A Collection of

NIDA NOTES

NATIONAL INSTITUTE ON DRUG ABUSE

Articles That Address

Research on Tobacco Addiction

Department of Health and Human Services
National Institutes of Health
National Institute on Drug Abuse

NN0031

A Collection of

NIDA NOTES

NATIONAL INSTITUTE ON DRUG ABUSE

Articles That Address

Research on Tobacco Addiction

Department of Health and Human Services
National Institutes of Health
National Institute on Drug Abuse

NN0031

Introduction

The National Institute on Drug Abuse (NIDA) supports most of the world's research on drug abuse and addiction. NIDA-funded research enables scientists to apply the most advanced techniques available to the study of every aspect of drug abuse, including:

- genetic and social determinants of vulnerability and response to drugs;
- short- and long-term effects of drugs on the brain, including addiction;
- other health and social impacts of drug abuse, including infectious diseases and economic costs;
- development and testing of medication and behavioral treatments for abuse and addiction; and
- development and evaluation of effective messages to deter young people, in particular, from abusing drugs.

Included in this document are selections of topic-specific articles reprinted from NIDA's research newsletter, *NIDA NOTES*. Six times per year, *NIDA NOTES* reports on important highlights from NIDA-sponsored research, in a format that specialists and lay readers alike can read and put to use. Selections like the current one are intended to remind regular *NIDA NOTES* readers and inform other readers of important research discoveries during the periods they cover.

We hope the information contained here answers your needs and interests. To subscribe to *NIDA NOTES* and for further information on NIDA's drug abuse and addiction research, please visit our Web site at www.drugabuse.gov.

Table of Contents

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 22, Number 3 (April 2009)

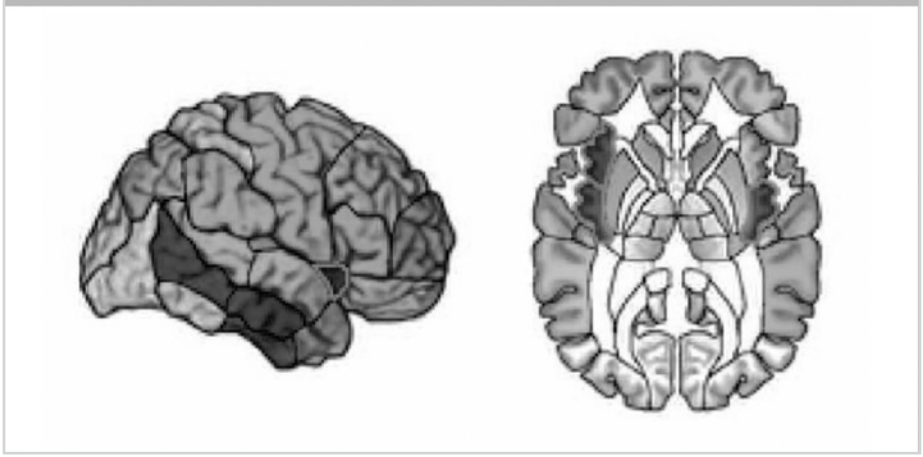
Damage to Brain Area May Immediately Halt Cigarette Addiction

Patients with injury to the insula lost the urge to smoke.

By Lori Whitten, *NIDA NOTES* Staff Writer

"My body forgot the urge to smoke." That's how one patient with damage to the insula, an area of the brain within the cerebral cortex, described the aftereffects of his stroke on his smoking habit. He is not alone. NIDA-funded investigators repeatedly heard of similar experiences while interviewing people who had sustained brain injuries.

BRAIN REGION LINKED TO SUDDEN CESSATION OF SMOKING In these two views of the brain, red indicates regions where damage was associated with the sudden disruption of cigarette addiction in 12 of 19 patients. The regions identified are the right and left insula, which other studies have linked to emotional feelings and cue-induced drug urges.



Many people who have suffered a stroke or other brain injury try to quit smoking out of concern for their health, says Dr. Antoine Bechara of the University of Southern California and the University of Iowa. Most have difficulty. "In some brain injury patients, however, the urge to smoke seemed to be switched off, while other desires, such as for food, were not disrupted," says Dr. Bechara. He and his colleagues found that the experience of quitting cigarettes immediately, easily, and without relapse was much more common among people with damage to the insula than those with injuries elsewhere in the brain. If Dr. Bechara's preliminary findings are validated, the insula is likely to become an important target for future addiction research.

Different Experiences of Smoking Cessation

Scientists suspect that in chronic abusers, drugs or drug-associated cues produce bodily sensations that the insula relays to other brain areas as urgent needs. To explore the insula's role in addictive behavior, Dr. Bechara's team contacted men and women who had suffered brain damage and were listed in the Patient Registry of the Division of Behavioral Neurology and Cognitive Neuroscience at the University of Iowa.

Before suffering brain damage, mostly from stroke, all the participants had been long-term, heavy cigarette smokers; on average, they had smoked a pack and a half a day for 27 years.

The patients' brains had been injured 8 years before the study, on average, and 32 of the 69 patients had quit smoking immediately following their injury or some time thereafter. The researchers used brain imaging to verify injury locations: 19 patients had insula lesions, and 50 showed damage to other regions. Patients with damage in the insula and those with damage to other regions were matched for the number of cigarettes smoked and duration of smoking before the injury.

Patients with insula and noninsula damage were equally likely to have quit smoking cigarettes after their brain injury. To identify those whose smoking addiction had ceased suddenly, the researchers settled on four criteria: quitting cigarettes less than a day after lesion damage; reporting no relapse after quitting; rating the difficulty of quitting as less than 3 on a scale of 1 (very easy) to 7 (very difficult); and reporting no urges to smoke since quitting.

Of the 32 patients who quit smoking, 16 met all four criteria and were designated as having "disrupted smoking addiction." They included 12 of the 13 patients with lesions in the insula who quit smoking, but just 4 of the 19 quitters with lesions only in other areas. "The much higher likelihood of disrupted smoking among patients with insula damage was striking and suggests that the area is a prime candidate in drug-taking urges," notes Dr. Bechara.

"For patients with insula damage, it seems that smoking quit them—they lost the desire to smoke—which is a provocative and unexpected finding," says Dr. Steven Grant of NIDA's Division of Clinical Neuroscience and Behavioral Research. "Dr. Bechara's results have cast a searchlight onto a relatively new area of interest among addiction researchers."

New Focus for Drug Abuse Research

Current interest in the role of the insula in drug abuse was sparked a few years ago by research that linked activity in that brain area with abstinence in methamphetamine abusers ("Brain Activity Patterns Signal Risk of Relapse to Methamphetamine," *NIDA Notes,* Vol. 20, No. 5). Recent studies have also tied insula activation to cravings and drug administration among substance abusers. According to Dr. Bechara, his team's next step is to examine urges for and abuse of substances—cigarettes, alcohol, and illicit drugs—in a larger number of patients who have recently suffered damage to the insula and other parts of the brain.

"Our findings so far suggest that the insula may be a structure to target in the development of new smoking cessation medications," Dr. Bechara says. "Obviously, damaging the insula is not a therapeutic option." But scientists could determine the types of receptors present in the insula, for example, and then test whether blocking them blunts nicotine reward.

Drs. Bechara and Grant agree that with animal protocols that mimic different aspects of addiction—reward, craving, and relapse—scientists may learn what specific role the insula plays in drug abuse.

Source

- Naqvi, N.H., et al. Damage to the insula disrupts addiction to cigarette smoking. *Science* 315(5811):531-534, 2007. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 22, Number 3 (April 2009)

Prenatal Nicotine Exposure May Damage Receptors That Influence Auditory Processing

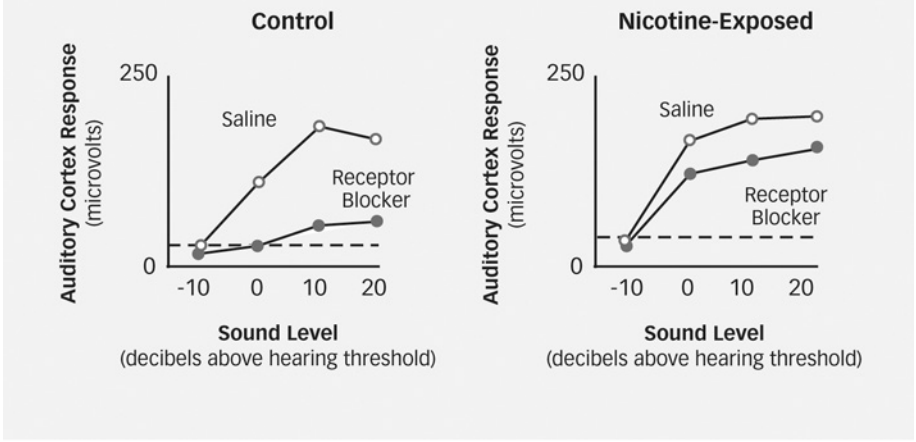
Tests correlate biochemical abnormality with deficits in rats' responses to sounds.

By *NIDA NOTES* Staff

Some children of women who smoked during pregnancy experience subtle difficulties processing auditory information; for example, they may have more than average problems recognizing slightly garbled words or understanding speech in a noisy environment. A recent series of animal experiments indicates that the cause of the problem is not in the ear but in the brain: Nicotine exposure during development damages a set of receptors in the brain's auditory processing center.

NICOTINE EXPOSURE DURING DEVELOPMENT ALTERS AUDITORY RESPONSE

Normal rats rely on nicotinic acetylcholine receptors in the auditory cortex to process auditory information. Rats exposed to nicotine shortly after birth have damaged nicotinic acetylcholine receptors and develop compensatory sound-processing mechanisms. As a result, blocking the receptors with mecamylamine reduces auditory cortex responsiveness dramatically in normal rats, but only slightly in rats exposed to the drug as pups.



Hearing Versus Heeding

The NIDA-funded experiments first demonstrated a deficit in sound processing in rats that had been exposed to nicotine at a developmental stage corresponding to that of a human fetus in the third trimester of gestation. Dr. Raju Metherate and colleagues at the University of California, Irvine, began by injecting rat pups with nicotine twice daily for 5 days (postnatal days 8 to 12). The injections produced nicotine blood levels approximating those of smokers, and presumably of pregnant smokers' fetuses. A group of same-aged control rats received injections of saline.

When the rats were 2 months old, a researcher trained them to escape an electrical shock by crossing from one chamber of an experimental box to another. The next day, a 5-second tone preceded each shock. All the animals immediately turned their heads toward the tone, indicating that they had heard it. Over 4 days, the rats had the opportunity to learn that the tone signaled an impending shock.

By the end of the training, all but one of the 12 control animals had learned the lesson well enough to routinely avoid the shock by crossing into the safe chamber during the tone. These animals moved to the safe chamber more rapidly as time went on, and eventually, many went into the safe chamber as soon as the tone began. Just 6 of the 11 rats exposed to nicotine, however, learned to associate the tone with the shock, and they responded more slowly than the control animals. The remaining 5 nicotine-exposed rats moved to the safe chamber only after receiving the shock.

A Less Responsive Cortex

The UC-Irvine researchers' next experiment linked the nicotine-exposed rats' poorer responses to warning tones to a difference in the animals' brains.

The auditory cortex is the brain's primary area for interpreting sounds. Normally, nicotine amplifies the cortex's responsiveness to auditory inputs. Researchers measure this effect by comparing electrical activity levels in the cortex before and after an injection of the drug.

Using this protocol when their rats were 2 to 3 months of age, Dr. Metherate's team documented smaller increases in cortical activity levels, on average, in the animals with early exposure to nicotine than in the control animals. Among adult rats not exposed to nicotine as pups, a stronger auditory cortex response to nicotine at 2 to 3 months

of age correlated with faster and more accurate learning to associate sound with electrical shocks. These observations may provide a hint why rats' early nicotine exposure leads to later difficulty using warning tones.

Underdeveloped Receptors

The researchers next investigated the underlying mechanism for their nicotine-exposed rats' diminished cortical responsiveness. The findings indicated that nicotine exposure during early development prevents a key receptor in the brain's acetylcholine signaling system from achieving full functionality.

Nicotine binds to the same receptors as acetylcholine, a chemical that neurons in the auditory cortex and elsewhere use to transmit electrical excitation to neighboring neurons. "When nicotine or acetylcholine binds to a receptor on the surface of a nerve cell, the binding process sets off chemical reactions inside the cell that help the cell function properly and fulfill its special physiological role," Dr. Metherate says.

The researchers measured electrical activity in the auditory cortex before and after injecting 2- to 3-month-old rats with mecamylamine, a compound that shuts down the nicotinic acetylcholine (nACh) receptors. The injection markedly reduced electrical activity in normal rats but made little difference in the rats that had been exposed to nicotine shortly after birth. This finding indicates that their nACh receptors were ineffective.

"Somehow, early nicotine exposure disconnects the receptors from the inside of the cell," Dr. Metherate says. "Acetylcholine and nicotine bind to the cell surface, but no chemical reactions take place in the interior."

A Clue and a Caution

Because human and rat brains process sounds similarly, the UC-Irvine findings may relate to the problems that people prenatally exposed to nicotine have interpreting sounds, and the experimental results may provide a clue to effective treatments as well. "If we can figure out how to reconnect the receptors to the activity inside the cells, we may be able to reverse these auditory-cognitive deficits in children, adolescents, or even adults," Dr. Metherate says.

He adds that nACh receptors also play a role in the development of other parts of the brain, including cortical areas that process vision and touch. So, prenatal nicotine exposure may undermine brain activity in those areas as well.

"Even though Dr. Metherate's rats were exposed to nicotine for only 5 days, the damage to their brains was long-lasting," says Dr. Thomas Aigner of NIDA's Division of Basic Neuroscience and Behavioral Research. "This is important information for women who think that smoking only intermittently during pregnancy is safe for the fetus. If they smoke during a critical period of brain development, in this case a few days into the third trimester, it looks as though the nicotine exposure can produce serious and long-lasting damage."

Sources

- Liang, K., et al. Neonatal nicotine exposure impairs nicotinic enhancement of central auditory processing and auditory learning in adult rats. *European Journal of Neuroscience* 24(3):857-866, 2006.
- Liang, K., et al. Nicotinic modulation of tone-evoked responses in auditory cortex reflects the strength of prior auditory learning. *Neurobiology of Learning and Memory* 90(1):138-146, 2008. NN

New Role for a Neurotransmitter and Its Receptor

Researchers have discovered a novel function of the nicotinic acetylcholine (nACh) receptor: It influences the propagation of signals along an axon.

Previous research had revealed nACh receptors along the myelinated axons that carry signals from the thalamus—a sensory processing center—to the auditory cortex. The new work, by Dr. Raju Metherate and colleagues Drs. Hideki Kawai and Ronit Lazar, at the University of California, Irvine, indicates that both nicotine and normally occurring acetylcholine activate nACh receptors along these axons, thereby increasing the effectiveness of a signal. This influence is distinct from the known mechanisms of acetylcholine activity at synapses.

"The regulation of axon excitability offers a powerful mechanism to control signal propagation," says Dr. Metherate. This action, he notes, might underlie nicotine's effect on the response of the auditory cortex to sound. However, that effect seems to be specialized. The team has recently found evidence that nACh receptors are not present along many other axons in the nervous system.

Source: Kawai, H.; Lazar, R.; and Metherate, R. Nicotinic control of axon excitability regulates thalamocortical transmission. *Nature Neuroscience* 10(9):1168-1175, 2007.

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 22, Number 3 (April 2009)

New Tracer for Nicotinic Receptors Promises Improved Specificity

Researchers at NIDA's Intramural Research Program have developed a radiolabeled compound for animal studies of nicotinic acetylcholine receptors in the brain. Tests in monkeys indicate that the new tracer readily enters the animals' brains and binds primarily to the nicotinic receptor subtype called $\alpha_4\beta_2$*. These receptors play a role in nicotine addiction and have been implicated in other neurological conditions, including dementia, epilepsy, depression, and anxiety.

In brain regions containing these receptors, the new radiotracer's accumulation is greater than that of 2FA, the tracer currently used in human imaging studies. As a result, the new tracer produces sharper and more detailed positron emission tomography images and may be especially useful for studying $\alpha_4\beta_2$* nicotinic receptors in brain areas where they are sparsely distributed. The specificity of the new radiotracer accumulation for the regions with these receptors is three- to four-fold that of 2FA, and tests in mice indicate that the new compound is equally safe, says Dr. Alexey G. Mukhin, now at Duke University in Durham, North Carolina.

If further animal and human imaging research confirms these results, the tracer could advance the study of the relationships between $\alpha_4\beta_2$* receptors and specific aspects of nicotine addiction and promote the development of medications for a wide variety of disorders. The chemical name for the new tracer is 6-chloro-3-((2-*(S)*-azetidinyl)methoxy)-5-(2-fluoropyridin-4-yl)pyridine ([^{18}F]NIDA522131).

Source

- *Journal of Neurochemistry* 104(2):306-315, 2008. NN

Adolescent Rats Self-Administer More Nicotine Than Adults

Studies comparing adolescent and adult rats have added to the evidence that the adolescent brain is particularly vulnerable to nicotine addiction. Dr. Edward D. Levin and colleagues at the Duke University Medical Center allowed male rats not previously exposed to nicotine to self-administer the drug for 4 weeks. During the first 2 weeks, the 13 adolescent rats took more than three times as much nicotine as the 13 adults. Nicotine consumption decreased as the adolescents matured, and it reached adultlike levels by the end of week 4.

In a prior study with female rats, the researchers found that adolescents self-administered twice as much nicotine as adults. Unlike the male rats in the current study, however, as the adolescent female rats matured, they continued to self-administer more nicotine than adults. Taken together, the team's results suggest that adolescent male rats may initially be more sensitive than females to nicotine, but females may experience a more persistent vulnerability.

Source

- *Neurotoxicology and Teratology* 29(4):458-465, 2007. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 22, Number 2 (December 2008)

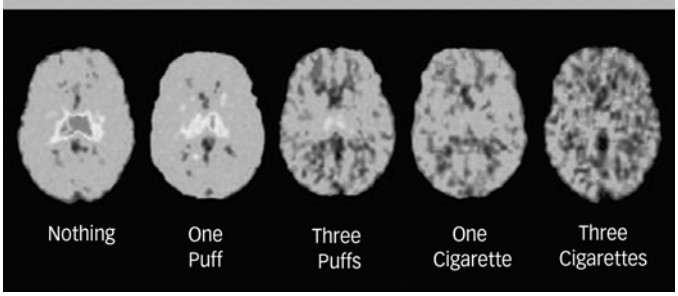
Imaging Studies Elucidate Neurobiology of Cigarette Craving

Researchers observe brain circuit activation, rapid receptor occupation.

By Lori Whitten, *NIDA NOTES* Staff Writer

One difference between a smoker and an ex-smoker is that the latter has successfully overcome cravings for tobacco. To learn how people achieve this feat, NIDA-funded researcher Dr. Arthur Brody has been looking inside the brains of would-be quitters. His findings, based on three separate imaging studies, indicate that when smokers actively resist cravings, they engage brain areas that focus attention and regulate emotion; that heavy smokers can stave off craving only by keeping virtually all nicotinic receptors in the brain filled; and that nicotine is the only component of cigarette smoke that occupies these receptors.

