Regulation of drug seeking by nucleus accumbens mGlur5 receptor is both drug intake and withdrawal dependent

Divyank Sharma1, Pouya Mirzaei1, Oscar Burgos1, M. Behnam Ghasemzadeh1
1Department of Biomedical Sciences, College of Health Sciences, Marquette University

Introduction

Context
According to the National Institute of Drug Abuse, cocaine is an addictive stimulant that is often mixed with opioids such as fentanyl which is a synthetic opioid2. The Wisconsin Department of Health Services indicates a general increasing trend over the previous 7 years in cocaine related overdose hospitalizations5. o Cocaine related overdose hospitalizations were 8.3 per 100,000 residents in 2019. o Southeastern Wisconsin had 2,433 total hospitalizations involving cocaine overdose hospitalizations5.

According to the National Institute of Drug Abuse, cocaine is an addictive stimulant that is often mixed with opioids such as fentanyl which is a synthetic opioid2. The Wisconsin Department of Health Services indicates a general increasing trend over the previous 7 years in cocaine related overdose hospitalizations5. Cocaine related overdose hospitalizations were 8.3 per 100,000 residents in 2019. Southeastern Wisconsin had 2,433 total hospitalizations involving cocaine overdose hospitalizations5.

Levels of mGlur5 protein decrease results in enduring alterations in the glutamatergic signaling in the reward center neurons (mGlur1 & mGlur5) have a critical role in regulation of both drug use and hospitalizations.

Cocaine overdose hospitalizations were 2,433 total hospitalizations involving cocaine overdose hospitalizations. According to the National Institute of Drug Abuse, cocaine is an addictive stimulant that is often mixed with opioids such as fentanyl which is a synthetic opioid. The Wisconsin Department of Health Services indicates a general increasing trend over the previous 7 years in cocaine related overdose hospitalizations. Southeastern Wisconsin had 2,433 total hospitalizations involving cocaine overdose hospitalizations.

Research Conducted
Previos studies have shown that group 1 metabotropic glutamate receptors (mGlur1 & mGlur5) have a critical role in regulation of both drug use and seeking behavior and withdrawal experienced after exposure to cocaine. Inhibition of mGlur5 receptor function results in reduced drug seeking behaviors in rats.

Neurobiology & Neuronal Levels LgA vs ShA

Impact
General exposure to cocaine results in increased levels of dopamine as a result of cocaine inhibition of dopamine reuptake in the synaptic cleft. Reinforcement of drug seeking behavior is, in part, a result of excess dopamine being left in the synapse due to inhibition of reuptake1. In addition, exposure to cocaine results in enduring alterations in the glutamatergic signaling in the reward circuit of the brain.

mGlur5 protein level decreases in NaShell in LgA rats

Drug intake (Self-Ad) in LgA vs ShA animal models

Glutamate Signaling

The prelimbic and infralimbic cortices.
The nucleus accumbens core and shell regions.

Methods

Self Administration of Cocaine (Acquisition/Maintenance Phase)

1. Mice were trained to self-administer cocaine (1 mg/kg, 4x weekly) for 21 days.
2. Mice were then given a cocaine withdrawal for 3 days.
3. Mice were then given a cocaine challenge (1 mg/kg) and their behavior was monitored.

Conclusion

(ShA) Decrease Drug Seeking in NA Shell but not Core

An experimental timeline of the study is shown below:

Day 7
Day 14
Day 21
Day 28
Day 35
Day 42
Day 49
Day 56
Day 63

Future Direction

o Analyzing molecular and cellular mechanisms mediating mGlur5 receptor plasticity: ShA vs. LgA.
- Identifying the mechanism responsible for selective modulation of mGlur5 receptors versus mGlur1 receptor by cocaine self-administration.
- Investigating the role of mGlur5 receptor in the development of incubation of craving.

References:


Cocaine Addiction - MTEP
- According to the National Institute on Drug Abuse (NIDA) the United States has and continues to face an opioid epidemic. In the past four years funding for opioid research has increased from approximately 1.4 billion dollars to 1.9 billion dollars. DeepLabCut implemented into society.
- o Major obstacle faced is high relapse rates individuals face due to cues consistently perceived by their environment.
- o Prior research has determined that glutamate receptors play a crucial role in the release of dopamine and is responsible for regulation of the reward system located in the nucleus accumbens. Therefore, indicating the positive feedback motivating individuals to repeat and relapse on cocaine is based on intercellular signaling of glutamate.1,2
- Current research focuses on studying group 1 metabotropic glutamate receptors, specifically mGluR5 and its relationship to MTEP, a known mGluR5 blocker.

Schizophrenia – DeepLabCut AI Program
DeepLabCut was developed to assist with behavioral studies, primarily with rating locomotion and behavior in rodent studies, such as those that involve Sprague-Dawley rats during schizophrenia studies. The fundamental problem solved, and reason DeepLabCut is a favorable program is because it removes the extensice time investment and labor necessary to collect data from video recorded experiments such as elevated plus maze (EPM), a test used to assess anxiety within a rat. During this experiment, a rat is left on an elevated platform that consists of two open arms and two closed arms for 15 minutes. After the experiment is complete, videos recorded must be rated to measure amount of time the rat spent in each arm for later analysis.1,3

Methods

Cocaine Addiction - MTEP
- Sprague-Dawley rats arrived and were left in colony room to habituate for 5-7 days post-travel & consistently handled.
- Rats were habituated to the operant chamber and food trained. o During habituation rats would be left in the operant chamber ranging from one to two hours to just sit.
- Rats were then food trained for up to 7 days during which they received a sugar pellet for every time they pressed the right lever, each session lasting 2 hours.
- After rats had successfully and consistently been hitting for food (i.e. 60-70 lever presses in the two hour interval) rats were divided into two groups, control & experimental group: o Control group received 0.5 µl of saline o Experimental group received 3.0 µg MTEP (mGluR5 receptor blocker) o Number of presses between control & MTEP groups were compared

Schizophrenia – Programming DeepLabCut
- EPM videos were uploaded to DeepLabCut and a configuration file was edited to set the parameters for what would be extracted from each video. A total of 426 frames were extracted from the videos, and were labelled with various markers. Markers indicated borders of the EPM maze and body parts of the rat. Labels were as follows: o Nose/Head/Body/Centerbody o Retropereoneosperoneal/Rhindendpo/Rhindendpaw o Tailbase/Tailend o Borders 1-4
- Markers placed were analyzed by the program at 95% confidence followed by a skeleton being built to teach the AI program what the shape of the rat is in comparison to the markers previously placed.

References: