Department of Pediatrics

COLLEGE OF MEDICINE

SUMMER RESEARCH OPPORTUNITIES FOR UNDERGRADUATE WOMEN

APLICATION DEADLINE: March 1, 2007

The Department of Pediatrics is pleased to offer the following research project for the summer of 2007. Interested students are urged to contact the faculty member(s) directing the project that most interests them. By contacting the faculty member, you can discover more about the project, learn what your responsibilities will be and if possible, develop a timetable for the twelve-week research period.

EFFECTS OF DRUGS OF ABUSE ON BRAIN AND BEHAVIOUR

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Project Description

Dr. Vorhees' laboratory investigates the effects of drugs of abuse on brain development and behavior and collaborates closely with the adjoining laboratory of Dr. Michael Williams. Both labs are interested in how 'club drugs' affect the brain when exposure occurs during early periods of brain development (prenatal) and what the long-term consequences are for later function, especially, cognitive function (learning and memory). The drugs currently investigated are methamphetamine, MDMA ('ecstasy') and 5-methoxy-diisopropyltryptamine ('Foxy'). For all three drugs we also investigate effects on adult brain and behavior because little is known about the cognitive effects of these drugs. The drugs are studied in rats exposed prenatally, neonatally, or as adults. Our results thus far show that these drugs cause changes in neurotransmitters, gene expression, circulating hormones concentrations (especially corticosterone), and learning and memory.

The lab also investigates genetically modified mice that have targeted deletions of genes that transcribe proteins found in high abundance in the brain, such as phosphodiesterase 1B, Npas3, Na-K-ATPases (3 alpha isoforms), a mucopolysaccaride knock-out, a prosaposin knockout, and 2 mouse models of ischemia-hypoxia (models of stroke). We are also currently developing a new mouse with targeted deletion of the

brain-specific creatine transporter protein. This mouse will serve as a model of a recently discovered human genetic disorder: creatine transporter deficiency syndrome.

Projects available for summer 2007: Projects that would be most suitable for summer research would be those on meth, ecstasy or foxy. For example, we need to characterize the basic pharmacology, neurotoxicity, and behavioral effects of foxy and explore the newly found effect of adult Meth exposure on a form of learning called path integration. We are also investigating the effects of MDMA after developmental exposure this summer and beginning a new study on a genetically engineered rat that has an 80% reduction in brain angiotensinogen, a protein our gene chip experiments suggested might be linked the cognitive effects seen after early MDMA exposure..

(2) How phosphodiesterases (of which there are 11 known families) affect brain function. Our focus is on the phosphodiesterase 1 family (1B (created here) and 1C (being created here)). Phosphodiesterases metabolize cAMP and cGMP. We are currently investigating which neurotransmitters pathways PDE1B may be affecting dopamine signaling. Our most recent evidence points to dopamine acting through the D2 receptor. Serotonin and GABA pathways also show some involvement. We find no evidence of effects on NMDA glutamatergic receptors. New evidence in collaboration with Dr. Ron Duman at Yale suggests that the PDE1B knockout mouse is reistent to depression. If this is verified, this mouse may be valuable for developing a new class of antidepressants that active this enzyme.

(3) Development of a creatine transporter knockout mouse. The gene has been targeted and inserted in ES cells. Positive clones were identified and injected into blastocystes and inserted into pseudopregnant mice at the UC ES Core. Chimeric progeny have been born and these are being bred to determine if the mutation is expressed in the germline. If it is, this would be the first model of the human disorder of brain creating transporter deficiency, which is a disease first discovered here only a few years ago, but which is know known to be the cause of mental retardation and speech delay in a significant number of cases of mental retardation whose cause has never before been know..

Projects currently under investigation are on (1) the long-term effects of prenatal and neonatal methamphetamine, MDMA (‘ecstasy’), and ‘Foxy’ exposure compared to that of adult exposure, particularly with regard to effects on learning and memory, on how these drugs alter the offspring’s stress response (HPA axis), and their effects on brain neurotransmitters and transporters, especially serotonin and the serotonin transporter; (2) the effects of the PDE1B knockout mouse in responses to drugs that affect dopamine neurotransmission and the use of this animal as a possible model for identifying antipsychotic drugs and a susceptibility gene for differential responses to drugs of abuse and developing a new mouse in which PDE1C (which is also expressed in the brain) is knockout out by homologous recomination; (3) This summer we hope to have founders of the new creatine transporter KO mouse (CrTr1). If we do, then characterizing its neurobehavioral effects will be the first project to be done in order to determine if it resembles the severe dystunction seen in children who have this genetic disease.