Effects of Medial Prefrontal Cortex-Laterodorsal Tegmental Nucleus Projection Inhibition on Cocaine-Induced Sensitization

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Optogenetics

- Manipulation of the activity of neurons with light

- Uses light-gated ionic pumps called opsins derived from microorganisms (ex: algae)

- Our study uses Halorhodopsin (NpHR) and Enhanced Yellow Fluorescent Protein (eYFP) through viral transfection into mice brains

Sensitization

- Sensitization is the heightened ability of drugs of abuse, like cocaine, to activate dopamine neurotransmission increasing locomotor activity and stimulating the reinforcement and reward systems.

- The Laterodorsal Tegmental Nucleus (LDTg) serves as an input of neurotransmitters, including glutamate (GLU) to the Ventral Tegmental Area (VTA).

- Our lab has shown previously, that LDTg GLU input to the VTA is important for sensitization. Also, the regulation of midbrain dopamine neuron firing along with the regulation of Nucleus Accumbens dopamine levels are implicated.

The medial prefrontal cortex (mPFC) has also been shown through studies involving lesioning of the mPFC to be integral in locomotor sensitization.

It is believed that sensitization induced by cocaine results from increased mPFC excitatory transmissions to its downstream targets, one of which is the LDTg.

As LDTg is a major input for the VTA, inhibition of mPFC projections to LDTg during cocaine exposure will test the roles of these projections in sensitization development.

Mice are given injections, of saline or cocaine, and placed into open boxes for a one-hour period.

Optical tethers are connected to mice throughout experimental days.

Movement and rearing of mice is tracked through a camera above each box.
Two phases of sensitization, pre-exposure and exposure post withdraw period
Histology: NpHR+ Neurons in the mPFC following viral transfection

- Figure A: DAPI and eYFP staining of mPFC expressing eYFP.
- Figure B: LDTg expressing eYFP.
- Figure B': Close up of image B.
Histology: Cresyl Violet Staining

- Cresyl Violet is a dye that stains nissl substance in the cytoplasm of neurons purple-blue as seen in the picture to the right.

- Single brain segment showing the probe tracks into the LDTg.
Results: Inhibition of PrL projections to LDTg affects acute locomotor activation induced by cocaine

- p-value within days = <.001
- p-value between groups = 0.002
Results: Cocaine Trial
Days Sex Comparison

- p-value between sexes = 0.181
Results: Inhibition of PrL projections to LDTg during repeated cocaine exposures reduces locomotor sensitization

- p-value for main effect of group = 0.001
- Post-Hoc test pairwise comparison (Fisher's LSD) = EC>ES (p-value < .001) and NS-NC (p-value = 0.097)
Results: Cocaine Challenge Timecourse

- p-value for main effect of group = 0.002
Inhibition of PrL projections to the LDTg during repeated cocaine exposures reduces the expression of drug-induced locomotor sensitization on a delayed challenge test.

We propose that cocaine-evoked increases in PrL dopamine results in enhanced PrL excitation of LDTg neurons. This in turn results in excitation of LDTg GLU input to the VTA known to be critical for the development of sensitization.

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