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Contacts: Emily Ortman, (202) 962-4090
Anne Nicholas, (202) 962-4060

New Insights Into How Stress and Other Factors Increase Risk of Drug-Addiction Relapse

Findings offer promising new leads for better understanding of brain health and addiction

CHICAGO — Researchers are uncovering new evidence about how stress and other factors lead to brain changes that increase the risk of relapse from a cocaine addiction. These findings have potential implications for the development of more effective treatments for cocaine and other drug addictions, which affect millions of people around the world. The research was presented at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Currently, there are no effective pharmacological therapies for cocaine or other drug addictions, and existing rehabilitation programs have low success rates. The National Institute on Drug Abuse estimates that up to 60 percent of Americans who undergo treatment for drug addictions experience a relapse within a year.

Today's new findings show that:

- People with a history of physical, emotional, or sexual abuse exhibit heightened brain responses to drug-related visual cues, a factor that may increase their risk of drug-addiction relapse (Paul Regier, abstract 315.05, see attached summary).
- Withdrawal from cocaine triggers an overexpression of certain molecules within neurons in mice, which increases cocaine-seeking behavior (Michael Cahill, abstract 506.14, see attached summary).
- Chronic stress during early withdrawal from cocaine addiction intensifies subsequent drug cravings in rats, making relapse more likely (Jessica Loweth, abstract 315.20, see attached summary).
- Stimulating a specific reward pathway in the brain decreased drug relapse without affecting mood in rats (Amy Loriaux, abstract 51.10, see attached summary).

"Changes in brain circuitry caused by stress and other factors play an important and incredibly complex role in the development of drug addiction — and in the frustratingly difficult process of overcoming an addiction," said Peter Kalivas, PhD, chair of the Department of Neuroscience at the Medical University of South Carolina. "These latest findings are deepening our understanding of the brain circuitry underlying drug addiction and suggesting new possibilities for more effective preventions and treatments."

This research was supported by national funding agencies such as the National Institute on Drug Abuse, as well as other private and philanthropic organizations. Find out more about the neurobiological mechanisms that underlie drug addiction at *BrainFacts.org*.

Related Neuroscience 2015 Presentation:
Symposium: Novel Ideas and Tools to Enhance the Neurobiological Study of Drug Addiction with an Eye Toward Intervention Development and Biomarker Identification
Tuesday, Oct. 20, 1:30-4 p.m., S100 B

Abstract 315.05 Summary

Lead author: Paul Regier (215) 222-3200
University of Pennsylvania pregier@mail.med.upenn.edu
Philadelphia

History of Abuse May Heighten Risk of Drug-Addiction Relapse

Findings may help scientists develop targeted treatments

People with a history of physical, emotional, or sexual abuse may have a heightened brain response to drug-related visual cues that puts them at greater risk of relapse, according to research released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. This finding could help lead to more effective interventions for treating drug addiction.

"Our study provides direct evidence that a history of abuse may have an impact on the brain that is linked to relapse," said lead author Paul Regier of the University of Pennsylvania. "It may also help explain why individuals with a history of abuse are two to three times more likely to develop a substance-abuse disorder than the general population."

For the study, Regier and his colleagues used functional magnetic resonance imaging (fMRI) to observe the brain activity of 25 individuals addicted to cocaine while they were exposed to four types of visual cues: sexual, cocaine-related, averse, and neutral. Eleven of the participants had experienced some kind of abuse in their past; the other 14 had no history of abuse. The imaging revealed that the cocaine-related cues (but not the others) elicited significantly more brain activity among the participants with a history of abuse. The increased activity was most pronounced in the mesolimbic pathway of the brain, a reward pathway that plays a central role in addiction.

"This finding suggests that patients with a history of abuse have an added challenge during their recovery from drug addiction," Regier said. "But knowing this information may also lead us to much more effective behavioral or pharmacologic interventions for their drug addiction — ones that may help us mitigate the impact of the abuse on the brain, thus improving the odds of recovery."

Research was supported with funds from the National Institute on Drug Abuse.

