

### Research News

#### **Contingency Management Helps Pregnant Women Abstain From Smoking**

Voucher-based reinforcement therapy (VBRT), in which participants may earn vouchers redeemable for retail goods and services for sustained abstinence from drug use, has shown promise in the treatment of a wide range of substance use disorders. In a randomized, controlled trial study, researchers funded in part by NIDA investigated the efficacy of abstinence-contingent vouchers for promoting cessation of cigarette smoking among pregnant women. Researchers recruited 82 women who were current cigarette smokers and less than 20 weeks pregnant (by self-estimation) and randomly assigned them to either the VBRT or control group (5 women withdrew from the study and thus were not included in the analyses). In the VBRT group, vouchers were earned for biochemically verified smoking abstinence (negative breath and urine samples submitted during clinic visits); women in the control group received vouchers at each test visit, regardless of their test results. Testing (and availability of vouchers) for both groups continued through the 12th week after delivery. Researchers found that women in the VBRT group achieved an average of almost 10 weeks of continuous abstinence from smoking, compared to 2 weeks for women in the control group. A greater percentage of women in the VBRT group (24 percent) than in the control group (3 percent) were also able to maintain abstinence throughout the third trimester of their pregnancy. Fetal development was also monitored during the study via ultrasound examination. Estimated fetal weight was significantly greater in the VBRT group compared to the control group, although the mean birthweight was not significantly different between the groups. "These results, coupled with those from previous trials provide compelling evidence supporting the efficacy of VBRT for promoting smoking cessation among pregnant women," conclude the authors.

Heil SH, Higgins ST, Bernstein IM, Solomon LJ, Rogers RE, Thomas CS, Badger GJ, Lynch ME. Effects of voucher-based incentives on abstinence from cigarette smoking and fetal growth among pregnant women. *Addiction*. 2008;103(6):1009-1018.

#### **Higher Prevalence of Sexual Risk Behavior Found in Teens Not Attending College**

In a study of 865 teenagers in the fall after their high school graduation, researchers funded by NIDA found that teens who went on to college (either on 2-year or 4-year programs) had a lower prevalence of sexual risk behavior (SRB) than those who did not, regardless of whether they still lived with their parents or had moved out on their own. The teenagers were all participants in the Raising Healthy Children project, a longitudinal study of students in a suburban Washington State school district, and had been followed by the researchers since the first or second grade. Using questionnaires and interviews, the researchers determined that about 23 percent of the college students reported using condoms inconsistently, compared to about 35 percent of teens not in college; about 15 percent of college students reported engaging in casual sex, compared to about 29 percent of teens not in college; and about 5 percent of college students reported engaging in high-risk sex (defined mainly as a combination of casual and unprotected sex), compared to about 16 percent of teens not in college. Although a large proportion of college students engaged in SRB, the prevalence was lower than among nonstudents. Interestingly, this difference could be explained by prior risk behavior and academic performance in high school. "College students in this sample reported lower rates of SRB largely because they were more likely to do well in school and less likely to use drugs and to engage in SRB during high school. Thus, patterns of behavior that had been established in high school were continued in the fall after high school," explain the authors. Prevention efforts targeting a reduction in substance use and SRB, and improving

academic performance during high school “should result in reductions in the prevalence of SRB in the transition to adulthood,” they conclude.

Bailey JA, Fleming CB, Henson JN, Catalano RF, Haggerty KP. Sexual risk behavior 6 months post-high school: Associations with college attendance, living with a parent, and prior risk behavior. *J Adolesc Health*. 2008;42(6):573–579.

### **Lofexidine Reduces Opioid Withdrawal Symptoms**

Medications such as methadone and buprenorphine are effective in helping drug-dependent individuals detoxify from heroin, morphine, and other opioid drugs. These medications are also opioids, however, and some individuals undergoing therapy for opioid addiction might prefer treatment with nonopioid medications. Investigators funded by NIDA performed a randomized, placebo-controlled trial of lofexidine, a nonopioid medication that has shown promise in the treatment of opioid withdrawal. The investigators enrolled 68 participants addicted to heroin, morphine, or hydromorphone into the study. After a 3-day period where all patients were placed on a fixed dose of morphine, investigators randomly assigned the patients either to 5 days of lofexidine treatment or to the placebo control group. Patients receiving lofexidine had fewer and less severe withdrawal symptoms than those receiving the placebo—this difference was so substantial that the trial was stopped early, as it was deemed unethical to continue giving patients the placebo in light of the benefits of lofexidine. Patients in the lofexidine group experienced more side effects such as loss of strength, dizziness, low blood pressure, and trouble sleeping; however, fewer patients in the lofexidine group discontinued treatment prematurely compared to the placebo group. “As a detoxification agent, lofexidine would represent a considerable advance over other detoxification medications currently approved for this use...because it is not a narcotic and is not considered to be an addictive drug,” conclude the authors.

