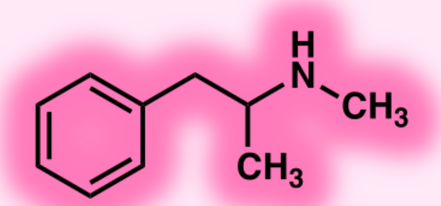
Mirtazapine and Methamphetamine Relapse Prevention

Hannah Borys and Dr. Daniel Widzowski,
Department of Biology, Kopchick College of Natural Sciences and Mathematics,
Indiana University of Pennsylvania, Indiana, PA 15705



Abstract

Methamphetamine is among one of the most highly abused drugs in the United States and worldwide. Part of what makes methamphetamine a particularly addictive substance is its ability to act as a substrate for monoamine transport proteins (MATs). When introduced to the body, methamphetamine binds to the MATs where it can then be taken up into the neuron.[4] Once inside the neuron, methamphetamine disrupts synaptic function by inhibiting vesicular monoamine transporter 2 (VMAT2). The inhibition of VMAT2 causes monoamine levels to build up inside the neuron. High monoamine levels within the neuron promotes monoamine leakage into the synaptic cleft by means of reverse transport. Post-methamphetamine use results in a deficit of neurotransmitter activity.[3] Mirtazapine is an atypical antidepressant that works as an a_2-adrenergic receptor and 5-HT_2 receptor antagonist. Mirtazapine notably enhances serotonin cell firing in the raphe nuclei, as well as dopamine release in the prefrontal cortex. It is hypothesized that Mirtazapine's ability to slightly increase monoamine levels will help alleviate methamphetamine withdrawal symptoms. [2]

Introduction/ Background

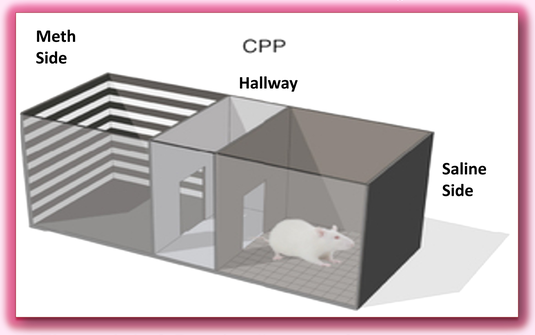
- Conditioned placement preference (CPP) is a commonly used preclinical behavioral model consisting of a specially crafted enclosure that holds a minimum of 2 separate chambers featuring opposing stimulus cues. [5]
- The multi-phase CPP approach is especially useful in the study of drug therapy options for methamphetamine/ other drugs of abuse as it allows the species to form a connection between the chamber and the administered substance.[5]
- **Phase 1: Pre-Conditioning/Habituation**. Mice allowed to explore the whole apparatus. it is expected that the mice will spend *50% of the total treatment time in the Meth chamber.*
- **Phase 2: Conditioning**. Mice receive either saline or methamphetamine (alternating) for 16 days and are restricted to the corresponding side of the chamber for the entire treatment period. It is expected that at day 16, the Post-Conditioning test will reveal that mice spend a minimum of *60% of total treatment time in the Meth the chamber.*
- **Phase 3: Extinction**. Mice split into control and experimental groups and receive either Mirtazapine or saline for 22 days. It is expected that by day 22, the mice will *spend 50% of the total treatment time in the Meth chamber.*
- **Phase 4: Reinstatement.** Mice given a priming dose of methamphetamine and allowed to explore both sides of the apparatus. It is expected that the control group will spend *70% of the total time in the Meth chamber.* If our hypothesis that Mirtazapine can prevent the reinstatement of preference for the Meth side of the chamber, the mice treated with Mirtazapine will spend approximately *50% of time in the Meth chamber.*

Materials & Methods

Subjects: 20 Male C57BL/6J mice (*Mus musculus*) obtained from our breeding colony at Indiana University of Pennsylvania. All protocols were approved by IACUC.

Materials:
- 4 CPP apparatuses.
- Training and test session were recorded with Sony video cameras.
- Methamphetamine dose: 2 mg/kg.
- Mirtazapine dose: 5mg/kg.

Methods:
- All behavioral sessions were 20 minutes long



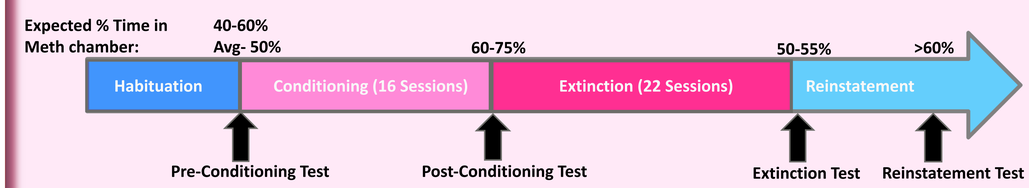


Figure 1: Left Panel – diagram of test apparatus. Right Panel - Experimental design and timeline showing different phases of CPP experiments.

