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 resistant 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
blastocysts 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 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 known.

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 recombination; (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 dysfunction seen in children who have this genetic
disease.