SMOKING SATURATES RECEPTORS As nicotine from a cigarette attaches to the $\alpha_4\beta_2$*-nACh nicotinic receptors in the brain, it displaces a radiolabeled tracer (red and yellow indicate high levels of the tracer, green indicates intermediate levels, and blue indicates low levels). The nicotine from three puffs displaced 75 percent of the tracer from study participants' receptors, and the nicotine from three cigarettes, nearly all.



Patterns of Resistance

In one study, Dr. Brody and his colleagues at the University of California, Los Angeles charted the changes in cerebral activity that accompanied willful resistance to videotaped smoking cues. One of the changes, intensification of activity in a specific brain area, parallels the effects of bupropion, suggesting that the anti-smoking medication may reinforce cognitive strategies that people naturally implement when they try to quit. Other specific brain activity changes identified in the study may provide leads for developing new medications and behavioral treatments for smokers.

Dr. Brody enlisted 42 men and women from the community at the Greater Los Angeles Veterans Affairs Healthcare System. On the morning of the study, each participant smoked a final cigarette and, 25 minutes later, put on a pair of special goggles to watch short video clips during brain scanning. The clips introduced the viewer to everyday situations—driving, writing a letter, standing outside a building. Two of every three clips also featured images that commonly incite nicotine craving, such as a view of someone taking out a lighter, preparing to light a cigarette, or actually smoking a cigarette. The researchers asked the participant to record the intensity of his or her craving, while either passively experiencing it or actively resisting it. The participants said that they usually resisted smoking cues by trying to distract themselves or ignore thoughts of smoking.

In the absence of smoking cues, the participants reported an average craving intensity of 2.4 out of a possible 5. The intensity rose to 3.0 when they saw a smoking cue. The intensity of the craving was similar whether or not the participants resisted the urge to smoke.

The researchers collected functional magnetic resonance images (fMRI) of the participants' brains while they were watching the videos. During efforts to resist smoking, activity increased in the dorsal anterior cingulate cortex (DACC) region, which participates in focusing attention and controlling emotions, as well as decisionmaking and planning, conflict avoidance, and error detection. Dr. Brody suggests that this DACC activation may reflect the participants' struggles to direct their attention away from cigarettes. Other researchers have noted intensified DACC activity when individuals employ specific trains of thought to try to control their emotional responses to anxiety-provoking stimuli. Engaging this area repeatedly may strengthen the neural circuit and bolster smokers' ability to resist cigarettes.

Dr. Brody and colleagues were intrigued by other changes in brain activity that occurred when their study participants resisted smoking cues. Among these were increased activity in the posterior cingulate cortex (PCC), which processes emotions and related sensory information, and in the precuneus, which has been related to consciousness of self.

Simultaneously, the team observed decreased activity in the lateral occipital and right postcentral gyri (LOG and RPG); the LOG deals with visual input and the RPG modulates movement. Changes in these areas had not been previously observed in the context of smoking ces-

sation and so may provide new clues to the cognitive and emotional dynamics that accompany that effort.

Taken together, these findings suggest that actively resisting the urge to smoke involves a redistribution of neural activity from sensory and motor areas of the brain to those that mediate rewards and emotions.

Smoking's Dramatic Effects on Receptors

In another study that underscores the challenge of quitting, Dr. Brody's team charted relationships between smoking, craving, and nicotinic receptors. They found that heavy smokers crave nicotine whenever the drug occupies less than 95 percent of the most common nicotinic receptors, the $\alpha_4\beta_2$*-nACh subset, in the brain. Smoking just a few puffs goes a long way toward saturating these receptors, which are the primary sites where nicotine attaches to brain neurons and exerts its psychoactive and physiological effects.

Although scientists have known that stimulation of these receptors underlies nicotine addiction, newly developed radiotracers have helped them measure receptor occupancy much more accurately and connect it to craving and other symptoms of withdrawal.

The 11 volunteers who took part in this study had smoked for 18 years, on average, and were currently smoking a pack a day. On the day of the study, following 2 days of abstinence, the participants smoked and reported their intensity of craving as the researchers used positron emission tomography (PET) imaging to observe $\alpha_4\beta_2$*-nACh receptors.

The images revealed that smoking occupied $\alpha_4\beta_2$*-nACh receptors throughout the brain with striking completeness, and for several hours. After the first puff, nicotine occupied one-third of the receptors; after the third puff, 75 percent; and after a full cigarette, 88 percent. As receptor occupancy increased, the participants' craving decreased, until—generally after 2.5 to 3 cigarettes—they achieved complete relief at about 95 percent occupancy.

"Our findings show how many receptors are taken up by nicotine," says Dr. Brody. "My colleagues and I were surprised that just one puff started to fill the receptors so substantially."

The team's findings suggest that some of the behaviors that characterize nicotine addiction may be explained by smokers' need to maintain receptor saturation. "Many smokers say they must have a cigarette to get their day going, which makes sense because receptor occupancy would be quite low after waking," says Dr. Brody.

Although near saturation of nicotinic receptors relieves craving, nicotine dependent people smoke beyond this point. Moreover, Dr. Brody notes that "blood levels of nicotine that accompany replacement therapies, such as the patch or gum, would likely saturate the receptors, yet only 20 to 25 percent of smokers on this treatment stay abstinent for a year." These observations suggest that other factors also drive smoking.

Evidence of Other Factors

To separate the impact of nicotine from other aspects of smoking—including the more than 4,000 chemicals other than nicotine in cigarette smoke—Dr. Brody and colleagues conducted a third study. The investigators followed a procedure that paralleled the one they had used to track the impact of smoking on $\alpha_4\beta_2$*-nACh receptors. Again, they charted the relationships between smoking, craving, and nicotinic receptors—this time in response to cigarettes with only a trace amount of nicotine.

The 15 volunteers who took part in this study had smoked for 14 years and were currently smoking 19 cigarettes a day, on average. In two sessions, each after 2 days of abstinence and separated by at least a week, they participated in PET imaging scans and reported their intensity of craving. On one study day, the participants smoked a denicotinized cigarette. On the other study day, seven participants did not smoke, and eight smoked a low-nicotine cigarette.

The images revealed that smoking a denicotinized cigarette, which contains only about 4 percent of the nicotine in a regular cigarette, resulted in a 26 percent occupancy of nicotinic receptors, compared with 79 percent after a low-nicotine cigarette (half the nicotine content of a regular cigarette), and no occupancy among those not given any cigarette. The 26 percent occupancy by smoking a denicotinized cigarette was predicted based on the amount of nicotine present.

This study demonstrates that of all the chemicals found in cigarette smoke, nicotine is responsible for virtually all $\alpha_4\beta_2$*-nACh receptor occupation, the researchers note. These findings also demonstrate that smoking a cigarette with only a trace amount of nicotine leads to substantial receptor occupancy in the brain.

Although smoking a denicotinized cigarette had a smaller impact on nicotinic receptors compared with the effects of a low-nicotine or regular cigarette, it did lessen craving. Before they smoked, the participants reported an average craving intensity of about 5 (on a scale of 0 to 6); these reports fell to 3.6 and 2.4 for those smoking a denicotinized and low-nicotine cigarette, respectively. This accords well with findings of prior studies indicating that denicotinized cigarettes reduce the urge to smoke. The taste, smell, and feel of cigarette smoke in the mouth contribute to smoking's appeal, Dr. Brody says, and denicotinized cigarettes do provide these sensory experiences. Additional

factors, such as stress and the perceived pleasure of smoking, also may play a role.

These findings elucidate why it is so difficult to give up cigarettes, according to Dr. Brody. "The many effects of smoking, including elevated mood and alleviation of anxiety, suggest that a long-term smoker may face considerable biochemical, cognitive, and emotional readjustments when he or she quits," says Dr. Brody.

Dr. Ro Nemeth of NIDA's Division of Clinical Neuroscience and Behavioral Research adds that inhalation is the fastest way for any drug to reach the brain. "The connection between a puff on a cigarette and the positive feelings it quickly generates helps maintain smoking, even when people know its negative consequences and want to quit," Dr. Nemeth says.

Sources

- Brody, A.L., et al. Brain nicotinic acetylcholine receptor occupancy: Effect of smoking a denicotinized cigarette. *International Journal of Neuropsychopharmacology*, published online 2008.
- Brody A.L., et al. Neural substrates of resisting craving during cigarette cue exposure. *Biological Psychiatry* 62(6):642-651, 2007.
- Brody, A.L., et al. Cigarette smoking saturates brain alpha 4 beta 2 nicotinic acetylcholine receptors. *Archives of General Psychiatry* 63(8):907-915, 2006.

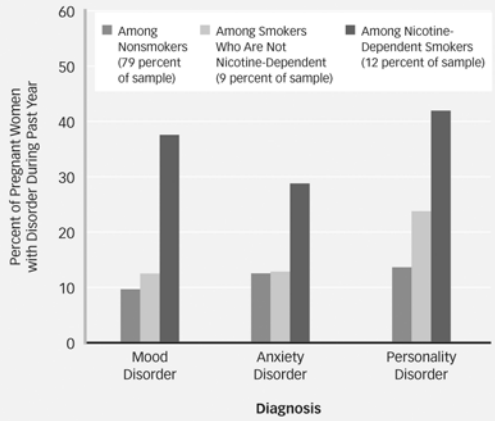
NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 22, Number 2 (December 2008)

Nicotine Dependence Is Linked With Mental Disorders in Pregnant Women



The link between mental disorders and nicotine dependence that had been previously observed in the general population also pertains to pregnant women, according to a U.S. survey that included 1,516 pregnant women. Taking into account important characteristics—including age, education, income, and marital status—associations appeared between nicotine dependence and having a mood, anxiety, or personality disorder. The presence of mental disorders may make smoking cessation particularly difficult. Smoking during pregnancy is of special concern because, according to prior research, it increases the risk of women having infants with low birth weight; such children subsequently face an elevated risk of health consequences and of learning and behavior problems.

SOURCE: An analysis of data from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions reported in Goodwin, R.D., Keyes, K., and Simuro, N. Mental disorders and nicotine dependence among pregnant women in the United States. *Obstetrics and Gynecology* 109(4):875-883, 2007.

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 21, Number 6 (June 2008)

Behavioral Problems Related to Maternal Smoking During Pregnancy Manifest Early in Childhood

Researchers find probable precursors of adolescent conduct disorders in the behavior of toddlers and schoolchildren.

By *NIDA NOTES* Staff

Many studies have established that a pregnant woman's smoking raises her child's risk of disruptive behavior disorders and of delinquency in the teen and young adult years, but its behavioral effects in early life have been been difficult to trace. Now, however, NIDA-funded researchers have revealed associations between a child's *in utero* exposure to smoking and specific patterns of aberrant behavior as a toddler, at school age, and as a teen. The researchers propose that these patterns form a continuum, united by an underlying theme of disrupted social information processing.

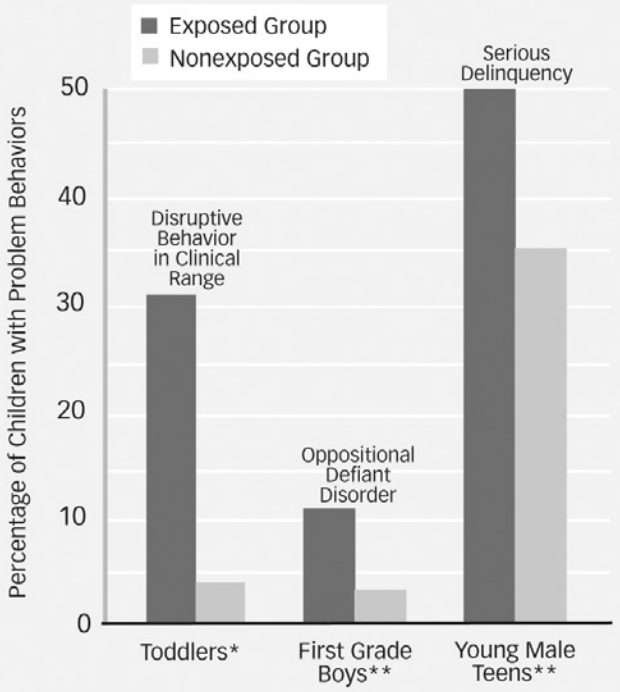
An Early Start to Disruptive Behavior

In an initial study, Dr. Lauren Wakschlag of the Institute for Juvenile Research at the University of Illinois at Chicago and her colleagues, Dr. Rolf Loeber of the University of Pittsburgh and Dr. Kate Pickett of The University of York in England, analyzed disruptive behavior patterns in first graders and subsequent problems that have been associated with later delinquency. Data were derived from the first-grade cohort of the Pittsburgh Youth Study (PYS), a community sample of boys at risk for delinquency who were followed over several decades under the direction of Dr. Loeber.

The researchers concentrated on 448 boys, who were roughly age 7 when the PYS study began. One hundred and sixty-six boys in this group had mothers who smoked during pregnancy. These boys developed the antisocial behavior pattern known as oppositional defiant disorder (ODD) at more than double the rate of the rest (see graph). Children with ODD demonstrate defiant, disobedient, and hostile behavior towards authority figures that persists for at least 6 months, and they are touchy, easily angered, and resentful. ODD is often considered a developmental precursor of conduct disorder (CD), a condition in older children and adolescents characterized by persistent antisocial behaviors such as lying, truancy, vandalism, and aggression.

Boys whose mothers smoked while pregnant did not have a higher incidence of attention deficit hyperactivity disorder (ADHD) without ODD than the nonexposed boys. However, the incidence of co-occurring ODD and ADHD—a combination that often results in chronic disruptive behavior problems—was nearly twice as high in the exposed group as in the nonexposed group. As the boys entered and traversed their teens, delinquent behavior began earlier and was more severe in the exposed group.

PATHWAY TO TROUBLE Children of mothers who smoked during pregnancy had higher rates of disruptive behavior throughout development. Toddlers were evaluated for disruptive behavior; first grade boys for oppositional defiant disorder; and young teenage boys for serious delinquency.



"All the children with ODD in the PYS study were diagnosed in first grade, meaning the disorder developed in the first 5 or 6 years of life. This provides evidence of a

coherent developmental pathway from prenatal exposure to cigarettes to a subsequent sequence of conduct problems," Dr. Wakschlag says. "While previous research established a link between prenatal exposure to cigarettes and CD in older children, this study is the first to establish connections to ODD and to do so as early as first grade."

Toddlers With Troubles

To look for exposure-related behavioral abnormalities at even younger ages, Dr. Wakschlag's team conducted the Family Health and Development Project (FHDP), in collaboration with colleagues from the University of Illinois, The University of York, the National Institute of Mental Health, and the University of Massachusetts-Boston. The researchers recruited 96 expectant mothers, age 18 and older, at several clinics. The women were predominantly white and working class. Along with the women's self-reports, the researchers collected biological data, such as measurements of the nicotine metabolite cotinine in urine samples, to assess fetal exposure to maternal smoking. These measurements, taken three times during pregnancy, indicated that 47 percent of the women smoked throughout their pregnancies. Ninety-three infants and their mothers completed the study's developmental phase, which lasted until the babies were 24 months old.

The babies were evaluated every 6 months. At the 12-, 18-, and 24-month evaluations, each mother filled out the Infant-Toddler Social Emotional Assessment (ITSEA). During 20-minute laboratory observations of the toddlers and their mothers interacting at 24 months, the researchers rated specific components of the toddlers' behavior using codes from the Disruptive Behavior Diagnostic Observation Schedule.

The results indicated that toddlers whose mothers had smoked during pregnancy demonstrated a high and escalating pattern of disruptive behavior from 12 to 24 months, whereas nonexposed toddlers exhibited a relatively stable pattern. A mother's smoking during pregnancy increased the likelihood of the observed atypical trajectory of behavior independent of several associated risk factors, including parental antisocial behavior, quality of parenting, and postnatal exposure to tobacco smoke. At 24 months, toddlers whose mothers had smoked while pregnant were more than 11 times as likely as nonexposed peers to exhibit clinically significant patterns of disruptive behavior, shown on the ITSEA.

To more precisely determine the nature of the boys' behavior problems, the researchers examined four components of disruptive behavior, each of which is considered a precursor to disruptive behavior patterns seen at later ages:

- Aggressive/destructive behavior, including threatening, hitting, and throwing or smashing toys;
- Dysregulated negative affect, characterized by persistent, uncontrolled outbursts of anger with loud yelling, intense crying, and temper tantrums;
- Stubborn defiance, marked by obstructive behavior that persists after the mother has increased expressions of support for her child and has tried several strategies to change her child's behavior; and
- Low social competence, where the child misses social cues and exhibits low social interest or concern.

These four behaviors, while viewed as normal in toddlers, are considered precursors to clinical problems if they are severe or pervasive.

The children whose mothers had smoked during pregnancy displayed lower social competence than other children and significantly higher levels of aggressive/destructive behavior and stubborn defiance. They were not more likely to exhibit dysregulated negative affect.

"Dr. Wakschlag has teased out some components of disruptive behavior problems when they first emerge between 18 and 24 months of age," says Dr. Nicolette Borek of NIDA's Division of Clinical Neuroscience and Behavioral Research. "This gives us a way to identify at-risk children early and raises interesting questions about the role of brain development in later-stage behavioral issues."

On to Adolescence

Dr. Wakschlag and colleagues have hypothesized that the resistant, hostile, and unresponsive patterns of behavior demonstrated in FHDP, PYS, and similar studies may reflect disruptions in social-information processing that resulted from prenatal exposure to cigarette smoke. To test this hypothesis, the team is conducting the NIDA-funded East Boston Family Study (EBFS), which includes 272 adolescents and is a followup to the Maternal-Infant Smoking Study of East Boston (MISSEB). Dr. Wakschlag and her colleagues are also examining the influence of genetic makeup on exposure-related disruptive behavior among these young people. The researchers are using maternal exposure data originally collected by MISSEB but applying more sophisticated methods to measure prenatal exposure to cigarette smoke. These new techniques, which combine maternal self-report and biological data, were developed from FHDP-derived data by Dr. Vanja Dukic at the University of Chicago in collaboration with Dr. Neal Benowitz of the University of California, San Francisco and Dr. Wakschlag.

"Maternal self-reports are affected by memory lapses and social pressure not to smoke, and biological methods can be inaccurate because the smoke-derived chemicals have a short half-life and rates of metabolism differ among individuals," says Dr. Wakschlag. "In addition, we know that smoking levels fluctuate throughout a pregnancy. The

new technique incorporates the unique information from both of these methods to provide a more precise estimate of prenatal exposure to cigarettes."

Sources

- Wakschlag, L.S., et al. A developmental framework for distinguishing disruptive behavior from normative misbehavior in preschool children. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 48(10; Special Issue on Preschool Psychopathology): 976-987, 2007.
- Wakschlag, L.S., et al. Is prenatal smoking associated with a developmental pattern of conduct problems in young boys? *Journal of the American Academy of Child and Adolescent Psychiatry* 45(4):461-467, 2006.
- Wakschlag, L.S., et al. Elucidating early mechanisms of developmental psychopathology: The case of prenatal smoking and disruptive behavior. *Child Development* 77(4):893-906, 2006. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 21, Number 4 (October 2007)

Endorphin Derivative Inhibits Reward From Morphine and Nicotine in Rats

Recent studies suggest therapeutic potential for glycyl-glutamine in opiate and nicotine addiction.

