

# NewsScan

## NIDA ADDICTION RESEARCH NEWS

NEWS UPDATE

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### Special Issue on Stress and Drug Abuse

Both research and clinical experience have demonstrated that stress increases the risk of substance abuse and is one of the major reasons why recovering drug abusers relapse. Many Americans are still experiencing high levels of stress as a result of the events of September 11, 2001, including the fear of new terrorist acts, the military action in Afghanistan, and the economic downturn. These individuals are potentially at increased risk for developing substance abuse problems or relapsing to previous addictions.

Prior to the events of September 11th, the editors of the journal *Psychoneuroendocrinology* had made the decision to publish a special issue on stress and drug abuse. That issue (Volume 27, Number 1/2, Jan/Feb 2002) was published in January 2002. Edited by Harold W. Gordon, Maria Dorota Majewska, and Pushpa Thadani from the National Institute on Drug Abuse (NIDA), the journal features selected papers from three NIDA-sponsored workshops on the complex relationship between stress and drug dependence.

This issue of NewsScan presents highlights of papers published in that special issue, as well as a summary of a paper by NIDA grantee Dr. Rajita Sinha, recently published in the journal *Psychopharmacology*. Her paper reviews the current state of knowledge and presents a framework for understanding how stress increases the risk of drug abuse and relapse.

### Understanding How Stress Increases the Risk of Drug Abuse and Relapse

Evidence from animal studies suggests that specific types of stressful experiences in early life may increase vulnerability to drug abuse. For example, animals that are isolated or separated from their mothers in early life increase self-administration of morphine and cocaine. Several human studies have reported a link between adverse life events, chronic stress, and increased drug abuse. Individuals with a history of physical or sexual abuse at a young age have an increased risk of abusing substances.

One proposed explanation for this link between stress and increased drug abuse has been that the use of addictive substances serves to both alleviate emotional distress and enhance mood, thereby reinforcing drug taking as an effective, but maladaptive, coping strategy. However, more recent animal studies suggest that stress may enhance the reinforcing effects of drugs that are commonly abused.

With those studies, scientists have sought to elucidate the neurological events in the brain that underlie the relationship between stress and substance abuse. The two main components of the brain's stress circuitry are corticotropin releasing factor, which originates in the hypothalamus and amygdala, and the noradrenergic activation initiated in the brain stem. Activation of the stress circuits also increases dopaminergic neurotransmission in the mesolimbic regions of the brain.

The mesocorticolimbic dopaminergic system is generally considered to be the brain's reward pathway, and increased transmission in this pathway has been shown to be critical for the reinforcing properties of drug abuse. Thus, it seems that exposure to stress stimulates some still-to-be-identified neural activity which in turn simultaneously activates both the stress circuitry and the reward pathway and, by doing so, enhances the likelihood of taking drugs and the pleasure obtained from taking drugs.

- **WHAT IT MEANS:** Research shows that stress, in addition to the drug itself, plays a key role in perpetuating drug abuse and relapse.

The paper, "How does stress increase the risk of drug abuse and relapse?" was published by Dr. Rajita Sinha in Volume 158, 343-359, 2001 of the journal *Psychopharmacology*.

### **Special Issue of *Psychoneuroendocrinology***

The following are selected papers from the special issue of the journal *Psychoneuroendocrinology* that describe studies that further elucidate the complex relationship between stress and substance abuse.

Among the major findings are:

- Stress and glucocorticoids sensitize animals for drug-seeking behaviors and facilitate drug self-administration;
- Animals that are hypoaroused and have low levels of glucocorticoids are more prone to develop drug-seeking behaviors;
- Severe stress early in life induces a cascade of physiological, neurobiological, and hormonal events that result in dysregulation of biological reward pathways in the central nervous system and in stress response systems; these changes seem to prompt self-administration of drugs and alcohol later in life; and
- Prenatal exposure to stress or drugs predisposes animals to drug-seeking behaviors in adulthood.

