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NewsScan
NIDA ADDICTION RESEARCH NEWS

NEWS UPDATE

NIDA News

Research Yields New Insights into Molecular Markers of Addiction

Building on previous research using microarrays that identified more than 400 human genes affected by long-term cocaine abuse, researchers at the Yerkes Regional Primate Research Center at Emory University have shown for the first time that long-term use of cocaine induces significant changes in gene expression in the human brain.

The scientists compared gene and protein expression patterns in specific brain areas—the ventral tegmental area (VTA) and the substantia nigra—in 10 cocaine overdose victims and 11 age-matched, drug-free control subjects.

They found significant increases in glutamate receptor subunits in the VTA of the cocaine abusers. Glutamate is a neurotransmitter, a class of compounds involved in regulating cell–cell communication. It is involved in neuronal excitability and is associated with learning, memory, and synaptic plasticity.

In addition, the scientists found significant increases in CREB (cyclic AMP responsive element binding protein), a molecule that regulates gene expression and is associated with addiction and memory, in the abusers' brains.

The scientists say this study marks the first attempt to identify molecular neuropathological markers that may be associated with cocaine addiction.

- **WHAT IT MEANS:** These results show that cocaine abuse can lead to significant alterations in the expression of specific genes in defined brain areas associated with addictive behavior. Identifying such molecular markers in human drug abusers broadens our understanding of the neuropathology associated with drug abuse and may help identify new biological targets for developing medications to treat addictive disorders.

The study, published by Dr. Scott Hemby and colleagues and supported by the National Institute on Drug Abuse, appeared in the May issue of the *Journal of Neurochemistry.*

The Value of Vouchers May Not Be as Relevant as the Timing

During contingency management (CM) treatment, drug abusers are given vouchers for goods and services when they refrain from using drugs for a given amount of time. With sustained abstinence, the value of the vouchers is increased. Earlier research showed that this escalation in voucher values helped maintain abstinence, but when only fixed-value vouchers were given for abstinence, sustained, continuous abstinence appeared to decrease. In some CM programs, the length of time abusers are required to abstain from drug use to receive a voucher also may increase at certain intervals. NIDA-funded researchers have found that although CM remained effective when voucher values became fixed, effectiveness was reduced when abusers were required to abstain from drug use for longer periods before receiving a voucher.

Dr. Thomas Kosten and coworkers at the Yale University School of Medicine recruited 75 individuals who abused cocaine and heroin simultaneously. They participated in a 24-week study where they received buprenorphine combined with the antidepressant desipramine and escalating CM vouchers during the first 12 weeks. (Combining CM with some medications for the treatment of cocaine and heroin dependence has shown to be more effective than either treatment alone.) During the second 12 weeks, participants continued to receive the medications and to participate in CM, but escalating CM values were eliminated so that the

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participants received a voucher worth a fixed amount for each submitted drug-free urine sample (samples were taken 3 times per week). During weeks 13 to 16, participants remained continuously abstinent, despite getting fixed-value vouchers. At 17 to 20 weeks, participants had to submit two consecutive drug-free urine samples to receive a voucher. At 21 to 24 weeks, three consecutive drug-free samples were required. The researchers found the fixed-value vouchers had little effect on abstinence from drug use in weeks 16 to 20. However, abstinence decreased in weeks 17 to 24, as participants were required to submit more drug-free samples to earn a voucher.

- **WHAT IT MEANS:** These findings suggest that to sustain the effects of CM, treatment programs need to focus on both broader psychosocial changes and reduction in drug use. Vouchers alone are not enough to maintain abstinence during treatment.

This study was published in the May issue of the journal *Addiction.*

Long-Term Treatment Yields Greatest Drug-Use Reductions

A team of NIDA-funded researchers from the University of Chicago, Brown University, and Rhode Island Hospital has found that, in general, the more time a person spends in treatment for addiction, the better.

The scientists found that treatment for up to 18 months in residential settings, or almost 14 months in outpatient nonmethadone treatment, yielded the greatest reductions in illicit drug use. Both overall and primary drug use declined after 18 months in long-term residential programs, at which point peak use measured about one-tenth the pretreatment level. After 18 months in this setting, the amount of improvement began to wane. A similar effect was seen in people treated in nonmethadone outpatient settings. Individuals in nonmethadone programs who reduced drug use on their own before entering a treatment program were better able to remain in recovery.

