

MSTP STUDENT DESCRIPTION

NAME: David Lee

e-Mail address: djlee4@buffalo.edu

Undergraduate College/University attended: Stanford

Major: Biological Sciences

Years in MSTP (1-8): 6

DEPARTMENT: Pharmacology and Toxicology

THESIS ADVISOR: Jerrold Winter

RESEARCH DESCRIPTION:

PhD Thesis title: Role of glutamate in the action of LSD

Date of Completion (or expected) of PhD: 2009

Research Description:

Hallucinogens, including the club drugs phencyclidine (PCP), ketamine, 3,4-methylenedioxy-N-methamphetamine (MDMA), and lysergic acid diethylamide (LSD), continue to be subject to widespread abuse by adolescents and young adults in this country. Among this class of drugs, the study of LSD and PCP offer perhaps a unique opportunity to elucidate and contribute to the understanding of psychosis as well as ameliorating the burdens of illicit and abusive drug use. Drug-induced stimulus control is a powerful tool for the study of behaviorally active drugs in intact animals that has identified clear distinctions in the mechanisms of action of non-competitive antagonists at the NMDA subtype of glutamate receptors, such as PCP, and serotonergic agents like LSD. However, it has also been observed that non-competitive antagonists of the NMDA receptor subtype potentiate the stimulus effects of both the phenethylamine hallucinogen (-)-2,5-dimethoxy-4-methylamphetamine (DOM) and LSD. Therefore, most recently, it has been hypothesized that glutamate release may be a final common pathway for the actions both of serotonergic and glutamatergic hallucinogens. This hypothesis draws support from behavioral studies using drugs that modify glutamate release in vivo that also have discriminative effects. However, a direct relationship between glutamate release and LSD-induced behavior in rats is lacking. The objectives of this research project are to use a combination of behavioral and biochemical approaches to clarify the role of cortical glutamate release in the stimulus effects of LSD, and determine the effect of drugs that modulate LSD-induced behavior on extracellular glutamate levels in the cortex of awake behaving male rats.

PUBLICATIONS / ABSTRACTS PRESENTED:

Abstract for Neuroscience day 2007

Title: The role of glutamate in the action of LSD

Authors: Lee, D; Rabin R; Winter J; Thompson A

Previous studies in our laboratory have found that the stimulus effects of the hallucinogenic serotonergic agonists (such as LSD) are potentiated by phencyclidine (PCP), a non-competitive NMDA antagonist. On the basis of electrophysiological evidence, it has been proposed that both antagonism of NMDA receptors by drugs such as PCP and stimulation of 5-HT_{2A} receptors by drugs such as LSD result in the release of glutamate. Also suggestive of behaviorally significant serotonergic/glutamatergic interactions is a finding by our laboratory that stimulus control by both PCP and LSD is partially antagonized by a mGlu_{2/3} agonist. It has been observed that antagonists and agonists at mGlu_{2/3} receptors increase and decrease, respectively, the release of glutamate. Furthermore, a previous microdialysis experiment in our laboratory has found that systemic administration of LSD increased extracellular glutamate levels in the medial prefrontal cortex (mPFC) of anesthetized rats. Based on these

observations, we have proposed that glutamate release in the mPFC underlies the interaction observed between different hallucinogens such as LSD and PCP. To test this hypothesis, the ability of LSD (0.1 mg/kg, i.p.) to increase extracellular glutamate in the mPFC was assessed by in vivo microdialysis in awake freely-moving rats. We have found that systemically administered LSD is able to induce both an increase and decrease in the extracellular concentration of glutamate in the mPFC. This suggests that the glutamate response to LSD is complex. Ongoing studies utilizing quantitative microdialysis methods could provide insight into the mechanism by which LSD changes extracellular glutamate levels in awake rats.

PROFESSIONAL/EDUCATIONAL MEETINGS ATTENDED (name of meeting, dates of attendance, location):

Society for Neuroscience Conference, 2008, Washington DC

AWARDS / HONORS:

Ruth L. Kirschstein National Research Service Award #DA021048-01A1

MEDICAL SCHOOL ACTIVITIES:

n/a

EXTRACURRICULAR INTERESTS:

n/a