Testing D1 Dopamine Receptors and Glutamate Combined Effects on Brain Stimulation Reward in the Extended Amygdala

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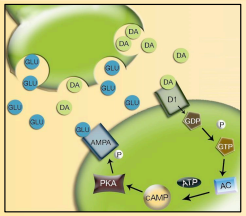
Introduction

- Purpose: To further understand the neural mechanisms underlying evaluation of rewarding stimuli in the mammalian brain. More specifically, to examine the effects of dopamine and glutamate manipulations in the central aspect of the sublenticular extended amygdala (SLEAc) on reward evaluation.
- Dopamine (DA) and glutamate (GLU) interact and are involved in reward evaluation. Our lab found a decrease in reward value when dopamine receptor 2 (D2) agonist/glutamate blocker combination solution was microinjected into the SLEAc but not the nucleus accumbens shell.
- Similar research suggests this effect may be more pronounced if dopamine receptor 1 (D1) drugs rather than D2 drugs are microinjected with GLU drugs.

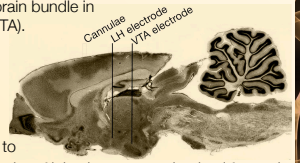
Hypotheses



- Administering a D1 receptor agonist with an AMPA receptor agonist will potentiate reward effectiveness.
- Administering a D1 receptor blocker with an AMPA receptor blocker will reduce reward effectiveness.
- Rationale: D1 receptor stimulation→ phosphorylates guanosine diphosphate (GDP to GTP)→ activates adenylyl cyclase (AC), producing cyclic adenosine monophosphate (cAMP)→ activates protein kinase A (PKA)→ phosphorylates hidden AMPA receptor→ AMPA receptor is presented to abundant glutamate available in the synapse

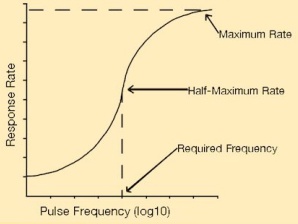
Methods

- Electrodes were surgically implanted along the medial forebrain bundle in the lateral hypothalamus (LH) and ventral tegmental area (VTA). Cannulae for microinjections were also implanted ipsilateral and contralateral to the stimulation site in the SLEAc.



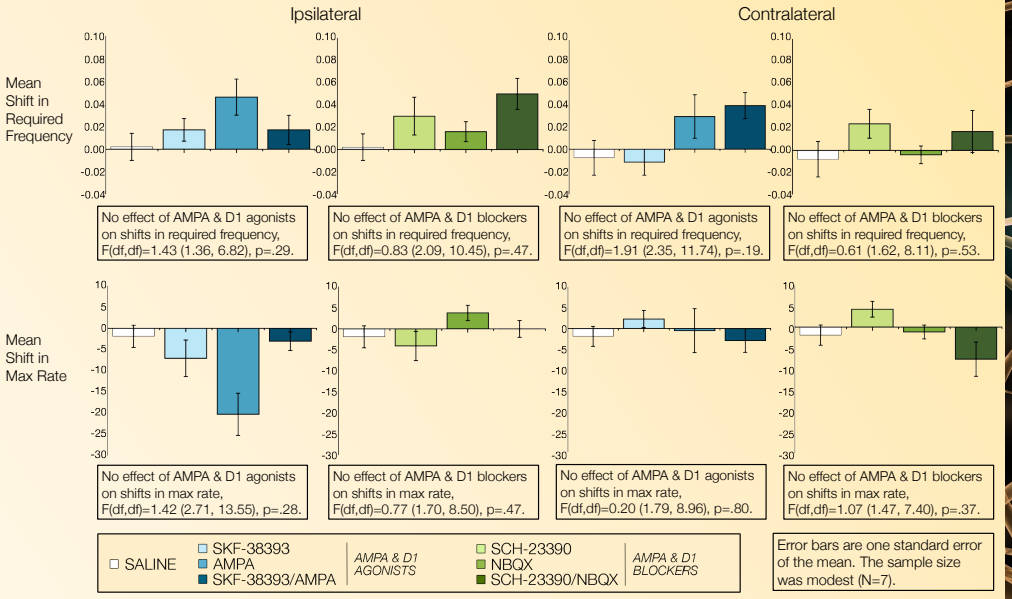
- Rats were trained to press a lever in exchange for rewarding stimulation.

Rate-Frequency Curve Shift Technique



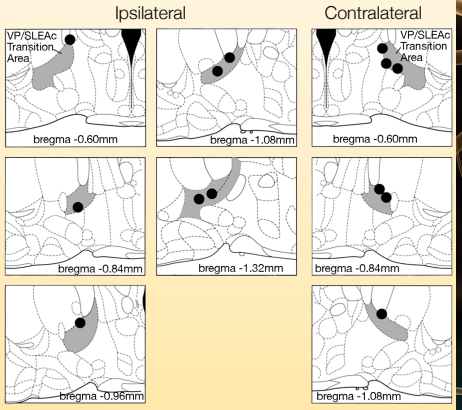
- All drugs were dissolved in 0.9% saline and titrated to a pH of 7.2-7.4. Order of injection was randomized for each rat. Drug solutions of the following concentrations were injected ipsilateral and contralateral to the stimulation site in 0.50 µL volumes.
  - Saline control (0.009 µg/µL)
  - D1 agonist SKF-38393 (10.0 µg/µL)
  - D1 blocker SCH-23390 (4.0 µg/µL)
  - AMPA agonist AMPA (0.20 µg/µL)
  - AMPA blocker NBQX (1.0 µg/µL)
  - SKF-38393/AMPA combination
  - SCH-23390/NBQX combination
- Stimulation reward efficacy and the rat's ability to respond for stimulation were assessed using the rate frequency curve shift technique. Shifts in required frequency and max rate induced by drug infusion were computed in comparison to surrounding non-injection (baseline) days. Max rate and required frequency data were collected daily for currents of 200µA, 400µA and 800µA.

Results



Error bars are one standard error of the mean. The sample size was modest (N=7).

Injection Sites



Conclusions

- Neither the D1 receptor agonist/AMPA receptor agonist combination injection nor the D1 receptor blocker/AMPA receptor blocker combination injection had a significant influence on required frequency or max rate.
- However, there may be a trend towards decreased reward value following administration of the D1 receptor blocker/AMPA receptor blocker (SCH-23390/NBQX) combination.
- Lack of effects may result from low statistical power because of small sample size. By continuing our work with a larger sample size we hope to elucidate possible influences of DA and GLU manipulations in the SLEAc on reward evaluation.

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