Neurokinin 1 (**NK1**) induced vomiting
- **Negative Feedback Loop**



# Measuring Nausea and Vomiting in Animals

---

- Vomiting

- Examples: Ferrets, Dogs, Nonhuman Primates, **Shrews**

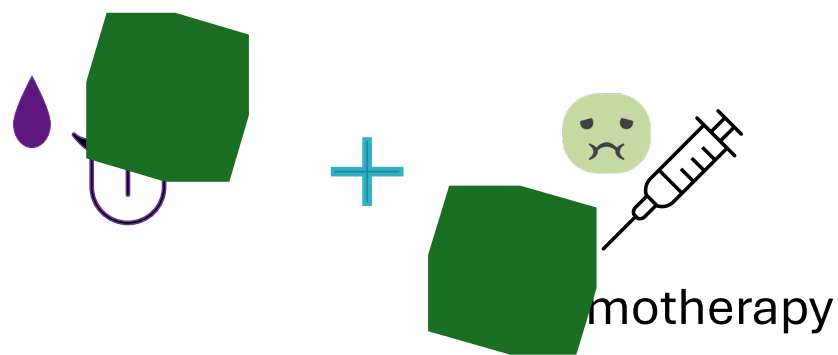
Darmani et al. 2003; Parker et al. 2015; Rock et al. 2012; Parker et al 2009



- Nausea?

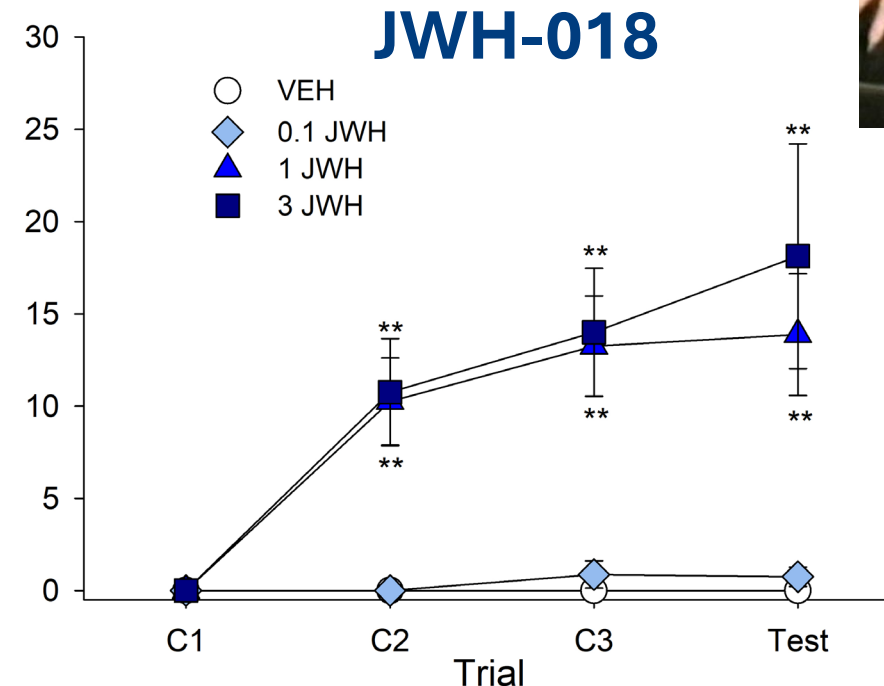
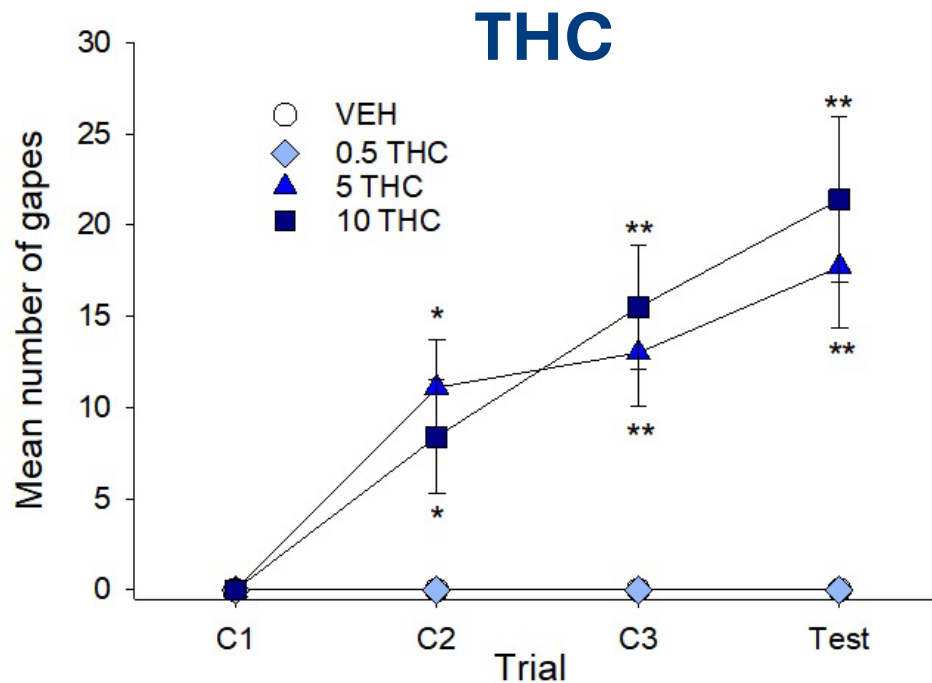
- Taste Reactivity Test
  - **Conditioned Gaping in rats**

