NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

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NewsScan

NIDA ADDICTION RESEARCH NEWS

NEWS UPDATE

NEUROSCIENCE ISSUE

Each year, neuroscientists from around the world gather to discuss the latest research findings that advance knowledge of the brain and nervous system. A highlight of the annual meeting of the Society for Neuroscience, held November 12–16, 2005 in Washington, DC, was the NIDA Mini-Convention: Frontiers in Addiction Research. Topics presented there included studies on addiction and obesity; comorbidity of substance abuse and mental illness; mGluR and the neurobiology of addiction; reconsolidation of memory; and adolescents and addiction.

Scientific advances are revolutionizing our understanding of drug abuse and addiction. NIDA has supported the majority of these advances, which have dramatic implications for how to best prevent and treat addiction. NIDA-supported science addresses the most fundamental and essential questions about drug abuse, ranging from research on the molecular level to managed care and community outreach. Below are examples of NIDA-supported studies that recently have been published in some of neuroscience's leading journals.

Epigenetics Offers New Avenues for Addiction Research

Epigenetics involves the transmission of information from a cell or multicellular organism to its descendants without that information being encoded in the chemicals that make up the DNA of a particular gene. Neuroscientists are beginning to investigate these mechanisms in neurobiological processes. These processes include memory, behavior, and long-lasting nervous system changes, such as those that result from drug abuse.

Two NIDA scientists—Dr. Christine Colvis and Dr. Jonathan Pollock—and their colleagues explain some of the latest research in this area in a review article that captures information presented at a special symposium at the 2005 annual meeting of the Society for Neuroscience. They describe new research in which:

- scientists show the effects of gene–environment interactions and how nurturing in early development can affect adult behavior;
- researchers uncover mechanisms involving the consolidation of short-term memory to long-term memory;
- certain protein–enzyme interactions may assist scientists in developing new drugs for a variety of degenerative diseases of the nervous system; and
- cocaine affects biochemical activity related to a specific protein and how these changes differ in acute versus chronic abuse.

■ **WHAT IT MEANS:** Epigenetics involves new concepts and new ways of thinking about fundamental processes that influence highly complex nerve functions, including those involved in the behavioral and biochemical aspects of drug abuse and addiction. These new paradigms may offer new avenues for therapy.

Dr. Colvis and Dr. Pollock, both at NIDA, published their review in the November 9, 2005 issue of the *Journal of Neuroscience*.

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Rat Study Shows Link Between Stress and Relapse to Drug Abuse

A recent NIDA study builds upon previous research findings into the relationship between stress and drug abuse, by identifying a direct link between stress- and reward-associated mechanisms in the brains of rats.

Dr. Roy Wise, of the National Institute on Drug Abuse, and colleagues from Tufts University and the University of Pennsylvania School of Medicine examined the effects of stress in adult male rats exposed to cocaine. The rats were trained to self-administer cocaine or saline (controls) and then subjected to withdrawal. Following training and withdrawal, the rats were exposed to a series of footshocks. The scientists then tested for the presence of stress-related chemicals in the brains of cocaine-exposed and control rats.

Researchers found that both cocaine-exposed and control rats had increased levels of the stress-related compound corticotropin-releasing factor (CRF) in the ventral tegmental area (VTA), a region of the brain associated with pleasure. Moreover, the presence of stress compound in the VTA was found to trigger a relapse to drug-seeking behavior by the cocaine-exposed rats.

- **WHAT IT MEANS:** These findings establish the VTA as the stress-associated release site for CRF. The presence of CRF in the brain activates reward systems—initiating relapse to drug-seeking behavior in cocaine-experienced rats—and highlights a link between stress mechanisms and drug reward pathways.

The scientists published their findings in the June 1, 2005 issue of the *Journal of Neuroscience*.

Nicotine, Hypocretin Have Similar Effects on Attention in Rats

Recent research in rats suggests that nicotine mimics the effects of hypocretin, a protein thought to help regulate sleep and wakefulness, in the prefrontal cortex, a part of the brain important in tasks requiring attention.

In the study, 10 adult male rats were trained to pay attention to a visual stimulus, upon which they would poke a target and be rewarded with food. After learning the task, the prefrontal cortices of all 10 rats were successively infused with saline, nicotine, and a low or high dose of hypocretin.

The researchers found that infusions of both nicotine and hypocretin improved the ability of the rats to pay attention and follow through on a task, even when conditions were demanding. Further analyses showed that nicotine and the higher dose of hypocretin improved accuracy in the task under the most demanding condition.

