Embargoed until Nov. 14, 11:30 a.m. PST
Press Room, Nov. 13-17: (619) 525-6640

Contacts: Kat Snodgrass, (202) 962-4090
Sarah Bates, (202) 962-4087

NEW ANIMAL RESEARCH SHOWS EFFECTS OF PRENATAL DRUG EXPOSURE AND EARLY LIFE INFECTIONS ON THE BRAIN

SAN DIEGO — New findings released today help identify the long-term impact of the prenatal environment and early parental care on the brain. Using animals as models, researchers help explain why early inflammation and a mother's exposure to drugs such as nicotine and high doses of pain killers have lasting consequences for children — and even future generations.

Maternal drug use has been associated with increased risk for learning disabilities, behavioral problems, and mental disorders for children. The new results provide greater insight into the neurobiological factors involved in these lifelong issues, and were reported at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news on brain science and health.

Today's new findings show that:

- Abuse of prescription pain relievers, such as morphine, during adolescence alters the brains of future offspring. The animal study suggests that a mother's history of drug use may have a significant impact on her children and grandchildren, even if she was not using drugs at the time of becoming pregnant (Elizabeth Byrnes, PhD, abstract 271.5, see attached summary).
- Prolonged prenatal exposure to nicotine decreases the number of newborn cells in the hippocampus, a brain area important in learning and memory. These results may lead to new approaches to treating learning disabilities and other behavioral deficits associated with exposure (Robin Lester, PhD, abstract 852.18, see attached summary).
- Smoking during pregnancy may interfere with brain development. New animal research shows maternal smoking affects genes important in the formation and action of a fatty brain substance called myelin that insulates brain cell connections (Ming Li, PhD, abstract 269.2, see attached summary).
- An episode of brain inflammation early in life may lead to long-lasting changes that increase the risk of developing drug addiction during adulthood (Lir-Wan Fan, PhD, abstract 879.10, see attached summary).

"Brain circuits, formed by genetic programs during embryonic development, are modified through interactions with the internal and external environment," said press conference moderator Yasmin Hurd, PhD, of the Mount Sinai School of Medicine, an expert in how drugs affect the brain, particularly prenatal and postnatal development. "These findings tell us new information about how the brain develops, and also highlight the social imperative of educating mothers on the importance of avoiding harmful substances."

This research was supported by national funding agencies, such as the National Institutes of Health, as well as private and philanthropic organizations.

# # #

Abstract 271.5 Summary

Lead author: Elizabeth Byrnes, PhD (508) 839-7986
Tufts University elizabeth.byrnes@tufts.edu
North Grafton, Mass.

Morphine Abuse During Adolescence Has Multigenerational Effects on Brain

Animal study suggests mother's previous drug abuse can have significant impact on her children and grandchildren

Abuse of prescription pain relievers, such as morphine, during adolescence alters the brains of future offspring, a new animal study found. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Abuse of prescription pain relievers among adolescents — girls as well as boys — is a growing concern," said Elizabeth Byrnes, PhD, of Tufts University. "Unfortunately, the long-term consequences of female adolescent drug use, particularly on future children, are unknown. Our findings suggest that a mother's history of drug use may have a significant impact on her children and grandchildren, even if the woman was not using drugs at the time she got pregnant."

For this study, female rats were given morphine for 10 days during adolescence. The doses were similar to what an abuser of prescription narcotics might use. After a drug-free period, the females were mated with healthy males, and the first and second generation offspring were subsequently studied when they reached adulthood.

First generation male adult offspring demonstrated decreased sensitivity to the drug quinpirole, a chemical that mimics the reward chemical dopamine in the brain. They also found this same effect in the second generation male offspring.

Disruption of dopamine is associated with addiction and psychiatric disorders. "Our model could be used to help determine how substance abuse and other reward-related disorders are passed down through several generations," said Byrnes. "We are currently examining changes in the expression of particular genes in both the mother and her offspring to determine how these effects are transmitted," she said.

Research was supported by the National Institute on Drug Abuse.

