NIDA
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ON DRUG ABUSE

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NewsScan
NIDA ADDICTION RESEARCH NEWS

NEWS UPDATE

Research News

Common Gene Variant May Offer Protection Against Marijuana Dependence

New research shows that specific variations in the cannabis receptor gene (CB1) may be associated with the development of one or more symptoms of marijuana dependence in adolescents. This is one of the first studies looking specifically at the link between marijuana dependence and CB1 variations.

Background: Marijuana is the most commonly abused illegal substance among adolescents and young adults, and those who begin using at this stage are about twice as likely as adults to become dependent. Genetic variations in the CB1 receptor—the brain target for the psychoactive ingredient in marijuana—is a logical candidate gene to study as a potential contributor to vulnerability to marijuana dependence. Therefore, researchers examined the associations between specific variants in the CB1 gene and the rates of marijuana dependence.

Study Design: The scientists collected DNA from 541 youths aged 17 or older who had used marijuana at least five times recently. After interviews to identify one or more DSM-IV symptoms of dependence, 327 were established as cases; the remaining 214 had no symptoms and served as controls. All subjects were genotyped for four specific DNA sequence variations of the CB1 gene.

What They Found: One CB1 variant (found in 21 percent of the general population) was associated with a lower rate of having one or more marijuana dependence symptoms, while two others (present in 12 percent of the general population) were linked to increased likelihood of developing dependence symptoms.

Comments from the Authors: Identifying gene variants that may afford some protection against marijuana dependence may have important implications for intervention. However, it is likely that multiple genes and their interactions with environmental events influence marijuana and other drug addictions. Therefore, some level of genetic protection may not necessarily protect an adolescent from becoming dependent on drugs or suffering other related health consequences.

What's Next: Future studies should examine these genetic variants for other drug-related traits, as well as additional DNA sequence variations for possible drug abuse associations.

Publication: The study, led by Dr. Christian J. Hopfer of the University of Colorado, was published in volume 141B, pages 895-901 (2006) of the *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*.

School-Based Drug Abuse Prevention Program Also Works Against Violence and Delinquency

Researchers determined that school-based intervention strategies used to prevent substance abuse may also work to reduce adolescent delinquency and violence. Participating students were mostly economically disadvantaged, non-White 6th graders.

Background: Prevention interventions that focus on the impact of social influences, making healthy choices, and promoting anti-substance abusing norms have proven effective in reducing adolescent drug use. The school-based drug abuse prevention program Life Skills Training (LST) teaches a variety of cognitive-behavioral skills for problem-solving and decisionmaking, resisting media influences, managing stress and anxiety, communicating effectively, developing healthy

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personal relationships, and asserting one's rights. Researchers wanted to know if these strategies may also be successfully applied to combat adolescent delinquency, verbal and physical aggression, and fighting.

Study Design: Researchers introduced LST to 2,374 students in 20 New York City public and parochial schools, and established a comparable control group. Sample composition was 39 percent African-American, 33 percent Hispanic, 10 percent White; 55 percent economically disadvantaged; and 30 percent living in mother-only households.

What They Found: After 15 school-based sessions, delinquency and frequent fighting were significantly reduced across the entire intervention group.

Comments from the Authors: This study supports the idea that multiple problem behaviors may have common causes. It further suggests that the development of comprehensive, integrated school-based approaches to prevention may more efficiently target an array of related behaviors, thereby reducing the burden on resources and increasing the likelihood for adoption and implementation.

What's Next: More research is needed to test the durability of the LST approach. It would also be useful to determine if these strategies can prevent more serious forms of violence, such as assault and homicide.

Publication: The study, led by Dr. Gilbert J. Botvin of the Department of Public Health at Weill Cornell University Medical College, was published in volume 7, pages 403-408 (2006) of *Prevention Science*.

Dual-Action Experimental Approach Looks Promising for Cocaine Addiction and Other Brain Disorders

Researchers have identified a novel strategy to reduce cocaine-seeking behavior. The approach uses a neurochemical normalization strategy that simultaneously releases two neurotransmitters deficient in the brains of those addicted to cocaine.

