Effects of morphine addiction and re-exposure on psychomotor and self-stimulation behavior at ILC-NAcSh glutamate inputs

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Introduction

- The infralimbic cortex (ILC), part of the medial prefrontal cortex, provides glutamatergic input to the nucleus accumbens shell (NAcSh), an area of the brain implicated in the reinforcement and motivation underlying drug addiction.[3,4]
- Morphine is an opiate drug that causes potentiation of excitatory synapses in ILC-NAcSh circuitry, which is thought to be a key component of the neural mechanism behind opiate-seeking behavioral reinstatement induced by re-exposure (RE-EXP) during forced abstinence (ABST).[1,4,5]
- Previous studies have shown that mice will self-stimulate ILC-NAcSh inputs, however, it is unknown exactly how morphine ABST and RE-EXP alters this circuitry and how it contributes to its effects on reward-motivated behaviors.[1,3]
- Intracranial self-stimulation (ICSS) is a useful paradigm for studying the effects of drug-mediated brain manipulations on reward systems.[2]

The goal of this study was to explore the relationship between MOR ABST and RE-EXP on self-stimulation of ILC-NAcSh inputs and reward-seeking behavior.

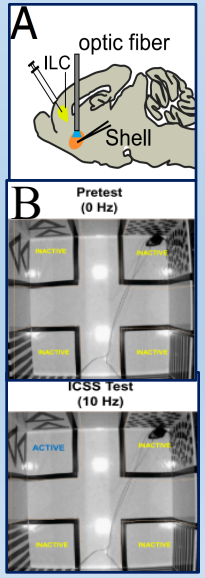
Methods

Animals: 9 Male C57BL/6J mice, individually housed, 12/12 hr light/dark cycle, food and water available *ad lib*

Surgery: Mice were injected with AAV2-CamKII-ChR2-EYFP bilaterally (0.5 µL per side) into the ILC (A/P +1.8, M/L+/-0.4, D/V -3.2 from skull). 2 weeks after viral infusion, mice had bilateral optic fibers implanted ~0.5 mm above the NAcSh (14°, A/P +1.6, M/L +/-1.64, D/V -4.1) **(Figure A).** [3]

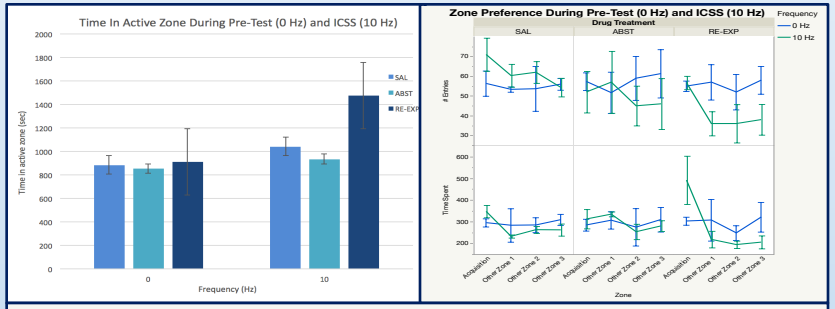
MOR psychomotor sensitization: Morphine exposure began ~4 weeks after viral surgery, to allow for opsin expression throughout the neuron and its projections, in the form of 5 once-daily injections of either saline or morphine (10 mg/kg, s.c.). Re-exposure occurred 11 days into abstinence.

Optogenetics and ICSS: Mice were placed in an open field chamber with unique contextual cues in each comer. A 30 minute pretest was conducted with no stimulation (0 Hz) to measure the time spent in each zone, after which an active (acquisition) zone was pseudo-randomly assigned for each animal **(Figure B).**[4] During self-stimulation (ICSS), the mouse's fibers would be stimulated with up to a 5 sec. pulse of blue light (473 nm) light if the mouse entered the active zone. Exiting the active zone would immediately result in cessation of light. Remaining in the zone for more than 5 sec., a 20 s timeout period would begin during which no stimulation would occur.

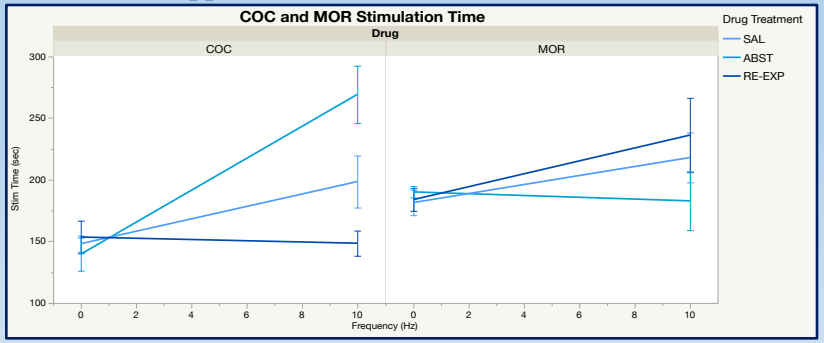


Results

MOR RE-EXP increases time spent in active ICSS zone



Effects of MOR RE-EXP and ABST on self-stimulation are opposite of COC RE-EXP and ABST



Summary & Conclusions

- MOR ABST and RE-EXP have opposing effects on the ability of glutamate to motivate self-stimulation and reward-seeking behavior.
- Exposure to morphine causes frequency-dependent ICSS of ILC-NAcSh synapses in drug-naïve mice, which supports the idea that morphine drives behavioral reinforcement of drug-seeking by inducing changes in plasticity at these inputs.[3]
- Morphine RE-EXP and ABST increase and decrease self-stimulation time, respectively, while cocaine RE-EXP and ABST exerts the opposite effects on behavior, suggests that while the rewarding effects of opioids and stimulants are both caused by increases in glutamate signaling, these classes of drugs may do so by affecting components of NAc circuitry differently.[3,4]
- **Overall, the findings of this experiment support that morphine influences reward-seeking behavior by affecting ILC-NAcSh circuitry.**

Future Directions

- To verify and further explore the significance of these findings, this experiment should be replicated with a larger sample size.
- Electrophysiological study is necessary to draw certain conclusions about the relationship between this data and changes in plasticity at ILC-NAcSh inputs.
- One important question that still remains is the role that other glutamate inputs to the NAcSh, such as the BLA and vHPC, play in controlling addiction behavior and the effects of MOR ABST and RE-EXP on these inputs.[1]
- While this data supports the findings that morphine-induced changes at ILC-NAcSh synapses influence reward-seeking behaviors, whether or not these changes are required for drug-directed behavior still needs to be explored.[3]

References

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