Scientific Presentation: Sunday, Nov. 14, 1–2 p.m., Halls B–H

271.5, Multigenerational effects of morphine exposure on the mesolimbic dopamine system
E. M. BYRNES, N. L. JOHNSON, L. M. CARINI; Tufts Univ. Cummings Sch. Vet Med., North Grafton, MA

TECHNICAL ABSTRACT: Familial transmission of drug abuse liability has been described in the human literature for years. Heritability estimates of substance abuse range from 0.4 to 0.6 depending upon the substance in question and the severity of the abuse. One frequent target in addiction genetics is the Dopamine D2 Receptor (D2). This emphasis is in part due to the critical role of mesolimbic dopamine in addiction processes. We have conducted a series of studies in rats to determine the influence of maternal morphine exposure occurring prior to pregnancy on adaptations in the mesolimbic dopamine system in both the F1 and F2 generation. Morphine exposure consisted of a 10 day, escalating dose regimen (5-25 mg/kg), with allometric scaling used to approximate human use. All females were at least 3 weeks post-withdrawal prior to mating. Using the D2/D3 agonist quinpirole in a sensitization model, we observed significant transgenerational effects of maternal exposure. Moreover, the direction of these effects was dependent upon the age at which the female was exposed. Specifically, offspring of females exposed during adolescent development demonstrated significantly reduced sensitization while offspring of females exposed as adults demonstrated enhanced sensitization. Similar effects were observed in the F2 generation. Significant alterations in D2 receptor mRNA expression in the nucleus accumbens were also observed suggesting a shift in both the number and function of D2 receptors in the mesolimbic dopamine system. Thus, maternal drug history in the absence of any in utero exposure may be a critical factor in familial transmission of drug abuse liability. Moreover, given the role of the mesolimbic dopamine system in natural rewards, maternal drug history may also influence any number of other reward-related behaviors.

Abstract 852.18 Summary

Senior author: Robin Lester, PhD (205) 934-4485
University of Alabama at Birmingham rlester@nrc.uab.edu
Birmingham, Ala.

Prenatal Exposure to Nicotine Affects Stem Cells in Hippocampus

Preliminary study may explain increased risk of learning disabilities among children whose mothers smoked during pregnancy

Prolonged prenatal exposure to nicotine decreases the number of newborn cells in the hippocampus, a brain area important in learning and memory, according to preliminary research presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The study offers a neurobiological explanation for why the children of women who smoke during pregnancy are at an increased risk of developing learning disabilities.

"Previous research has shown that nicotine, cocaine, and other addictive drugs decrease the number of newborn cells in adults. Our research suggests that these effects may be even more dramatic in newborn animals," said Robin Lester, PhD, of the University of Alabama at Birmingham, who directed the study. "These findings provide further warnings to expectant mothers that they should seek help in refraining from smoking during pregnancy," Lester said.

To mimic the conditions of moderate to heavy smoking in a pregnant mother, Lester and his colleagues treated pregnant rats with nicotine through an implanted mini-pump, which acts similarly to a nicotine patch. The researchers then counted the number of newborn cells in the offsprings' dentate gyrus, a section of the hippocampus known to contain neuronal stem cells. They also monitored synaptic plasticity — the reorganization of neural pathways considered essential to learning.

"We found a reduced number of dividing stem cells and altered plasticity in the newborn animals exposed to nicotine," Lester said. These findings may lead to new approaches to treating learning disabilities and other behavior deficits associated with prenatal nicotine exposure.

Research was supported by a United States Public Service Grant and the Evelyn F. McKnight Brain Institute.

Scientific Presentation: Wednesday, Nov. 17, 2–3 p.m., Halls B–H

852.18, Neurogenesis and LTP is altered in the rat dentate gyrus after chronic gestational exposure to nicotine
S. HYMAN[1], A. KIDWELL[2], **R. A. J. LESTER[1]**; [1]Neurobio., [2]Univ. of Alabama In Birmingham, Birmingham, AL

TECHNICAL ABSTRACT: More than 20 percent of pregnant women in the United States smoke, despite FDA warnings that smoking during pregnancy is associated with a number of negative outcomes. Long-term effects of this behavior on the offspring include: a higher rate of drug abuse during adolescence and learning disabilitiesi. Here we evaluate how neuronal stem cells and synaptic plasticity in the dentate gyrus may be affected after gestational exposure to nicotine. Pregnant dams were implanted with osmotic minipumps on gestational day 4 with either saline or a moderate to high dose of nicotine [6mg/kg/day] for the duration of gestation and through post-natal day10 (PN 10). ii This time period after birth is analogous to the third trimester in human gestation. After injection of pups on PN 10 with BrdU we show that the rate of neurogenesis, as reported by BrdU activity, decreases after gestational exposure to nicotine by 75 +/- 20 percent (s.e.m.; n = 3 saline; n=5 nicotine) in PN 10 animals. The rate of survival for these stem cells is the same however, in both groups, over a four-day period [saline = 45 percent +/- 20 (s.e.m.; n = 3), nicotine = 37 percent +/- 20 (s.e.m.; n = 5)]. This change in neurogenesis rate is accompanied by an increase in synaptic activity as measured by a shift to the left on extracellular input-output curves; in addition to a decrease in LTP threshold. A decrease in LTP threshold was determined by a decrease in the number of stimuli necessary for LTP induction. Both the changes in excitability and neurogenesis in the dentate gyrus may contribute to the observed behavioral changes in the offspring of pregnant rats exposed to nicotine. i Abdel-Rahman, A, Dechkovskaia, AM, Sutton, JM, Chen WC, Guan X, Khan WA, Abou-Donia MB (2005) Maternal exposure of rats to nicotine via infusion during gestation produces neurobehavioral deficits and elevated expression of glial fibrillary acidic protein in the cerebellum and CA1 subfield in the offspring at puberty Toxicology 209:245-261 ii Fewell, JE, Smith, FG, Ng, VKY. (2001) Threshold level of Maternal Nicotine that Impairs Protective Responses of Newborn Rats to Intermittent Hypoxia. J Appl Physiol 90: 1968 -76