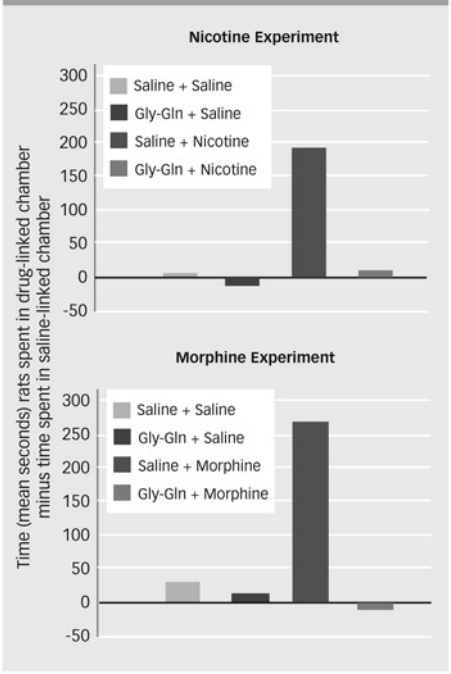
By Sarah Teagle, *NIDA NOTES* Contributing Writer

A naturally occurring brain chemical has shown early promise as a treatment for addiction. NIDA-funded researcher Dr. William Millington and colleagues at Albany College of Pharmacy demonstrated that glycyl-glutamine (Gly-Gln), a product of the conversion of one form of beta endorphin to another, reduces the rewarding effects of morphine and nicotine and the severity of withdrawal from these drugs in rats.

The researchers utilized an animal model called conditioned place preference (CPP; for more on CPP, see "Animal Experiments in Addiction Science," *NIDA Notes*, Vol. 20, No. 5). When pretreated with Gly-Gln, rats stopped preferring a cage in which they received morphine infusions over another in which they received a physiologically inert substance. The investigators concluded that Gly-Gln completely blocked the brain-rewarding effects of morphine. They used the same experimental technique to demonstrate that Gly-Gln pretreatment also blocks the rewarding effects of nicotine in rats.

GLY-GLN BLOCKS THE REWARDING EFFECTS OF NICOTINE AND MORPHINE

Rats trained to associate nicotine or morphine infusions with a particular chamber showed a clear preference for the drug-linked chamber when later allowed to roam freely between it and a second chamber. Rats that were pretreated with Gly-Gln prior to receiving nicotine or morphine divided their time roughly equally between drug-linked and saline-linked chambers.



Some chemicals that block the rewarding effects of drugs of abuse also take away subjects' pleasure in normal healthy activities. Again using CPP, Dr. Millington's team demonstrated that Gly-Gln does not have this drawback, at least in regard to one food—a sweetened cereal—that rats enjoy.

Subsequently, Dr. Millington and his coinvestigators examined Gly-Gln's effect on withdrawal from morphine. They induced morphine dependence in the rats, injected some with Gly-Gln 72 hours later, and then administered the opioid antagonist naloxone to induce withdrawal. Across all measures, the Gly-Gln pretreated rats exhibited significantly fewer behavioral and physiological signs of withdrawal than the others. The researchers observed a similar effect when they induced withdrawal from nicotine with the agent mecamylamine.

Safe Analgesia, Too?

In separate studies, Dr. Millington and colleagues found evidence that Gly-Gln has potential for improving pain treatment by slowing the development of morphine tolerance. The investigators treated rats with morphine twice daily for 7 days and, each day, measured the rats' reaction to pain with tail-flick latency tests. They observed that the pain-relieving effects of morphine declined 20 percent by the second day, an indication that tolerance had developed rapidly. However, rats pretreated with Gly-Gln did not begin showing evidence of morphine tolerance until the fourth day of treatment. Their level of pain relief had dropped to 75 percent of the maximum by day 4, compared with 39 percent for rats that were not pretreated.

These findings offer new hope for making pain treatment more effective, but without adding to the problems of painkiller abuse and prescription drug diversion. Dr. David Thomas of NIDA's Division of Basic Neuroscience and Behavioral Research explains, "It is like a tug-of-war; we want better pain treatment, but we do not want more addiction. If we can find a medication that improves the management of chronic pain without causing addiction or the negative physical side effects, then it really is a win-win situation. Gly-Gln may give us that."

"We need to learn much more about Gly-Gln's pharmacology before we can develop it into a drug that is useful clinically," says Dr. Thomas. "The profile of its effects brought out by Dr. Millington's work is striking. It makes a strong argument for taking the research to the next step: understanding its mechanism of action in the brain. In our world of preclinical animal research, we really could not ask for better findings. So far, everything we know about Gly-Gln is promising."

Sources

- Cavun, S.; Goktalay, G.; and Millington, W.R. Glycyl-glutamine, an endogenous beta-endorphin-derived peptide, inhibits morphine-induced conditioned place preference, tolerance, dependence, and withdrawal. *Journal of Pharmacology and Experimental Therapeutics* 315(2):949-958, 2005.
- Goktalay, G., et al. Glycyl-glutamine inhibits nicotine conditioned place preference and withdrawal. *European Journal of Pharmacology* 530(1-2):95-102, 2005. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 21, Number 3 (April 2007)

Genes and Smoking

By NIDA Director Nora D. Volkow, M.D.

Most of the 44.5 million American adults who smoke cigarettes would prefer not to. Why do so many would-be quitters fail, even with the help of stop-smoking interventions like nicotine replacement? Why, for that matter, do people become addicted to smoking in the first place? The answers lie partly in our genes.

NIDA researchers in collaboration with Perlegen Sciences, Inc., a private company, recently completed a search of the entire human genome for differences between individuals who are nicotine-dependent and those who smoked but never became dependent. Their target: single nucleotide polymorphisms (SNPs), locations on the genome where individuals differ by just one chemical unit in the makeup of their DNA. From 2.2 million known SNPs, researchers have identified roughly 40 to 80 that are highly correlated with nicotine addiction.

Once researchers link an SNP statistically to drug abuse, the question becomes: Does the gene do anything that might explain why people with one of its forms are more vulnerable to drugs than people with another? Some of the genes researchers have implicated in addiction affect the dopamine reward circuit. Others involve neurotransmitter systems and neural pathways not previously known to figure in smoking's effects. Researchers will use techniques such as brain imaging to correlate genetic differences with differences in brain structure or function and psychological tests to match them to behavior. Findings from the genome exploration may ultimately yield novel, more effective interventions.

Genetic variations can only partly explain why people become addicted to nicotine: A person's genetic makeup, experiences, and surroundings all combine to determine whether he or she will smoke and, if so, how difficult quitting will be. NIDA-funded epidemiologists and behavioral scientists are conducting a large longitudinal study to elucidate these interactions. They have been following pairs of twins, now 17 years old, collecting information about participants' smoking and environmental factors like stressors and peer relationships that can increase the risk of substance abuse or protect against it. The next step will be to analyze these data, together with information on the twins' genetic and biological traits.

NIDA-supported researchers are also working to discover why interventions like nicotine replacement therapy (NRT) work for some people and not others. By comparing smokers who have successfully used pharmacotherapy with those whose efforts to quit have failed, the researchers hope to identify groups of genes that predict who will do well with NRT, with bupropion, or with varenicline, the newest smoking cessation drug. The ultimate goal is to tailor the treatment to the smoker. Ultimately, we hope genetic studies will lead to strategies that protect vulnerable young people from addiction. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 21, Number 3 (April 2007)

Standard Treatments Help Depressed Smokers Quit

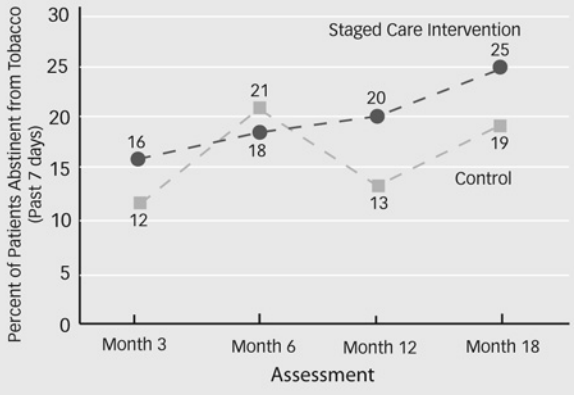
As smoking rates fall in the United States, mentally ill individuals comprise a larger percentage of people who continue to light up.

By Lori Whitten, *NIDA NOTES* Staff Writer

Smoking cessation interventions that are effective in the general population also help for depressed smokers, suggests a study of outpatients at four mental health clinics. Dr. Sharon Hall and colleagues at the University of California, San Francisco; the University of Rhode Island; and Kaiser Permanente Northern California found that depressed smokers who were treated with a combination of motivational counseling, nicotine patches, and behavioral therapy were more likely than their counterparts who did not receive the interventions to be smoke-free at 12- and 18-month assessments.

"Patients in our study mirrored the general population of smokers in their readiness to quit, acceptance of treatment, and cessation outcomes—findings that surprised me and my colleagues," says Dr. Hall, lead investigator of the study. Further, patients with severe symptoms of depression both accepted the interventions and benefited from them. "Our findings suggest that clinicians should offer depressed outpatients nicotine addiction treatment and should start with available smoking cessation interventions. They need not be overly concerned about patients' levels of depression," says Dr. Hall.

MORE DEPRESSED SMOKERS QUIT WITH STAGED CARE INTERVENTION Among smokers in outpatient treatment for depression, more who participated in the Staged Care Intervention achieved abstinence at the 12- and 18-month followups compared with participants in the control group.



The investigators recruited 322 men and women from a university-based clinic and three sites of a health maintenance organization who were being treated for depression and smoked daily. Most of the volunteers (79 percent) were taking psychiatric medication for moderate depression. On average, they had smoked for 24 years, smoked 15 cigarettes a day, and had tried to quit six times.

At the start of the study, the participants provided information on their depression severity and treatment, smoking behavior (confirmed by expired air carbon monoxide measurements), nicotine dependence level, readiness to quit smoking, previous quit attempts, and commitment to abstinence. They repeated these self-reports 3, 6, 12, and 18 months later.

The active intervention in the study was Staged Care Intervention (SCI). At the outset and months 3, 6, and 12, participants assigned to SCI answered a computerized questionnaire about smoking, its advantages and disadvantages, triggers for smoking-related thoughts and behaviors, and ways to change these thoughts and behaviors. The computer provided an individualized feedback report that the patients and counselors reviewed together in a 15-minute session. The report classified each patient's readiness to quit based on the Stages of Change model, compared his or her responses with those of others in the program, showed changes from earlier reports, and identified triggers for smoking and strategies to move to the next stage. If the patient expressed a desire to quit, he or she began an 8-week cessation treatment. Each participant in the control group received a self-help guide to smoking cessation and a list of programs in the area, but no therapeutic contact or advice about smoking cessation.

Opportunity to Engage

About one-third (34 percent) of SCI participants entered cessation treatment. They received nicotine patches (7, 14, or 21 mg, depending on level of smoking and week of study) and six 30-minute counseling sessions. The focus of counseling was immediate and complete cessation at an agreed-upon date. During sessions, patients developed a commitment to abstinence, established a quit plan, identified reasons for smoking, reviewed the benefits of quitting, and received information on nutrition and exercise.

Patients who did not attain abstinence with nicotine patches were prescribed bupropion if their mental health care provider deemed it medically appropriate.

The researchers included all SCI participants, including those who did not enter cessation treatment, in their data analysis. At the 12-month assessment, 20 percent of participants in the SCI group and 13 percent in the control group had verified 7-day tobacco abstinence. The SCI group's advantage persisted at the 18-month assessment (25 percent versus 19 percent). More SCI (44 percent) than control group participants (34 percent) endorsed permanent abstinence—an attitude the researchers say predicts success in changing behavior. The intervention was particularly effective for heavy smokers: Among participants who smoked more than a pack of cigarettes a day, those assigned to SCI were about twice as likely as controls to report a quit attempt during the study.

Computer Feedback Nurtures Change

Excerpts from two feedback reports illustrate indivualized care:

Feedback for a person who has no immediate intention to stop smoking: Your answers on the last survey show that you need to begin to change the way you look at yourself as a smoker. You can do this by thinking more about your attitudes and beliefs about your smoking. For example:

- If you think smoking could be bad for your health, be specific about how smoking is affecting you. (For example: Cigarettes give me a sore throat—or cause my cough—or make me feel tired all the time.)
- How would your life change if you quit? (For example: I would set a better example for others—or I'd have more money to spend on things I enjoy.)
- What might be difficult if you quit? Can you plan in advance how you will handle those difficulties? (For example: I could get more exercise so I won't gain weight.)

Feedback for a person who intends to quit in the next 6 months: You seem to be well aware of the risks of smoking … you're doing as well as others who have used this program to help themselves quit smoking! To make more progress:

- Weigh the "pros" and "cons" of smoking;
- Learn more about quitting; and
- Keep thinking of how you're doing.

"The findings of Dr. Hall and her colleagues suggest that, even among severely depressed smokers who are not motivated to quit, the SCI increases abstinence rates compared with a standard control," says Ms. Debra Grossman of NIDA's Division of Clinical Neuroscience and Behavioral Research. The finding adds to the justification for American Psychiatric Association and Agency for Health Care Research and Quality recommendations to offer smoking cessation therapy to people with mental disorders.

"The high prevalence of smoking in mental health clinics presents an opportunity to engage people with depression in smoking cessation," says Dr. Hall. She adds that one advantage to doing so is the supportive environment of such settings: if cessation worsens depression, then patients can obtain additional help. Dr. Hall notes that the treatment benefits seen among the study population of mostly employed patients enrolled in a health maintenance organization might not apply to depressed people who are disadvantaged or in treatment at publicly funded hospitals. Dr. Hall's team plans to conduct a cost-effectiveness analysis of the intervention to help clinic directors decide on resource allocation.

Source

- Hall, S.M., et al. Treatment for cigarette smoking among depressed mental health outpatients: A randomized clinical trial. *American Journal of Public Health* 96(10):1808-1814, 2006. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 21, Number 3 (April 2007)

Vaccine May Reduce Fetal Exposure to Nicotine

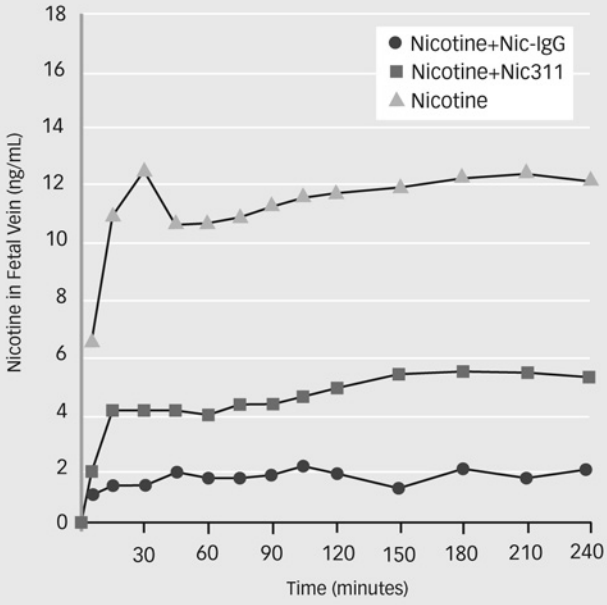
Antibodies that block nicotine's path across the blood brain barrier may also inhibit placental absorption.

By Carl Sherman, *NIDA NOTES* Contributing Writer

Vaccine-induced antibodies that facilitate smoking cessation by blocking nicotine penetration into the brain also markedly reduce the drug's passage across the *ex vivo* human placenta, a NIDA-funded study has demonstrated. The finding suggests that maternal immunization during pregnancy may be safe and may to some extent protect the fetus from exposure to nicotine.

The adverse effects of maternal smoking during pregnancy include increased rates of miscarriage, premature delivery, low birth weight, neonatal mortality, and sudden infant death syndrome (SIDS). Increasingly, research has linked prenatal smoking exposure to children's neurobehavioral problems, such as attention deficit-hyperactivity disorder. The role of nicotine in causing this damage is not entirely clear, but animal studies suggest the drug may compromise fetal development directly or through its effects on the placenta. "We desperately need medications that can help women quit smoking during pregnancy, medications that are both effective and do not themselves harm the fetus. This study supports the potential use of immunization," says Dr. Paul Pentel of the University of Minnesota Medical School, one of the investigators.

RESULTS OF MEASURING THE CONCENTRATION OF NICOTINE IN THE FETAL VEIN The addition of a nicotine-specific antibody significantly reduces the appearance of nicotine in the fetal vein. Of two antibodies tested, Nic-IgG was more effective than NIC311.



The Experimental Procedure

NicVAX, a vaccine being developed by Florida-based Nabi Biopharmaceuticals with NIDA support, joins the nicotine molecule to a protein. The resulting molecule provokes the production of antibodies that combine with circulating nicotine to create a complex molecule that is too large to cross the blood-brain barrier. When the amount of nicotine reaching the brain drops far enough, the concept goes, "the smoker will no longer get a rewarding effect and will quit," says Dr. Scott Winston, a Nabi researcher. A recent small-scale clinical study found dose-related improvements in 30-day quit rates among 68 immunized smokers ("Nicotine and Cocaine Vaccines Move Forward," *NIDA Notes*, Vol. 20, No. 5).

The two antibodies used in the placenta transfer study, nicotine immune globulin (Nic-IgG) and a monoclonal antibody (Nic311) were taken, respectively, from rabbits and mice that produced them in response to immunization with NicVAX. The research team, headed by Dr. Mahmoud Ahmed of the University of Texas Medical Branch, Galveston, tested the antibodies' effects on placental tissue and cross-placental nicotine transfer using a method developed in the mid-1980s: An intact lobule was dissected from placentas taken immediately after delivery and placed in phosphate-buffered saline. The researchers inserted catheters into blood vessels on the maternal and fetal side of the placental lobule and perfused each with tissue culture medium from a separate reservoir, creating distinct maternal and fetal circuits. They monitored placental function and viability for 2 hours, and then added nicotine to the fluid in the maternal reservoir. "We used a concentration (40 ng/mL) that has been reported in the circulation of mothers who smoke," Dr. Ahmed says. Either Nic311 or Nic-IgG along with nicotine was added to the maternal reservoir. Following these infusions, the researchers continued to monitor placental tissue health and tracked nicotine and antibody concentrations in both maternal and fetal circuits for 4 more hours.

Safety Reassurance

"Our primary interest in these studies was vaccine safety: Would it be safe to vaccinate women who may become pregnant, or during pregnancy? Antibodies might protect the fetus, but we also worried that they might escort nicotine across the placenta or sequester it in the fetus, increasing exposure," says Dr. Pentel. "The studies look reassuring."