Grill & Norgren, 1978; Parker, 2014

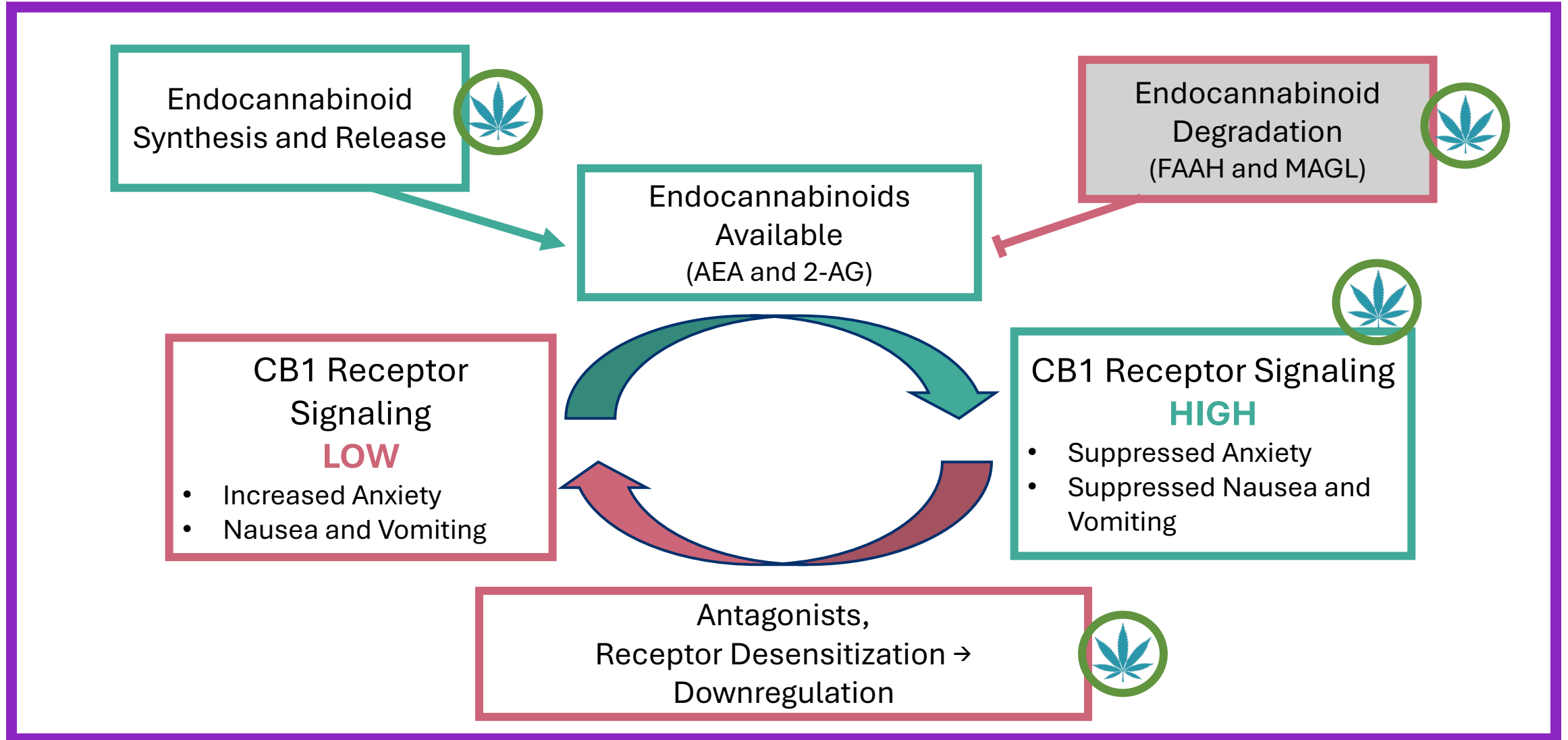


# Can Cannabinoids Produce Conditioned Gaping?

- THC and JWH-018 produce *dose-dependent* conditioned gaping
- \* Prevented by blocking the CB<sub>1</sub> receptor
- \* Vomiting in Shrews