Results

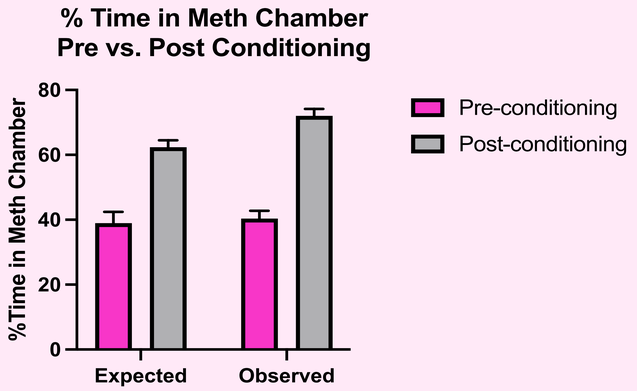


Figure 2: Bar graph showing avg time spent in Meth chamber pre vs. Post Conditioning. Expected values shown for comparison.

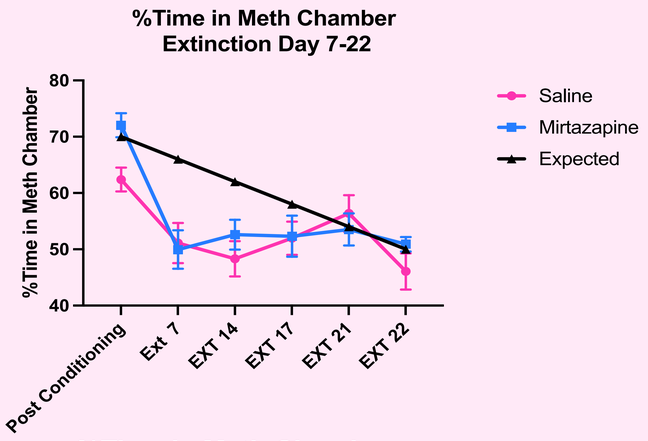


Figure 3: Line graph showing extinction curve of both control and experimental groups vs. expected.

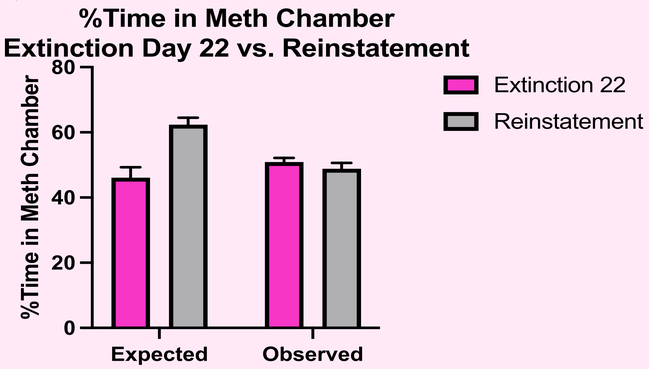


Figure 4: Bar graph showing avg time spent in Meth chamber on Extinction day 22 vs. Reinstatement. Expected values are shown for comparison.

Conclusion

- No mice showed initial bias for either side of the chamber. (See Figure 2).
- All mice met the conditioning criteria of spending at least 60% of the total time in the Meth side of the chamber. (See Figure 2).
- Mice extinguished their preference for Meth side much faster than expected. (See Figure 3).
- Control group failed to show any reinstatement. (See Figure 4).
- A confounding error prevented the data from being useful in determining the effect of the Mirtazapine treatment.

Discussion

The exact cause of the rapid extinction of preference to the Meth side of the chamber is unknown. In the future, the study will be repeated with a modified procedure to minimize the possibility of external factors influencing animal behavior.

Future modifications include using mice that are slightly older in age, implementing a minimal disturbances policy in the lab, and using cage covers during the treatment period.

The search to find an effective pharmaceutical treatment for managing methamphetamine withdrawal symptoms is ongoing. Mild monoamine agonists remain strong candidates for future studies.

Existing literature indicates that Mirtazapine has been successful at minimizing relapse to methamphetamine use in humans. A research article made available in 2011 by the American Medical Association titled: *Mirtazapine to Reduce Methamphetamine Use: A Randomized Controlled Trial,* where 60 MSM that met the qualifications for methamphetamine dependency were treated with either Mirtazapine or a placebo for a 12-week period in conjunction with substance abuse counseling. What they found was that participants who received Mirtazapine exhibited a decrease in methamphetamine urine positivity from 73% to 44%.[1]

References

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