Endocannabinoid regulation of incentive cues

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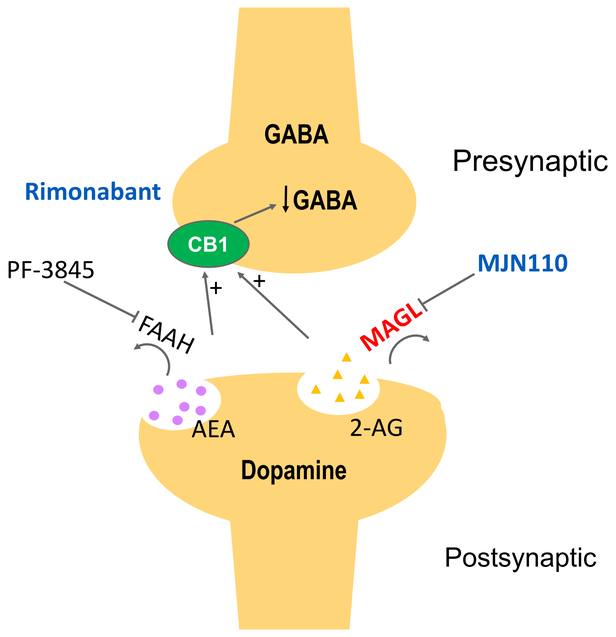
Introduction

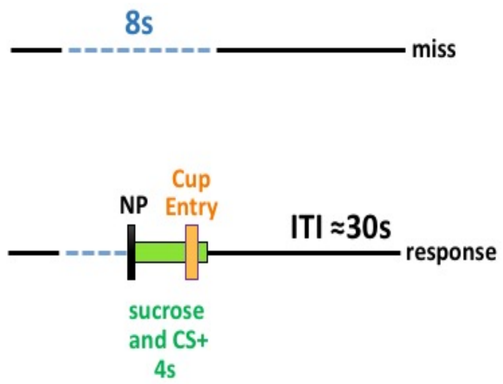
- Previously neutral cues that are repeatedly paired with a reward can become powerful incentives for reward seeking.
- We have recently shown that activating VTA GABA neurons attenuates responding to incentive cues (ICs).
- Others have shown that endocannabinoids (eCBs), particularly 2-arachidonyl glycerol (2-AG), enhance dopamine release during cue presentation and induce reward seeking by inhibiting VTA GABA neurons.
- Presumably, these effects occur via retrograde transmission of 2-AG from dopamine neurons, which activates CB1 receptors on GABA interneurons, leading to decreased GABA release and less GABA inhibition of the postsynaptic dopamine neurons (disinhibition).
- We hypothesize that blocking the CB1 receptor will decrease responding to ICs by attenuating VTA GABA disinhibition, while enhancing 2-AG will increase responding by increasing disinhibition.
- Understanding the mechanisms contributing to incentive cue (IC)-induced reward seeking may reveal unique treatment targets for addiction.

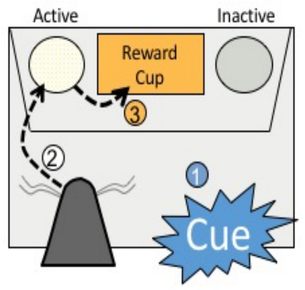
Endocannabinoid System



Compound	Class	Activity	Hypothesized Effect on GABA
Rimonabant	CB antagonist	blocks eCBs	increase
MJN110	MAGL inhibitor	enhances 2-AG	decrease
PF-3845	FAAH inhibitor	enhances AEA	no effect

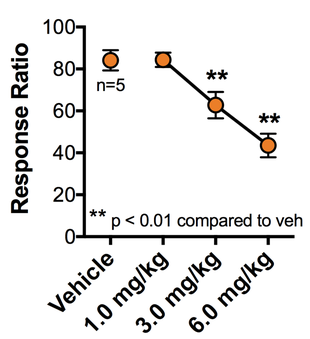
Methods: IC Task



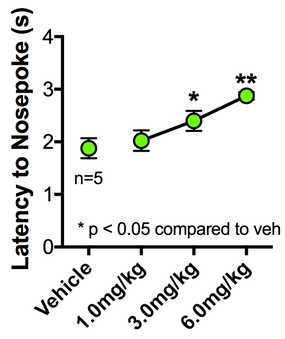


Results

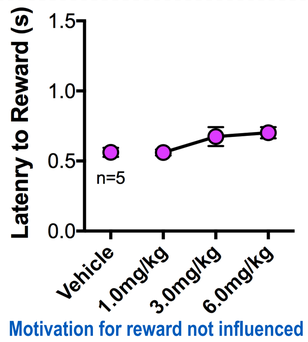
Rimonabant



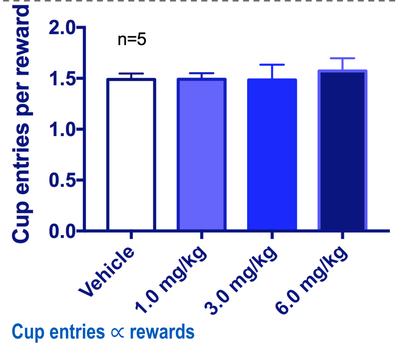
Decrease in IC responding



Decrease in motivation for IC



Motivation for reward not influenced



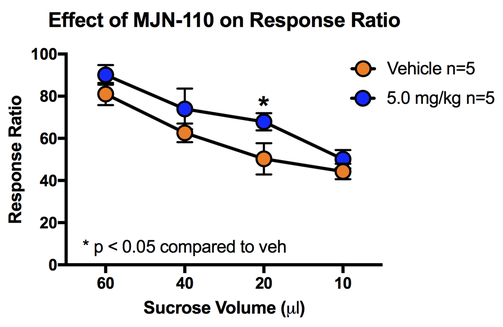
Cup entries ∝ rewards

Decreasing Reward Volume

60 µl	40 µl	20 µl	10 µl

- training volume is 60 µl, but produces a ceiling effect.
- in this variation of the task the volume of the reward decreases every 15 min.
- allows us to study improvements in responding.

MJN-110



Summary

- Rimonabant dose dependently decreased responding to ICs
  - increases in nosepoke latency indicate that the reinforcing efficacy of the IC is decreased
  - no change in latency for the reward
  - together these data indicate that rimonabant affects motivation for the IC but not the primary reinforcer
- reward cup entries after rimonabant administration was proportional to the number of rewards acquired
  - activating VTA GABA neurons *increased* the ratio of cup entries to rewards obtained
  - may indicate that other brain regions are involved in rimonabant's effect on IC responding
- MJN-110 produced an overall increase in responding to ICs of different sucrose volumes, though more subjects are needed.

Future Aims

- Microinfusions to determine if these effects are VTA specific.
- Test additional inhibitors (e.g. CB2 receptor antagonists), which has recently been found in the brain.
- Examine the role of anandamide and FAAH.

Funding

K.T.W. was supported by the SUNY Brain Network of Excellence Post-doctoral Fellow program and the RIA Research Training on Alcohol Etiology and Treatment Post-doctoral Fellow program.

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