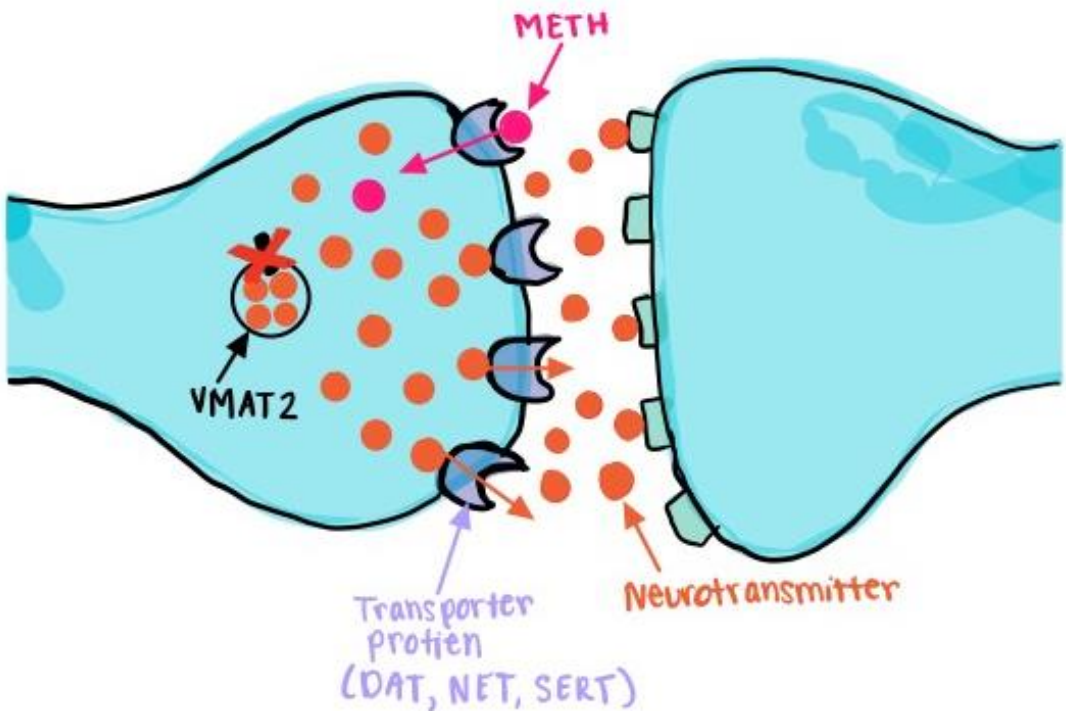
Mirtazapine and Methamphetamine Relapse Prevention

Hannah Borys

Abstract: Methamphetamine is among one of the most highly abused drugs in the United States and worldwide. The United States National Institute on Drug Abuse reports that approximately 2.6 million people of age 12 or older have used methamphetamine in the past 12 months. Among these individuals, nearly 1.6 million reported having a methamphetamine use disorder.[1] With these statistics in mind, it is no surprise that the deaths related to overdose of methamphetamine are of major concern. 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. 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. Monoamine leakage into the synaptic cleft is associated with the profound neurotoxicity of methamphetamine.[4] In addition to the inhibition of VMAT2, methamphetamine blocks the re-uptake of monoamines as well as monoamine oxidase; an enzyme that metabolizes monoamines. Post-methamphetamine use results in a deficit of neurotransmitter activity.[5] 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.[2] It is hypothesized that Mirtazapine's ability to slightly increase monoamine levels will help alleviate methamphetamine withdrawal

symptoms. 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. 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. Thus, drug-seeking behaviors can be analyzed in the presence and absence of the drug of abuse and are then compared to behavior post-administration of the experimental substance.[3]



Literature Review: A research article made available in 2011 by the American Medical Association titled: *Mirtazapine to Reduce Methamphetamine Use: A Randomized Controlled Trial* demonstrates Mirtazapine as a promising candidate for the treatment of methamphetamine use disorder. The research model consisted of a randomized, controlled, double-blind 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%.[7]

In 2019, the Saudi Arabian Medical journal posted a research article on behalf of Yusuf S. Althobaiti *Pharm D, Ph.D.* titled: *Role of Venlafaxine in Relapse to Methamphetamine Seeking: Potential Treatment Option for Drug Dependence.* In this study, Venlafaxine was used as a treatment to prevent the reinstatement of METH-induced condition placement preference in male Wistar rats. Venlafaxine is a commonly used anti-depressant that is thought to play a role in the glutaminergic system by blocking evoked glutamate released caused by the influx of dopamine into the substantia nigra that is characteristic of methamphetamine use. What Althobaiti found was that Venlafaxine was able to reduce the amount of time the rats spent in the METH chamber by a factor of over 25%.[6]

Marta Rodríguez-Arias, Ana Castillo, et al. composed the article: *Effects of Extended Cocaine Conditioning in the Reinstatement place Preference* wherein, they performed many rigorous experiments to determine the optimal CPP conditions for the study of cocaine relapse prevention. The study consisted of 12 different experimental groups in which the dosage of cocaine and length of the conditioning period was varied. After the data was collected, ANOVA statistical analysis determined that a 16-day conditioning period where the dosage of cocaine is kept constant yields the highest sensitivity to reinstatement of CPP.[8]

Objectives: Revise the model, collect data, determine whether Mirtazapine reduces time spent in the METH side of the CPP chamber, and propose further testing.

Methods: A Sony video camera will be used to collect time data. 20 male C57BL/6J mice obtained from the Indiana University of Pennsylvania breeding colony will be used in this study. 4 conditioning placement enclosures will be crafted. The enclosures will feature two separate chambers. One chamber will have black horizontal striped walls, the other will have solid grey walls. The mice will then be divided into 2 separate groups (n=10). The experimental group will receive METH (2 mg/kg) during the conditioning phase and Mirtazapine (MIR) (5mg/kg) during the extinction phase. The control group will receive METH during the conditioning phase and saline during the extinction. The experiment will consist of 4 phases. The habituation phase will take place on days 1-3. During this time, the mice will be free to explore both sides of the enclosure. The time that each mouse spends on either side of the enclosure will be recorded. Any mouse that shows an initial preference for either side of the enclosure will be removed from the study. On day 4, a pre-conditioning test will be performed in which the mice will be free to explore both sides of the CPP apparatus. Following the habituation phase is the 16-session conditioning phase in which each mouse receives the appropriate dosage of METH. At the time of treatment, the mice will be restricted to their assigned chamber for 20 minutes so that they are able to form an association between the chamber and the administered substance. On day 20, the enclosure will be opened up for the mice to explore both sides. The time each mouse spends on either side of the enclosure will be recorded as a post-conditioning test. Day 21 will mark the beginning of the extinction phase which will last for 21 consecutive days. In this phase, the mice will be treated will either MIR or saline per their assignment. Again, the mice will be restricted to their assigned room for 20 minutes. After the 21-day period, a post-extinction test will be performed to assess whether MIR was able to reduce the

amount of time the mice spend in the METH room after the 21-day treatment. The final phase is the reinstatement phase where mice in the experimental group will be given a dose of METH and allowed to explore both sides of the enclosure for 20 min. It is hypothesized that the time spent by the mice in the METH chamber during the reinstatement phase will be significantly reduced as a result of the Mirtazapine treatment.

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