### **Psychobiology of Trauma Helps Explain Increased Susceptibility to Substance Abuse**

The preface of the Stress and Drug Abuse issue of the journal *Psychoneuroendocrinology* includes a brief synopsis of the relationship between stress and the risk of substance abuse. Understanding the cascade of hormonal and neurobiological events that are set off by experiencing trauma helps to explain the linkage between stress and substance abuse. Both clinical experience and research have shown that posttraumatic stress disorder (PTSD) is a risk factor for substance abuse.

Traumatic stress may have negative effects on the neurotransmitter systems and neuroendocrine axes that are activated during acute stress. Although stress affects practically all aspects of physiology, the most important physiological stress responses include activation of the central nervous system, the autonomic nervous system, and the limbic-hypothalamic-pituitary-adrenal (LHPA) axis.

Animal studies examining catecholamine function show that traumatic stress activates the locus coeruleus, the major catecholamine-containing nucleus in the brain, leading to the biologic changes of the "fight-or-flight" reaction. Increases in catecholamine turnover in the brain lead to increases in heart rate, blood pressure, metabolic rate, alertness, and in the circulating catecholamines epinephrine and dopamine. During severe stress, the HPA axis is stimulated, setting off a neurochemical cascade that results in anxiety and hypervigilance, core behavioral symptoms of PTSD.

Glucocorticoids released during chronic stress alter gene expression and influence functions of practically all tissues. Research has shown that chronic exposure to glucocorticoids can result in many deleterious health effects, including acceleration of heart disease and diabetes, reduced volume of the hippocampus and cerebral cortex, cognitive impairments and psychiatric disorders.

The link between stress and drug abuse is supported by studies that show that administration of cocaine to humans evokes similar physiological reactions, such as secretion of adrenaline and corticosteroids, and psychological arousal that are evoked by stress. Discontinuation of cocaine in long-time addicts is associated with lasting disturbances of HPA axis functions, somewhat similar to those observed after chronic stress. And animals that maintain low levels of arousal and manifest relatively low concentrations of plasma glucocorticoids in response to a stressor are more likely to develop drug-seeking behaviors than are those with a normally functional HPA axis.

- **WHAT IT MEANS:** Stress is clearly interwoven with increased predisposition to psychiatric disorders and drug abuse.

## **Traumatic Experiences in Childhood Associated with Increased Risk of Substance Abuse during Teen Years**

This review paper by Michael D. DeBellis from the University of Pittsburgh Medical Center discusses studies that look at the developmental effects of traumatic events in early childhood. The evidence points to the conclusion that maltreatment or other stresses during childhood disrupt the major biological stress response systems, resulting in adverse effects on brain development.

Dysregulation of biological stress response systems may lead to an increased vulnerability to psychopathology, particularly posttraumatic stress disorder (PTSD) and depression. These disorders, in turn, may put a child at increased risk for adolescent-onset or young-adult-onset alcohol or substance abuse disorders.

- **WHAT IT MEANS:** Changes in biological stress response systems in childhood can increase vulnerability to “self-medicating” with alcohol and various illicit substances.

## **Sexual Abuse in Childhood Increases Risk of Developing Substance Abuse Problems Later in Life**

Researchers from the Harvard Medical School and McLean Hospital found that repeated sexual abuse during childhood causes physical changes in the brain, changes that can explain why abused children often develop substance abuse problems later in life.

The investigators found that young adults who had been sexually abused as children had changes in the blood flow and function of a brain region called the cerebellar vermis, a portion of the brain that may play a role in modulating response to addictive drugs.

Testing revealed that the young adults with a history of childhood sexual abuse had substantially higher scores in some psychiatric symptoms associated with substance abuse.

- **WHAT IT MEANS:** The findings suggest that early trauma may interfere with the development of the vermis and produce neuropsychiatric symptoms associated with drug use.

Dr. Carl M. Anderson of McLean Hospital led the study.