Background: Biogenic amine transporters (BATs) are proteins that transport dopamine and other neurotransmitters across cell membranes. As a result, they are principal sites of action for psychotropic drugs, including cocaine and methamphetamine. Previous studies have suggested that withdrawal from long-term cocaine abuse produces a dual deficit of dopamine and another neurotransmitter known as serotonin. Researchers wanted to know if normalizing those deficits would reduce cocaine-seeking behavior.

Study Design: Researchers reviewed preclinical and clinical data suggesting that developing compounds that release both dopamine and serotonin, the two neurotransmitters most affected by chronic cocaine abuse, is a promising strategy for the treatment of cocaine addiction.

What They Found: Previous studies have shown that administration of dopamine and serotonin releasing agents alone or together reduces drug-seeking behavior in animals. However, a major limitation with the use of dopamine releasers (such as amphetamines) has been their stimulant and reinforcing properties. The studies reviewed here show that combining dopamine and serotonin releasers may reduce this abuse potential. Finally, the authors identified a compound, PAL287, which potently releases both dopamine and serotonin and found that it reduces cocaine self-administration in animal models without being reinforcing itself.

Comments from the Authors: Although additional work must be done to refine PAL287, it represents the prototype for a new generation of medications that target BATs. Medications like these may also be useful for treating depression, obsessive-compulsive disorder, attention-deficit disorder, and obesity.

What's Next: Further work must be done on PAL287 to increase its selectivity and evaluate any potential adverse effects. However, it should be possible to test dopamine-serotonin releasers in humans using clinically available compounds.

Publication: The review's lead author was Dr. Richard B. Rothman of the Clinical Psychopharmacology Section at the National Institutes of Health Intramural Research Program at NIDA in Baltimore. It was published in volume 27, number 12, pages 612-618 (2006) of *TRENDS in Pharmacological Sciences*.

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Different Models of Buprenorphine Treatment for Opioid Addiction Offer Hope for Undertreated Regions of the World

Buprenorphine programs in Europe, Australia, and the United States have been successful in treating opioid addiction. Expanded access to opioid treatment programs with the introduction of buprenorphine may help stem the co-occurring epidemic of HIV and drug abuse in undertreated regions of the world, including Eastern Europe, Asia, and the former Soviet Union.

Background: Of the estimated 13 million injection drug users—primarily heroin abusers—worldwide, more than 10 million live in developing or transitional countries. These numbers reflect a dramatic increase in the number of opioid abusers in these countries between 1990 and 2000. Accompanying this increased prevalence of injection drug use (IDU) has been a rapid increase in HIV infection rates. In some parts of Asia and the former Soviet Union, HIV infection prevalence has reached 80 to 90 percent among those addicted to opioids. Although methadone is the opioid treatment that has been available the longest worldwide, the global availability of buprenorphine has steadily increased; now both methadone and buprenorphine are included in the World Health Organization's (WHO) Model List of Essential Medicines. However, availability of methadone or buprenorphine treatment varies widely from country to country.

Study Design: The researchers examined the international experience with buprenorphine and attitudes of various countries toward methadone maintenance treatment (MMT) or buprenorphine maintenance treatment (BMT) when used to combat opioid addiction and HIV transmission.

What They Found: Responses to opioid dependence vary widely in countries around the world. High-dose buprenorphine tablets are currently approved for use in 44 countries and are already being marketed in 31 of these countries. Three predominant treatment models have emerged. In the United States and France, physicians and drug abuse treatment specialists are the major prescribers; in Australia, community-based pharmacies supervise dispensing and work closely with primary care physicians and specialty clinics; and in Italy and Germany, specialty clinics or a combination of these systems dispense and prescribe buprenorphine. Maintenance treatment is just beginning to become available in Eastern European countries and the independent states that were part of the Soviet Union. HIV infection prevalence among injection drug users is lowest in Croatia and Slovenia, where methadone and buprenorphine treatment have been available the longest. International data to date suggest that expanded access to opioid treatment reduces the morbidity and mortality related to IDU, improves the health and social conditions of patients, and plays a critical role in curbing the spread of HIV.