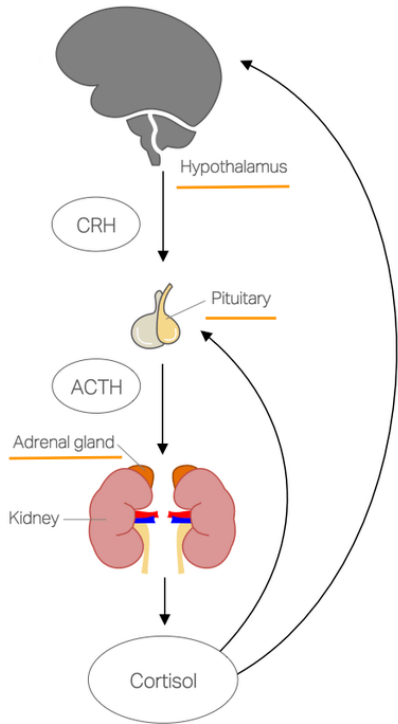


# High Dose Cannabis Wears Out Endocannabinoid System Brakes



# THC Activates the Stress Response Dose-Dependently

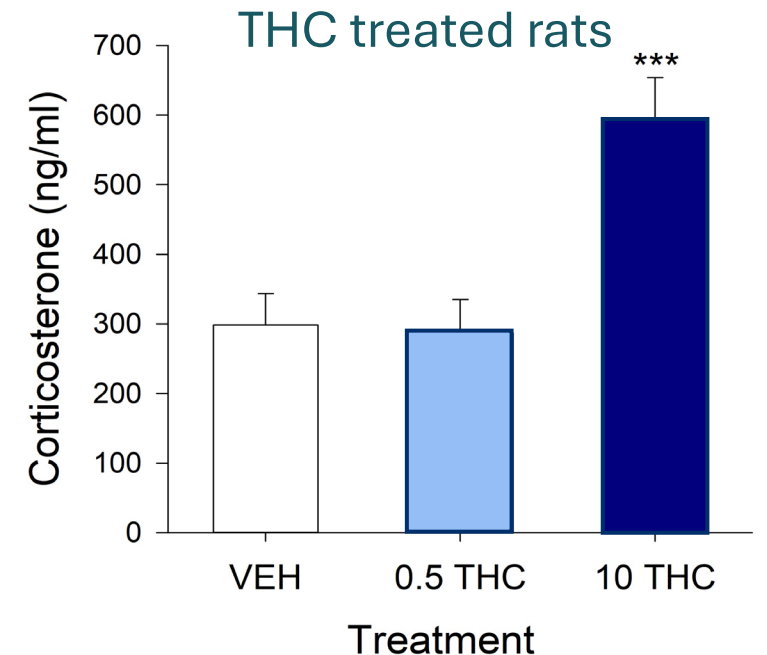
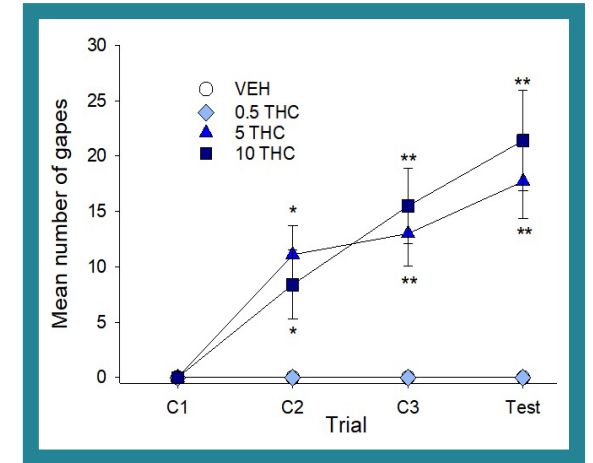
## HPA Axis



