The Synthetic Psychedelic 2,5-methoxy-4-iodoamphetamine (DOI) Attenuates the Positive Appetitive and Reinforcing Effects of Methamphetamine

Bo J. Wood, and Kevin Murnane

Abstract ID 56697 Poster Board 468

INTRO: Methamphetamine is a highly addictive psychomotor stimulant, which despite posing a growing public health threat, has no Food and Drug Administration approved pharmacotherapies. Psychedelics, whose early studies have had success in addiction and other psychiatric conditions, offer a new approach to treating methamphetamine addiction. Despite the growing examination of these psychedelics in clinical research, these compounds have not been evaluated in the context of attenuating the positive appetitive and reinforcing effects of methamphetamine.

METHODS: To investigate this, the synthetic phenethylamine R(-) 2,5-methoxy-4-iodoamphetamine (DOI) was used in two well validated behavioral models, conditioned place preference (CPP) and operant self-administration, to evaluate its capacity to attenuate the positive appetitive and reinforcing effects of methamphetamine, respectively. For the positive appetitive effects of methamphetamine, CPP was utilized, where animals were administered DOI intraperitoneally directly following each methamphetamine conditioning session. For the reinforcing effects of methamphetamine, operant self-administration was used where animals were trained to respond at a fixed ratio 5 schedule of reinforcement. Once stably responding, animals received a pretreatment of DOI 15 minutes prior to the start of the operant session. To ensure any potential decrease in drug-associated responding, a food-maintained control was used.

RESULTS: At the peak dose in CPP of methamphetamine (0.56mg/kg), DOI blocked the development of a methamphetamine place preference. DOI (3.2 mg/kg) significantly reduced the percent change of time spent in the methamphetamine-paired side compared to animals who received saline as a post-treatment. Additionally, DOI (0.32 mg/kg) produced a robust decrease in operant responding for methamphetamine. When evaluating food-maintained behavior, we found that DOI more potently suppresses methamphetamine self-administration compared to the food-maintained control.

DISCUSSION: Although psychedelics such as psilocybin have shown promise in both preclinical and clinical settings for addiction and various psychiatric disorders, there is a large gap of this research in the context of methamphetamine addiction. Consistent with previous findings from our lab showing that DOI suppresses alcohol CPP and decreases voluntary drinking, DOI suppressed methamphetamine CPP and voluntary methamphetamine self-administration. Together the data presented here demonstrate that DOI attenuates the positive appetitive and reinforcing effects of methamphetamine. These results indicate the potential that psychedelics have in the treatment of methamphetamine addiction.

This work was supported by the Louisiana Addiction Research Center, the Department of Pharmacology, Toxicology & Neurosciece, and the Center of Biomedical Research Excellence in Redox Biology and Cardiovascular Disease (P20GM121307).