The Disruptive Effects of the CB_1 Receptor Antagonist Rimonabant on Extinction Learning in Mice are Task-Specific

Presented by Josh Zuk

Journal

- *Psychopharmacology* is an international journal that covers studies related to drugs that affect the CNS.
- Impact Factor: 4.077
- First published in 1959

Lichtman Cannabinoid Lab at Virginia Commonwealth University

Lab Focus: Understanding the physiological functions of the endocannabinoid system and the mechanisms of action underlying these functions. Exploring medicinal uses of cannabinoids.

Principle Investigator:

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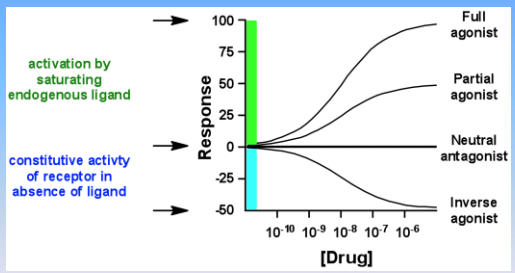
- Andrew J. Thorpe – postdoc
- Rene J. Stokes – MD
- Jenny L. Wiley – Associate professor

What is the difference between an agonist and an antagonist?

- **Agonist**: A substance that binds to a neuronal receptor and fully activates it.
- **Antagonist**: A substance that binds to a neuronal receptor and does not activate it but blocks agonists from binding.

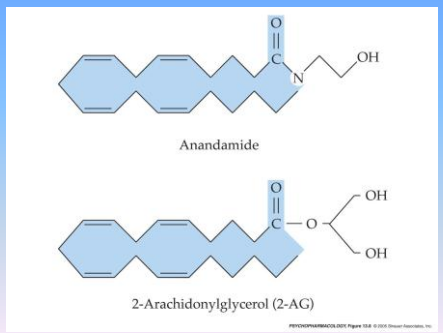


Two major types of cannabinoid receptors

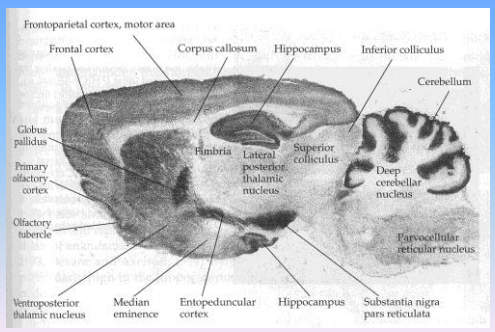
- CB1
  - Mediates psychoactive effects of cannabinoids
- CB2
  - Found in immune tissues
  - Found in brain after stroke or inflammatory disease
  - CB2 agonists can help protect from stroke and neuropathic pain

What normally binds to CB1 receptors?

Endocannabinoids



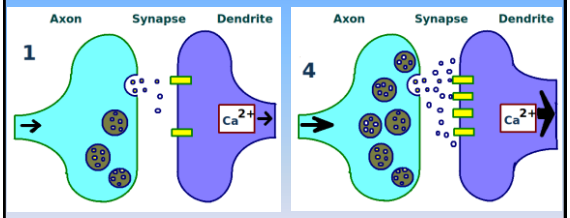
Distribution of cannabinoid binding sites in rat brain



Endocannabinoid pathway is involved in LTP and LTD

- **Long-Term Potentiation**:
  - Strengthening of synapses
  - Occurs when two adjacent neurons fire simultaneously
  - One of the major mechanisms underlying learning and memory
- **Long-Term Depression**:
  - Weakening of synapses
  - Occurs after persistent weak synaptic stimulation

Long-Term Potentiation



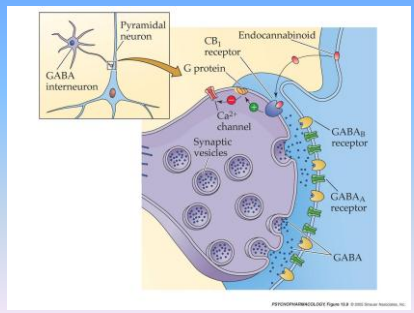
Endocannabinoid pathway is involved in LTP and LTD

- LTP is inhibited by CB1 agonists
- LTP is enhanced in CB1 KO mice
- CB1 agonists enhance LTD

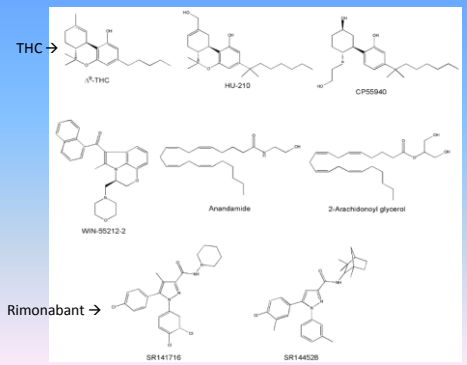
Endocannabinoids

- Anandamide and 2-AG are retrograde messengers.
- Synthesized postsynaptically and act presynaptically.

