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NATURE AND NURTURE WORK TOGETHER TO SHAPE THE BRAIN

New animal research finds life experiences influence brain development, behavior

Washington — Scientists presented new research today demonstrating the impact life experiences can have on genes and behavior. The studies examine how such environmental information can be transmitted from one generation to the next — a phenomenon known as epigenetics. This new knowledge could ultimately improve understanding of brain plasticity, the cognitive benefits of motherhood, and how a parent's exposure to drugs, alcohol, and stress can alter brain development and behavior in their offspring.

The findings were presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Today's new findings show that:

- Brain cell activation changes a protein involved in turning genes on and off, suggesting the protein may play a role in brain plasticity (Ian Maze, PhD, abstract 660.03, see attached summary).
- Prenatal exposure to amphetamines and alcohol produces abnormal numbers of chromosomes in fetal mouse brains. The findings suggest these abnormal counts may contribute to the developmental defects seen in children exposed to drugs and alcohol *in utero* (Jerold Chun, MD, PhD, abstract 166.04, see attached summary).
- Cocaine-induced changes in the brain may be inheritable. Sons of male rats exposed to cocaine are resistant to the rewarding effects of the drug (Chris Pierce, PhD, abstract 371.05, see attached summary).
- Motherhood protects female mice against some of the negative effects of stress (Tracey Shors, PhD, abstract 219.12, see attached summary).

Another recent finding discussed shows that:

- Mice conceived through breeding — but not those conceived through reproductive technologies — show anxiety-like and depressive-like behaviors similar to their fathers. The findings call into question how these behaviors are transmitted across generations (David Dietz, PhD, see attached speaker's summary).

"Research in the last few years has dramatically changed what we know about how behaviors are inherited," said press conference moderator Flora Vaccarino, MD, from Yale University, an expert on the developing brain. "Today's findings show how our genes and environment work together to influence brain development throughout a lifetime."

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

Related Presentation:

Presidential Special Lecture: **Genes, the Environment, and Decisions: How Fixed Circuits Generate Flexible Behaviors**
Monday, Nov. 14, 5:15–6:25 p.m., Hall D

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Abstract 660.03 Summary

Co-author: Ian S. Maze, PhD (614) 301-4222
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Brain Cell Activity Changes Key Epigenetic Protein

Animal study points to role protein may play in synaptic function, plasticity

New animal research indicates a novel epigenetic process — specifically, that brain cell activation leads to changes in histones, the protein spools upon which DNA is wound. The research was presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Genes are constantly being turned on and off, according to the needs of a cell. When not in use, DNA is tightly looped around protein spools called histones. Cells are constantly adding or removing chemical groups to genes or histones, signaling the DNA to loosen its coil — which exposes the genetic instruction manual for the cell — or to coil tighter, ensuring the gene remains off-limits.

In the new study, Ian Maze, PhD, and colleagues, of The Rockefeller University, found brain cell activation changed the amount and the location of a histone called H3.3. Following activation, this histone moved along the strand of DNA. After activation, the histone was found near gene promoters — the on/off switches for genes. The findings suggest a new way for the environment to affect genes.

"Understanding how plasticity is regulated by genes and histones will provide critical clues into the basic mechanisms of brain cells, and will help identify target genes involved in many neurological diseases," said Maze.

Research was supported by the National Institute of Mental Health.