Scientific Presentation: Monday, Oct. 19, 8-9 a.m., Hall A

315.05, A history of physical, emotional, or sexual abuse predicts higher mesolimbic response to drug cues in cocaine-dependent patients
***P. REGIER**[1], Z. A. MONGE[1], J. J. SUH[1], K. JAGANNATHAN[1], Z. WANG[1], J. F. MAGLAND[2], A. TEITELMAN[3], T. R. FRANKLIN[1], R. R. WETHERILL[1], K. YOUNG[1], M. J. GAWRYSIAK[1,4], D. D. LANGLEBEN[1], C. P. O'BRIEN[1], A. R. CHILDRESS[1];
[1]Psychiatry, [2]Radiology, [3]Sch. of Nursing, [4]VA Med. Ctr., Univ. of Pennsylvania, Philadelphia, PA

TECHNICAL ABSTRACT: **Aims:** Previous studies have reported that a history of adverse experiences is associated with higher rates of mental health issues, including addiction. Here, we investigated whether a history of physical, emotional, or sexual abuse in cocaine-dependent patients was associated with greater cocaine cue-triggered activity in nodes of the mesolimbic reward circuitry. **Methods:** Treatment-seeking cocaine-dependent patients (n=26) were recruited as part of a 6-month treatment study. Before the start of the study, participants were administered the Addiction Severity Index (ASI), which contains questions measuring prior abuse (emotional, physical, or sexual). After inpatient stabilization, participants were scanned with event-related blood-oxygen-level-dependent functional MRI during exposure to brief (500 msec) evocative (cocaine, sexual, aversive) vs. neutral cues. Forty-eight images of each cue type were presented in a quasi-random order. Imaging preprocessing (alignment, registration, normalization, smoothing, and motion correction) and first level analysis were conducted within a standard SPM8 pipeline. The responses to the abuse questions were used to create a split (abuse yes - abuse no) for the *cocaine-neutral* cue contrast. **Results:** From the ASI, there were 12 patients that reported a history of abuse and 14 that reported no abuse. As predicted, patients reporting abuse had greater brain activation to the cocaine (vs. neutral) cues in several mesolimbic regions, including the midbrain (VTA), ventral striatum, dorsal striatum, and caudal orbitofrontal cortex to drug cues compared to patients reporting no abuse ($2<t<5$). **Conclusions:** Individuals with adverse life events have been found to be more susceptible to drug addiction. In our study, even though all patients were cocaine dependent, our results provide initial evidence that a history of abuse could have a brain impact (i.e., heightened limbic response to drug cues) that drives drug seeking. Our results highlight heterogeneity within a cocaine-dependent population, indicating the need for individually tailored treatment. Importantly, to our knowledge, this is the first evidence of a history of abuse on brain vulnerability that is linked to relapse.

Abstract 506.14 Summary

Lead author: Michael E. Cahill, PhD 630-880-3970
Icahn School of Medicine at Mount Sinai michael.cahill@mssm.edu
New York

Molecules in Brain's 'Pleasure Center' Linked to Cocaine Relapse

Findings may lead to more effective approaches for preventing relapse

Scientists have identified molecules in the brain's "pleasure center" that may play a role in cocaine withdrawal and relapse, offering new insights into the neurobiological mechanisms of addiction. The research was released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest sources of emerging news about brain science and health.

Cocaine is among the most abused addictive substances in the United States. An estimated 1.4 million Americans are currently addicted to the drug, and cocaine addicts have a high incidence of lifetime relapse.

Previous research has shown that short-term cocaine withdrawal increases the formation of new dendritic spines on neurons in the nucleus accumbens, a "pleasure center" region of the brain known to play an important role in addiction-associated drug-seeking behavior. Neurons use dendritic spines to communicate with each other, so the spines' number and shape are crucial.

For this study, the researchers first identified molecules whose expression level is increased in dendritic spines of mice during short-term cocaine withdrawal. They then forced these specific molecules to overexpress in the nucleus accumbens of mice. This not only resulted in an increase in the number of dendritic spines, but also caused an increase in cocaine-seeking behavior. One of these molecules, Rap1b, belongs to a class of proteins that regulate the growth and structure of dendritic spines.

"By mimicking the overexpression of Rap1b that occurs during cocaine withdrawal, we were able to produce a similar level of dendritic spine growth — and increase the cocaine-seeking behavior of the mice," said lead author Michael Cahill of the Icahn School of Medicine at Mount Sinai in New York.