Yu E, Miotto K, Akerele E, Montgomery A, Elkashef A, Walsh R, Montoya I, Fischman MW, Collins J, McSherry F, Boardman K, Davies DK, O'Brien CP, Ling W, Kleber H, Herman BH. A Phase 3 placebo-controlled, double-blind, multi-site trial of the alpha-2-adrenergic agonist, lofexidine, for opioid withdrawal. *Drug Alcohol Depend*. 2008;97(1–2):158–168.

### **Dopamine Helps Balance Striatal Synaptic Plasticity**

Neurotransmitters, or brain chemicals, play a key role in the long-term changes that allow a brain to adapt continuously in response to experience. This hinges on the ability of neurotransmitters to change the efficiency with which neurons communicate with one another. In the striatum, a brain region critically involved in certain types of learning, dopamine is the main chemical responsible for tuning the efficiency of this communication up and down. Two types of dopamine receptors (D1 and D2) were previously thought to have completely opposite functions in this process, whereby D1- and D2-expressing neurons could only tune the strength of the connections either up or down, respectively. A new study funded in part by NIDA dispels that notion, demonstrating that conditions in the local brain environment can make it possible for both cell types to carry out either function, thereby resolving a long-standing scientific puzzle. Drugs of abuse can elevate dopamine to abnormally high levels and disrupt the carefully balanced actions of dopamine and other neurotransmitters in the striatum. This study reveals a mechanism by which exposure to drugs can corrupt the adaptive training of neural circuits and lead to the deleterious learned behaviors that characterize addiction. A better understanding of the molecular processes that regulate this type of learning may bring to light novel strategies to weaken these behaviors and provide new targets for treatment development.

Shen W, Flajolet M, Greengard P, Surmeier DJ. Dichotomous dopaminergic control of striatal synaptic plasticity. *Science*. 2008;321(5890):848–851.

### **Substance Abusers' Brains Hypersensitive to Normal Rewards**

The ventral striatum (VS) is an area of the brain that is known to be highly sensitive to cues associated with drug use. Scientists are unclear, however, about how neurons in the VS of substance-dependent (SD) individuals respond to cues associated with other forms of reward. To better understand how these neurons respond to non-drug-related rewards, researchers led by a NIDA investigator performed functional magnetic resonance imaging (fMRI) on treatment-seeking alcohol-dependent patients—most of whom also had a history of abuse or dependence on drugs other than alcohol—and nonaddicted control subjects while they played a money-based reward game. During the game, all participants—23 alcohol-dependent and 23 control participants—had the potential to win a small monetary reward (50 cents), win a larger monetary reward (5 dollars), receive no reward, or lose 5 dollars based on their ability or failure to respond to certain stimuli

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presented during the game. Before each trial began, participants were told what amount of money they could win or lose. Overall, SD participants responded to targets faster than controls, regardless of the amount of the incentive. Compared to controls, SD participants also showed significantly increased activation of the VS when notified of a reward during the game. Conversely, the VS was less active when SD patients were notified that they failed to win money, or when they won money but were instructed to play additional rounds before they could receive their reward (reward delay). While brain activity in anticipation of winning or losing money was similar between groups, the VS of SD subjects were highly responsive to the actual outcomes. Whether these differences are a result of chronic alcohol or drug abuse or predisposing risk factors will need to be clarified with future research.

Bjork JM, Smith AR, Hommer DW. Striatal sensitivity to reward deliveries and omissions in substance dependent patients. *Neuroimage*. 2008;42(4):1609–1621.

### **Increased Hormone Processing in the Brain May Result in Transition From Drug Use to Drug Abuse**

Both neurotransmitter and hormone systems contribute to the altered brain states associated with drug abuse. Little is known, however, about how drug intake—whether acute or chronic—regulates levels of enzymes that control the processing of larger, inactive prohormones into smaller, active hormone forms. Investigators funded in part by NIDA have performed a study examining the effects of chronic and acute morphine exposure on levels of the proteins PC1/3 and PC2, which activate several important hormones, and P-CREB, which regulates the expression of PC1/3 and PC2. In the study, researchers exposed rats to morphine for either 24 hours (acute exposure) or 7 days (chronic exposure) and compared brain levels of PC1/3, PC2, and P-CREB to control rats that were not exposed to morphine. Researchers found that levels of all three of the proteins were more pronounced in the hypothalamus, a part of the brain that plays an important role in addiction, following chronic morphine treatment. On the other hand, acute morphine exposure decreased protein levels. In order to determine if changes in PC1/3 and PC2 protein levels can directly affect the synthesis of biologically active hormones, the researchers measured levels of the hormone pro-thyrotropin-releasing hormone (TRH) after exposure to morphine—PC1/3 and PC2 convert TRH into its active form. Chronic morphine exposure, compared to acute exposure, significantly increased brain TRH levels. The authors suggest that after long-term drug use, compensatory changes in the synthesis of neurohormones could be part of the brain's way of adjusting to its new environment. "The down-regulation of PC1/3, PC2 and P-CREB by short-term morphine and up-regulation by long-term morphine treatment may be a signal mediating the switch from drug use to drug abuse," explain the authors.

