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

Methods: IC Task

Results

Rimonabant

- Decrease in IC responding
  - ** p < 0.01 compared to veh
  - ** p < 0.05 compared to veh

- Decrease in motivation for IC
  - * p < 0.05 compared to veh

- Motivation for reward not influenced

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.

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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.

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