Cahill and his colleagues also discovered that the same molecules that overexpressed early in the withdrawal period were under-expressed a month later. Reproducing this reduced expression of the molecules in a new group of mice led to a decrease in the formation of dendritic spines in the nucleus accumbens— and a reduction in cocaine-seeking behavior.

"Our study identifies molecules that appear to have functions that both contribute to and prevent relapse from cocaine addiction," Cahill said. "This finding suggests that the anti-relapse function — the decreased expression of molecules in long-term withdrawal — may not be working properly in cocaine addicts who experience relapse."

Research was supported with funds from the National Institute on Drug Abuse.

Scientific Presentation: Tuesday, Oct. 20, 9-10 a.m., Hall A

506.14, Cocaine augments local synaptic translation in the nucleus accumbens through a small GTPase network

***M. E. CAHILL**[1], R. C. BAGOT[1], D. WALKER[1], J. FENG[1], H. SUN[1], J. KOO[1], R. NEVE[2], A. GANCARZ[3], G. L. SCHROEDER[3], Z. WANG[3], D. M. DIETZ[3], E. J. NESTLER[1];
[1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Massachusetts Insititute of Technol., Cambridge, MA; [3]SUNY Buffalo, Buffalo, NY

TECHNICAL ABSTRACT: Dendritic spines are the sites of most excitatory synapses in the central nervous system, and withdrawal from drugs of abuse alters the density and morphology of dendritic spines on medium spiny neurons (MSNs) of the nucleus accumbens (NAc), a primary reward region. Members of the Rho subfamily of Ras-like small GTPases are critical regulators of spine morphogenesis in MSNs, and guanine nucleotide exchange factors (GEFs) directly activate small GTPases. Our studies indicate that early withdrawal from both investigator-administered and self-administered cocaine increases the synaptic expression of the Rap1 small GTPase in the NAc. Conversely, late withdrawal from cocaine decreases synaptic NAc Rap1 levels. To date, no downstream effectors of Rap1 in NAc MSNs have been identified, and here we characterize a novel role for Rap1 in stimulating the activity of an AKT/mammalian target of rapamycin (mTOR) local translation network within dendritic spines. Via viral-mediated gene transfer and pharmacological manipulations, we found that altered Rap1-AKT-mTOR signaling controls NAc spine morphogenesis with resulting time-dependent effects on cocaine-mediated behavioral reward. Using optogenetic methods we dissected the excitatory inputs to the NAc that regulate Rap1-AKT-mTOR signaling. These optogenetic studies revealed a specific role for prefrontal cortex (PFC) to NAc projections in increasing synaptic Rap1-AKT-mTOR activity, and we found that PFC terminal stimulation in the NAc increases behavioral reward through Rap1. Our recent work has identified specific proteins that are locally synthesized in NAc synaptosomal fractions through mTOR, and current studies are aimed at determining how these locally formed proteins regulate cocaine-mediated spine morphogenesis and behavioral reward.

Abstract 315.20 Summary

Lead author: Jessica Loweth, PhD (773) 383-0650
Rosalind Franklin University of Medicine and Science jessica.loweth@rosalindfranklin.edu
North Chicago, Ill.

Chronic Stress Intensifies Cocaine Cravings in Rats After Withdrawal

Findings may lead to more effective therapies for preventing relapse

Chronic stress during early withdrawal from cocaine addiction can intensify subsequent drug cravings, making relapse more likely, according to animal research released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The National Institute on Drug Abuse estimates that up to 60 percent of Americans who undergo treatment for cocaine or other drug addictions experience a relapse within a year. "Studies have shown that people who experience chronic adverse life events are particularly vulnerable to relapse, although the interactions between chronic stress and drug withdrawal at the cellular level are not well understood," said lead author Jessica Loweth of the Rosalind Franklin University of Medicine and Science.