Comments from the Authors: It is important that countries learn from each other's unique experiences in managing opioid addiction. Research from several countries shows us that BMT can be established rapidly and safely in primary health care settings and that access to a choice of treatments has important public health implications. This is particularly true when we consider, first, that the rising heroin epidemic in some parts of the world fuels a co-occurring HIV infection epidemic among injection drug users, and second, that treatment with either methadone or buprenorphine is an essential and proven tool in reducing the rate of HIV infection.

What's Next: Countries that do not offer MMT or BMT should consider the findings of this report—Treatment can be effective. Countries that offer MMT should consider BMT to expand access to treatment. Flexibility of care models available with BMT and its successful use in primary care settings increase opportunities for effective individual treatment and better regional management of the HIV epidemic. Finally, additional research must be done to evaluate the use of buprenorphine in diverse populations such as pregnant women, prison populations, HIV-infected individuals, and those with comorbid health conditions.

Publication: The overview article was written by a group of researchers from the United States, Australia, and Europe, and led by Dr. Maria Patrizia Carrieri of the Institut Nationale de la Santé et de la Recherche Médicale in Marseilles, France. It was published in volume 43 (Supplement 4), S197 (2006) of *Clinical Infectious Diseases*.

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Chronic Abuse of Different Drugs Causes Similar Brain Changes

The results of this study suggest that many drug abusers may experience similar changes in the patterns of global gene expression in their brains, irrespective of their drug of choice. Whether longtime drug abusers favor cocaine, marijuana, or PCP, their autopsied brains showed a number of common gene changes consistent with diminished brain plasticity—i.e., the ability to learn from new experiences and adapt to new situations. Therefore, brain functions may be similarly impaired as the result of chronically abusing different drugs.

Background: Chronic drug abuse can change the structure and function of several brain regions. Recent advances in genomic technologies allow us to monitor the expression level of thousands of genes simultaneously in specific parts of the brain, including the anterior prefrontal cortex (aPFC), a region that plays an important role in decisionmaking. A dysfunctional aPFC appears to be a characteristic feature of the brains of drug abusers. Researchers wanted to know if different drugs of abuse can compromise the normal patterns of gene expression that converge in common pathways, resulting in similar changes in the brains of drug abusers.

Study Design: NIDA scientists compiled clinical case histories and toxicology reports to establish the primary drug of abuse of 42 deceased drug abusers. The drugs examined included cocaine, marijuana, and PCP. The researchers then measured the level of expression of more than 9000 individual genes in small brain tissue samples obtained from the aPFC.

What They Found: Although many effects were specific to each drug, the scientists also found that nearly 80 percent of the drug abuse cases displayed similar alterations in genetic output compared to the controls. For example, genes involved in calcium signaling were turned down, while genes involved in lipid- and cholesterol-related pathways were turned up.

Comments from the Authors: The aPFC is characterized by a particularly dense and complex network of neural connections. Our results show that cocaine, marijuana, and PCP can alter the function of this critical brain area in similar ways, which could threaten the drug abuser's ability to make sound decisions.

What's Next: Many of the gene families identified here point to common downstream pathways that should be studied further in order to understand their specific contributions to the long-term effects of abused drugs on the human brain.

Publication: The study, led by Dr. Elin Lehrmann of the Cellular Neurobiology Research Branch in NIDA's Intramural Research Program in Baltimore, was published in the open access journal *PLoS ONE* on December 27, 2006 (PLoS ONE 1:e114).

New Tool Is Available for Characterizing Nicotine Receptors in the Brain

Nicotine addiction relies on brain receptors that have been difficult to fully study and characterize. Scientists at the University of Colorado in Boulder have demonstrated that an immunolabeling technique can effectively analyze receptor subunits.

Background: Nicotine's effects on the brain are triggered upon its binding to nicotinic acetylcholine receptors, each of which consists of five subunits: two alphas, one beta, one delta and one gamma. Different combinations of these subunits produce different receptor subtypes, which may vary in their pharmacology, biophysical properties, and distribution. To more fully understand how to interfere with nicotine's effects in the brain, scientists must first understand where these different receptors are and how they work. Two of the most important subunits, $\alpha 4$ and $\beta 2$, have been hard to study because current study methods can only locate the fully assembled receptor unit. Researchers wanted to know if an alternative strategy of immunolabeling (i.e., using antibodies to tag individual proteins), which has been fraught with technical challenges, would be able to identify, map, and quantify separate subunits.