The 4,005 patients in the study were treated for addiction to cocaine, heroin, or marijuana in 62 drug treatment units throughout the United States. As part of the National Treatment Improvement Evaluation Study, they were interviewed at admission, discharge, and one year after therapy ended between 1993 and 1995.

Treatment programs included methadone maintenance programs, outpatient nonmethadone programs, short-term residential programs, and long-term residential programs.

There was no significant relationship between treatment duration and overall drug use improvement for individuals in methadone maintenance and short-term residential programs.

- **WHAT IT MEANS:** Remaining in treatment for an extended time has beneficial outcomes for people in residential or outpatient drug treatment programs. Insurers may consider changing their policies to include a longer length of stay so people can be more effectively treated for their addictions.

Lead author Dr. Zhiwei Zhang of the National Opinion Research Center (NORC), a national organization for research at the University of Chicago, and his colleagues published this analytic study in the May issue of *Addiction.*

Cocaine Use May Cause Alterations in Brain Regions Involved in Decisionmaking

Scientists may have uncovered a biological mechanism that could help explain why cocaine users continue to use the drug despite their inability to relive the powerful, pleasurable feelings that they experienced at first use. The researchers found that cocaine use may cause changes in an area of the brain involved in decisionmaking called the orbitofrontal cortex (OFC).

In humans, the OFC shares neural connections with many brain regions that affect decisionmaking, compulsive behaviors, and feelings of reward. Damage to the OFC may result in personality changes that include irresponsibility and persistence in self-destructive behaviors, such as drug use.

For the study, the research team led by Dr. Karen I. Bolla at the Johns Hopkins University School of Medicine recruited cocaine users who reported using the drug regularly for at least 2 years and nonusers. Participants were admitted to the Clinical Inpatient Research Unit at the NIDA Intramural Research Program. They were asked to remain abstinent from drug use during their stay, and random drug testing verified abstinence. On day 3 of the residential stay for nonusers and day 25 for cocaine users, changes in cerebral blood flow were measured during a rest period, during a control task, and while engaged in a decisionmaking task known as the Iowa Gambling Task. The task measures the ability to choose between high gains with high risk and low gains with low risk.

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The researchers found that while performing the Iowa Gambling Task, the abstinent cocaine users had increased blood flow—an indicator of increased brain activity—in the OFC compared to nonusers. This finding suggests that during the task, the cocaine users may have had an abnormally intense focus on winning and its rewarding aspects, which may have suppressed thoughts of losing. This may mean that the cocaine users may be more likely to focus on the rewarding effects of the drug, while ignoring its destructive consequences.

In a related study by lead author Dr. John Matochik at the NIDA Intramural Research Program, the same core team of researchers found structural differences in the brains of the cocaine users and nonusers who had participated in the previous study. Cocaine abusers had less gray matter tissue than nonabusers in the same brain regions that showed increased blood flow during the Iowa Gambling Task. Gray matter is primarily composed of neuron cell bodies and is considered to play a role in thought processes. Some researchers believe that a reduction in gray matter may indicate damage to or a loss of neurons.

- **WHAT IT MEANS:** These findings suggest that cocaine users have structural and functional abnormalities in the areas of the brain involved in decisionmaking and that these effects are related to cocaine use. Impairments in the ability to make decisions may play a role in the development of addiction and undermine attempts to stop abusing drugs. Therefore, understanding how these abnormalities are related and their role in drug abuse could contribute to the development of more appropriately targeted treatment and prevention interventions.

These studies, funded by the National Institute on Drug Abuse, were published in the July issue of *Neuroimage.*

Natural Fat Compound May Be Basis For New Class of Drug Targeting Obesity and Other Compulsive Disorders, Including Addiction

A naturally occurring lipid called oleylethanolamide (OEA) is known to curb appetite and regulate body weight. Although it is structurally related to a neurotransmitter similar to marijuana's active ingredient, it does not bind to cannabinoid receptors. Now, NIDA-funded researchers have found that in mice, OEA controls hunger and contributes to weight maintenance by binding to peroxisome proliferator-activating receptors (PPAR-alpha), which regulate several aspects of lipid metabolism.

In the study, a team of researchers led by Dr. Daniele Piomelli at the University of California, Irvine, fed a high-fat diet to mice that were either normal or had their PPAR-alpha receptors genetically removed. After the mice became obese, the researchers administered OEA for 4 weeks.