To study the effect of chronic stress on relapse vulnerability, Loweth and her colleagues first trained rats to self-administer cocaine for 10 days. Each infusion of cocaine was accompanied by a light cue so that, over time, the rats learned to associate the light with cocaine availability. The rats then underwent forced abstinence from cocaine and were divided into two groups for separate experiments designed to model chronic stress. In one experiment, half the rats were fed a mildly restricted amount of food, while the other half were free to eat whatever they wanted. In a second experiment, half the rats were restrained for 20 minutes once a day for seven days, while the others were allowed to move about freely in a normal cage. On the first day after self-administration ended and again two weeks later, the rats in both experiments were tested to see how strongly they sought cocaine in response to light cues. All the animals, including those in the control groups, exhibited a greater desire for cocaine than they had on the first day they had lost access to the drug — evidence of "incubation," the progressive intensification of drug craving that occurs during withdrawal. Interestingly, the animals in the stressed groups showed stronger intensification of cravings for cocaine than the controls.

"This finding suggests that exposure to chronic stress may intensify incubation of craving after drug withdrawal — and make it more likely that individuals will experience a relapse," Loweth said. "The next step is to try to figure out how to reverse this effect."

Research was supported with funds from the National Institute on Drug Abuse.

Scientific Presentation: Monday, Oct. 19, 11 a.m.-noon, Hall A

315.20, Chronic stress exposure during early withdrawal from extended access cocaine self-administration facilitates incubation of cue-induced cocaine craving
***J. A. LOWETH**[1], R. M. GLYNN[1], J. A. ROSENKRANZ[2], M. E. WOLF[1];
[1]Neurosci., [2]Cell. and Mol. Pharmacol., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

TECHNICAL ABSTRACT: A major challenge for treating cocaine addiction is the propensity for abstinent users to relapse. Two important triggers for relapse are cues associated with prior drug use and stressful life events. Human studies indicate that exposure to chronic adverse life events is associated with increased relapse vulnerability, indicating a need for animal models that explore interactions between chronic stress and drug withdrawal. However, the majority of studies investigating stress-induced relapse vulnerability have examined the effects of acute stressors on the reinstatement of previously extinguished drug seeking behavior, a model which may not accurately depict the situation of addicts, who typically do not undergo extinction training and may relapse after a long drug-free period. To study the effect of chronic stress on withdrawal-dependent changes in relapse vulnerability, we used the incubation model of craving and relapse in which cue-induced drug seeking progressively intensifies ("incubates") during withdrawal from extended-access cocaine self-administration. Food restriction or repeated restraint stress were used as chronic stressors. Rats self-administered cocaine under extended-access conditions (6 h/d for 10 d) that have been shown to produce incubation of craving. On the day after the last self-administration session [withdrawal day (WD) 1], rats received a test for cue-induced cocaine seeking, during which nose-pokes resulted in presentation of the light cue but not cocaine. Rats were then divided into 2 groups destined for either control or stress conditions. In the food restriction studies, rats underwent a 2 week period of mild, chronic food restriction stress starting on WD2 (body weight maintained at 90% of their baseline weight). Control rats had ad libitum access to food. On WD15, rats underwent a second seeking test. In the repeated restraint studies, rats underwent 7 daily restraint sessions (20 min) over a 9 day period from WD6 to WD14 and received a seeking test on WD15, a day after the last repeated restraint session. Controls were placed in a cage with bedding on the same schedule. As expected, we found that controls showed greater cue-induced cocaine seeking on WD15 compared to WD1 (i.e. incubation of craving). Interestingly, rats in both stress groups showed a more robust increase in seeking on WD15, indicating acceleration or facilitation of incubation. Separate studies showed that the enhanced cocaine seeking observed was due to chronic and not acute stress. These data indicate that chronic stress during early withdrawal facilitates incubation of cocaine craving, which is thought to contribute to enhanced relapse vulnerability.

Abstract 51.10 Summary

Lead author: Amy Loriaux, PhD (214) 648-5164
University of Texas Southwestern Medical Center amy.loriaux@utsouthwestern.edu
Dallas

Activating Specific Brain Pathway Decreases Addictive Behavior in Rats Without Affecting Mood

Discovery may lead to targeted treatments for drug addiction

Stimulating a specific pathway in the brain can decrease drug relapse without producing depressive episodes commonly seen in withdrawal, according to new animal research released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Addiction and depression are strongly linked, and withdrawal from chronic drug use is often marked by depressive episodes," said lead author Amy Loriaux of the University of Texas Southwestern Medical Center. "Drug relapse may be a form of self-medication for the depression."