## **Stress Reduction May Help Promote Abstinence in Recovering Cocaine Addicts**

Researchers at the Louisiana State University Health Sciences Center used rats to study the role of the HPA axis in the acquisition, maintenance, and relapse of cocaine use. They found that corticosterone, a stress hormone produced by the HPA axis, is necessary for the acquisition of drug-taking behavior, and that the animals did not self-administer cocaine unless the level of corticosterone was increased above a threshold critical for reward.

It was also found that corticosterone is involved in the stress- and cue-induced relapse of cocaine abuse.

- **WHAT IT MEANS:** Stress reduction, either alone or in combination with medication targeting the HPA axis, may help promote abstinence in individuals seeking treatment for cocaine addiction.

The Louisiana research team was led by Dr. Nick E. Goeders.

## **Maternal Deprivation Affects Sensitivity to Stress, Cocaine Later in Life**

Investigators led by Dr. Michael J. Meaney of the Douglas Hospital Research Center in Montreal, Canada, found that, in rodents, maternal separation during early postnatal life alters the development of the ascending mesocorticolimbic dopamine system.

As adults, animals raised under conditions of prolonged maternal separation showed decreased dopamine transporter binding in one part of the brain, increased dopamine release in response to acute stress, and enhanced behavioral sensitivity to cocaine.

- **WHAT IT MEANS:** These findings suggest that parental care in early life could alter the development of the mesocorticolimbic dopamine system and thus form the basis for a vulnerability to certain forms of drug abuse in later life.

### **Prenatal Stress Shown to Alter Patterns of Alcohol Consumption During Adolescence**

Researchers led by Dr. Mary L. Schneider from the University of Wisconsin present evidence from studies using monkeys that prenatal stress and exposure to alcohol result in offspring with reduced attention span and delayed motor development in infancy.

The researchers also addressed the issue of whether prenatal alcohol exposure or stress contributes to increased risk for alcohol or substance abuse later in life. In some of the monkeys, increased alcohol consumption during adolescence was associated with prenatal stress.

- **WHAT IT MEANS:** The effects of stress during pregnancy (alone or in combination with fetal alcohol exposure) need to be better understood in humans.

### **Strength, Duration of Stress Early in Life May Influence Adult Susceptibility to Substance Abuse**

The investigators used a rat model to study the impact of chronic injection of the tricyclic antidepressant desipramine and 24-hour maternal deprivation on the developing rat brain.

At 80 days of age, the animals that received desipramine during the newborn period consumed more alcohol than did those that were not injected. History of maternal deprivation had no impact on alcohol consumption.

The investigators noted 5-HT<sub>1B</sub> receptor down-regulation in the animals subjected to chronic injection treatment. Low 5-HT<sub>1B</sub> receptor levels have been associated with cocaine self-administration.

- **WHAT IT MEANS:** The investigators conclude that 5-HT<sub>1B</sub> receptor down-regulation may be one of the biological mechanisms whereby early life stress increases vulnerability to substance abuse later in life.

Dr. Delia M. Vazquez led the research team from the University of Michigan.

Other papers appearing in this special issue include:

- Prenatal opiate exposure and long-term CNS consequences in the stress system of the offspring;
- The HPA axis and cocaine reinforcement;
- Temporal concordance of cocaine effects on mood states and neuroendocrine hormones;
- Environmental regulation of the development of mesolimbic dopamine systems: A neurobiological mechanism for vulnerability to drug abuse?;
- Cortisol levels in adult offspring of Holocaust survivors: Relationship to PTSD symptom severity in the parent and child;
- Developmental traumatology: A contributory mechanism for alcohol and substance abuse disorders;
- Pre-adoption stress and its association with child behavior in domestic special needs and international adoptions; and
- Social regulation of the cortisol levels in early human development.

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

- Reporters, call Michelle Person at 301-443-6245.
- Congressional staffers, call Mary Mayhew at 301-443-6071.

The National Institute on Drug Abuse 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 can be ordered free of charge in English and Spanish by calling NIDA Infobox at 1-888-NIH-NIDA (644-6432) or 1-888-TTY-NIDA (889-6432) for the deaf. 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>.

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