Scientific Presentation: Tuesday, Nov. 15, 3–4 p.m., Washington Convention Center, Halls A–C

660.03, Epigenomic profile and function of the histone variant H3.3 during periods of activity-dependent neural plasticity
C. D. ALLIS[1], **I. S. MAZE**[1], K.-M. NOH[1], P. W. LEWIS[1], L. A. BANASZYNSKI[1], S. J. ELSAESSER[1], E. MOUZON[2], *E. J. NESTLER[2];
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TECHNICAL ABSTRACT: Exciting new discoveries have demonstrated that in addition to post-translational modifications of histones and nucleosomal remodeling, eukaryotic cells have evolved another physiologically relevant means of generating significant variation in chromatin architecture via the introduction of histone variant proteins. Although the variant histone H3.3 differs from the canonical H3.2 and H3.1 histone proteins at only four to five amino acids, respectively, H3.3 has been shown to be specifically enriched at transcriptionally active genes and within gene promoters, at specific heterochromatic loci, such as telomeres, and at regulatory elements in mammalian embryonic stem cells and in neural precursors. Unlike other H3 variants, which require mitosis for active nucleosomal deposition, H3.3 is efficiently transcribed and incorporated into chromatin in a DNA replication-independent manner in post-mitotic neurons, suggesting a potential role for H3.3 in activity-dependent nucleosomal remodeling/assembly. We have recently discovered that H3.3 expression and genomic deposition are tightly regulated by alterations in cortical activity in vitro. These findings indicate that activity-dependent epigenomic reorganization of this 'mark' may occur to maintain altered patterns of transcription that might contribute to synaptic function and neural plasticity. Now, with our laboratory's development of a collection of novel histone variant specific tools [e.g., tagged H3.3 knock-in mice, histone variant specific antibodies (recognizing untagged endogenous H3.3 and H3.1/2, as well as tagged knock-in forms), gene copy specific/conditional knockdown strategies (shRNA viruses and H3.3A/B knockout mice), etc.], we are beginning to expand our studies to investigations of H3.3 in the central nervous system using a combination of genome-wide (ChIP-/RNA-seq), biochemical (H3.3 complex purification in brain) and genetic techniques (knockdown vs. exogenous expression) to further elucidate the biological relevance of H3.3 deposition/eviction in guiding various aspects of neuronal function.

Abstract 166.04 Summary

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Amphetamine, Alcohol Change Chromosome Number in Fetal Brain Cells

Animal study suggests new way abused substances may interfere with normal brain development

Exposure to amphetamines or alcohol in the womb alters the number of chromosomes in fetal brain cells, a new animal study shows. The research was presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Traditionally, researchers believed normal cells always contain the same number of chromosomes, which in humans is 46. Past studies in cancer cells have revealed that chromosomes are not always equally distributed between cells during cell division, resulting in an addition or loss of a chromosome — a phenomenon known as aneuploidy. Aneuploidy is known to affect brain function, as observed in Down Syndrome (trisomy 21, with an extra chromosome 21).

Researchers led by Jerold Chun, MD, PhD, of The Scripps Research Institute, previously found that normal brains contain many diverse forms of aneuploidy. In the current study, they tested the effects of alcohol and amphetamines on aneuploidy by exposing pregnant mice to the substances. Exposed embryos displayed marked increases in the amount of total aneuploidy compared with the brains of mice whose mothers were not exposed to drugs or alcohol.

Prenatal exposure to alcohol versus amphetamine led to different types of aneuploidy. Amphetamine-exposed embryos displayed three times as much mild aneuploidy (5 or fewer chromosomes missing) compared with unexposed animals. In contrast, embryos exposed to alcohol had three times as much severe aneuploidy (more than 5 chromosomes missing) as unexposed mice.

"Our data identifies major increases in fetal aneuploidy produced by prenatal exposure to drugs of abuse or alcohol," said Chun. "This represents a new, unrecognized basis for altered neural function, which could contribute to developmental defects seen in animal models and human patients," he said.

Research was supported in part by the National Institute on Drug Abuse. Dr. Chun has a proprietary interest in lysophospholipid research, none of which were used in the current study.