When nicotine alone was added to the maternal circuit, it readily crossed the placenta; its concentration in the fetal circuit increased rapidly over the first 30 minutes. It did not change in the next 210 minutes. The addition of either antibody markedly reduced the rate at which nicotine crossed the placenta. With Nic311, nicotine reached a concentration of 1.8 ± 0.8 ng/mL in the fetal circuit in the first 5 minutes—about one-fourth of the transfer in the absence of the antibody. There was no significant increase in fetal circuit nicotine after the first 30 minutes. Nic-IgG had an even more pronounced effect: The concentration of nicotine in the fetal circuit was about one-half what it had been with Nic311 after the first 5 minutes (1.0 ± 0.04 ng/mL); it, too, rose little after that. Both antibodies also reduced the amount of nicotine retained in placental tissue.

"There was no effect of nicotine or either antibody on placental function or viability," Dr. Ahmed says. No appreciable amount (less than 1 percent) of either antibody appeared in the fetal circuits at any point in the experiment, suggesting that placental transfer was negligible.

Whether vaccination would protect the fetus from nicotine if a mother continued smoking is not yet clear. "I'm not sure that the effect would be large enough," Dr. Pentel says. Previous animal studies in which he was involved found that while antibodies sharply slow the rate at which a single dose of nicotine reaches the brain, they do not stop the process altogether. "When nicotine is administered chronically in a way that approximates daily smoking, its long-term accumulation in the fetal brain looks the same in vaccinated and unvaccinated animals." Vaccination of pregnant rats reduced nicotine transfer to the fetal circulation and brain for 25 minutes after a single dose, but did not change accumulation in the fetal brain when nicotine was administered chronically. In another study, maternal vaccination did not prevent nicotine-induced upregulation of nicotinic cholinergic receptors or changes in gene expression (*c-fos*) in the fetal rat brain, Dr. Pentel observes. The *ex vivo* system used in the current study is not intended to model the effects of continual daily smoking, he says, but rather provides insight into the shorter term effects of antibodies on nicotine transfer across the placenta, as well as placental viability.

Dr. Amrat Patel, of NIDA's Chemistry and Pharmaceutics Branch, says the current study represents an important advance beyond animal research in suggesting that nicotine-specific antibodies can reduce placental transfer of nicotine in humans as well, but more work is needed to know whether the effect will be sufficient to prevent neurotoxicity. "We need to determine how much nicotine is necessary to cause fetal damage, and how to make sure nicotine does not approach that level." Antibodies with higher affinity for nicotine may make a difference, he says; as vaccine research continues, "we'll probably progress to develop antibodies that are even better able to sponge up nicotine."

Source

- Nekhayeva, I.A., et al. Effects of nicotine-specific antibodies, Nic311 and Nic-IgG, on the transfer of nicotine across the human placenta. *Biochemical Pharmacology* 70(11):1664-1672, 2005. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 21, Number 2 (February 2007)

Nicotine Alters the Developing Rat Brain

Exposure to the drug during gestation or adolescence may cause lasting alterations in reward and motivation circuits.

By Carl Sherman, *NIDA NOTES* Contributing Writer

Most people who become chronic smokers start in adolescence, and the risk of addiction at this time is even greater among those whose mothers smoked while pregnant. NIDA-funded animal studies recently identified two neurobiological effects of nicotine that could underlie these vulnerabilities. Investigators at the University of Tennessee, led by Dr. Burt Sharp, found that prenatal nicotine exposure reduces the availability during adolescence of a receptor that mediates the drug's impact on cells in the brain's reward system. At the University of Wisconsin, Dr. Charles Landry and his research team found that nicotine stimulates a set of genes involved in synapse formation to a higher level of activity in adolescent than in adult rats.

LOWER BINDING CAPACITY SUGGESTS LOWER NICOTINE REWARD The capacity to bind epibatidine is a marker for the concentration of nicotinic cholinergic receptors in a tissue sample. In the brain regions tested, this capacity was significantly lower in adolescent rats that had been exposed to nicotine during gestation. This suggests that prenatal exposure reduces later nicotine sensitivity in a brain circuit believed central to the drug's rewarding effect.

	Male		Female	
	Control	Nicotine	Control	Nicotine
Binding capacity (fmol / mg protein)				
NAc	38.2	30.2	37.7	27.1
PFC	55.1	45.6	55.7	41.9
VTA	59.5	43.3	45.9	39.3

Nicotine's Impact on Receptors

The University of Tennessee researchers pursued a clue from previous work in which they examined the effects of prenatal nicotine exposure on the mesolimbic reward pathway. Nicotine and other drugs of abuse stimulate neurons in the brain area where this pathway originates, the ventral tegmental area (VTA), to release the neurotransmitter dopamine in the nucleus accumbens (NAc) and prefrontal cortex (PFC). The dopamine influx into the NAc produces the feelings of reward and pleasure that are primary motivators of continued drug-taking. Dr. Sharp and colleagues found, however, that exposing rats prenatally to nicotine reduced the amount of dopamine released in the NAc when the animals were given the drug again as adolescents.

"We asked ourselves, 'What causes this?'" Dr. Sharp says. "We decided to look at nicotine's impact on the expression of nicotinic cholinergic receptors—the principal sites where nicotine molecules interact with brain cells to exert their stimulating effects." The researchers hypothesized that exposure to nicotine during gestation would reduce the number of such receptors present on dopamine-producing cells in the VTA in adolescence.

They gave nicotine to pregnant rats via an implanted pump at the rate of 2 mg/kg/day (the equivalent of a human smoking a pack a day) throughout gestation. At birth they increased the nicotine infusions to 6 mg/kg/day and continued them for 2 more weeks, while the rat pups nursed. Because rat pups are born at an earlier stage of development than humans, the weeks of continued exposure were necessary to give them cumulative nicotine exposure equivalent to a smoking mother's baby at full-term. A control group of rats received the nicotine delivery solution without the drug.

The researchers took brain sections from the rat pups when they were 35 days old, developmentally equivalent to mid-adolescence in humans, and assayed them for nicotinic cholinergic receptors. In confirmation of their hypothesis, the results showed significantly fewer receptors in the VTA, NAc, and PFC of the adolescent rats that had been exposed to nicotine *in utero*. Messenger RNA (mRNA) for the receptors declined only in the VTA, suggesting that gestational nicotine had primarily affected dopaminergic neurons that originate in that area. The total number of VTA neurons also dropped in the brains of nicotine-exposed rats.

These findings "show how gestational exposure to nicotine may alter maturation, literally changing the brain," Dr. Sharp says. Although it is not clear how such changes could enhance the likelihood of dependence, "one hypothesis might be that prenatally exposed adolescents, having fewer nicotinic receptors, must take more puffs to release

a rewarding amount of dopamine into the NAc, and this leads to stronger conditioning," he says.

Dr. Allison Chausmer of NIDA's Division of Basic Neuroscience and Behavioral Research says, "The findings confirm the long-term effect of smoking during pregnancy and underscore the importance of smoking cessation at this time."

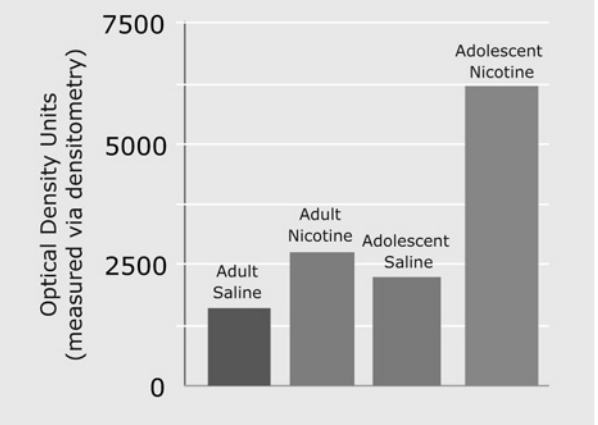
Nicotine Affects Synapse Development

The University of Wisconsin team studied the impact of nicotine on genes that contribute to neural plasticity. This process—the formation of new synaptic connections between neurons and pruning of old ones—wires the brain during development and reaches a crescendo during adolescence. The researchers specifically focused on the genes—including *arc*, *c-fos*, and *NGFI-B*—that produce a set of neurochemicals involved in building synapses. Using rats as subjects, they compared the expression—roughly, the production rate—of these genes following exposure to nicotine in adolescents (average age 30 days) and adults (average age 70 days).

The investigators injected the rats with nicotine at a dose large enough (0.4 mg/kg) to cause a behavioral response—increased motor activity—or with saline. An hour later, they examined slices of the rats' brains, with particular attention to areas that play central roles in learning and motivation: the medial PFC, ventral and lateral orbital cortex (VLO), cingulate cortex, somatosensory cortex, ventral striatum, and dorsal striatum. They assessed the expression of plasticity-related genes by measuring the amount of their corresponding mRNA.

***arc* EXPRESSION INCREASES WITH NICOTINE**

The height of the bars represents the expression of *arc*, a gene involved in neural plasticity. Administration of nicotine increases *arc* in the ventral and lateral cortex of both adolescent and adult rats, but significantly more in adolescents. This suggests that nicotine triggers synaptic development—a key process in learning—in a region important in motivation and goal-directed activity. Because the effect is greater in adolescents, they may more readily "learn" the nicotine habit.



Throughout the brain, they found higher amounts of mRNA for *arc* and *c-fos* in the adolescent than the adult brains, an indication of more synaptic plasticity overall, Dr. Terri Schochet suggests. In both age groups, *arc* and *c-fos* mRNA jumped after injection of nicotine, compared with saline, indicating that the drug "switched on" these genes. In certain prefrontal regions, the nicotine-evoked increase in *arc* mRNA was significantly greater in adolescent animals. In the VLO, for example, *arc* expression increased by 182 percent in adolescents after nicotine injection, compared with 98 percent in adults.

"These findings show that at the basic biochemical level, the adolescent brain responds differently to a single dose of nicotine," says Dr. Landry, principal investigator for this study. "The enhanced expression of *arc,* a gene involved in dendrite formation, in adolescent forebrains following acute nicotine reflects a very dynamic synaptic milieu. It's difficult to speculate further, but my suspicion is that the adolescent brain responds to the drug with a greater increase in synaptogenesis and pruning."

"The adolescents' greater changes in molecular systems involved in learning may indicate that this age group is more susceptible to developing the nicotine habit," Dr. Schochet suggests. The striking effect of a single dose of nicotine could have implications for treatment, she adds: "It's really important to intervene as early as possible to prevent adolescents from trying nicotine in the first place."

Research that explores and compares adult and adolescent behavior and neurobiology is a particular interest of NIDA's, says Dr. Susan Volman of the Institute's Division of Basic Neuroscience and Behavioral Research. This study was valuable because it "looks at both what's different in general between the maturing and adult brain and how that difference interacts with nicotine."

Dr. Volman notes that the adult/adolescent disparity in response to nicotine was greatest in the ventrolateral PFC. "Neural adaptations here could have to do with altering motivation and the value placed on particular rewards," she says. Smoking might be equally pleasurable to adults and adolescents, that is, but the experience would be more highly valued by the adolescent—a difference with potential implications for tailoring behavioral treatments to this age group.

Sources

- Chen, H., et al. Gestational nicotine exposure reduces nicotinic cholinergic receptor (nAChR) expression in dopaminergic brain regions of adolescent rats. *European Journal of Neuroscience* 22(2):380-388, 2005.
- Schochet, T.L., Kelley, A.E., and Landry, C.F. Differential expression of arc mRNA and other plasticity-related genes induced by nicotine in adolescent rat forebrain. *Neuroscience* 135(1):285-297, 2005. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 20, Number 6 (July 2006)

Sensory Aspects May Drive Addiction in Obese Smokers

Obesity appears to reduce nicotine's rewarding effect in mice and humans.

By Patrick Zickler, *NIDA NOTES* Contributing Writer

For obese smokers, the taste and smell of a lit cigarette may play as powerful a part in addiction as does the nicotine buzz. For these smokers, nicotine replacement therapies that also replace some of the sensory aspects of smoking—lozenges, gum, or nasal spray—may be more effective than a patch, according to researchers at the University of Pennsylvania's Transdisciplinary Tobacco Use Research Center (TTURC).

Lead investigator Dr. Caryn Lerman and TTURC colleagues asked 37 smokers to describe the experiences of smoking two "brands" of cigarettes; although the smokers did not know it, one brand contained nicotine and the other did not. Obese smokers rated the two nearly equal, while nonobese smokers gave higher marks to the conventional cigarettes. When allowed to choose freely, nonobese smokers preferred conventional cigarettes, while obese smokers were equally likely to choose either type.

To validate these observations and investigate their physiological basis, Dr. Julie Blendy and colleagues tested nicotine's rewarding effect in mice. Given access to two chambers, nonobese mice gravitated to the one in which researchers had dosed them with nicotine, whereas mice made obese by a high-fat diet showed no preference. These results suggest that the nicotine provided the nonobese mice, but not the obese mice, with an experience they wanted to repeat. When the researchers examined the brains of the mice, they found that the obese animals, compared with those fed a normal diet, had reduced levels of opioid receptors, which have been implicated in nicotine addiction.

"For obese smokers, sensory cues such as sights and smells and taste may be at least as rewarding as the pharmacological reward of nicotine," says Dr. Lerman. "The mouse experiment suggests a possible biological mechanism for the observation in human smokers. Diet may influence nicotine reward through effects on the opioid system," Dr. Blendy adds.

OBESE SMOKERS DERIVE LESS PLEASURE FROM NICOTINE THAN OTHER SMOKERS

Obese smokers rated regular and nicotine-free cigarettes very similarly.

Item/Scale	Cigarette	Mean	
		Nonobese (n=20)	Obese (n=17)
Satisfaction	Nicotine-Free	2.1	2.9
	Nicotine	3.4	3.0
Psychological relief	Nicotine-Free	1.5	1.2
	Nicotine	1.7	1.4
Liking	Nicotine-Free	2.3	2.8
	Nicotine	3.7	2.9

Obesity and Human Response to Nicotine

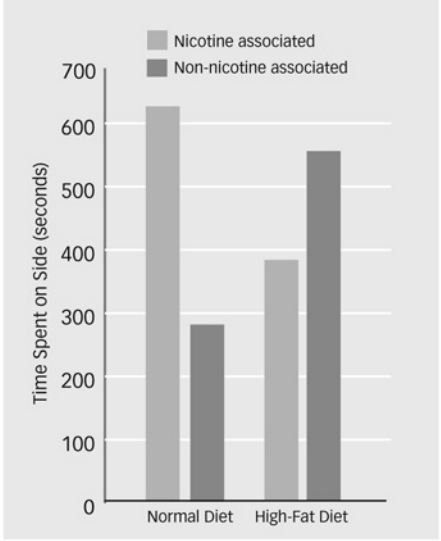
The research team recruited 17 obese and 20 nonobese men and women who were regular smokers. The obese and nonobese study participants' average body mass indexes were 39.1 (range, 31.0 to 59.4) and 23.0 (range, 18.3 to 26.3), respectively. In the first part of the study, the participants smoked one cigarette from each of two color-coded sets, one that contained nicotine and one that was nicotine-free, without being informed about the difference. Participants rated the two smokes on a scale ranging from 0 (none) to 7 (complete)—for "satisfaction," "liking," and "psychological relief." On average, obese smokers gave the conventional and nicotine-free cigarettes almost identical ratings for satisfaction (3.0 for nicotine versus 2.9 for nicotine-free), liking (2.9 versus 2.8), and psychological relief (1.4 versus 1.2). Nonobese smokers gave the conventional cigarettes higher ratings for satisfaction (3.4 versus 2.1) and liking (3.7 versus 2.3) and showed no significant preference in psychological relief (1.7 versus 1.5).

Next, the smokers were allowed to smoke cigarettes from either color-coded set in four sessions, spaced 30 minutes apart, but limited to four puffs per session. On average, obese smokers took as many puffs on the conventional (48 percent) as the nicotine-free (52 percent) cigarettes. Nonobese smokers took 70 percent of their puffs from the conventional cigarettes.

"Tobacco addiction involves an interplay of physiological influences, such as the effects of nicotine or other components of tobacco, with sensory influences associated with taste or aroma, the physical manipulation of cigarettes and lighters, or the sight of smoke," Dr. Lerman says. "It appears that for obese smokers, non-nicotine factors play

a considerable part in maintaining addiction and therefore need to be considered in developing a treatment to help obese smokers quit. Obesity and smoking are both serious health risks, and some research suggests they act synergistically to create an even greater risk. If so, helping obese smokers to quit may have a greater impact on public health than an equivalent cessation among nonobese smokers."

MICE RAISED ON A HIGH-FAT DIET HAVE DIMINISHED RESPONSE TO NICOTINE Mice fed a normal diet spent most of a 15-minute test period on the side of a cage in which they had been given nicotine, whereas mice fed a high-fat diet showed no such preference.



Obese Mice and Nicotine

In the animal component of their investigation, the researchers simulated human obesity in mice by feeding them a high-fat diet (45 percent fat, 35 percent carbohydrates, 20 percent protein) for 15 weeks. A control group of mice received a normal laboratory diet (12 percent fat, 60 percent carbohydrates, 28 percent protein). The researchers injected each animal with nicotine while confining it to one compartment of a two-compartment test chamber daily for 8 days. Subsequently, they placed each mouse in the test chamber and allowed it free access to either compartment for 15 minutes. Nonobese mice spent most of this time in the compartment where they received the drug, indicating that the nicotine injections had given them pleasure they would like to repeat. However, obese mice showed no preference for the side associated with the drug.

The investigators next examined the brains of the mice and found evidence that the animals maintained on a high-fat diet had less precursor associated with structures called mu-opioid receptors on cells in the ventral tegmental area (VTA) of the brain. The VTA is where nicotine acts to increase the availability of dopamine, a chemical that causes the pleasurable sensations associated with many drugs of abuse. Other animal research has implicated mu-opioid receptors in neurochemical processes that lead to nicotine addiction, and the finding that fewer of these receptors are activated in the brains of the high-fat-diet mice could in part explain their blunted response to nicotine's rewarding effect.

"In this mouse study, the animals could not control their diet. But humans choose what and when to eat," says Dr. Allison Chausmer of NIDA's Division of Basic Neuroscience and Behavioral Research. "The observations made in these mice suggest a fascinating chain of events leading from a behavior, selecting what to eat, to a measurable biochemical change in the brain and altered response to an addictive drug. They illustrate the complexity of factors that contribute to the powerful addictive grip of tobacco and—conversely—can potentially be manipulated to improve the effectiveness of treatments that help smokers quit."

Source

- Blendy, J.A., et al. Reduced nicotine reward in obesity: Cross-comparison in human and mouse. *Psychopharmacology* 180(2):306–315, 2005. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 20, Number 5 (April 2006)

Bupropion Helps People With Schizophrenia Quit Smoking

Data address physicians' concerns about prescribing the medication for smokers with schizophrenia.

