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STUDIES IMPROVE KNOWLEDGE OF UNDERLYING BRAIN CHANGES CAUSED BY ADDICTION

Research into specific cells and circuitry affected by addiction may help guard against relapse

CHICAGO — New research using animal models is enabling a deeper understanding of the neurobiology of compulsive drug addiction in humans — knowledge that may lead to more effective treatment options to weaken the powerful cravings that cause people to relapse. The findings were released today at Neuroscience 2009, the Society for Neuroscience's annual meeting and the world's largest source of emerging news about brain science and health.

Drug addiction is known to change the structure and function of the brain, affecting a person's self control and decision-making ability. According to the Substance Abuse and Mental Health Services Administration's latest survey, 23.6 million persons aged 12 or older needed treatment for an illicit drug or alcohol abuse problem in 2006. These new studies have identified brain mechanisms that help explain how addictions form, as well as the cognitive problems associated with them. Additional research findings discussed could also offer hope against addiction relapses.

Today's new findings show that:

- Chronic alcohol consumption reduces the number of new brain cells that form in the hippocampus of primates. The hippocampus plays a key role in memory, perhaps explaining the association between chronic alcoholism and memory problems (Chitra Mandyam, PhD, abstract 30.17, see attached summary).
- After exposure to cocaine, rhesus monkeys developed impairments in learning, cognitive flexibility, and memory. This finding suggests that cognitive problems associated with cocaine addiction in humans result directly from the cocaine abuse rather than from a pre-existing trait or lifestyle factor (Charles W. Bradberry, PhD, abstract 158.4, see attached summary).
- A chemical already found in the body reduces cravings in addicted rats and appears to restore normal functioning in a brain circuit associated with cocaine addiction (Khaled Moussawi, abstract 346.14, see attached summary).

Other research findings being discussed at the meeting show that:

- Advanced neuroimaging technologies and behavioral research suggest that addiction disrupts the fine balance underlying reward, motivation, memory, and cognitive control. This research has important implications for developing therapies to treat addictive disorders (Nora D. Volkow, MD, see attached speaker's summary).
- Increasing evidence suggests chronic drug use may alter the brain's reward circuits on a genetic level, contributing to addiction. Focusing on the genetic effects of addiction may open new avenues for improved treatment (Eric J. Nestler, MD, PhD, see attached speaker's summary).

"The brain is the body's most complex organ and chemical alterations caused by drug abuse have significant overarching impact on neuroplasticity," said press conference moderator George F. Koob, PhD, of The Scripps Research Institute, an expert on addiction and stress. "Today's findings offer a better understanding of the impacts of this disease and provide a clearer approach toward treating addiction and guarding against relapse."

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

– more –

Related Presentations:

Presidential Special Lecture: **Addiction and Self-Control**
Monday, Oct. 19, 5:15–6:25 p.m., Hall B1

Special Lecture: **Transcriptional and Epigenetic Mechanisms of Drug Addiction**
Wednesday, Oct. 21, 1–2:10 p.m., Hall B1
# # #

Abstract 30.17 Summary

Lead author: Chitra Mandyam, PhD (858) 784-9039
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Chronic Voluntary Alcohol Consumption Impairs Neurogenesis

Findings suggest new therapeutic approach to alcohol addiction

A new study found that chronic alcohol consumption reduces the number of new brain cells that form in the hippocampus of adolescent rhesus monkeys. This finding suggests these cells are vulnerable to alcohol and their presence may be essential for preventing alcohol dependence. The findings were presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"We've found a potential mechanism for alcohol's harmful effects on the hippocampus and other brain regions associated with executive function and memory," said Chitra Mandyam, PhD, of the Scripps Research Institute in San Diego and lead author of the study. "This may lead to more effective medications for helping alcoholics overcome their addiction."

In this study, male rhesus monkeys (aged four to five years early in the study and five to six years at the end) were allowed to voluntarily consume a Tang-sweetened solution containing 6 percent alcohol during one-hour sessions, Monday through Friday. A control group of monkeys had similar access to alcohol-free Tang. The alcohol group consumed an average of 1.78 g/kg of alcohol per session.