Scientific Presentation: Sunday, Nov. 13, 11–12 p.m., Washington Convention Center, Halls A–C

166.04, Alterations in neural aneuploidy by drugs of abuse during fetal brain development
D. BUSHMAN[1], H. MIRENDIL[2], **J. CHUN**[2]; [1]Biomed. Sci. Grad. Program, UCSD, LA JOLLA, CA; [2]Mol. Biol., The Scripps Res. Inst., La Jolla, CA

TECHNICAL ABSTRACT: Mosaic aneuploidy, defined as coincidental chromosome losses and/or gains to deviate from the haploid chromosome complement, has been identified in both the developing and the adult mammalian central nervous system, including neural progenitor cells and functionally integrated mature neurons. Aneuploidy arises through altered cellular mechanisms controlling growth, DNA synthesis and replication, and neurogenesis; during development, these processes are influenced by neurotransmitters and their associated signaling cascades. Exposure to non-endogenous agonists such as amphetamines and nicotine can result in cell damage including oxidative stress or cleavage regulation problems and may contribute to DNA damage and misrepair through which aneuploidy can arise. When used during pregnancy, drugs of abuse and alcohol can cross the placental barrier from the mother into the fetal brain, and are linked to developmental defects including abnormalities of cell proliferation, differentiation and death, loss of synaptic activity, Sudden Infant Death Syndrome (SIDS), as well as pre- and postnatal growth retardation and Fetal Alcohol Disorders (FAD). Here we show that in utero exposure to amphetamines or alcohol increases the incidence of aneuploidy in the developing brain. Using metaphase spread analysis, embryos exposed at embryonic day 13.5 (E13.5) show a two-fold increase in total aneuploidy, from 23-25% in vehicle control versus 52% with d-amphetamine (10mg/kg) and 55-65% with ethanol (3-4.5mg/kg). For both drugs, hypoploidy (loss of chromosomes) was more prevalent than hyperploidy (chromosomal gains). Metaphase spreads were also categorized by severity of aneuploidy: a mildly aneuploid spread has fewer than five chromosomes lost or gained; severe spreads have lost or gained more than five chromosomes. Embryos exposed to d-amphetamine show a three-fold increase in the amount of mild aneuploidy compared to vehicle controls, while levels of severe aneuploidy remained consistent between treated and control embryos. In contrast, embryos exposed to either 3mg/kg or 4.5mg/kg of ethanol display a three-fold increase in severe aneuploidy and less than twice as much mild aneuploidy. These data identify alterations in neural aneuploidy as a new component in the etiology of disorders associated with prenatal exposure to alcohol and drugs of abuse.

Abstract 371.05 Summary

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Philadelphia, Pa.

Cocaine-Induced Changes in Brain May Be Heritable

Sons of addicted male rats are more resistant to rewarding effects of drug

Male pups of rats addicted to cocaine appear to find the drug less rewarding, a new study finds. The research was presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

To study the effect of cocaine across generations, Chris Pierce, PhD, of the University of Pennsylvania, and colleagues mated cocaine-exposed male rats with females that were not exposed to the drug. After the female rats became pregnant, the males were removed and had no role in rearing offspring. Once the offspring reached adulthood, they too were given access to cocaine.

The researchers found that the male — but not female — offspring took cocaine less readily and took less of the drug overall, compared with the offspring of male rats that were not exposed to drugs. Additionally, the sons of cocaine-exposed males did not work as hard to access cocaine as the sons of non-exposed males, suggesting they found the drug to be less rewarding.

"These results indicate that paternal exposure to toxins such as cocaine can have profound effects on gene expression, and on the behavior of the offspring," said Pierce. "Our data suggests cocaine-induced changes in the brain can be inherited by sons from their fathers," he said.

Research was supported by the National Institute on Drug Abuse.