Abstract 269.2 Summary

Senior author: Ming Li, PhD (434) 243-0566
University of Virginia ml2km@virginia.edu
Charlottesville, Va.

Smoking During Pregnancy Affects Myelin Genes in Offspring

Problems with brain cell "insulation" may explain increased risk of psychiatric disorders among children whose mothers smoked during pregnancy

Smoking during pregnancy may interfere with brain development. New animal research shows maternal smoking affects genes important in the formation and action of a fatty brain substance called myelin that insulates brain cell connections. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The finding may explain why the children of mothers who smoked during pregnancy are more likely to develop attention deficit hyperactivity disorder, depression, autism, drug abuse, and other psychiatric disorders. "Myelin deficits have been previously observed in adults with various psychiatric disorders," said Ming Li, PhD, of the University of Virginia, who directed the study. "Our findings suggest that abnormal myelination may also contribute to the psychiatric disorders associated with maternal smoking," Li said.

The study found that when rats were given nicotine during pregnancy, their offspring showed changes in myelin genes in specific regions of their brain's limbic system — structures involved with emotion. The effect was strongest in the prefrontal cortex, a brain region important for decision-making.

The researchers also identified sex differences in nicotine's effects. Myelin-related genes increased in the prefrontal cortex of the male offspring, but decreased in the females. The opposite was observed in the hypothalamic paraventricular nucleus, a brain region involved in the regulation of stress and appetite, among other functions.

"These findings suggest that maternal smoking may affect daughters and sons differently," Li said.

Research was supported by the National Institute on Drug Abuse.

Scientific Presentation: Sunday, Nov. 14, 2–3 p.m., Halls B–H

269.2, Prenatal nicotine exposure modifies expression of myelin-related genes in the limbic system of adolescent rats in a brain region- and sex- dependent manner
J. CAO[1], J. B. DWYER[3], F. M. LESLIE[3,4], **M. D. LI[2]**; [1]Dept. of Psychiatry & Neurobehavioral Sciences, Univ. of Virginia, CHARLOTTESVILLE, VA; [2]Dept. of Psychiatry & Neurobehavioral Sciences, Univ. of Virginia, Charlottesville, VA; [3]Pharmacol., [4]Anat. & Neurobio., Univ. of California, Irvine, Irvine, CA

TECHNICAL ABSTRACT: Maternal smoking during pregnancy (MS) has long-lasting neurobehavioral effects on the offspring. Many MS-associated psychiatric disorders begin or change symptomology during adolescence, a period of continuous development of the central nervous system. Most of these disorders are thought to be mediated by dysfunction of the limbic system, a collection of brain nuclei that mature during adolescence. Given that deficits in central myelination are convergently observed in many psychiatric disorders, we hypothesized that myelin is impaired by gestational treatment with nicotine (GN), the major psychoactive component in tobacco, in adolescent limbic system. Pregnant Sprague Dawley rats were treated with nicotine (3 mg/kg/day) or saline via osmotic minipumps from gestational days 4 to 18. Both male and female offspring were sacrificed on postnatal day 35, and five limbic brain regions, including prefrontal cortex (PFC), hypothalamic paraventricular nucleus (PVN), caudate putamen (CPu), nucleus accumbens (NAc) and the amygdala (AMY) were dissected. Twenty-nine myelin genes, including those encoding major myelin proteins, lipid-related enzymes and transcriptional factors, were assayed with quantitative RT-PCR array. We found that GN significantly modified myelin gene expression in a brain region dependent manner. Specifically, we found that more genes were altered in the PFC compared to other brain regions, while AMY showed the least response to GN. In the striatum, more genes were changed in the CPu as compared to NAc. Further, we detected striking sex differences in each brain region. In the PFC, myelin genes were significantly upregulated by GN in males, but downregulated in females. In contrast, myelin genes in the PVN were downregulated in males but upregulated in females. In the AMY, only seven genes were significantly upregulated in females while none of them were changed in males. In the striatum, most myelin genes were upregulated in both males and females, with more genes affected in males. Taken together, we conclude that GN impaired myelination in a brain region- and sex-dependent way. Abnormal myelination may contribute to MS-linked psychiatric disorders. Furthermore, the substantial and long-lasting changes by the low dose of nicotine imply that nicotine replacement therapy during pregnancy may carry many of the same risks to the offspring as does MS.