The researchers found that the normal mice ate less and lost weight while OEA feeding had no effect on mice that lacked PPAR-alpha receptors. They also found that in normal mice, OEA lowered blood cholesterol levels.

- **WHAT IT MEANS:** This study suggests that OEA plays a role in weight maintenance and satiety by activating PPAR-alpha. Identifying the receptors that contribute to the compound's weight maintenance properties may lead to the development of a new class of medications that target obesity and other eating disorders. The researchers also say that because neural mechanisms underlying reward for drugs and food can overlap, these findings may contribute to the development of medications for the treatment of other compulsive behaviors such as drug addiction.

This study, funded by the National Institute on Drug Abuse, was published in the September 4, 2003 issue of *Nature*.

Study Investigates Short-Term Effects of Marijuana Use on HIV+ Patients

Researchers from the University of California, San Francisco, have found that patients infected with the human immunodeficiency virus (HIV) may not experience adverse effects on cell counts or viral load from short-term marijuana use.

In the 3-week trial, the researchers assigned 62 HIV+ patients to use marijuana cigarettes, cannabinoid capsules, or a placebo three times a day before meals. All of the patients were on antiretroviral regimens containing protease inhibitors for at least 8 weeks before the study began. Fifty-eight percent of the patients entered the study with levels of HIV circulating in their blood below the limit currently detectable by the usual tests.

Overall, there were no significant changes in the levels of HIV in the patients' blood. Compared to the placebo group, CD4+ and CD8+ T cell levels rose slightly in the marijuana and cannabinoid capsule groups.

- **WHAT IT MEANS:** This study indicates that short-term use of marijuana may not substantially elevate viral load in individuals with HIV infections who are receiving stable antiretroviral regimens containing protease inhibitors. However, the researchers say that these findings need to be confirmed with larger and longer trials. They also caution that these results cannot be extrapolated to the potential effects of marijuana available on the street because the marijuana used in this study was of known potency and content.

Dr. Donald Abrams and colleagues published this study, funded in part by the National Institute on Drug Abuse, in the August 19 issue of the *Annals of Internal Medicine*.

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Scientists Seek To Identify Patterns in Injection Drug Users

Researchers from the Johns Hopkins University Bloomberg School of Public Health and the Ben-Gurion University of the Negev in Beer-Sheva, Israel, who followed but did not treat 1,339 injection drug users for 12 years, showed that fewer than 20 percent were able to completely cease injection drug use.

Perhaps the most important finding from this study is that so few injection drug users were able to resolve their addiction. While 71 percent did experience some period of abstinence, most took up the practice of injecting drugs again. Only 19.6 percent succeeded in ceasing injection drug use completely during the study.

A younger age at enrollment, especially being younger than 30 years, was significantly associated with cessation of drug use or with cessation followed by relapse. Women were more likely than men to stop using injected drugs.

A total of 29 percent of the study population remained persistent drug users, the authors report. Fourteen percent relapsed once during the study period, and 37 percent relapsed at least twice.

The scientists say their data show that the average time to first relapse is 10–18 months. They suggest that intervention efforts should continue throughout this critical period to support injection drug users who try to overcome their addiction.

Study participants in all four groups—persistent drug users, those who ceased drug use completely, those who relapsed once and continued using drugs, and those who had multiple relapses—could not be differentiated by educational level, marital status, and the presence of dependent children, the authors report. Only a history of incarceration differentiated people who successfully stopped using injection drugs from those who continued to use them. However, the scientists also report that daily use of alcohol was strongly associated with persistent injection drug use.

Participants who relapsed once were younger than persistent drug users. These male participants also were 4 times more likely to report engaging in homosexual sex.

The highest mortality rates were seen in the persistent drug users. The principal causes of death were overdose, violence, AIDS, and other infections.

- **WHAT IT MEANS:** Patterns noted in the study are consistent with the view of drug addiction as a chronic disease, the researchers say. The data presented emphasize the need to develop and make available effective cessation programs for people who use injection drugs to prevent adverse health and social outcomes.

The NIDA-funded study by Dr. Noya Galai and colleagues was published in the October 1 issue of the *American Journal of Epidemiology.*

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

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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 more than 85 percent 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**.