After five months the primates' brain tissue was analyzed, with careful attention to sections containing the hippocampus for signs of neurogenesis. The researchers found that chronic alcohol consumption significantly altered neurogenesis in the region of the hippocampus that produces self-renewing neural stem cells. Specifically, the alcohol-consuming monkeys exhibited a 58 percent decrease in proliferation — stem cell birth — and a 63 percent decrease in differentiation and neurogenesis — stem cell survival.

"Our results demonstrate that in addition to causing existing cells to degenerate, excessive alcohol keeps new stem cells from forming," Mandyam said.

Research was supported by the National Institutes of Health.

Scientific Presentation: Saturday, Oct. 17, 1–2 p.m., South Hall A

30.17, Chronic voluntary alcohol consumption produces permanent impairment of hippocampal neurogenesis in adolescent nonhuman primates
C. D. MANDYAM, R. W. KOTZEBUE, E. F. CRAWFORD, R. D. CREAN, M. A. TAFFE; Scripps Res. Inst., San Diego, CA

TECHNICAL ABSTRACT: The adult hippocampal subgranular zone of the rodent continuously produces neural precursor cells that generate pools of proliferating progenitors which mature into functional granule cell neurons. Using endogenous markers for proliferation, differentiation and neurogenesis, we demonstrate that the young adult primate hippocampus similarly generates distinct types of proliferating progenitors that later mature into granule cell neurons. Using a model for chronic alcohol self-administration (mean of 1.78g/kg alcohol per session), we explored alcohol's effects on type 2a/2b/3 proliferating progenitors, differentiation and neurogenesis. Alcohol distinctly altered proliferation (58 % decrease) versus differentiation and neurogenesis (63 % decrease), with robust effects on neurogenesis. Mechanistic details demonstrate that the alcohol-induced reduction in hippocampal neurogenesis paralleled an increase in hippocampal neuronal degeneration which is mediated by non-apoptotic pathways. Taken together these results demonstrate that alcohol decreases the neuronal turnover in the young adult primate hippocampus which may produce spatial memory deficits seen with chronic alcoholism.

Abstract 158.4 Summary

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New Animal Research Suggests Cognitive Problems Are Direct Result of Cocaine Exposure

Finding is part of multi-year cognitive assessment study

New animal studies suggest that memory and other cognitive problems experienced by cocaine-addicted people can result directly from the cocaine abuse in addition to pre-existing traits or lifestyle factors. The findings were presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our results clearly demonstrate the negative impact that even limited access to cocaine can have on cognitive function," said senior author Charles W. Bradberry, PhD, of the University of Pittsburgh. "These findings may lead to the development of therapies for cognitive impairments as a way to improve addiction treatment."

Cocaine users display a range of cognitive deficits, including problems with decision-making, planning, and memory. The greater these deficits, the more likely treatment will fail. The current finding is part of a multi-year longitudinal study of cognitive assessment in cocaine-exposed rhesus monkeys, which offer an ideal model for study because their brain structure and function are similar to that of humans.

For the study, 14 animals were trained to perform two tasks on a touch screen. One test first assessed how well the animals learned to associate pictures with rewards and then measured cognitive flexibility by reversing high- and low-reward pictures. The other task was a visual working memory task, in which animals had to remember an abstract stimulus for varying periods of delay. After initial training they were separated into two groups, with one group self-administering cocaine on Tuesdays through Fridays. Cognitive testing for both groups was conducted on Mondays, after the cocaine-administering animals had been drug-free for about 72 hours.

The animals showed impairments in learning, cognitive flexibility, and, to a lesser degree, working memory. "The types of errors suggest that poor attention and distractibility were significant contributors to the deficits, for they were similar to those made on cognitive tasks by people with attentional deficit disorders," Bradberry said. His lab plans to investigate whether the brain mechanisms that lead to impaired attention in people with attention deficit disorders may be causing similar problems in people chronically addicted to cocaine.

Research was supported by the Veteran's Administration Medical Research Service and the National Institute on Drug Abuse.