- **WHAT IT MEANS:** This is the first study to suggest that hypocretin plays a role in attention, and further demonstrates that hypocretin and nicotine act similarly to enhance attention and performance. An implication is that the cognitive effects of nicotine—normally administered in intermittent bursts through smoking—need to be considered in smoking cessation treatments. The scientists suggest that a constant, low level of nicotine infused into the body from a patch may desensitize rather than activate nicotine receptors.

The study, led by Dr. Evelyn Lambe of Yale University School of Medicine, was published in the May 25, 2005 issue of the *Journal of Neuroscience*.

Research in Mice Shows Naloxone Blocks Activity in Brain Pathways Key to Nicotine Addiction

Results of a study performed in mice show that naloxone was able to block activation of the brain's molecular pathways that reinforce smoking behaviors and keep the mice from seeking out more nicotine. Naloxone belongs to a class of compounds known as opiate antagonists, which can prevent certain drugs, such as morphine and heroin, from latching onto receptors in the brain.

The scientists saw that when they gave nicotine to normal mice, activity of a particular protein known to play a role in the rewarding properties of many drugs of abuse increased in various brain regions. They again observed

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increased activity of this protein when normal mice previously given nicotine were placed in the environment they associated with receiving the drug. But when the scientists treated mice with naloxone before exposing them to the nicotine-associated environment, the activity of this protein was blocked, as was the behavioral response associated with reward.

The researchers suggest that future studies evaluating the efficacy of opiate antagonists or other drugs capable of blocking the activity of this protein would be useful in humans to see if they block the craving in quitters exposed to visual or olfactory stimuli that may rekindle the desire to smoke.

- **WHAT IT MEANS:** Environmental cues related to smoking activate some of the same molecular pathways in the brain as direct exposure to nicotine. However, this study shows that medications such as naloxone may help block this action in nicotine addiction, thereby offering promise for smokers who want to quit, and alternatives or additions to current smoking cessation therapies.

Dr. Julie Blendy and her colleagues at the University of Pennsylvania published their findings in the June 16, 2005 issue of the journal *Neuron*.

New Brain Scan Study Suggests Differences in Smokers in Response to Smoking Cues

New research suggests that different levels of sensitivity to drug cues may exist in the brains of smokers. These differences may be influenced by the degree to which smokers crave cigarettes.

Dr. Joseph McClernon and colleagues from the Duke University Medical Center in North Carolina examined brain activity in regions associated with attention, motivation, and reward. All of the 13 adult smokers completed two brain scan sessions (1 following a period of overnight abstinence, and the other following smoking as usual) while viewing a series of pictures, including smoking-related objects and people smoking cigarettes. Study participants provided self-reports of cravings before, during, and after each session.

Although all smokers reported cravings following both sessions, the researchers found that smokers who reported a greater urge to smoke following the period of abstinence also exhibited stronger brain activity after viewing smoking-related images. In contrast, smokers who reported fewer cravings displayed stable or decreased brain activity, despite viewing the same smoking-related images after a period of abstinence.

- **WHAT IT MEANS:** These findings suggest that important differences may exist in the brains of smokers. These differences may influence levels of cigarette craving following abstinence and may also affect the impact of smoking cues. Smokers who experience a greater sensitivity to smoking cues may have difficulty quitting smoking and may also be more prone to relapse.

The researchers published these study findings in the May 2005 issue of *Neuropsychopharmacology*.

Compound Blocks Cocaine-Associated Environmental Cues in Rats

Scientists at the University of California, Irvine have been able to block learned associations between environmental cues and cocaine-seeking behavior in rats via an experimental drug that acts on a specific signaling pathway in the brain.

Dr. John Marshall and Courtney Miller trained rats, to associate a particular location with the rewarding effects of cocaine. The scientists then administered an experimental compound called U0126 that blocked the extracellular signal-regulated kinase (ERK) pathway, which has been implicated in the central nervous system effects of drugs of abuse.

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They found that inhibiting this pathway interfered with the ability of the animals to maintain the environment–drug association, and the rats lost their preference for the drug-associated site.

- **WHAT IT MEANS:** Memories associated with drug-related stimuli are responsible for much of the relapse seen in drug abuse and addiction. These findings suggest there is a way to disrupt and "unlearn" these memories, breaking the bond between environmental cues and drug-seeking behavior. This opens the possibility of developing new therapies to treat cocaine abuse and addiction.