Using rats addicted to cocaine, the researchers employed optogenetic technology to selectively activate a neural pathway that extends from the nucleus accumbens to the ventral pallidum, two brain structures that help modulate mood and the rewarding properties of addictive drugs and other stimuli. Activating the pathway significantly decreased the rats' willingness to work for cocaine, as demonstrated by how many times the animals pressed levers on the cocaine-delivery apparatus in their environment. The pathway activation did not appear to have an effect on mood-related behavior, as measured by the rats' willingness to escape a forced swim test or their interest in a pleasurable sugar stimulus.

This response was in stark contrast to the effect that optogenetic activation has on another important reward pathway in the brain, which projects from the nucleus accumbens to the lateral hypothalamus. Previous animal studies by these researchers demonstrated that activation of the lateral hypothalamus pathway promotes both addiction and depression.

The results of this research offer a clearer picture of the reward circuitry in the brain, suggesting that various outputs from the nucleus accumbens mediate pro- and anti-addictive properties.

"Our findings may lead to innovative treatments that target specific brain pathways," Loriaux said. "For example, a treatment that selectively stimulates the nucleus accumbens-ventral pallidum pathway might decrease cocaine craving without having a deleterious side effect on mood or on motivation for natural rewards, such as food."

Research was supported with funds from the National Institute on Drug Abuse.

Scientific Presentation: Saturday, Oct. 17, 2-3 p.m., Hall A

51.10, The role of projections from the nucleus accumbens shell to the ventral pallidum in mood and motivation for cocaine
***A. L. LORIAUX**, D. W. SELF;
Dept. of Psychiatry, UT Southwestern Med. Ctr., Dallas, TX

TECHNICAL ABSTRACT: Cocaine users often cite negative affect as a key factor behind relapse. However, the relevant neurocircuitry behind mood and motivational changes in cocaine addiction, and their relationship to one another, is not fully understood. We have recently shown that selective stimulation of nucleus accumbens shell (NAcSh) neural projections to the lateral hypothalamus (LH) increases motivation for cocaine, while producing depression-like despair in rats trained to self-administer cocaine. Global stimulation of NAcSh cell bodies also produces despair, but decreases motivation for cocaine, suggesting that other NAcSh outputs may override the motivational effects of NAcSh-LH terminal stimulation. Activity in NAc projections to ventral pallidum (VP) has been associated with depressed mood in drug naïve animals, but with conflicting effects on the motivation for cocaine. In the present study, we used a target-specific optogenetic approach to selectively activate NAcSh projections to the VP in male rats. We tested the hypothesis that increased activity in the NAcSh-VP depresses both mood and motivation for cocaine, and, thus, is behaviorally differentiated from the effects of NAcSh-LH projections. Rats were bilaterally injected with either AAV2-hSyn-hChR2(H134)-EYFP or AAV2-hSyn-EYFP control virus into the NAcSh, and implanted with optic fibers in the terminal fields of the NAcSh in the VP. Rats were trained to self-administer intravenous cocaine (0.5 mg/kg/infusion, i.v.) 4 h/day for 3 weeks. We measured the effect of laser stimulation of the NAcSh-VP pathway (30 min pretreatment, 10 sec/min, 20 Hz, 50 mW) on motivation for cocaine as assessed by 1) performance on a progressive ratio (PR) schedule of reinforcement for cocaine, 2) drug-paired lever presses under extinction conditions and 3) cocaine-primed reinstatement. We measured behavioral despair and anhedonia with the forced swim and sucrose preference tests, respectively. Optogenetic stimulation of NAcSh-VP terminals significantly decreased the effort to self-administer cocaine in ChR2 animals compared to eYFP controls, as indicated by 43.6% lower breakpoints. ChR2 animals also had a 43.6% reduction in lever presses during early extinction and a 32.9% decrease during reinstatement compared to eYFP controls. However, in contrast to global stimulation of the NAcSh, we found no differences in measures of immobility in the forced swim test, or a difference in preference for a 1% sucrose solution. These findings suggest that activity in the NAcSh-VP circuit may decrease motivation for cocaine independent of changes in mood, and thus may serve as a possible neural substrate for addiction treatment.