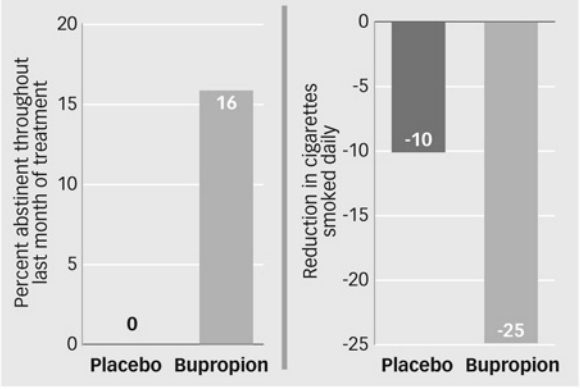
By Lori Whitten, *NIDA NOTES* Staff Writer

The smoking cessation aid bupropion is safe and effective for people with schizophrenia, researchers at Massachusetts General Hospital and Harvard Medical School have found. In a NIDA-funded study of smokers with schizophrenia, those who took sustained-release bupropion were more likely to stop smoking by their quit date and to achieve continuous abstinence for a month than those who received placebo, and they also remained abstinent longer. The researchers did not observe any adverse interactions with the patients' antipsychotic medications or exacerbation of psychiatric symptoms.

The U.S. Food and Drug Administration (FDA) approved sustained-release bupropion as a treatment for depression in 1996 and as a smoking-cessation aid in 1997, but physicians have been reluctant to prescribe the medication for patients with schizophrenia. "Although 75 to 85 percent of people with schizophrenia smoke, we have lacked data on treatments for nicotine addiction in this population, resulting in many not receiving advice to quit," says Dr. A. Eden Evins, lead investigator of the study.

Dr. Evins and her colleagues treated 53 patients, aged 24 to 66, for nicotine dependence. When they began treatment, the patients smoked 30 cigarettes a day, on average, and typically had made two previous quit attempts. During the 12-week study, each participated in weekly sessions of group cognitive-behavioral therapy (CBT) and received either 300 milligrams a day of sustained-release bupropion or placebo. The CBT program was adapted for patients with schizophrenia from standard smoking-cessation therapy. Each patient visited the clinic once a week for evaluations of smoking (self-report confirmed by expired air carbon monoxide measurements), changes in psychiatric symptoms, medication compliance, and side effects.

BUPROPION ENHANCES OUTCOME OF COGNITIVE-BEHAVIORAL THERAPY Patients with schizophrenia who participated in weekly group cognitive-behavioral therapy for smoking cessation were more likely to remain abstinent throughout the last month of a 12-week study if they also took bupropion. Among patients still smoking at study's end, those receiving bupropion smoked fewer cigarettes daily than those on placebo.



Therapists encouraged all patients to set a quit date before the 4th week of treatment, and 36 percent of those taking bupropion—compared with 7 percent of those on placebo—achieved this goal, demonstrating abstinence at the 4-week assessment. Sixteen percent of patients in the bupropion group, but none taking placebo, achieved abstinence throughout the last month of treatment. Among patients who were not abstinent at the end of the study, those in the bupropion group reduced the average number of cigarettes smoked daily from 34 to 9, compared with a drop from 25 to 15 in the placebo group.

Bupropion was generally well tolerated and did not exacerbate the symptoms of schizophrenia. Depression and flat affect, as well as cognitive function, tended to improve among patients taking the medication. Common side effects experienced by people taking antipsychotic medications, such as muscle stiffness and shuffling gait, were not worsened by nicotine abstinence or bupropion. About 80 percent of patients in both the medication and placebo groups kept to their regimens throughout the study.

The findings confirm promising results from several smaller studies. Dr. Evins points out that the relapse rate was high after treatment discontinuation—75 percent of those who were abstinent at week 12 had relapsed to smoking at the 3-month followup. Only about 4 percent of patients in either group were abstinent in the week before the 3-month followup. Other studies of bupropion in the general population have shown that about half of patients tend to relapse after treatment discontinuation. "Patients with schizophrenia may need a longer course of bupropion with CBT or a combination of bupropion and nicotine replacement therapy to avoid relapse," says Dr. Evins.

Source

- Evins, A.E., et al. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *Journal of Clinical Psychopharmacology* 25(3):218-225, 2005. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 20, Number 4 (March 2006)

Genetic Predisposition and Depression Both Influence Teen Smoking

By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA-supported scientists have found that a gene, called *DRD2*, partly determines whether an adolescent who takes a first puff on a cigarette will progress to regular smoking. Adolescents who carry one of the two known forms of the gene (*A1*) are more likely than those with the other variant (*A2*) to become daily smokers. If the teen also suffers from depression, the genetic effect is amplified, further increasing the likelihood of smoking escalation, according to Dr. Janet Audrain-McGovern and colleagues at the University of Pennsylvania Transdisciplinary Tobacco Use Research Center (TTURC).

The new findings result from a large-scale study that Dr. Audrain-McGovern and her research group undertook to clarify outstanding issues surrounding *DRD2* and smoking. Scientists have suspected for some time that variations in *DRD2* might influence people's responses to tobacco, based on the gene's function: It helps guide construction of sites where the neurotransmitter dopamine—which plays a key role in producing the pleasurable effects of nicotine—attaches to brain cells. Some previous studies have found that, indeed, men and women who smoked or were nicotine-dependent were more likely to have the *A1 DRD2* variant than the *A2*. However, other studies did not confirm the link.

DRD2 Variants and Smoking Progression

Dr. Audrain-McGovern's team recruited 615 adolescents (322 girls, 293 boys) to participate in their study. Because genetic diversity would increase the difficulty of interpreting results, all the youths were of European ancestry. Analysis of DNA obtained from cheek swabs showed that the frequencies of the alternative *DRD2* forms, or alleles, were roughly the same among the participants as have been seen in general population samples of people of European stock: Two-thirds (67 percent) had inherited the *A2* allele from both parents, 30 percent had one *A1* and one *A2*, and 3 percent had two copies of the *A1*.

The researchers interviewed the teens in ninth grade, asking questions used in the Youth Risk Behavior Survey, including, "Have you ever tried or experimented with cigarette smoking, even a few puffs?" "Have you smoked at least one whole cigarette?" "How many cigarettes have you smoked in the last 30 days?" and "How many cigarettes have you smoked in your lifetime?" Based on their responses, the teens were categorized as never smokers, puffers (a few puffs, but never a whole cigarette), experimenters (at least one but fewer than 100 lifetime cigarettes), and current smokers (smoked in the past 30 days and 100 or more lifetime cigarettes).

The teens answered the same questions again in the fall and spring of their 10th-grade year and in the spring of their 11th-grade year. Analyzing the teens' sequential responses together with their genetic data, the researchers found no association between variation in *DRD2* alleles and the likelihood that participants who had never smoked would start, Dr. Audrain-McGovern says. "However, among adolescents who had taken at least a single puff, we found a clear association between the *A1* allele and progressing up the ladder of smoking frequency—for example, moving from puffer to experimenter, or experimenter to current smoker. Each additional copy of the *A1* allele nearly doubled the odds of progression," she says. Among teens who had at least puffed once, those with a single *A1* allele were 1.8 times as likely, and teens who had inherited *A1* alleles from both parents were 3.4 times as likely as those with two *A2* alleles to progress to heavier smoking before they finished 11th grade.

"These results clearly illustrate the important interplay between a gene and the environment," Dr. Audrain-McGovern says. "The *DRD2* variant appears to play no

role in whether or not these teens took that first puff. Its effect isn't seen until there is some biological exposure. Then, we see a markedly different response to nicotine, perhaps because the *A1* allele is associated with reduced density of dopamine receptors. If individuals with this allele have lower baseline levels of dopamine activity, they might experience greater reward when nicotine triggers an enhanced dopamine release."

DRD2 and Depression

During the ninth-grade interviews, the researchers administered the Center for Epidemiological Studies Depression Scale (CES-D Scale) to the study participants. Each teen rated how frequently he or she had experienced each of 20 depression symptoms during the past week. One hundred teens (16 percent) scored 23 or higher on this scale, which indicates clinically significant depression. Of the 100, 52 had at least one *A1* allele. Teens without an *A1* allele had an average CES-D score of 12.3; those with one *A1* and one *A2* had an average score of 15.1; and those with two copies of the *A1* allele averaged 16.7. There also was a significant association between the CES-D score and smoking status at the initial interview: The average score was 12.5 for never smokers, 14.6 for puffers, 13.7 for experimenters, and 20.8 for current smokers.

Teens with high depression scale scores and the *A1* allele were at the highest risk of smoking progression. Among teens with at least one *A1* allele, 33 percent of depressed teens, compared with 25 percent of nondepressed teens, reported smoking progression within 2 years.

The interaction of the *DRD2* allele and depression on smoking progression highlights the intricate interplay of genetic, psychological, and social factors that influence adolescents' smoking behavior, observes Dr. Allison Chausmer of NIDA's Division of Basic Neurosciences and Behavior Research. "This research group has previously shown that adolescents who have depression are more receptive than nondepressed teens to the messages contained in tobacco advertising. This is not a trivial number of potential smokers. Roughly one in five high school students has symptoms that represent clinically significant depression. Those who succumb to the appeal of tobacco manufacturers' advertising and have this particular genetic makeup may be more likely to progress to higher levels of smoking and ultimately experience consequences of reduced health and longevity."

Source

- Audrain-McGovern, J., et al. Interacting effects of genetic predisposition and depression on adolescent smoking progression. *American Journal of Psychiatry* 161(7):1224-1230, 2004. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 20, Number 3 (October 2005)

Study Points to Acetaldehyde-Nicotine Combination in Adolescent Addiction

By Patrick Zickler, NIDA NOTES Staff Writer

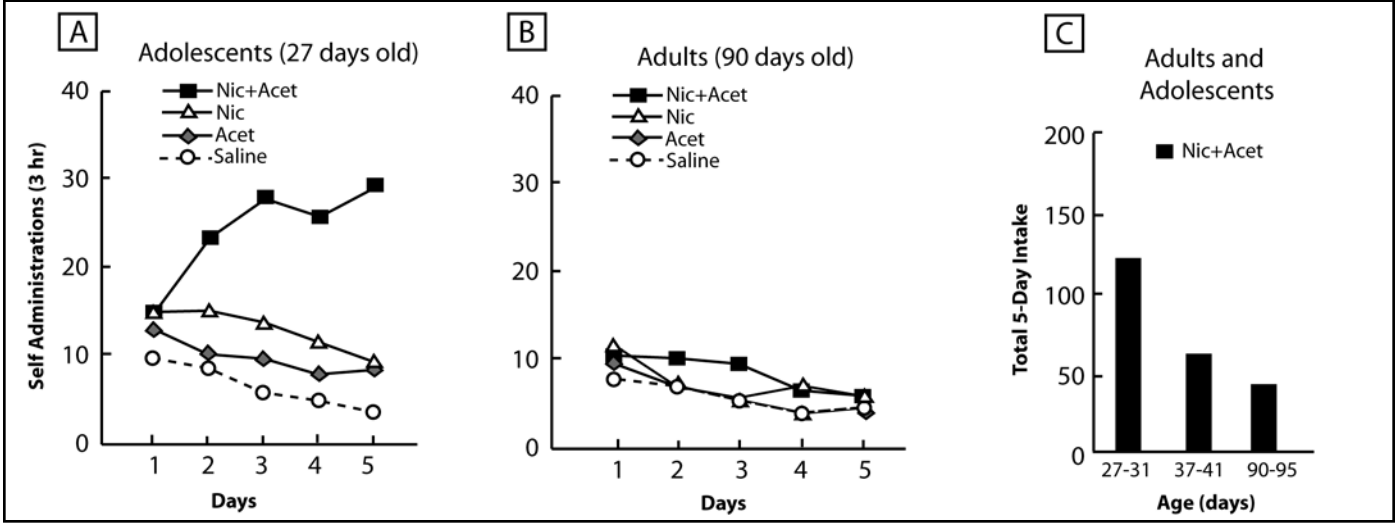
The teen years are when most smokers first light up, and adolescents become addicted to tobacco faster than adults. Research has suggested that young people are particularly vulnerable to smoking addiction in part because their brains are more sensitive to nicotine, but that other factors also contribute. Now, NIDA-funded investigators have produced evidence pointing to another chemical constituent of tobacco smoke, acetaldehyde, as one of those factors. A recent study demonstrated that in adolescent but not adult laboratory rats, acetaldehyde and nicotine together produce a much stronger pleasure-producing, or reinforcing, effect than either chemical alone.

Dr. James Belluzzi and colleagues at the Transdisciplinary Tobacco Use Research Center at the University of California at Irvine hypothesized that acetaldehyde might play a role in smoking addiction for several reasons. Among them:

- Smokers exhibit more drive to take another puff on a cigarette than laboratory animals do to push a lever for another nicotine infusion, a difference that might be explained if smoke contains an additional reinforcing constituent besides nicotine;
- Smokers are abundantly exposed to acetaldehyde, which occurs naturally in tobacco leaves and also is formed as a combustion product of sugars added to tobacco during cigarette manufacture;
- Research has suggested that acetaldehyde, which also is produced during alcohol metabolism, contributes to alcohol reinforcement and withdrawal symptoms, raising the possibility that it might play a similar role in tobacco dependence.

To test their hypothesis that acetaldehyde contributes to tobacco addiction, particularly in adolescents, Dr. Belluzzi's research team conducted an animal self-administration study with early-adolescent (27-day-old), adolescent (37-day-old), and adult (90-day-old) rats. The researchers placed the animals in cages where they could poke their noses through holes in the cage wall to obtain injections of nicotine (30 μg/kg) plus acetaldehyde (16 μg/kg), nicotine or acetaldehyde alone, or saline. In such studies, the

Adolescent Rats, but Not Adults, Increase Intake of Nicotine When it Is Combined With Acetaldehyde, a Component of Tobacco Smoke



(A) Adolescent rats self-administered nicotine combined with acetaldehyde—but not nicotine alone, acetaldehyde alone, or saline—with increasing frequency over 5 days. (B) Adult rats did not demonstrate any preference for nicotine, acetaldehyde, or the combination over saline. (C) Total 5-day intake of nicotine plus acetaldehyde was greatest for the youngest group of animals, suggesting that vulnerability to tobacco addiction decreases with age.

frequency and persistence with which animals nose-poke for a particular substance is a measure of how rewarding it is for them, which in turn may correspond to how addictive it is for people. Over the course of five daily 3-hour sessions, the youngest rats worked up to poking their noses for nicotine plus acetaldehyde roughly three times as frequently than for either chemical alone or saline. The older adolescent rats also demonstrated a preference for the two-drug combination, but a less-marked one than the 27-day old animals. The adult rats responded no differently to the drugs, alone or in combination, than they did to the saline solution.

"Our results show that acetaldehyde, at the same relative concentration found in cigarette smoke, dramatically increases the reinforcing properties of nicotine," says Dr. Belluzzi. "Furthermore, the effect is age-related, with adolescent animals far more sensitive than adults."

To buttress their interpretation of their results, the researchers tested a potential alternative explanation for the rats' behavior: The animals might not be seeking pleasure when they poked their noses into the holes for nicotine and acetaldehyde, but simply exhibiting random activity due to chemically induced locomotor stimulation. To evaluate this possibility, the researchers put a control group of rats into the test cages and gave them injections of nicotine plus acetaldehyde at the test dosage. They predicted that these rats should nose-poke less than the original animals if pleasure-seeking was a main motivation for the behavior (because they were getting the chemicals' reinforcing effects automatically without having to work for them), or nose-poke the same amount if locomotor stimulation was the primary cause (because the test animals and control animals received similar doses of the chemicals). The data showed that the control rats nose-poked less than the original animals.

"This research underscores the point that nicotine alone may not cause the intensity of dependence seen in smokers, and nicotine replacement does not, by itself, eliminate withdrawal or craving for people trying to quit. Other factors clearly are at play," says Dr. Allison Chausmer of NIDA's Division of Basic Neurosciences and Behavioral Research. "Dr. Belluzzi's experiment strongly suggests that acetaldehyde is one of those factors, and it offers a potential explanation for age-related differences that we observe in epidemiological studies of the impact of tobacco."

Source

- Belluzzi, J.D.; Wang, R.; and Leslie, F.M. Acetaldehyde enhances acquisition of nicotine self-administration in adolescent rats. *Neuropsychopharmacology* 30(4):705–712, 2005. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 20, Number 2 (August 2005)

NIDA Research Illuminates Associations Between Psychiatric Disorders and Smoking

By Patrick Zickler, *NIDA NOTES* Staff Writer

Nearly half of all cigarettes sold in the United States are sold to people with mental illness, and men and women with mental disorders are twice as likely as the general population to smoke. A recent NIDA-supported epidemiological analysis reveals relationships between psychiatric disorders and smoking that have important implications for public health. The findings suggest that treating psychiatric illness can contribute to reductions in smoking intensity and nicotine addiction, and that addressing smoking during substance abuse treatment is vital to counter an increased risk for nicotine addiction that may accompany recovery.

Active Psychiatric Disorders Increase Likelihood of Daily Smoking, Nicotine Addiction

	Relative Risk of Transition to Daily Smoking		Relative Risk of Developing Nicotine Addiction	
	When Symptomatic	When Remitted	When Symptomatic	When Remitted
Depressive Disorders				
Major Depression	1.6	0.6	2.2	NE
Dysthymia	1.6	1.5	1.2	NE
Anxiety Disorders				
Agoraphobia	1.4	0.1	1.8	NE
GAD	2.1	NE	1.8	NE
Simple Phobia	1.5	0.9	1.8	13.6
Social Phobia	1.3	2.8	1.8	1.6
Panic Disorder	0.9	1.7	1.4	5.8
PTSD	2.0	2.5	2.1	0.7
Substance Use Disorders				
Alcohol A/D	1.5	0.5	1.7	5.2
Drug A/D	1.8	0.9	1.5	4.1

GAD indicates general anxiety disorder; NE, not evaluated; PTSD, posttraumatic stress disorder; and A/D, addiction/dependence.

Researchers found that active psychiatric disorders, with the exception of agoraphobia and panic disorder, were associated with increased risk of transition to daily smoking. In contrast, past disorders (those that had been inactive for a year or more) generally did not predict transition to daily smoking. Researchers also found an increased risk of transition to nicotine addiction associated with a wide range of active disorders, but only four past disorders. Risks are presented as odds ratios; a relative risk of 2.0 indicates twice the likelihood.

Dr. Naomi Breslau, at Michigan State University in East Lansing, used data from the Tobacco Supplement to the National Comorbidity Survey (NCS) to study the relationships between the temporal onset of psychiatric disorders, psychiatric symptoms, and smoking. The NCS, mandated by Congress to assess the prevalence of psychiatric disorders in the United States, surveyed a representative sample of the national population between 1990 and 1992, eliciting information about the onset of psychiatric disorders—as defined by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised* (DSM-III-R)—and the time course of their symptoms. Disorders included in the NCS are major depression, dysthymia (similar to clinical depression, but with longer-lasting and milder symptoms), agoraphobia, generalized anxiety disorder, simple and social phobias, panic disorder, posttraumatic stress disorder, and alcohol or drug abuse or addiction. The NCS Tobacco Supplement asked respondents whether they smoked, when they began smoking daily, at what age they experienced symptoms matching DSM criteria for nicotine dependence, and whether they had stopped smoking regularly a year or more before they took part in the survey.