Scientific Presentation: Sunday, Oct. 18, 11 a.m.–noon, South Hall A

158.4 Longitudinal studies of cocaine self-administration on cognition in rhesus monkeys
J. N. PORTER[1,3], A. S. OLSEN[1], K. GURNSEY[2], B. P. DUGAN[2], H. P. JEDEMA[2], **C. W. BRADBERRY**[2,4,1]; [1]Neurosci., [2]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [3]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [4]VA Pittsburgh Hlth. Services, Pittsburgh, PA

TECHNICAL ABSTRACT: Background: Cocaine users display a range of cognitive impairments, and greater deficits predict poorer treatment outcome. It is still unknown whether these deficits are pre-existing traits or the neurobiological consequences of cocaine exposure. Other factors not easily controlled for in a clinical population are polydrug use, poor diet, etc. The aim of this study was to examine effects of chronic cocaine self-administration (SA) on cognition in monkeys, an ideal model for studies of addiction related cognition. They have similar cortical structure and function and are suited to clinically relevant tasks and methods such as brain imaging approaches. Methods: We used rhesus monkeys in a longitudinal study in which 14 animals were characterized prior to assignment to matched control (n=6) and cocaine SA (n=8) groups. We used a delayed match to sample (DMS) task to assess visual working memory, and a discrimination/reversal task to assess the establishment of reward/stimuli associations and the cognitive flexibility needed to reverse them. SA took place Tues-Fri, maximum of six 0.5 mg/kg infusions separated by 10 min timeout. They performed the two cognitive tasks at biweekly intervals on Mondays, and were thus drug free for approx. 72 hours. A weekly assessment of efficacy of the water reward used for cognitive testing took place on Tues morning, with SA in a separate session Tues afternoon. All procedures utilized touch screens in sound attenuating audiometric booths. Results: Soon after initiating self-administration, deficits in the DMS and the discrimination/reversal task were observed. Overall accuracy in the DMS task was decreased in the experimental group relative to their baseline performance suggesting impaired working memory. However, there was not an interaction with delay period, suggesting

working memory alone is not impaired. There was also a delay-dependent increase in omissions, indicative of attentional deficits consistent with other evidence of attentional effects (see accompanying poster). Consistent with previous work in our lab, the experimental group showed impaired stimulus discrimination, when compared to baseline performance, and marginally significant deficits on discrimination reversal. Progressive ratio evaluation of water reward efficacy showed no change. Conclusion: These data indicate that cocaine SA causes deficits in a broad range of cognitive function. Effects on selective attention may be contributing to the breadth of effects observed. Deficits are seen very early in the course of SA, and do not appear linked to a devaluation of the reward that motivates performance on the tasks.

Abstract 346.14 Summary

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Amino Acid May Help Reduce Cocaine Cravings

Animal study may offer promising therapeutic strategy for addiction

A new study in rats has found that N-acetylcysteine (NAC), a commonly available and generally nontoxic amino acid derivative, reverses changes in the brain's circuitry associated with cocaine addiction. The reversal appears to lessen the cravings associated with cocaine, thus providing protection against relapse. The findings were presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our finding suggests a promising therapeutic strategy for cocaine addiction, for which there is no approved treatment," said lead author Khaled Moussawi of the Medical University of South Carolina in Charleston.

Cocaine is a highly addictive drug characterized by frequent relapses. Recent advances in brain imaging are helping scientists uncover what happens in the brain when an addicted person is exposed to the drug-associated "cues" that trigger craving — and lead to relapse. They've found that repeated exposure to psychoactive drugs such as cocaine causes an imbalance in the brain circuits regulating reward and cognitive control.

One of these circuits is a pathway involving the neurotransmitter glutamate. In the current study, Moussawi and his colleagues found that NAC restored normal functioning to this circuit in rats that had been previously addicted to cocaine. In addition, after receiving NAC, the previously cocaine-addicted rats did not reengage in drug-seeking behavior, even in the presence of drug-associated cues.