Retrograde signaling



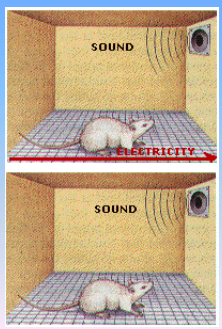
Drugs that affect CB1 receptors



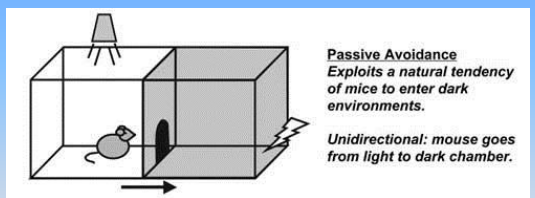
Methods

- Conditioned Freezing Test
- Passive Avoidance Task
- Appetitively Motivated Operant Conditioning Task
- Assessment of Locomotor Activity

Conditioned Freezing Test



Passive Avoidance Task



Appetitively Motivated Operant Conditioning Task

- 2 levers
- 1 lever gives sweetened milk when pressed
- Mice trained to press lever and receive food reward
- Reward was removed and the number of lever presses was recorded

Assessment of Locomotor Activity

- Traveled distance, speed, and time spent immobile were measured

Results

How did the behavior of rimonabant treated mice differ from the vehicle treated mice in the conditioned freezing test, the passive avoidance task, and the operant conditioning task?

Figure 1

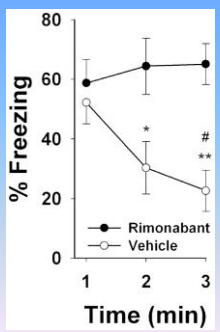


Figure 2

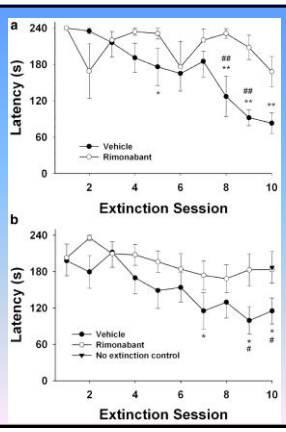


Figure 3

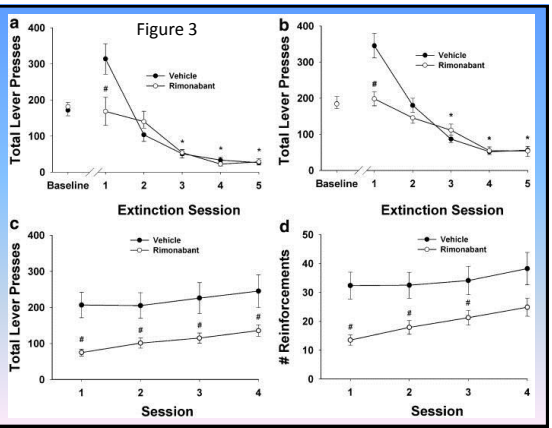


Table 1 Rimonabant failed to have significant effects on gross locomotor behavior (n=7–9 mice per group)

Treatment	Total distance traveled (m±SEM)	Speed (cm/s±SEM)	% Immobility (mean±SEM)
Vehicle	21.63±3.24	2.4±0.4	4.1±1.4
Rimonabant (1 mg/kg)	17.87±3.09	2.0±0.3	6.4±1.5
Rimonabant (3 mg/kg)	19.10±3.22	2.1±0.4	7.3±2.1

Conclusions

- Endocannibinoid system plays an important role in extinction of aversively motivated behaviors
- This system does not appear to be involved in extinction of appetitively motivated behaviors

Implications

- Researchers are currently studying CB1 agonists as a potential treatment for PTSD
- Rimonabant was used as a diet pill because of its ability to decrease appetite. It was taken off the market because it frequently led to severe depression and suicidal thoughts.
  - Possibly due to inability to forget negative memories?