Analyzing the responses from 4,414 survey participants, Dr. Breslau found that:

- Men and women with histories of substance abuse, major depression, and most anxiety disorders reported increased rates of transition to daily smoking, but only during periods when they were experiencing symptoms. When their illnesses had been asymptomatic for a year or more, they became daily smokers at rates no higher than respondents who never experienced psychiatric illness;

- Substance abuse and major depression predicted transitions from voluntary smoking to nicotine addiction when actively symptomatic (the association was borderline for drug, as opposed to alcohol, abuse). In the case of substance abuse, this relationship became markedly stronger when the problems had remitted for at least a year;
- Most anxiety disorders increased risk for nicotine addiction when symptomatic. For individuals with simple phobia or panic disorder, these risks multiplied during periods of remission. For those with post-traumatic stress disorder, the risk reverted to baseline when symptoms had been absent for a year; and
- None of the psychiatric disorders studied affected respondents' chances of successfully quitting smoking, either when active or when remitted.

"We found that the majority of the psychiatric disorders, when active, predicted the onset of daily smoking," Dr. Breslau says. "Respondents with one active disorder were 1.3 times as likely, and those with four or more active disorders were 2.2 times as likely to begin daily smoking as those with no active disorders. This suggests that early treatment may be able to prevent patients who are not currently daily smokers from progressing to that status."

"Similarly," Dr. Breslau says, "most disorders—when active—predicted that smokers would progress from daily smoking to nicotine addiction. In this transition from one stage of smoking to another, daily smokers with one active disorder were on average 1.8 times as likely as those with no active disorder to develop addiction, and the odds of developing nicotine addiction increased with the number of active disorders. This suggests that successful control of psychiatric symptoms before smokers become addicted can prevent them from making that transition."

Substance abuse, however, is an important exception to this general observation. Respondents with past but not active alcohol and drug abuse disorders had risk ratios two to three times as high as respondents with current active disorders involving these substances. "This association suggests that cessation of substance abuse may induce greater smoking intensity. In treatment for substance use disorders it is important to be conscious of smoking behavior, to guard against the possibility that a person in treatment for one damaging condition might increase the danger posed by another. Treatment should assist patients who are abusing alcohol or drugs and who smoke to quit both," Dr. Breslau says.

When Dr. Breslau looked for a relationship between mental disorders and quitting smoking, she found that neither active nor remitted disorders made respondents more or less likely to quit smoking successfully during the year preceding the survey.

"The relationship between tobacco use and comorbid psychiatric disorders is complex," says Dr. Kevin Conway of NIDA's Division of Epidemiology, Services and Prevention Research. "While we see variations across the range of disorders included in the comorbidity survey, the consistent pattern in this study emphasizes the importance of active expression of psychiatric disorders—not simply a history of the disorder—in relation to smoking stages."

Source

- Breslau, N.; Novak, S.P.; and Kessler, R.C. Psychiatric disorders and stages of smoking. *Biological Psychiatry* 55(1):69-76, 2004. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

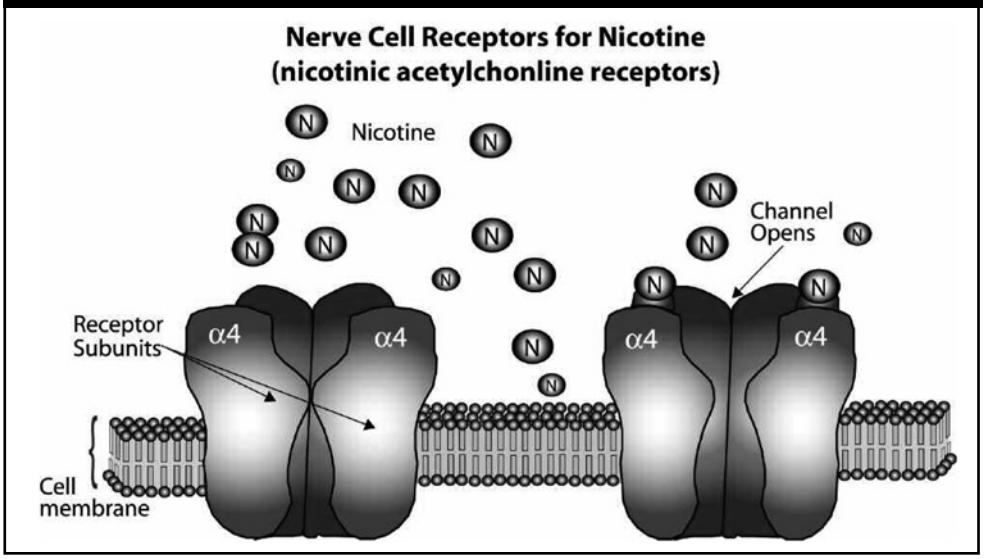
Volume 20, Number 2 (August 2005)

Site on Brain Cells Appears Crucial To Nicotine Addiction

By Patrick Zickler, *NIDA NOTES* Staff Writer

Using genetic engineering, NIDA-supported scientists have produced a strain of mice with special characteristics that can help researchers identify and study key steps in the development of nicotine addiction. By altering a single amino acid in just one of a mouse's 30,000 genes, the scientists produced mice that are exceptionally sensitive to the effects of nicotine. The modified mice show behaviors associated with addiction when exposed to nicotine doses far too small to cause similar effects in other mice. Their dramatically increased sensitivity suggests that the brain cell site affected by the modified gene is crucial to development of nicotine addiction.

Brain Pathway to Nicotine Addiction



Nicotine attaches to nerve cells in the brain at receptors on the cell membrane. The receptors comprise five subunits that fit together like sections of an orange. When a nicotine molecule binds to one of these subunits, the segments pull away from each other, creating an open channel through the cell membrane. This initiates a series of electrical and chemical signals that trigger release of dopamine by other brain cells. One type of subunit, designated α4, appears to play a central role in development of nicotine addiction; mice engineered to have especially sensitive α4 subunits exhibit behaviors characteristic of nicotine addiction when exposed to a dose of nicotine just one-fiftieth of that normally needed to elicit these behaviors.

Dr. Andrew Tapper and colleagues at the California Institute of Technology in Pasadena and at the University of Colorado in Boulder built on work by other scientists which indicated that a site on some brain cells—the α4 subunit of nicotine receptors—plays a key role in the brain's response to nicotine. The previous work involved "knock-out" mice, in which scientists had disabled a gene that directs development of the α4 site. When exposed to nicotine, the α4 knock-out mice did not respond with increased release of the pleasure-causing brain chemical dopamine, a reaction thought to be a key factor in the development of nicotine addiction.

The results with knock-out mice suggested that α4 sites on brain cells are necessary for development of nicotine addiction, but didn't address the question of whether the sites are sufficient by themselves to initiate the behaviors associated with addiction. To answer that question, says Dr. Henry Lester of the California Institute of Technology, "We decided to create animals with hypersensitive α4 receptors. That way, instead of eliminating the response to nicotine, we could emphasize it and study the processes that lead to nicotine addiction. So we developed the α4 'knock-in' mouse."

The scientists compared the behavioral effects that are in part characteristic of nicotine addiction—reward, tolerance, and sensitization—in their knock-in mice and unmodified mice. According to Dr. Lester, the results indicate that activation of the α4 site by nicotine is sufficient to initiate the effects.

Reward: The researchers measured nicotine reward in their mice with a technique called "conditioned place preference," which is based on the assumption that if animals like an experience, such as receiving nicotine, they will gravitate to the place where they have had that experience rather than another where they haven't. In the experiment, mice with unmodified α4 receptors exhibited a preference for a compartment associated with a nicotine dose of 0.5 mg/kg of body weight—a typical

dose ingested by a human smoker. The investigators then tested the rewarding effect of one-fiftieth of that amount, 10 μg/kg, on the unmodified and the α4 knock-in mice. When allowed to move freely between the chambers for 20 minutes following nicotine administration, the unmodified mice showed no preference for the nicotine-associated compartment; they spent slightly less time in that chamber than they had before. In contrast, modified mice showed a marked preference for the compartment associated with nicotine, spending an average of 2 minutes more in that chamber following nicotine administration.

Tolerance and sensitization: To test tolerance to nicotine, the investigators subjected the unmodified and knock-in mice to repeated doses of nicotine, 15 μg/kg daily over 9 days, and then compared the changes in nicotine-induced hypothermia. The unmodified mice showed no change in body temperature, but the knock-in mice exhibited a decrease of 3°C on the first and second days, and smaller decreases each successive day, suggesting they had developed tolerance to the nicotine-induced hypothermia. In tests for sensitization, only the genetically engineered mice increased activity levels (measured by counting the number of times the animals cross a beam of light in the 60 minutes following injection) in response to daily injections of 15 μg/kg over 9 days.

"This work represents a significant step forward in understanding how nicotine hijacks the brain's normal signaling process," says Dr. Joni Rutter of NIDA's Division of Basic Neurosciences and Behavior Research. "And the research approach—moving from manipulation of a single protein to an animal's behavioral response to nicotine—also holds great promise. If the α4 site is also found to play a large role in human nicotine addiction," Dr. Rutter adds, "it is a promising focus for research into medications that might block nicotine's effects."

Source

- Tapper, A.R., et al. Nicotine activation of α4 receptors: Sufficient for reward, tolerance, and sensitization. *Science* 306(5698):1029-1032, 2004. NN

Genetic Engineering Reveals Proteins' Key Role in Sensitivity to Cocaine

Genetic engineering strategies like those used at the California Institute of Technology to study nicotine addiction have helped other investigators identify a pair of proteins that seem to influence cocaine addiction.

Dr. Peter Kalivas and his colleagues at the Medical University of South Carolina in Charleston developed a strain of mice lacking two genes, called *Homer1* and *Homer2,* that direct production of proteins linked to cocaine's effects in the brain. The researchers found that the *Homer* "knock-out" mice were more sensitive than unmodified mice to the behavioral effects of cocaine.

Compared with unmodified mice, animals missing either *Homer1* or *Homer2* developed stronger place conditioning—when allowed to move freely, they would spend more time in a compartment where they had received cocaine than in a compartment with no drug association. The knock-out mice also were more sensitive to cocaine's stimulatory effect; when placed in a chamber equipped with photoelectric beams that could measure activity, the knock-outs were approximately 50 percent more active than unmodified mice following cocaine injections. To verify the role of the *Homer* genes in increased sensitivity to cocaine, the researchers restored *Homer* genes in the brains of the knock-outs, eliminating the previously seen differences in stimulation and place conditioning.

"The fact that *Homer* deletions result in these augmented responses to cocaine suggests that disruption of Homer protein-regulated signaling in the brain is a central step in development of cocaine addiction," Dr. Kalivas says. Additional evidence of this role is seen in changes that *Homer* deletion causes in levels of the brain messenger chemical glutamate, he adds. *Homer* knock-out mice that had never been exposed to cocaine had nucleus accumbens (NAc) glutamate concentrations about 50 percent lower than mice with the genes—an effect similar to that seen in mice after cocaine withdrawal. This effect, too, was reversed when the scientists injected *Homer* genes into the NAc.

The association between *Homer* activity and the conditions of cocaine withdrawal is particularly intriguing, according to Dr. Kalivas, because other researchers have shown that Homer protein levels rise and fall in response to environmental cues and changing levels of stress. "*Homer* may be a window to study the molecular basis of the important link between environmental stress and cocaine addiction."

Source: Szumlinski, K.K., et al. Homer proteins regulate sensitivity to cocaine. *Neuron* 43(3):401-413, 2004. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 19, Number 6 (May 2005)

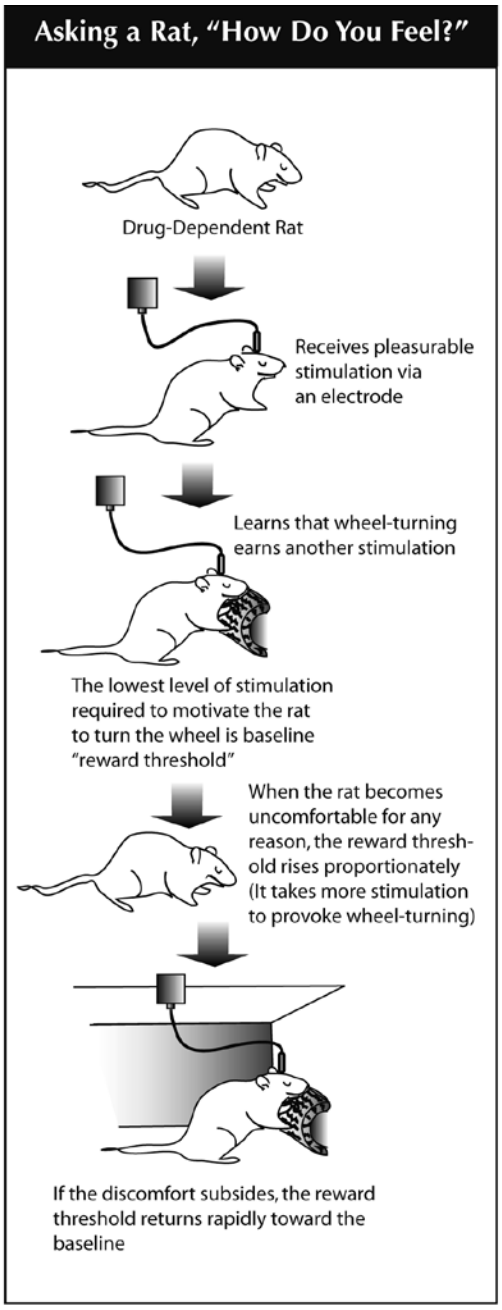
Nicotine Withdrawal Linked to Disrupted Glutamate Signaling

By Patrick Zickler, *NIDA NOTES* Staff Writer

More than a third of America's 46 million adult smokers try to stop each year, but fewer than 10 percent succeed. Some relapse because they cannot tolerate the discomfort and craving associated with nicotine withdrawal. In recent animal studies, NIDA-supported scientists identified sites on some brain cells that appear to be key promoters of the negative psychological symptoms of nicotine withdrawal. The sites, called glutamate receptors, are part of the communication network that uses the neurotransmitter glutamate as a chemical messenger.

Neurobiologists have previously shown that glutamate helps produce the good feelings smoking causes. When nicotine attaches to receptors on cells in the brain's ventral tegmental area (VTA), the cells release glutamate, which in turn triggers other VTA cells to release dopamine, a neurotransmitter that produces pleasure. Dr. Athina Markou of The Scripps Research Institute (TSRI) in La Jolla, California, and colleagues reasoned that just as glutamate surges caused by nicotine give rise to smoking pleasure, glutamate depletion related to nicotine abstinence might underlie the displeasure of withdrawal. The researchers speculated that when nicotine is withdrawn after chronic use, the feedback system that restores glutamate to normal levels following surges could overshoot its mark, resulting in a glutamate dearth—and symptoms of depression and irritability.

To test this idea, Dr. Markou and Dr. Paul Kenny at TSRI, along with Dr. Fabrizio Gasparini of Novartis Institutes for Biomedical Research in Basel, Switzerland, focused on a specific group of glutamate receptors called group II metabotropic glutamate (mGluII) receptors. These inhibitory receptors are key components of the glutamate feedback system: They detect high glutamate levels and signal glutamate-producing cells to reduce their activity to bring the levels back down. Inactivating the mGluII receptors interrupts this process, leaving glutamate levels high. The researchers hypothesized that if they inactivated rats' mGluII receptors while subjecting the animals to nicotine withdrawal, the plunge in glutamate levels may be avoided, and the animals' withdrawal symptoms attenuated.



Dr. Athina Markou and her colleagues used this experimental technique, known as intracranial self-stimulation, to assess animals' discomfort from nicotine withdrawal and evaluate the role of mGluII receptors in withdrawal.

The scientists implanted tiny pumps under the skin on the backs of adult male rats. The pumps dispensed a nicotine solution that maintained high nicotine levels equivalent to those produced in a human who smokes 30 cigarettes per day. After the rats had been exposed to nicotine for 7 days, the investigators removed the pumps, depriving the animals of nicotine and thus leading to nicotine withdrawal. Then, after 18 hours of withdrawal, half the rats were injected with a chemical that blocks the action of mGluII receptors, in effect switching off the inhibitory feedback signals to the glutamate-producing cells. Over the next 72 hours the scientists evaluated the rats at regular intervals using a technique, called intracranial self-stimulation (see "Asking a Rat, 'How Do You Feel?'"), that measures withdrawal-like depression in laboratory animals. As the scientists had predicted, the rats with active mGluII receptors exhibited significant discomfort; the withdrawal discomfort rapidly

dissipated in those in which mGluII receptors were turned off.

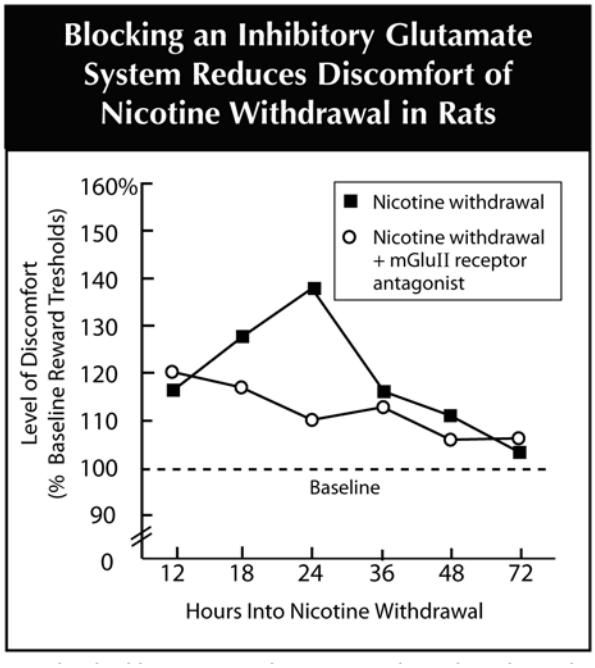
To help confirm the association between mGluII receptors and withdrawal-like symptoms, Dr. Markou's team treated nicotine-dependent rats with a compound that stimulates the same receptors. In these animals, activation of the inhibitory glutamate loop triggered discomfort comparable with that in nicotine withdrawal.

"Other research has shown how nicotine changes regulation of excitatory glutamate signaling," Dr. Markou says. "Our study helps explain how nicotine also commandeers inhibitory glutamate circuits. The altered function of the mGluII receptors appears to mediate, at least partly, the depression-like aspects of nicotine withdrawal." The effect, she explains, is a carrot-and-stick influence strong enough to thwart the most sincere attempts to quit smoking. "Nicotine provides a positive effect through the excitatory circuits, making smoking a rewarding and reinforcing experience. Now we see that nicotine has a similarly powerful aversive effect through the inhibitory circuits, making withdrawal an unpleasant experience."

The role of mGluII receptors in withdrawal suggests that these receptors might also offer a target for therapeutic intervention, Dr. Markou adds. "Easing the depression-like aspects of withdrawal would significantly decrease discomfort and make it easier for people to maintain abstinence and resist the temptation to relapse to smoking."