Abstract 879.10 Summary

Senior author: Lir-Wan Fan, PhD (601) 984-2786
University of Mississippi Medical Center littlelifan@yahoo.com
Jackson, Miss.

Early-Life Brain Inflammation May Increase Susceptibility to Drug Addiction in Adulthood

Study offers new insight into the neurological underpinnings of addiction

An episode of brain inflammation early in life may lead to long-lasting changes in the brain that increase the risk of developing drug addiction during adulthood, a new animal study found. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. Brain inflammation is most often caused by head injury or a viral infection such as encephalitis or meningitis.

Senior author Lir-Wan Fan, PhD, of the University of Mississippi Medical Center, and her colleagues previously showed that adult rats exposed to lipopolysaccharide, a toxin produced by certain bacteria that triggers a strong inflammatory immune response, are more likely to exhibit addictive-like behavior in response to a dose of methamphetamine. In this new study, the researchers found that adult rats exhibited the same increased tendency toward an addictive-like response to methamphetamine even when their exposure to lipopolysaccharide — and the resulting brain inflammation — had occurred early in the animals' development. The response was greater in male than in female rats.

"Our findings suggest that early-life brain inflammation leads to long-lasting damage of the brain's reward system," said Fan. "But this damage may not become apparent unless later unmasked by exposure to an addictive drug, like methamphetamine," Fan said.

Research was supported by the National Institute of Health Human Development, the National Institute of Neurological Disorders and Stroke, the University of Mississippi Medical Center, and the Shin Kong Wu Ho-Su Memorial Hospital in Taipei, Taiwan.

Scientific Presentation: Wednesday, Nov. 17, 2–3 p.m., Halls B–H

879.10, Neonatal exposure to lipopolysaccharide enhances methamphetamine-induced behavioral sensitization in adult rats
L.-T. TIEN[1], Z. CAI[2], P. G. RHODES[2], **L.-W. FAN[2]**; [1]Fu-Jen Catholic Univ., Hsingchuang, Taipei, Taiwan; [2]Dept. of Pediatrics, Univ. of Mississippi Med. Ctr., Jackson, MS

TECHNICAL ABSTRACT: Perinatal brain inflammation may lead to long-lasting dopaminergic injury and is associated with the subsequent development of motor disturbances in the adult. Our previous studies have shown that neonatal exposure to lipopolysaccharide (LPS) resulted in brain dopaminergic injury in adult rats. The neonatal LPS-injected male rats showed significantly increased methamphetamine (METH)-induced abnormal locomotion compared to that of the control male rat. To further investigate the effect of neonatal LPS exposure induced dopaminergic injury, we have used our neonatal rat model of LPS exposure (1 mg/kg, intracerebral injection in postnatal day five, P5, neonatal rats) to examine the METH sensitization, as an indicator of drug addiction, in the adult rats. On P70, animals began a treatment schedule of five METH subcutaneous (s.c.) administration (0.5 mg/kg) or saline once per day (P70-P74) to induce behavioral sensitization. 96 hours after the fifth treatment with METH or saline (P78), animals received a single dose of 0.5 mg/kg METH (s.c.) or saline. The locomotion, including distance traveled and rearing events, and stereotypy were monitored for three hours following injection. The distance traveled, rearing events (exposure rearing and sniffing-air responses) and stereotypy (standing, grooming, scratching, head-swinging, sniffing and freezing) progressively increased with repeated treatment of METH, indicating behavioral sensitization in all of the METH-treated groups. Neonatal LPS exposure potentiated the level and rates of development of behavioral sensitization, including distance traveled, rearing events and stereotypy, to METH administration in both male and female rats. Neonatal LPS exposure also potentiated the reinstated rearing events and stereotypy sensitization in both male and female rats after chronic administration had ceased for 96 hours. However, neonatal LPS exposure only potentiated the reinstated distance traveled sensitization to METH administration in male, but not in the female rats. These results indicate that neonatal brain LPS exposure produces a persisting lesion in the dopaminergic system and potentiates METH-induced locomotor and stereotyped behavioral sensitization in later life. These findings show there are interactions between early-life brain inflammation and the development of addiction to drugs in later life.