Study Design: Scientists at the University of Colorado worked with brain sections of mice genetically engineered to express particular $\alpha 4$ and $\beta 2$ subunit combinations. Using a sensitive immunolabeling technique, they explored the expression of the $\alpha 4$ and $\beta 2$ subunits at both the gene and protein levels. Additional mice strains, missing the subunits under study, were used as controls.

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What They Found: The two predominant nicotinic receptor subtypes (α4 and 2) were reliably detected using immunolabeling. Expression of the α4 subunit protein was almost universally dependent on 2, whereas most, but not all, 2 subunit protein expression was α4-dependent.

Comments from the Authors: Immunolabeling using specific antibodies offers a powerful approach for mapping the distribution of nicotine receptor subunits and can produce reliable quantitative results.

What's Next: Similar studies can be designed to locate other nicotine receptor subtypes. In many cases, the antibody recognition sites are inside the cell membrane. It will likely take alternative biochemical approaches to uncover these less accessible sites. A better understanding of receptor composition and function may eventually have important implications for developing interventions at the receptor level.

Publication: The study, led by Dr. Paul Whiteaker of the Institute for Behavioral Genetics at the University of Colorado, Boulder, with Dr. Jon Lindstrom of the University of Pennsylvania, was published in volume 499, number 6, pages 1016-1038 (2006) of the *Journal of Comparative Neurology*.

NIDA Researchers Identify 89 Genes Implicated in Addiction—At Least 21 Are Likely to Affect Brain's Memory Processes

An analysis that compared the DNA of drug abusers with that of non-abusing controls has identified 89 genes that are likely to contain variants that contribute to addiction vulnerability.

Background: Vulnerability to addiction is a complex trait with strong genetic influences. Since the mid-1990s, scientists have been developing methods and tools to identify and evaluate the functional role of genes and their variants. The impact of such efforts has been greatly enhanced by the Human Genome and International HapMap Projects. By 2001, the first low-resolution genome-wide association studies from the NIDA-IRP's Molecular Neurobiology Branch were published. Genetic research technology is now able to reliably scan the genome of individuals for genetic variants linked to specific functions.

Study Design: From 1990 to 2005, thousands of people participated in studies at NIDA-IRP's Molecular Neurobiology Branch, providing self-reports and DSM Diagnostic Interview Schedule scores. From among this pool, researchers identified 980 African-American and European-American "drug abusers" (heavy lifetime use of illegal substances) and 740 controls (no significant history of addictive substances, no abuse, no dependence). Pooled DNA samples, prepared from blood extracted from each group were used to examine a panel of close to 640,000 genetic variations.

What They Found: Using strong statistical models that focused on the overlaps between the samples, this screen identified 89 genes that display clusters of genetic variants that are likely involved in addiction vulnerability. Most of these genes are expressed in the brain. Twenty-one of these genes influence cell adhesion, and nearly all of those are expressed in brain regions implicated in memory processes.

Comments from the Authors: The nature of the addiction-associated genes identified in this study, especially those involved in cell adhesion, suggest the critical role played by dysfunctional nerve cell connections in the addicted brain.

What's Next: Other genes that emerged from the analysis are being tested in the context of where they are located in the brain and their likely functions: enzymes, transporters, receptors, protein processing, and transcriptional regulation. Results like these highlight characteristics that are common to human addiction and may facilitate efforts to develop targeted prevention and treatment strategies.

Publication: The study, led by Drs. George Uhl and Qing-Rong Liu of the Molecular Neurobiology Branch at the National Institutes of Health Intramural Research Program at NIDA in Baltimore, was published in volume 141B, pages 1-8 (2006) of the *American Journal of Medical Genetics Part B* (*Neuropsychiatric Genetics*).

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- 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 www.drugabuse.gov.

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