Source:

- Kenny P.J.; Fabrizio, G.; and Markou, A. Group II metabotropic and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/kainate glutamate receptors regulate the deficit in brain reward function associated with nicotine withdrawal in rats. *Journal of Pharmacology and Experimental Therapeutics* 306(3):1068-1076, 2003. NN



Rats that had been exposed to nicotine for 7 days showed discomfort 12 hours after withdrawal from nicotine. Rats that were injected, at 18 hours into withdrawal, with a compound that blocked mGluII receptors showed no increase in withdrawal-associated discomfort. (Discomfort measurement technique is described in "Asking a Rat, 'How Do You Feel?'" on the previous page). Untreated rats experienced increasing discomfort through 24 hours of withdrawal.

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 19, Number 4, (December 2004)

Smoking Exposure *In Utero* Increases Risk of Later Addiction

By Arnold Mann, *NIDA NOTES* Contributing Writer

An expectant mother's smoking during pregnancy does not increase the likelihood that her child will later try smoking or become a regular smoker. Her pack-a-day smoking, however, doubles the risk that if her child does become a smoker, he or she will become addicted to tobacco, according to the first study to examine rates of tobacco addiction in adults who were prenatally exposed.

The study was led by Dr. Stephen L. Buka of the Harvard School of Public Health in Boston and cosponsored by the National Cancer Institute, the National Institute of Mental Health, the Robert Wood Johnson Foundation, and NIDA. Dr. Buka, together with Drs. Edmond D. Shenassa and Raymond Niaura, both of Brown Medical School in Providence, Rhode Island, collected data from 1,248 individuals aged 17 to 39. All the study subjects' mothers had participated in the Providence cohort of the National Collaborative Perinatal Project (NCPP) between 1959 and 1966. As part of the NCPP, pregnant women provided information about their smoking and gave blood samples for measuring nicotine levels.

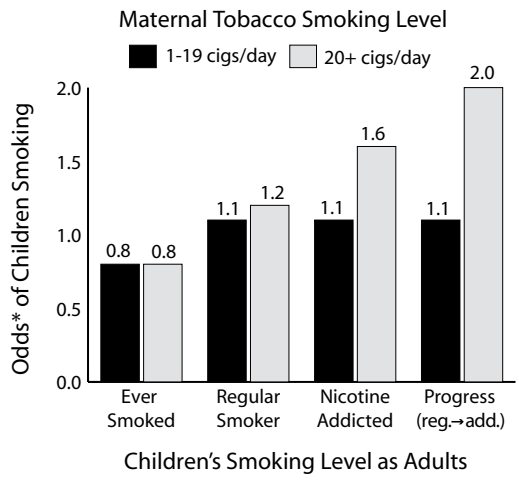
Among the men and women in the new study, 62 percent had smoked regularly and 45 percent met the medical criteria for tobacco dependence at some time in their lives. The criteria, as defined by DSM-III (Diagnostic and Statistical Manual of Mental Disorders, Revision III), include persistent, unsuccessful attempts to quit or control smoking, continued use despite smoking-related problems, and smoking to reduce withdrawal symptoms. Thirty-eight percent were born to mothers who did not smoke, 25.6 percent to mothers who smoked less than a pack a day, and 36.4 percent to mothers who smoked a pack or more per day at some point during pregnancy.

Among children who had smoked at least once, those whose mothers smoked up to a pack a day during pregnancy had a 20 percent higher, and those whose mothers smoked a pack a day or more had a 60 percent higher odds of having at some time been addicted to tobacco, compared with those whose mothers had not smoked. Among children who had at some time in their lives smoked daily for a month or more, those exposed *in utero* to a mother's pack-a-day smoking had double the odds of progressing to addiction.

"The evidence from this study, which reinforces the findings of experimental research with animals, is compelling," says Dr. Buka. "Early exposure to tobacco during pregnancy apparently affects the individual's response to cigarettes in later adolescence and adulthood."

The researchers' statistical analyses indicated that the associations between maternal smoking during pregnancy and offspring's future smoking were independent of socioeconomic status, maternal age at pregnancy, offspring sex, and offspring age at the time of the interview. What's left, then, is a biological factor. "The most likely hypothesis is that the toxins in cigarettes cross the placental barrier and interact with the genes that control cell differentiation, permanently altering cells' responsiveness in ways that increase vulnerability to tobacco addiction," Dr. Buka says.

Heavier Maternal Smoking During Pregnancy Increased Children's Odds of Nicotine Addiction as Adults



Children of women who smoked at least 20 cigarettes a day during pregnancy were more likely to become addicted to nicotine or progress from regular smoking to nicotine addiction as adults compared with children of women who smoked fewer than 20 cigarettes a day. Children of heavier smokers were no more likely to try smoking or to smoke regularly than children of lighter smokers.

The cross-generational impetus to tobacco addiction documented by the study is a serious national health concern. Almost half of women who smoke continue to do so when they become pregnant, says Dr. Buka. The smoking mothers-to-be constitute about 12 percent of women who give birth—a national potential for 500,000 prenatal exposures every year.

The researchers also collected information about the study participants' marijuana abuse and found no tie to prenatal nicotine exposure. This suggests, the investigators say, that the "pathophysiological pathway" that promotes vulnerability to tobacco addiction among offspring differs from the pathway that leads to marijuana addiction.

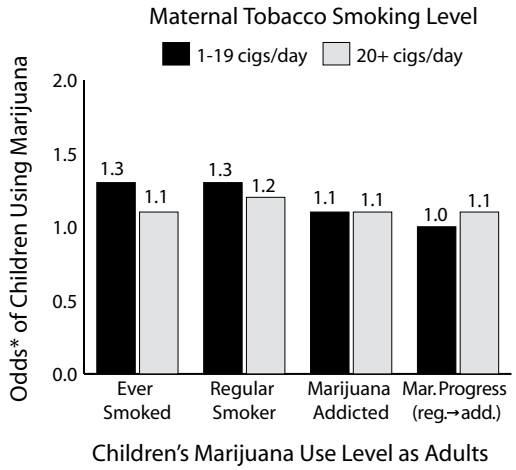
The study confirms the need for energetic efforts to deter women from smoking, especially during pregnancy, says Dr. Kevin Conway, deputy chief of NIDA's Epidemiology Research Branch. Preventing smoking by pregnant women will improve nicotine addiction rates of the next generation. "This study highlights opportunities for physicians to intervene with mothers who smoke, for the health of themselves and their children," says Dr. Conway.

"Healthy-baby prenatal visits, labor and delivery, and postnatal-care visits are golden opportunities for providers to offer assistance to quit smoking and prevent relapse, thereby reducing the risk of children's progression to nicotine addiction," says study coauthor Dr. Niaura. "Health care providers must take advantage of every opportunity to ask, advise, and assist patients in efforts to quit smoking."

Source

- Buka, S.L.; Shenassa, E.D.; and Niaura, R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: A 30-year prospective study. *American Journal of Psychiatry* 160(11):1978-1984, 2003. NN

Maternal Tobacco Smoking During Pregnancy Did Not Affect Children's Odds of Marijuana Use as Adults



** Odds ratio, calculated by dividing the odds of the children in the maternal smoking group by the odds of those with nonsmoking mothers.*

The finding that in utero *exposure to tobacco did not affect later marijuana use indicates that the two drugs have different physiological pathways.*

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 19, Number 2 (July 2004)

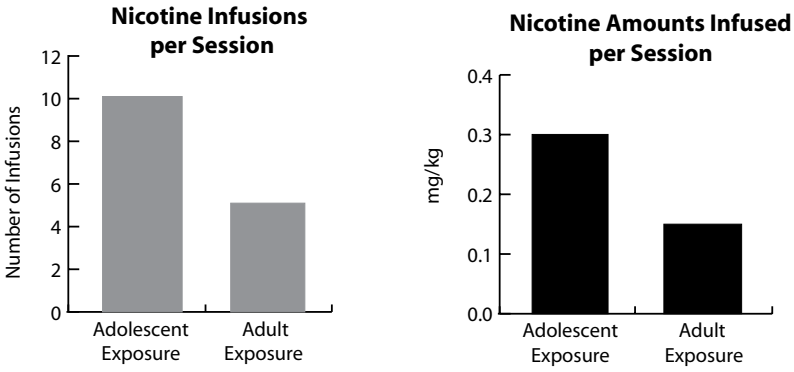
Early Nicotine Initiation Increases Severity of Addiction, Vulnerability to Some Effects of Cocaine

By Patrick Zickler, *NIDA NOTES* Staff Writer

Most tobacco use begins during adolescence, and people who start in their teens are more likely to become life-long smokers than are those who first light up as adults. Adolescent smokers are more likely than adult smokers to become dependent on nicotine. And when compared with nonsmoking peers, young smokers are more likely to be abusers of other drugs: In 2002, the National Survey on Drug Use and Health reported that roughly half (48.1 percent) of youths aged 12 to 17 who smoked cigarettes in the past month also used an illicit drug, whereas only 6.2 percent of nonsmoking youths reported using an illicit drug in the past month.

These observations suggest that teen smokers are especially vulnerable to the physiological effects of nicotine. Two recent NIDA-supported animal studies lend support to this interpretation of the epidemiological data. The results indicate that smoking may be more addictive if it is initiated during adolescence and that early exposure to nicotine may heighten response to other addictive drugs. An additional finding was that males and females may differ in their susceptibility to these effects.

Rats Exposed to Nicotine in Adolescence Self-Administer More Nicotine Than Rats First Exposed as Adults



Female rats first exposed to nicotine as adolescents self-administered nicotine more often and in higher total doses per session than rats first exposed as adults.

Early Initiation to Nicotine

Dr. Edward Levin and colleagues at Duke University in Durham, North Carolina, investigated whether the developmental period during which rats are first exposed to nicotine makes a difference in their subsequent drive to obtain the drug. One experiment looked at short-term effects, the other at long-term effects.

In the first experiment, the researchers showed that adolescent initiation to nicotine produced a greater intensity of nicotine taking in the days immediately following exposure than was seen in rats initiated to nicotine in adulthood. The researchers trained eight female adolescent rats and seven female adult rats to press a lever to obtain an intravenous injection of nicotine. Following this 2-week training, the researchers gave the rats, now 54 to 62 days old (adolescents) and 84 to 90 days old (adults), free access to the lever daily for 1 hour. The nicotine dosage delivered with each lever push changed each day, in different order for each rat, but over the 8 days of the study every animal had one day each with dosages of 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, or 0.08 mg/kg of its body weight. Regardless of dose, the adolescent animals administered more injections each day (average 10.4) than the adults (average 7.5).

Dr. Levin and colleagues next demonstrated that this greater propensity of adolescent-initiated female rats to self-administer nicotine persists into their adulthood. The researchers trained 13 adolescent and 7 adult rats to self-administer nicotine, then tracked their nicotine self-administration for 4 weeks, during which time the adolescents matured into adulthood. Throughout this period, the rats exposed as adolescents pressed the lever for nicotine (at a dose of 0.03 mg/kg) more often than the rats initially exposed as adults (10.1 times per session versus 5.1 times per session).

"At the end of this 4-week period, the adolescent-onset rats were at least 82 days old and were themselves adult," says Dr. Levin. "This finding suggests that those who begin smoking during adolescence are at greater risk for increased smoking over the long term."

These findings are likely to be meaningful for humans as well as lab animals, Dr. Levin observes, since human brains as well as rat brains continue to develop during adolescence. "Self-administration of nicotine during teenage years, when the brain is still developing, may cause some of the developmental processes to proceed inappropriately, in effect sculpting the brains of these adolescents in ways that facilitate the addiction process."

Animal self-administration studies have become a standard tool in nicotine research, but investigation into a possible link between adolescent exposure and severity of addiction has been limited and most work has involved male animals, Dr. Levin points out. In humans, there are notable differences between adult men and women smokers. Men tend to be heavier smokers than women, for example, and women report more severe withdrawal symptoms than men. It is possible that sex differences also occur in adolescent smoking, Dr. Levin observes. "An animal study that uses female rats will more closely model adolescent-onset smoking in teenage girls, a group that is showing a rise in smoking rates," he says.

Smoking may be more addictive if it is initiated during adolescence, and early exposure to nicotine may heighten response to other addictive drugs. Males and females may differ in their susceptibility to these effects.

"Epidemiological data show that adolescent girls exhibit signs of nicotine dependence sooner than adolescent boys. Animal studies show that adult females exhibit greater motivation to self-administer nicotine than do males," points out Dr. Cora Lee Wetherington, NIDA's women and gender research coordinator. "The growing body of evidence on sex differences in response to nicotine emphasizes the importance of including females in animal models of adolescent nicotine use. Dr. Levin's plan to follow up these intriguing findings with a parallel study with males is particularly important," she adds.

Sensitization Differs in Males, Females

Repeated exposure to the same dose of an addictive drug may result in increasingly more intense behavioral response. A dose of cocaine, for example, may elicit more activity on the second day of exposure than did the same dose a day before. This phenomenon, called sensitization, involves drug-induced brain changes that may underlie addiction and can be used to identify differences in susceptibility to the effects of drugs.

Dr. Sari Izenwasser and Dr. Stephanie Collins at the University of Miami found that female adolescent rats show more rapid and pronounced sensitization to behavioral effects of nicotine than adolescent males or adult rats of either sex. In addition, when the researchers administered cocaine to adolescent and adult rats previously exposed to nicotine, adolescent males, but not adolescent females or adults of either sex, exhibited sensitization to some effects of cocaine.

The researchers administered nicotine (0.4 mg/kg of body weight) daily for 7 days to 20 rats, 5 adolescents and 5 adults of each sex. After each injection, the animals were placed in activity monitors—chambers equipped with infrared light beams aimed at detectors on the opposite wall—for 60 minutes while the researchers monitored two aspects of their behavior. Horizontal locomotion was measured by counting the number of times an animal broke light beams. Stereotypy, which involves repetitive actions such as head bobbing, was measured by counting repeated breaks of the same beam. Adolescent females showed increased stereotypy and locomotion in response to nicotine on their second exposure, signifying sensitization, which persisted over the 7 days of repeated administration. Adolescent males, in contrast, showed no locomotor sensitization to nicotine and no stereotypy sensitization until the fourth day of repeated exposures. Adult male and female rats showed sensitization (stereotypy and locomotion) after the fifth day of repeated exposures.

On the eighth day of the study, the researchers investigated the extent to which nicotine exposure affected sensitization to cocaine. They administered cocaine to all the rats in three sequential injections (1, 2, and 7 mg/kg) and monitored the animals' activities for 10 minutes after each injection. For females, previous exposure to nicotine was associated with cocaine sensitization as evidenced by cocaine-induced stereotypy—but not by horizontal movement. Adult males that received nicotine exhibited sensitization to cocaine's effect on horizontal movement but not stereotypy. Adolescent males exposed to nicotine also exhibited greater sensitization than did adult males to cocaine's effect on horizontal movement and were the only group to exhibit sensitization in both stereotypy and horizontal movement.

"Overall, it appears that sensitization to cocaine is more pronounced in adolescent than in adult rats after treatment with nicotine. This suggests that early nicotine use may create an increased risk for young people who subsequently use cocaine, and that adolescent males who smoke may be particularly vulnerable to the risk of cocaine abuse," Dr. Izenwasser says.

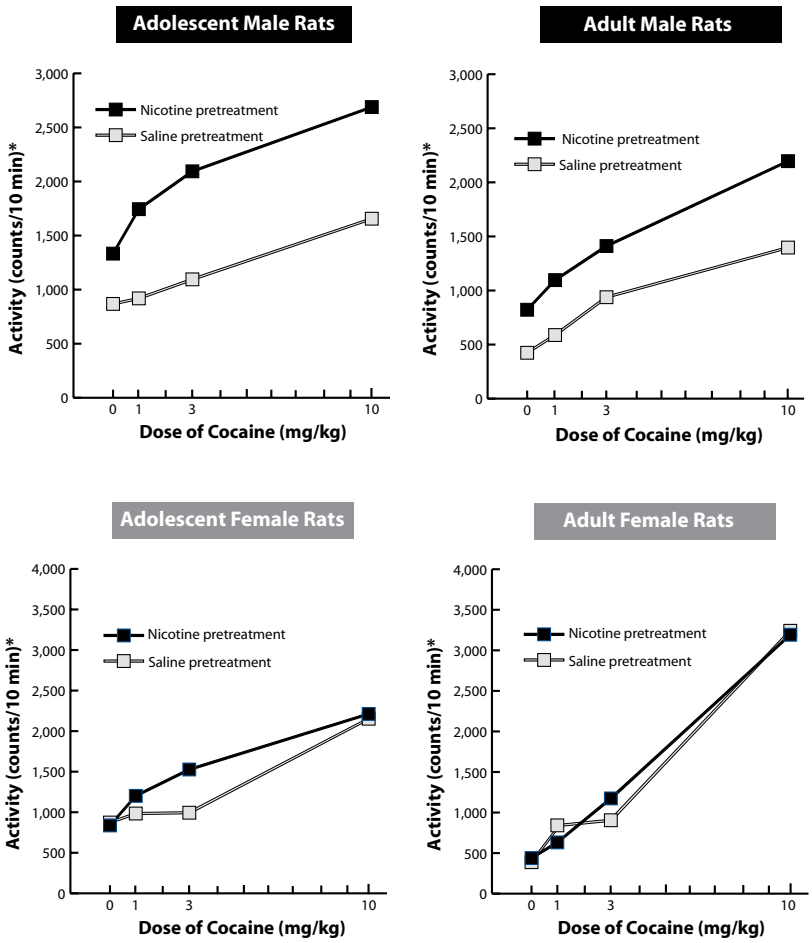
"Animal studies such as these are an important addition to a research base that suggests that adolescents show a very different responsiveness to nicotine—upon both

acute and chronic or repeated administration—than do adults. The rapid sensitization of adolescent females to nicotine's behavioral effects highlights the need to be aware of gender differences in addictive processes during adolescence," observes Dr. Minda Lynch of NIDA's Division of Neuroscience and Behavioral Research. "Studies such as these also raise important questions about vulnerability to nicotine addiction and on nicotine's potential for cross-sensitization to other drugs of abuse in adulthood or adolescence. And they illustrate the importance of studying drug effects, and the neurological changes they trigger, in the context of the dynamic processes that characterize adolescent brain development."

Sources

- Collins, S.L., and Izenwasser, S. Chronic nicotine differentially alters cocaine-induced locomotor activity in adolescent vs. adult male and female rats. *Neuropharmacology* 46(3):349-362, 2004.
- Levin, E.D., et al. Adolescent-onset nicotine self-administration modeled in female rats. *Psychopharmacology* 169(2):141-149, 2003. NN

Rats First Exposed to Nicotine in Adolescence Show Greater Sensitization to Cocaine Than Rats First Exposed as Adults



**Activity level after cocaine administration was measured by counting the number of times in 10 minutes each rat crossed light beams projected in a grid across its cage.*

Rats exposed to nicotine in adolescence and then exposed to cocaine were more sensitive to cocaine's locomotor stimulating effects than rats first exposed to nicotine as adults. Nicotine-induced presensitization to cocaine was greatest in young male rats.

