Novel noninvasive voluntary methamphetamine inhalation paradigm for long-term studies of neuroinflammation and drug-seeking behavior

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Rationale: The mechanisms underlying repeatedly anticipating and seeking methamphetamine (MA) are largely unknown. We have developed a non-invasive protocol for long term behavioral studies of mechanisms supporting the anticipation and voluntary intake of MA. A noninvasive voluntary intake paradigm is essential to understanding how MA breeches the BBB, how MA provokes inflammatory and neurotoxic responses, and how the latter responses change with repeated use.

Objectives: We developed a protocol for voluntary intake of MA in mice that mimics, as closely as possible, the conditions under which humans repeatedly self-administer the drug. In this novel protocol mice are maintained in their home cage and they self-awaken from sleep in the hours before MA is available, in anticipation of the opportunity to acquire MA. If motivated, they then can enter a tunnel connected to a chamber to obtain access to nebulized MA which is available briefly for 1hr/day.

Behavioral Results/Conclusion: We established a concentration of nebulized MA at which motor activity increases following voluntary intake were similar to those seen following MA injection. Mice regulate their exposure to nebulized MA, self-administering for durations inversely proportional to the concentration of nebulized MA. Mice acquire the MA by running repeatedly in and out of the nebulizing chamber for brief bouts of intake lasting about 3 min. total This exposure duration is sufficient to augment plasma levels for the next several hours. We conclude that nebulization is an effective route of MA self-administration and our protocol provides a useful tool for examining the transitions from initial intake to long term use and its behavioral, immune and neural consequences in a non-invasive protocol.

Voluntary MA intake effect on blood brain barrier (BBB) and CNS inflammation: We compared MA exposed to control animals and found that MA exposure breaches the BBB, measured by leakage of Evans Blue. We also demonstrated inflammatory responses in the brain following MA, including microglial activation. We next explored whether decreasing the neuroinflammation and protecting the BBB would affects MA intake in the voluntary self-administration paradigm. The results indicate that animals given the broad-spectrum tetracycline antibiotic minocycline, reduced their intake of MA. Minocycline also reduced microglial activation, Evans Blue penetration and IgG levels.

Overall Conclusions: This study presents a novel and noninvasive method for studying long and short term effects of MA exposure, for studying neural and vascular consequences of MA intake, and for identifying individuals or genetic mutations that develop a high preference for MA compared to conspecifics or littermates. Our goal at the meeting is to share our protocol and to develop collaborations to explore its potential.