*High dose* cannabinoids increase stress related hormones and neurotransmitters:

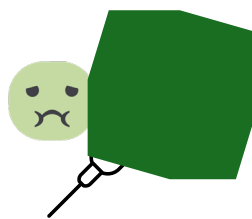
- Corticotropin Releasing Hormone (CRH)
- Cortisol/Corticosterone (CORT)
- Norepinephrine (NE)
- Serotonin (5-HT)

⚡ *Stress and nausea also related!*





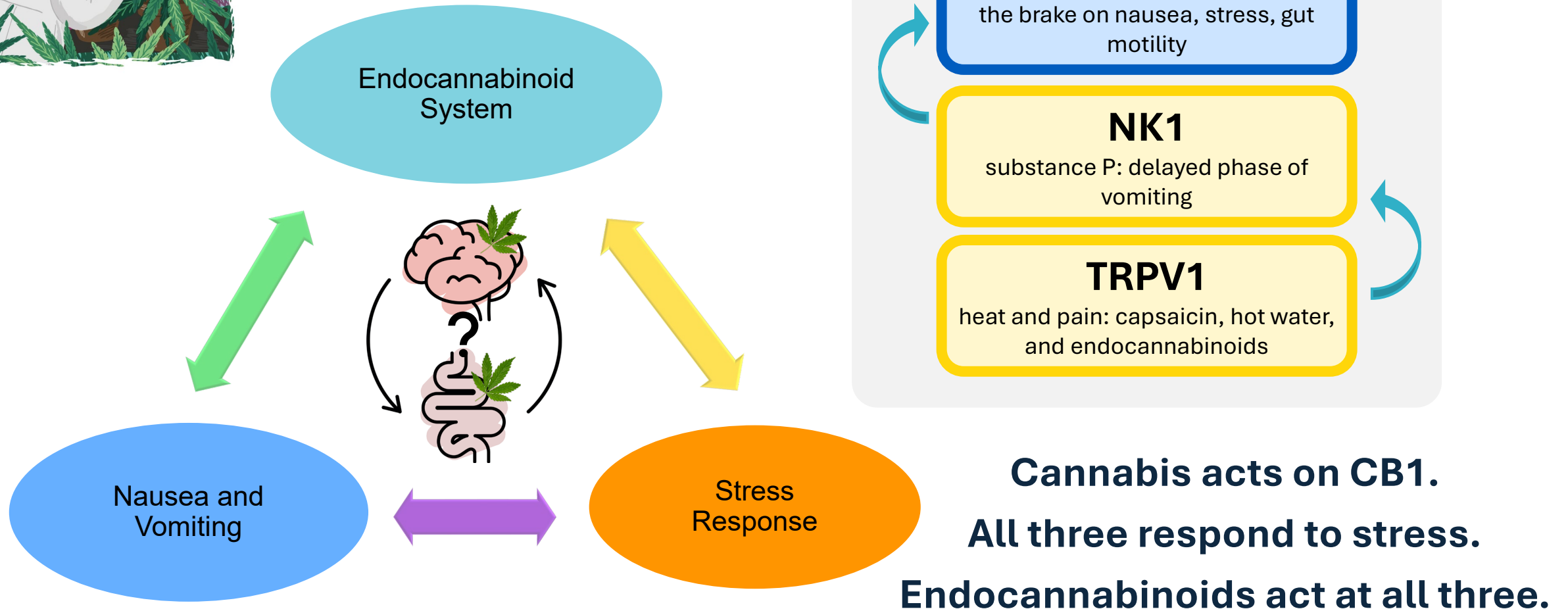
+



| Pre-treatment                               | What it targets                                              | Worked in rats? | Helps patients?   |
|---------------------------------------------|--------------------------------------------------------------|-----------------|-------------------|
| Propranolol                                 | $\beta$ -adrenergic receptor<br>Sympathetic nervous system   | Yes             | Yes               |
| Chlordiazepoxide                            | Benzodiazepine, Anxiety                                      | Yes             | Yes               |
| Antalarmin                                  | Corticotropin Releasing<br>Hormone (CRH), stress<br>response | Yes             | <i>Not tested</i> |
| Increase AEA and 2-AG<br>(URB 597 & MJN110) | Endocannabinoid enzymes                                      | Yes             | <i>Not tested</i> |
| <b>Ondansetron</b>                          | <b>Serotonin (5-HT3)</b>                                     | <b>No</b>       | <b>No</b>         |