Espinosa VP, Liu Y, Ferrini M, Anghel A, Nie Y, Tripathi PV, Porche R, Jansen E, Stuart RC, Nilni EA, Lutfy K, Friedman TC. Differential regulation of prohormone convertase 1/3, prohormone convertase 2 and phosphorylated cyclic-AMP-response element binding protein by short-term and long-term morphine treatment: Implications for understanding the "switch" to opiate addiction. *Neuroscience*. 2008;156(3):788–799.

### **Defects in Dopamine-Regulating Mechanisms Found in Obese Rats**

Dopamine signaling pathways in the brain help mediate the feelings of enjoyment associated with eating. To better understand whether changes in the brain's dopamine circuitry contribute to obesity, investigators funded in part by NIDA measured dopamine signaling, synthesis, and packaging within the brain in rats prone to obesity versus obesity-resistant rats. At 15 weeks of age, obesity-prone rats ate 14 percent more food and weighed 20 percent more than obesity-resistant rats. Dopamine levels in the nucleus accumbens, a part of the brain associated with addiction, of obesity-prone rats were twofold lower compared to obesity-resistant rats. Changes in dopamine levels in several brain areas also were accompanied by significant decreases in dopamine signaling (which reflects release of dopamine from its neurons) in obesity-prone rats compared to obesity-resistant rats. Interestingly, similar differences were observed in the brains of 4-week-old obesity-prone and obesity-resistant rats, even though their body weights were not yet significantly different. Further, experiments in neurons taken from neonates showed that lower dopamine levels in obesity-prone rats were present at birth. Finally, genetic experiments showed that obesity-prone rats had lower levels of genes encoding for several proteins involved in dopamine synthesis, packaging of dopamine into vesicles in neurons, and dopamine signaling. "This report represents the first demonstration that there are impairments in all midbrain dopamine systems in obesity-prone rats and that these deficiencies are distinctly in place early in postnatal life," state the authors. Their results "underscore the importance of motivational and hedonic pathways in...the regulation of appetite and feeding behavior."

Geiger BM, Behr GG, Frank LE, Caldera-Siu AD, Beinfeld MC, Kokkotou EG, Pothos EN. Evidence for defective mesolimbic dopamine exocytosis in obesity-prone rats. *FASEB J*. 2008;22(8):2740–2746.

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## Cocaine-Induced Cellular Stress Inhibits Neural Development

Cocaine use during pregnancy is known to have negative effects on neural progenitor cells, the cells that will eventually develop into neurons. However, the mechanisms by which cocaine interferes with the process whereby cells replicate (the cell cycle) are not completely understood. Researchers, who were funded in part by NIDA, found that in cultured human fetal cells and rat primary neural progenitor cells, cocaine inhibited cells from dividing near the beginning of the cell cycle and that a protein, cyclin A, played an important role in how cocaine inhibited the cell cycle. Levels of this protein were reduced in fetal rats exposed to cocaine in the early and middle stages of neurogenesis, the process through which neurons are created. When the researchers exposed cells first to cyclin A and then to cocaine, they no longer saw a decrease in cell division/replication. Experiments in cells further showed that cocaine metabolism induced the production of reactive oxygen species—a marker of cellular stress—resulting in a reduction in cyclin A. Interestingly, the medication cimetidine, which is used to treat stomach ulcers, reversed the down-regulation of cyclin A and the inhibition of neural progenitor cell proliferation in fetal rats when given to the pregnant rats before cocaine injection.

While the full extent of the effects of prenatal cocaine exposure on a child are not completely known, scientists now are finding that exposure to cocaine during fetal development may lead to subtle yet significant deficits in some aspects of cognitive performance, information processing, and attention to tasks—abilities that are important for the realization of a child's full potential. Therefore, understanding how cocaine exposure *in utero* affects developing neurons is important for developing prevention and treatments strategies to combat the problems that can result from exposure to cocaine during gestation.

Lee CT, Chen J, Hayashi T, Tsai SY, Sanchez JF, Errico SL, Amable R, Su TP, Lowe RH, Huestis MA, Shen J, Becker KG, Geller HM, Freed WJ. A mechanism for the inhibition of neural progenitor cell proliferation by cocaine. *PLoS Med.* 2008;5(6):e117.

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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>. To order publications in English or Spanish, call NIDA's new *DrugPubs* Research Dissemination center at 1-877-NIDA-NIH (1-877-643-2644) or 240-645-0228 (TDD), or fax or e-mail requests to 240-645-0227 or [drugpubs@nida.nih.gov](mailto:drugpubs@nida.nih.gov).

(58)



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