This NIDA-supported study was published in the September 15, 2005 issue of the journal *Neuron*.

Scientists Correlate Cocaine Craving, High with Regional Brain Activity

Using functional magnetic resonance imaging (fMRI)—a neuroimaging technique that shows which brain structures are active during particular mental operations—scientists have shown that the same brain regions associated with animal models of cocaine reinforcement also are engaged in human drug-taking behavior. In addition, they observed that craving and the drug-induced "high" involve the same areas of the brain but in different ways.

The researchers analyzed brain scans on a minute-to-minute basis from six adult male cocaine addicts who self-administered the drug during a 1-hour session. The participants, who did not abuse other drugs, rated their levels of high, rush, craving, and anxiety once per minute. This allowed the scientists to track the developing relationship between the drug's subjective effects and changes in brain activity.

Not surprisingly, the participants' "high" ratings reached peak levels soon after cocaine administration, while craving ratings decreased to minimal levels about 2–3 minutes after giving themselves a dose of the drug. The scientists observed that the drug-induced highs correlated with reduced activity in the limbic, paralimbic, and mesocortical regions of the brain, while craving was associated with increased activity in these same regions.

The pathway between these brain regions is a major highway for transport of the chemical dopamine, associated with pleasure and reward. The limbic system also is involved in emotional behavior.

- **WHAT IT MEANS:** Understanding the neurochemical mechanisms that drive drug-seeking behavior is central to developing effective therapies for drug abuse and addiction. Information derived from this and future studies may lead to the development of pharmaceuticals targeting specific brain regions that show enhanced activity during drug craving.

Dr. Robert Risinger and his colleagues at the Medical College of Wisconsin and NIDA's Neuroimaging Research Branch published their study in the July 15, 2005 issue of the journal *NeuroImage*.

New Brain Scan Technology Confirms the Effects of Acute Cocaine Abuse in the Human Brain

Scientists at the Medical College of Wisconsin have developed a new form of functional magnetic resonance imaging (fMRI) that has helped them determine that cocaine activates a midbrain pathway involving dopamine and that the drug also stimulates frontal brain networks associated with learning, motivation, and memory.

The new technology, developed by Dr. Shing-Jiang Li and his colleagues, enhances visibility of neural activity in regions of the brain previously distorted by imaging artifacts. A total of 15 nontreatment-seeking cocaine abusers were recruited to complete two 15-minute brain scan sessions—1 with a single dose of cocaine and 1 with saline substitution.

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The team of scientists observed that an acute dose of cocaine, a dose with the ability to induce a significant high and craving (20mg/70kg), triggered activity in both mesolimbic and mesocortical dopaminergic pathways—regions of the brain associated with reward, motivation, learning, and memory. These study findings support the involvement of dopaminergic pathways in cocaine addiction and suggest that hierarchical networks involved in reinforcement and cognitive functions, such as planning and task management, may also mediate cocaine addiction in the human brain.

- **WHAT IT MEANS:** Although the compulsive nature of drug abuse is generally attributed to a powerful desire for the drug, understanding the neurobiological process of addiction remains a central challenge in addiction research. These research findings suggest that acute cocaine abuse may activate pathways and networks in the brain that are responsible for reward, motivation, learning, memory, and reinforcement. Thus, these processes may play a significant role in the compulsive nature of drug abuse. Additional research is needed to better understand the neural pathways and systems involved in cocaine addiction in the human brain.

This article was published in the December 2005 issue of *NeuroImage*.

Rat Study Suggests Chromatin Remodeling Affects Brain Circuits Involved in Addiction

Researchers studying the molecular machinery that underlies short-term gratification from drug abuse and the brain changes that fuel addiction have honed in on a key process that involves the activation of specific genes.

In rat studies, the scientists investigated a process called chromatin remodeling, in which histones (proteins that bind to DNA, help give chromosomes their shape, and help control gene activity) enfolding certain genes are modified in an effort to activate the genes. They found that the acute effects of cocaine at this level differ from the chronic effects of the drug—acute cocaine activated a gene called cFos (an important regulator of other genes) while chronic administration of cocaine desensitized that gene. Acute administration of cocaine was defined as a single injection of the drug, while chronic cocaine was an injection given once daily for 7 days.