"Clinical trials involving people addicted to cocaine and nicotine have already suggested that N-acetylcysteine may be useful in decreasing cravings for those drugs," said Moussawi. "Our research adds support to that suggestion." A phase III clinical trial using NAC to treat cocaine addiction is currently underway.

Research was supported by the National Institute of Drug Abuse.

Scientific Presentation: Monday, Oct. 19, 9–10 a.m., South Hall A

346.14, N-acetylcysteine persistently prevents reinstatement of cocaine seeking by countermanding cocaine induced synaptic potentiation in the nucleus accumbens

K. MOUSSAWI[1], W. ZHOU[3], D. B. CARR[2], P. W. KALIVAS[2]; [2]Neurosci., [1]MUSC, Charleston, SC; [3]Ningbo Addiction Res. and Treatment Ctr., Ningbo Univ., Ningbo, China

TECHNICAL ABSTRACT: Cocaine addiction, characterized by compulsive drug seeking and increased vulnerability to relapse, ensues upon loss of the ability of prefrontal cortex (PFC) glutamatergic projections into the nucleus accumbens (NAc) to regulate motivated behavior. This is thought to be rooted in the impaired glutamate homeostasis and enduring neuroplasticity at excitatory synapses in the NAc caused by repeated exposure to cocaine. Therefore, a therapeutic strategy for cocaine addiction lies in the reversal of these neuroadaptations. Here we show that repeated N-acetylcysteine (NAC) administration restores glutamate homeostasis, reverses certain neuroadaptations at the PFC-NAc synapses, and provides enduring protection against relapse to cocaine seeking. Rats were trained to self-administer cocaine for 2 weeks, then underwent 2-3 weeks of extinction during which they received daily NAC injections (100 mg/kg, i.p.), followed by 2-3 weeks of abstinence without NAC treatments. Our results show that cues and cocaine priming failed to reinstate drug seeking in NAC treated rats even up to 3 weeks after the last NAC injection, and that NAC treatment facilitated extinction training. In addition, the behavioral effects of NAC were correlated with persistent normalization of synaptic transmission at the PFC-NAc synapses. In vivo field potential recordings in the NAc after PFC stimulation showed that NAC treatment normalized potentiated PFC-NAc synapses, a major neuroadaption by chronic cocaine. Moreover, using whole cell recordings, we demonstrated a restoration of normal AMPA/NMDA ratio and normal release probability (mini-epsc frequency) at excitatory synapses in the NAc. We also found that dendritic spine plasticity in response to cocaine was normalized by chronic NAC. Altogether, our data indicate that reversing cocaine induced plasticity at PFC-NAc synapses is a promising therapeutic strategy for cocaine addiction, and that through this action NAC provides durable protection against relapse to cocaine seeking.

Speaker's Summary

Speaker: Nora D. Volkow, MD (301) 443-6480
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Rockville, Md.

Presidential Special Lecture: **Addiction and Self-Control**
Monday, Oct. 19, 5:15–6:25 p.m., Hall B1