Scientific Presentation: Monday, Nov. 14, 8–9 a.m., Washington Convention Center, Halls A–C

371.05, Trans-generational epigenetic transmission of a cocaine-resistance phenotype
F. M. VASSOLER[1], **C. PIERCE[1]**, S. L. WHITE[1], P. I. ORTINSKI[1], G. SADRI-VAKILI[2]; [1]Univ. Pennsylvania Sch. of Med., PHILADELPHIA, PA; [2]Harvard Med. Sch., Boston, MA

TECHNICAL ABSTRACT: Genetic factors contribute significantly to the risk of cocaine abuse in humans. However, the potential role of epigenetic influences on addiction phenotypes has not been addressed. A growing body of evidence indicates that environmental information can be inherited. Thus, epigenetic changes in the mammalian germline can act as a trans-generational carrier of environmental information. Here, we describe a rat model developed in order to delineate a heritable phenotype resulting from the self-administration of cocaine. Male Sprague-Dawley rats were allowed to self-administer cocaine (25 mg/kg/infusion) for 60 days (controls received yoked saline injections). Twenty-four hours later, they were introduced to naïve females and allowed to mate. Behavioral, electrophysiological and molecular phenotypes of the F1 offspring were examined at adulthood (approximately P60). We found that while the male offspring of cocaine-experienced sires had delayed acquisition of cocaine self-administration relative to the offspring of yoked saline controls, there was no difference in the acquisition of cocaine self-administration in female offspring. The delayed acquisition of cocaine self-administration in male cocaine-sired rats was not due to deficits in operant learning since the acquisition of food self-administration was normal in these animals. Our results also indicated that male cocaine-sired rats did not develop behavioral sensitization to cocaine, which suggests altered neuronal plasticity in the mesocorticolimbic system. Preliminary electrophysiological evidence indicated increased synaptic GluA2-lacking AMPA receptors in the nucleus accumbens shell. Also, male cocaine-sired rats had increased levels of BDNF protein and mRNA in the prefrontal cortex (PFC). It remains to be determined how increased GluA2-lacking AMPA receptors in the shell and increased BDNF in the PFC influence behavior in the male offspring of cocaine-experienced sires. In conclusion, these results suggest that cocaine experienced sires confer a resistance to cocaine reinforcement in their male offspring.

Abstract 219.12 Summary

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Motherhood Protects Female Rats from Negative Effects of Stress

Animal study finds effect lasts long after pups have grown up, separated from mother

Maternal experience may offer life-long protection against the negative effects of stress, according to new animal research. The research was presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

In virgin female rats, it's known that stressful experiences diminish the ability to learn associations between events in the environment. This study found that the impairment does not occur in female rats that are either lactating or taking care of young, suggesting they are somehow immune to the negative consequences of stressful experiences.

To determine how long the protective benefits of maternal experience might last, Tracey Shors, PhD, and colleagues at Rutgers University, examined how a stressful experience affected female rats that had given birth to offspring at least once. Unlike virgin females, which did not learn after exposure to a stressful event, female mothers performed as well on a learning task as females that had not been exposed to the stressful event.

"In our study, learning after a stressful experience is altered for the better after motherhood, and apparently this effect remains long after the offspring have matured," said Shors.

Research was supported by the National Institute of Mental Health and National Science Foundation.

Scientific Presentation: Sunday, Nov. 13, 3:45-4 p.m., Washington Convention Center, Halls A–C

219.12, Once a Mother, Always a Mother: Maternal experience protects females from the negative effects of stress on learning throughout their lifetime.
*L. Y. MAENG, **T. J. SHORS**;
Dept. of Psychology & Ctr. for Collaborative Neurosci., Rutgers, The State Univ. of New Jersey, PISCATAWAY, NJ