The researchers also observed that chronic cocaine administration activated two other genes, BDNF and Cdk5. Previous research has implicated the Cdk5 gene in the rewiring of brain circuitry in a region of the brain called the striatum, which is known to be important in cocaine's behavioral effects. In humans, the striatum becomes active in the presence of dopamine, a brain chemical associated with pleasure and reward; involved in coordinating movement, it also becomes engaged in decision-making processes.

In behavioral experiments, the scientists found that enhancing histone modification increased the cocaine reward response. In contrast, when the animals received drugs that reduce histone modification, they showed diminished reward effects.

- **WHAT IT MEANS:** Long-term changes in chromatin remodeling might be a crucial mechanism driving brain changes that occur in response to drug abuse and lead to addiction. This line of research suggests that drugs designed to short-circuit these processes hold promise as addiction therapies.

Dr. Arvid Kumar, Dr. Eric Nestler, and their colleagues at the University of Texas Southwestern Medical Center published their findings in the October 20, 2005 issue of *Neuron*.

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Study Identifies Cerebellum's Involvement in Addiction

Researchers report they have new evidence suggesting that the cerebellar vermis, a worm-shaped structure that plays a role in concentration that was once thought to have modest involvement in addiction, may be a key factor in modulating the brain's dopamine and reward systems. Dopamine is a brain chemical that plays a significant role in drug abuse and addiction through its effects on reward and motivation.

Dr. Carl Anderson, of McLean Hospital and Harvard Medical School, and his colleagues took a closer look at data from a previous study in which 10 crack cocaine abusers viewed two videos (one of butterflies, one of people using the drug) while undergoing brain scans. Their analysis showed that the cerebellar vermis was particularly active when the participants watched the cocaine video.

The researchers also determined that the cerebellar vermis may contain dopamine transporters, so it may be a target for cocaine and other stimulants. The dopamine transporter is a protein that assists in the movement of dopamine from the intercellular space back into the nerve cell. When the dopamine transporter is blocked by drugs like cocaine, dopamine remains in the synapse for prolonged periods and can produce intense pleasurable sensations when it occurs in parts of the brain associated with reward. Prolonged activation in other areas may have different outcomes, but still represents a failure of the exquisitely regulated neuronal communication system.

- **WHAT IT MEANS:** Scientists have not focused much attention on the cerebellum as a brain region involved in drug-associated behaviors due to its low concentration of dopamine and dopamine receptors, although its importance in certain types of learning is well known. These findings offer new insights into how brain regions may interact in addiction.

The scientists published their study in the October 12, 2005 issue of *Neuropsychopharmacology*.

Brain Protein May Elicit Neuroprotective Effects on Brain Nerve Cells

Findings from a recently published NIDA-funded study suggest a brain protein may combat nerve cell damage in the brain.

Dr. Shang-Yi Tsai and colleagues from the National Institute on Drug Abuse in Baltimore, Maryland, cultured a hybrid of mouse and rat brain cells with the delta opioid peptide enkephalin (DADLE)—a powerful brain protein with properties to prevent nerve cell damage—to examine the effects of DADLE on nerve growth factor (NGF), a biological compound that stimulates nerve cell growth and differentiation in the brain.

Researchers observed significant increases in NGF when brain cells were exposed to small amounts of DADLE. Because DADLE was found to raise NGF levels by selectively increasing transcription factors (proteins that regulate the gene expression of NGF), DADLE may be one of the most potent agents known to increase NGF in the biological system.

- **WHAT IT MEANS:** DADLE has been found to mediate a host of neuroprotective and biochemical effects in the brains of mice, including protection from nerve cell damage. These research findings suggest that DADLE may be effective in the production of growth factors important for the survival of brain cells. Thus, DADLE may effectively combat methamphetamine-induced brain damage and neurodegenerative diseases such as Parkinson's.

These research findings were published in the September 2005 issue of *Synapse*.

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For more information about any item in this *NewsScan*:

- **Reporters**, call **Sara Rosario Wilson** at 301-443-6245.
- **Congressional staffers**, call **Geoffrey Laredo** at 301-594-6852.

The National Institute on Drug Abuse (NIDA) is a component of the National Institutes of Health, U.S. Department of Health and Human Services. NIDA supports most of the world's research on the health aspects of drug abuse and addiction. The Institute carries out a large variety of programs to ensure the rapid dissemination of research information and its implementation in policy and practice. Fact sheets on the health effects of drugs of abuse and other topics are available in English and Spanish. These fact sheets and further information on NIDA research and other activities can be found on the NIDA home page at **http://www.drugabuse.gov**.

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