Advances in science have generated compelling evidence that addiction is a complex disease of the brain. Often, the first time a drug is taken it is, in fact, by choice, to achieve a pleasurable sensation or emotional state that is relatively short-lived. Repeated use of drugs of abuse, on the other hand, disturbs this ordinarily well-balanced system, disrupting what once was the addict's normal hierarchy of needs and desires and displacing it with drives centered solely around drugs. This happens because drugs activate the very same brain circuits that are triggered by events or things in our environment which have been linked to behaviors indispensable to survival such as eating, bonding, and procreating, though in more efficient ways. There are two basic mechanisms that operate in the brain to motivate these vital behaviors —pleasure and distress — and both can be hijacked by drugs. Though we seek food because eating it is pleasurable; when food is not available the mounting distress from hunger overtakes other competing drives to ensure that we focus our efforts on obtaining and consuming food. In the same way, a drug is initially sought because it produces pleasure, but with repeated use, and as addiction develops, the absence of the drug generates an even greater level of distress than hunger does, displacing other competing motivations and making all else seem irrelevant. The drug is no longer sought by the addict because of liking it (pleasure) but because of needing it (to relieve distress). The addict's drive to seek and use the drug becomes overwhelming regardless of the severity of its negative consequences. Research on the neuroscience of addiction is helping to identify specific brain changes that are responsible for such a dramatic shift. Brain imaging has been particularly useful in helping identify the brain circuits that are disrupted in addiction and how this results in the behavioral changes that characterize this disease. Brain imaging studies have shown that in the human brain just as had been reported by preclinical studies the rewarding effects of drugs of abuse depend upon their ability to induce large and very rapid upsurges in levels of a neurochemical (dopamine) that is critical to our ability to experience pleasure and to motivate behavior. These drug-induced dopamine surges mimic but greatly exceed in intensity and duration those that occur in response to everyday stimuli that typically signal pleasure, such as the sight or smell of food. However, repeated exposures to these large dopamine surges have an insidious consequence — they reduce the normal dopamine bursts that activate frontal areas of our brain responsible for assigning value to stimuli. This results in neuroadaptations in the connections of the frontal cortex with the limbic brain (glutamatergic efferents) and behaviorally in an enhanced value placed on stimuli associated with the drug and a reduced value given to the natural rewards of everyday life. These frontal brain regions also normally allow us to exert inhibitory control over our desires and emotions and their dysfunction in the addicted person impairs this process. If "self control" is the ability to consciously choose our actions and act accordingly, then when the areas of the brain responsible for this complex function become disrupted, just as the damaged heart can no longer propel blood to our bodies, the damaged brain can no longer propel nerve impulses to control our desires and emotions. Behavior becomes reflexive and much less amenable to cognitive interference. Like any other medical disorder that impairs the function of vital organs, repair and recovery of the addicted brain depends upon targeted and effective treatments that must address the complexity of the disease, the brain circuitry that has been changed, and the behavioral manifestations that result. Discovery of these disruptions in the fine balance that normally exists between brain circuits underling reward, motivation, memory, and cognitive control are leading to the design of new and improved pharmaceutical, behavioral and combined treatments for drug addiction.

Speaker's Summary

Speaker: Eric J. Nestler, MD, PhD (212) 659-5656
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Special Lecture: **Transcriptional and Epigenetic Mechanisms of Drug Addiction**
Wednesday, Oct. 21, 1–2:10 p.m., Hall B1

Drug addiction can be viewed as a stable form of drug-induced neural plasticity, whereby long-lasting changes in gene expression mediate some of the stable behavioral abnormalities that define an addicted state. Our laboratory has focused on two main transcriptional pathways in addiction. Chronic exposure to cocaine or opiates causes the prolonged activation of the transcription factor CREB within the brain's reward circuits and several other brain regions, and this adaptation mediates aspects of drug tolerance and dependence. In contrast, induction of another transcription factor, DeltaFosB, in brain reward regions by virtually all drugs of abuse exerts the opposite effect and contributes to sensitized responses to drug exposure.

Studies are underway to explore the detailed molecular mechanisms by which CREB and DeltaFosB regulate target genes and thereby contribute to the complex state of addiction. One way to approach such molecular mechanisms of drug action in vivo is through the study of chromatin remodeling, that is, changes in the acetylation or methylation of histones that bind to certain drug-regulated gene promoters, or changes in methylation of the promoters themselves, as revealed by chromatin immunoprecipitation (ChIP). We are utilizing ChIP to examine chromatin changes at specific candidate genes for CREB and DeltaFosB, as well as genome-wide measures to gain a more global view of target genes for these transcription factors. Prominent among these targets are those that regulate synaptic function and plasticity as well as the morphology of drug-regulated neurons. We have also demonstrated drug regulation of some of the enzymes that catalyze chromatin modifications, which indicates that chromatin remodeling mechanisms are themselves important targets of drug action.

These findings establish chromatin remodeling as an important regulatory mechanism underlying drug-induced neural and behavioral plasticity, and provide fundamentally new insight into how CREB and DeltaFosB, and several other drug-regulated transcription factors, contribute to addiction by regulating the expression of specific target genes in the brain's reward circuitry. These advances can now be mined to develop improved diagnostic tests and treatments for addictive disorders.