# Decoding the Mechanism

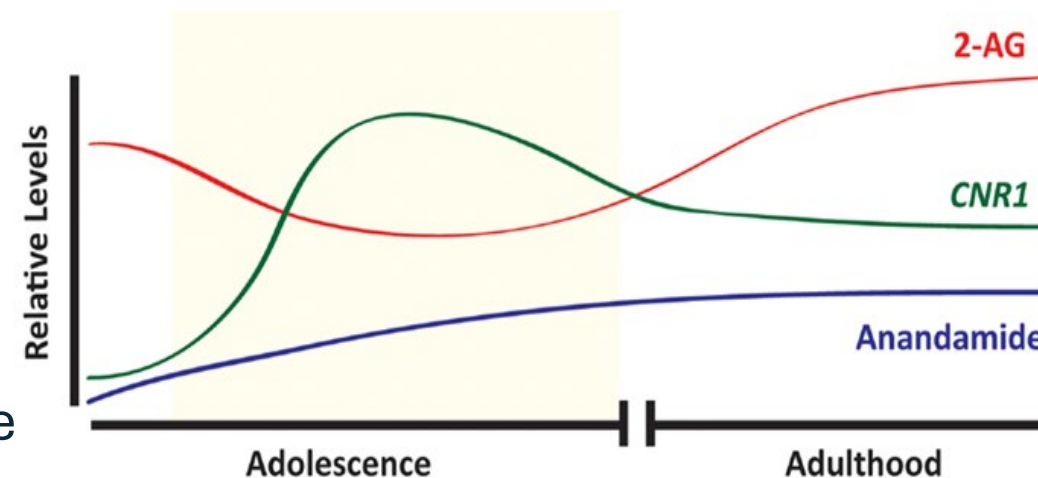




# A Vulnerable Gut-Brain Axis

- Adolescence is a period of major brain reorganization
  - Dependent on the endocannabinoid system
- High rates of cannabis use at this age
- Adolescent cannabis use associated with :
  - Increased psychiatric risk
  - Increased CHS risk?
- **What is the effect on the gut-brain endocannabinoid system?**

DeVuomo et al. unpublished



# Adolescent THC Reshapes Gut-Brain Signalling into Adulthood

## GUT

ileum and colon

### Endocannabinoid system

CB2 · NAPE-PLD · DAGL $\alpha$  · **DAGL $\beta$**  ·  
MAGL

### Inflammation and lipid sensors

COX-2 · IL-1 $\beta$  · IL-6 · TNF $\alpha$  · PPAR $\beta/\delta$  ·  
**PPAR $\gamma$**

### Serotonin

**SERT**



## BRAIN

Mesocorticolimbic regions

### Endocannabinoid system

CB1 · CB2 · **DAGL $\beta$**  · FAAH

### Inflammation and lipid sensors

COX-2 · IL-1 $\beta$  · TNF $\alpha$  · PPAR $\beta/\delta$  ·  
**PPAR $\gamma$**

### Serotonin

**SERT**

**The same three systems are dysregulated at both ends of the gut-brain axis**

Bold = changed in both gut and brain



# Thank You!

---

Dr. Linda Parker  
Dr. Cheryl Limebeer  
Dr. Erin Rock  
Dr. Kelly Hrelja  
Olivia La Caprara  
Dr. David Mutch  
Alex Rajna

Dr. Matthew Hill  
Dr. Gavin Petrie

Dr. Steven Laviolette  
Dr. Daniel Hardy  
Dr. Hanna Szkudlarek  
Dr. Marta De Felice  
Dr. Mohammed Sarikahya  
Samantha Anderson  
Erynn Lonnee  
Jenna Flemming

Dr. Elyanne Ratcliffe  
Chiara Fricano  
Selena Chiarini



**Western**  
**BrainsCAN**  
Transforming brain research.



**NSERC**  
**CRSNG**



**CANADA**  
**FIRST**  
RESEARCH  
EXCELLENCE  
JND



**McMaster**  
University



**CIHR IRSC**



Canadian Institutes  
of Health Research

Instituts de recherche  
en santé du Canada



[Marieka.devuono@uwo.ca](mailto:Marieka.devuono@uwo.ca)



[/marieka-devuono](#)