TECHNICAL ABSTRACT: Women experience profound hormonal fluctuations throughout their reproductive lives. Pregnancy into motherhood/postpartum is one such transitional stage during which women and other female species are especially susceptible to disturbances in mood and/or cognition (Brummelte & Galea, 2010). Responses to stressful stimuli are also altered. Virgin female rats express a severe learning deficit in associative eyeblink conditioning after a stressful life event (Wood & Shors, 1998; Wood et al., 2001). Interestingly though, females that are lactating and/or caring for young learn as well as unstressed females (Leuner & Shors, 2006). The deficit in learning is nonetheless evident if the young are removed and lactation ceases. Thus, it seems as though the protective effect of motherhood relies on the presence of offspring and maternal behavior. These previous studies tested females during their first pregnancy. Here, we hypothesized that females that had been maternal at some time in their lives would learn well even after exposure to a stressful event. To test this hypothesis, we examined females that had at least one brood of young and expressed a normal estrus cycle. During diestrus, they were exposed to an acute stressful event that reliably impairs learning in virgin females. They were trained 24 h later with classical eyeblink conditioning. In contrast to the virgin females that did not learn after stressor exposure, those females that had been mothers performed as well as those that were not stressed ($p>0.05$). These data suggest that motherhood is protective. Maternal experience appears to impart a resistance to stress that is long-lasting and perhaps permanent.

Speaker's Summary

Speaker: David Dietz, PhD (212) 659-5656
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Paternal Transmission of Stressed–Induced Pathologies (792.07)
Poster Session: Mood Disorders: Animal Models: Epigenetic and Intracellular Signaling Mechanisms
Wednesday, Nov. 16, 10–11 a.m., Washington Convention Center, Halls A–C

Major depressive disorder (MDD) is a common and disabling disorder with an overall lifetime risk estimated to be ~15% in the general U.S. population. Depression is thought to be caused by a combination of genetic and environmental factors. In humans, there has been a rich amount of literature suggesting MDD is a familial disorder, with up to a 2-fold increased risk in offspring from depressed patients compared to offspring from control patients. More recently, there has been a great deal of interest into what epigenetic mechanisms may contribute to the trans-generational transmission of susceptibility to depression.

The use of rodent models have allowed for tremendous insight into the biology of depression. For example, in adult male mice, exposure to chronic social defeat stress induces a syndrome of behavioral deficits that closely models subtypes of human depression including: anxiety, anhedonia (reduced pleasure), changes in weight, and social withdrawal. We hypothesized that these behavioral adaptations might be transmitted to subsequent generations, ultimately leading to enhanced susceptibility to depressive-like behaviors in the offspring of mice sired from defeated fathers. Using social avoidance (withdrawal) as a measure of depressive-like behavior, our initial findings confirmed that male mice bred from defeated fathers, but not from control fathers, showed pronounced social avoidance when subjected to defeat stress.

To further study the role of paternal influences in heritability of depressive-like behaviors, we performed an experiment that allowed us to directly compare both male and female offspring sired from the same males before and after having been subjected to social defeat. We performed a battery of behavioral tests (forced swim test, elevated plus maze, sucrose preference, and social defeat) that together examine depressive- and anxiety-like behaviors. Compared with pre-defeat offspring (which were indistinguishable from controls), both male and female offspring from the defeated fathers demonstrated robust depressive- and anxiety-like phenotypes. Similar to what has been observed in depressed humans, the offspring of defeated fathers also had increased circulating blood levels of the stress hormone, corticosterone. Taken together, these studies demonstrate the clear transmissibility of depressive- and anxiety-like phenotypes to the F1 generation offspring of socially defeated mice.

To directly assess the role of epigenetic mechanisms, we used in vitro fertilization (IVF) to investigate if the behavioral phenotypes observed in the above experiments were directly transmissible through the sperm of socially defeated mice. Sperm from defeated and control mice was used to impregnate female mice, and the offspring were tested for depressive- and anxiety-like behaviors. Unlike our previous findings, animals derived using IVF from defeated fathers did not exhibit a robust increase in susceptibility for a depressive- or anxiety-like phenotype, with only very modest differences seen.

Our IVF experiments indicate that most of this trans-generationally transmitted behavioral phenotype likely occurs through behavioral mechanisms. Nevertheless, our data suggest that a small contribution of epigenetic modifications is possible, which now requires further examination.