JPC-077 Interacts with VMAT2 to Decrease the Neurochemical and Behavioral Effects of Methamphetamine

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Background: Methamphetamine (METH) abuse continues to be a health care burden. Currently, no approved treatments are available for METH addiction. Lobeline, an alkaloidal constituent of Lobelia inflata, has efficacy in attenuating reward induced by METH, primarily via interaction with the vesicular monoamine transporter-2 (VMAT2). Lobeline also inhibits high affinity nicotinic receptors, revealing a lack of selectivity at VMAT2. Chemical defunctionalization of lobeline afforded lobelane, which demonstrated improved VMAT2 selectivity.

Purpose/Hypothesis: The current study provides preclinical data in support of a novel lead analog of lobelane, JPC-077, as a treatment for METH abuse.

Methods: The effects of JPC-077 at VMAT2 and the dopamine transporter (DAT), and as an inhibitor of METH in slice preparations, were evaluated. Also, translation to the whole animal was pursued by determining JPC-077-mediated inhibition of responding for METH in self-administration assays.

Results: Results show that JPC-077 exhibited a 6-fold increase in affinity (Ki=0.15 μM) for the [3H]dihydrotetrabenazine binding site on VMAT2, and a 5-fold increase in affinity (Ki=9.3 nM) for the dopamine (DA) translocation site on VMAT2 in relation to lobelane, as well as a competitive inhibition of DA uptake at VMAT2. JPC-077 evoked [3H]DA release (EC50 =54 nM) from synaptic vesicles with 130-fold greater potency than lobelane or METH. JPC-077 had 370-fold greater selectivity for VMAT2 over the plasmalemma DAT, indicating that JPC-077 likely has low abuse liability. Importantly, JPC-077 inhibited (IC50=0.86 μM; Imax=71.9%) METH-evoked DA release from striatal slices, while concurrently increasing extracellular dihydroxyphenylacetic acid. JPC- 077 (56 mg/kg) decreased the number of methamphetamine infusions self-administered, but did not alter responding for food when given across repeated pretreatments.

Conclusions: Thus, in vitro effects of JPC-077 translated to in vivo efficacy, decreasing METH self-administration. As a result of these studies, JPC-077 has emerged as a lead compound in the development of a treatment of METH abuse.

Supported by DA13519, DA016176, TR000117