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 19, Number 1 (April 2004)

Smoking Decreases Key Enzyme Throughout Body

By Patrick Zickler, *NIDA NOTES* Staff Writer

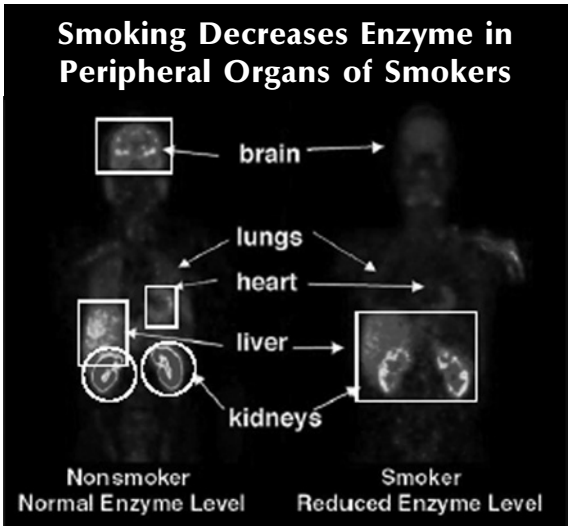
Nicotine addiction and tobacco use wreak enormous worldwide health consequences, including more than 400,000 deaths in the United States each year from tobacco-related diseases. Most of this health toll involves disease related to the effects of inhaled smoke on the lungs and respiratory system and on the heart and circulatory system. However, recent NIDA-supported research has demonstrated that a compound found in cigarette smoke reduces levels of an important enzyme throughout the body—in the spleen, kidneys, and brain as well as the lungs. The enzyme, monoamine oxidase B (MAO-B), plays a critical role in breaking down neurotransmitters and helping to regulate blood pressure. Too much or too little of the enzyme can affect mental or physical health.

Dr. Joanna Fowler and colleagues at the Brookhaven National Laboratory in Upton, New York, and the State University of New York at Stony Brook used positron emission tomography (PET) imaging to show reduced levels of MAO-B in the kidneys, heart, lungs, and spleen of smokers. "When we think about smoking and smoking toxicity, we usually think of the lungs," Dr. Fowler observes. "But here we see a very marked effect of smoking on one of the major enzymes in the body, and we see that this effect extends far beyond the lungs."

In earlier research, the Brookhaven scientists—whose research also is supported in part by the Department of Energy and the National Institute of Biomedical Imaging and Bioengineering—had found decreased levels of MAO-B in the brains of smokers. "Because smoking exposes the entire body to the tobacco compounds that inhibit MAO-B, we believed it had the potential to limit MAO-B activity elsewhere in the body," Dr. Fowler says.

The study involved 10 men and 2 women (average age 41 years) who had been smoking for an average of 21 years. Each participant underwent PET scanning of his or her torso after receiving injections of radioactive MAO-B tracers. When the researchers compared these scans with scans previously performed on nonsmokers, they found that MAO-B distribution in the heart, lungs, kidneys, and spleen of smokers was 33 to 46 percent lower than levels seen in nonsmokers.

The reduction in MAO-B levels is not due to nicotine, but to an unidentified component of tobacco smoke—one of roughly 4,000 chemicals to which smokers are exposed with each puff. "With the whole body exposed to the thousands of compounds in tobacco smoke, we need to be aware that these may contribute to the physiological effects of smoking," Dr. Fowler adds.



PET scans compare the distribution of the enzyme MAO-B in a nonsmoker and smoker. Circled areas indicate the highest MAO-B concentrations, areas captured in squares show intermediate levels, and areas with the lowest concentrations are unmarked. The smoker has lower MAO-B concentrations in peripheral organs than the nonsmoker.

"Nicotine establishes the addiction, and continuous smoking maintains levels of all these compounds throughout the body," Dr. Fowler says. "The health consequences of reduced MAO-B levels in the organs are unclear. There may be adverse effects that are indirect and associated with the dietary substances or environmental compounds normally broken down by the enzyme. At the very least, however, it is clear that enzyme levels in smokers' peripheral organs are significantly affected by their tobacco use."

Source

- Fowler, J.S., et al. Low monoamine oxidase B in peripheral organs of smokers. *Proceedings of the National Academy of Sciences* 100(20):11600-11605, 2003. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 18, Number 6 (February 2004)

The Neurobehavioral Legacy of Prenatal Tobacco Exposure

By Jill Schlabig Williams, *NIDA NOTES* Contributing Writer

More than 17 percent of pregnant women between the ages of 15 and 44 smoke, according to the 2002 National Survey on Drug Use and Health. Much is known about the adverse effects of smoking during pregnancy: Cigarette smoke reduces blood flow through the placenta by as much as 38 percent, and pregnant smokers are more than twice as likely as nonsmokers to have an infant with low birthweight. New research by NIDA-funded investigators now provides the first evidence of toxic effects of prenatal exposure to tobacco smoke on newborn neurobehavior. This finding begins to fill in our picture of how the adverse neurological effects of prenatal exposure manifest from the earliest days of life to later observed effects, including lower IQ and increased risk of developing attention-deficit/hyperactivity disorder.

Drs. Barry M. Lester and Karen L. Law and their colleagues at Brown Medical School in Providence, Rhode Island, used the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) to document the effects of maternal smoking on 1- to 2-day-old infants. The researchers found significant differences in short-term neurobehavioral status in tobacco-exposed newborns compared with unexposed newborns and noted that neurobehavioral impact worsened as the mothers' smoking levels rose.

"This study offers the first solid evidence of a dose-response relationship between maternal smoking during pregnancy and newborn neurobehavior," says Dr. Lester. "Babies born to mothers who smoked while pregnant are stressed, which could affect their development."

"Focusing on newborn neurobehavioral outcomes is important," comments Dr. Vincent Smeriglio, Chair of NIDA's Child and Adolescent Work Group. "It invites us to think about the continuity of consequences, as we

Tobacco-Exposed Infants Exhibit Significant Neurobehavioral Effects

NNNS Category	Tobacco-Exposed Infants (N=27)	Non-Exposed Infants (N=29)	Measure Description, Number of Items, and Range
Handling	0.57	0.44	Mean number of strategies used to maintain infant's alert state (8 items, 0-1)
Excitability	3.08	1.91	Sum of items measuring excitable behavior (15 items, 0-15)
Hypertonicity	0.37	0.00	Sum of items measuring excess muscle rigidity response (10 items, 0-10)
Total Stress/Abstinence (Withdrawal)	0.12	0.05	Mean number of observed stress/abstinence signs (50 items, 0-1)
Central Nervous System Stress	0.16	0.09	Subscale of total stress/abstinence score (range 0-1)
Gastrointestinal Stress	0.16	0.02	Subscale of total stress/abstinence score (range 0-1)
Visual Stress	0.11	0.01	Subscale of total stress/abstinence score (range 0-1)

The NICU Network Neurobehavioral Scale (NNNS), developed with NIDA funding to study prenatal drug exposure, was used to assess the effects of prenatal nicotine exposure on 56 newborns within 48 hours of birth. Infants prenatally exposed to tobacco were highly aroused and reactive, with more rigid muscles than non-exposed infants. Tobacco-exposed infants also scored higher on a checklist of 50 items that serve as markers of stress or drug withdrawal in high-risk babies, with significant results evident for central nervous system, gastrointestinal, and visual stress. Data shown are adjusted scores; statistical analyses controlled for parity, 5-minute Apgar score, and birthweight.

see these very early behavioral differences in prenatally exposed children and consider them in light of effects in older children" (see below, "Cognitive Deficits Persist Into Early Adolescence for Children of Smoking Mothers"). "This research is providing an important piece of the puzzle linking prenatal exposure to cigarette smoke and long-term behavioral outcomes," Dr. Smeriglio says.

The researchers conducted their study with 56 new mothers, ages 18 to 35, and their newborns at a Providence hospital. Recruited shortly after they had given birth, the mothers—27 smokers and 29 nonsmokers—had not used any illegal drugs during their pregnancy and consumed fewer than four alcoholic drinks per month. Mothers who smoked reported smoking fewer than seven cigarettes per day, with tobacco use confirmed by measuring saliva levels of cotinine, the primary metabolite of nicotine. Only healthy newborns whose weights were appropriate to their gestational ages were included in the study; the researchers controlled for birthweight so the effects they found on neurobehavior could not be attributed to the effects of maternal smoking on birthweight.

A certified examiner who was unaware of the mother's smoking status administered the NNNS to each newborn within 48 hours of birth. The test examines an infant's

Cognitive Deficits Persist Into Early Adolescence for Children of Smoking Mothers

Teenage children of mothers who smoked during pregnancy perform more poorly on tests of general intelligence and on tasks requiring auditory memory than do children who were not exposed to cigarette smoke before birth, according to NIDA-supported researchers at Carleton University in Ottawa, Canada. Dr. Peter Fried and his colleagues, who have followed the development of children born to smoking mothers as part of the Ottawa Prenatal Prospective Study, previously reported poorer cognitive abilities in children of smokers when the children were ages 5 to 6 and 9 to 12. "The results we see now that the children are 13- to 16-year-olds continue to suggest that exposure to cigarettes before birth has negative impact on general IQ and on auditory memory. And the effects are dose-related: The deficits are more severe in children of heavy smokers," Dr. Fried says.

The scientists administered a battery of tests to 145 13- to 16-year-olds (78 boys, 67 girls) whose mothers smoked heavily (more than a pack per day), lightly (less than a pack per day), or not at all during their pregnancies. The tests included measures of general achievement (reading and language skills), visual memory (identifying a missing number from a random sequence of numbers from 1 to 10), auditory memory (repeating tape-recorded sentences of increasing length and complexity), and general intelligence (IQ scores). In some tests there were no significant differences among the children. In tests of general intelligence and auditory memory, however, children born to smokers had lower scores than did children of nonsmokers, and children born to heavy smokers had poorer scores than children of light smokers. For example, in the general intelligence test, for which scores from 99 to 109 are considered "normal," children of nonsmokers had an average score of 113.4; of light smokers, 109.8; and of heavy smokers, 105.2.

In some areas of cognitive function, the gap in test results between exposed and unexposed children has narrowed as the children have grown, observes Dr. Fried. This improvement is most notable in tests that measure achievement rather than innate ability. For instance, although measured IQ remains lower for exposed children, their scores on reading and language skills are equivalent to those of unexposed children. "This comparative improvement in achievement is associated most strongly with the educational level of the parents. Achievement tests are in many ways a measure of formal learning acquired at home and in school. It appears that family and environmental factors that support learning can help moderate the negative effects seen in measures of ability," Dr. Fried explains.

"The improvements found in this most recent evaluation of these children are encouraging," says Dr. Vincent Smeriglio, chair of NIDA's Child and Adolescent Work Group. "Nonetheless, the continued finding of poorer performance as the exposed children enter adolescence underscores the damage that appears to be done by smoking during pregnancy. These kids may be catching up in some ways, but they started out with a serious disadvantage."

Source

Fried, P.A.; Watkinson, B.; Gray, R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. *Neurotoxicology and Teratolgy* 25(4):427-436, 2003.

neurological state, considering muscle tone, reflexes, and integrity of the central nervous system (CNS); behavior, including attention, arousal, and excitability; and a checklist of 50 items shown by previous research to be markers of stress or—in high-risk babies—of drug withdrawal. Dose-response effects were determined by evaluating the relationship between measures of maternal smoking (cotinine and self-report) and NNNS scores.

"Infants exposed to tobacco in the womb showed statistically significant differences that suggest toxic effects of prenatal tobacco exposure on the newborn neurological system," says Dr. Lester. The tobacco-exposed infants were highly aroused and reactive as indicated by the higher excitability and handling scores, and their muscles were more rigid. They also showed signs of stress and drug withdrawal consistent with what has been reported in infants exposed to other drugs. When the total stress/abstinence scores were broken down into subscales, exposed infants showed significant CNS, gastrointestinal, and visual effects. Further, infants prenatally exposed to tobacco required more handling to keep them in a quiet and alert state.

"These infants' higher scores in such areas as excitability and arousal reflect that nicotine is a stimulant," says Dr. Lester. The researchers also found consistent dose-response relationships for both the cotinine bioassay results and the self-reports of number of cigarettes smoked per day. "These results indicate that greater exposure to tobacco smoke is related to increasingly negative neurobehavioral effects," he adds, "and that these children may be at increased risk for future neurobehavioral problems."

Dr. Lester is currently designing a larger, multisite study focusing on the neurobehavioral effects of prenatal exposure to cigarette smoke. Future research will attempt to pinpoint which components of tobacco are responsible for the known neurobehavioral effects; determine whether those effects are long-term; clarify whether newborns experience nicotine withdrawal; and separate the effects of prenatal exposure from those of postnatal exposure through second-hand smoke or breastfeeding.

With valid information on the potential neurobehavioral effects of prenatal tobacco exposure, more pregnant women may be swayed to quit smoking, notes Dr. Lester. "The smoking effects observed in our study underscore the importance of smoking cessation programs, particularly for women of childbearing age," he says.

Source

- Law, K.L.; Stroud, L.R.; LaGasse, L.L.; Niaura, R.; Liu, J.; Lester, B. Smoking during pregnancy and newborn neurobehavior. *Pediatrics* 111(6):1318-1323, 2003. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 18, Number 5 (December 2003)

Hard-to-Treat Smokers May Benefit From Medication That Acts on Dopamine

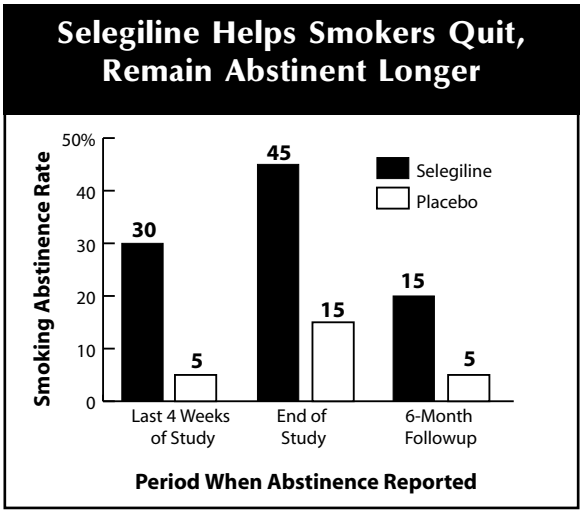
By Patrick Zickler, *NIDA NOTES* Staff Writer

Nearly 23 percent of Americans 18 and older smoke cigarettes. Although this figure represents a substantial decrease since smoking rates were at their highest in 1965, most current smokers say they would like to quit. According to the Centers for Disease Control and Prevention, 71 percent of smokers interviewed in 2000 said they wanted to quit smoking, with 41 percent having tried to quit in the preceding year.

Many of those who still smoke are the hardest to treat, having failed to stop despite numerous attempts. Their efforts to quit are frustrated by nicotine's addictive effects, which result in large part from the drug's ability to trigger and sustain release of the pleasure-producing neurotransmitter dopamine in the brain. At Yale University in New Haven, Connecticut, NIDA-supported researchers have found that selegiline, a medication currently used by physicians primarily to delay the progression of symptoms in Parkinson's disease, can help smokers who want to quit but have been unsuccessful with other treatments.

"Our research group focused on difficult-to-treat smokers, who aren't responsive to nicotine replacement therapy or to bupropion," says Dr. Tony George of Yale University School of Medicine. "Many smokers who attempt to quit fail because of the powerful withdrawal symptoms smokers experience when they stop smoking. There is strong evidence that the symptoms of nicotine withdrawal are associated with sharp declines in dopamine levels, so we thought a medication that acts to boost dopamine levels might be of benefit." In Parkinson's disease, which involves massive loss of dopamine-producing cells, treatment with selegiline helps the brain retain its stores of dopamine longer by inhibiting the activity of monoamine oxidase-B, an enzyme that breaks down dopamine.

To evaluate the effect of selegiline in smoking cessation treatment, the researchers recruited 40 smokers (75 percent Caucasian, 15 men, 25 women, average age 49) who had unsuccessfully tried (at least 3 times and some as many as 20) to stop smoking and described themselves as highly motivated to quit. Over 8 weeks, all participants received weekly smoking cessation counseling that included motivational enhancement for the first 3 weeks of the study and work on relapse prevention strategies for the last 5 weeks. They took pills containing either placebo or 5 mg selegiline once a day for the first week and twice a day for the remaining 7 weeks. Twenty participants (8 men, 12 women) received selegiline and 20 (7 men, 13 women) received placebo. All participants were allowed to smoke during the first 2 weeks of the study, and a "quit date"was set for the first day of the third week.



Smokers who received selegiline plus counseling were more likely to stop smoking and remain abstinent than smokers who received placebo and counseling.

At the end of the eighth week, 45 percent of the participants who received selegiline reported they had not smoked during the preceding week, compared with 15 percent of those receiving placebo. Measurement of carbon monoxide levels in the participants' exhaled breath verified their self-reports. The difference between the two treatment groups was even more pronounced when reports of 4-week abstinence were considered: Compared with 5 percent of the placebo group, 30 percent of those who received selegiline reported they had not smoked in the last 4 weeks of the study. Six weeks after the study ended, 20 percent of the selegiline group were still not smoking, compared with 5 percent of those who received placebo.

"In this study, selegiline appeared to substantially improve outcomes for smokers who have had a difficult time stopping," says Dr. Ivan Montoya of NIDA's Division of Treatment Research and Development. "The results,

which are better than those typically achieved by smokers using nicotine replacement therapy to help them quit, offer strong confirmation that controlling the dopamine system could be an important approach to successful treatment of nicotine addiction, particularly for smokers with a history of unsuccessful quit attempts. Our next step is to confirm this in a much larger trial with several hundred smokers."

Source

- George, T.P., et al. A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. *Biological Psychiatry* 53(2):136-143, 2003. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

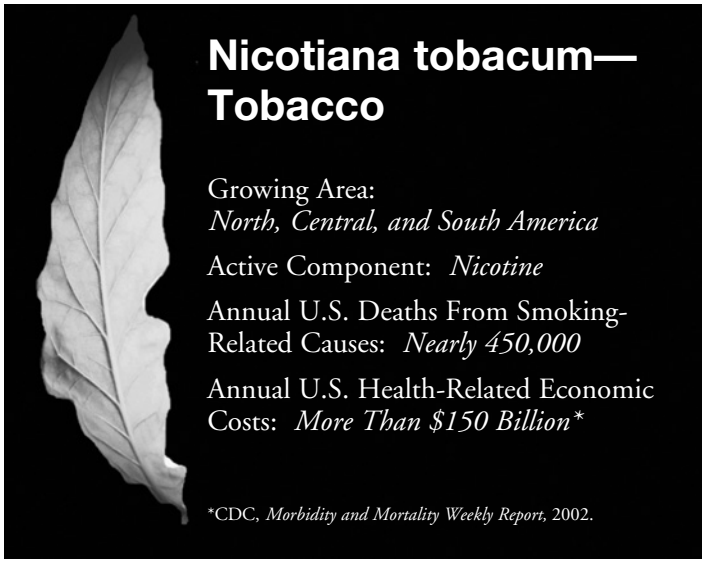
Research Findings

Volume 18, Number 3 (October 2003)

Discovering, Developing, and Delivering Smoking Cessation Medications Is Focus of NIDA Symposium

By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA, joined by the National Cancer Institute (NCI) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), sponsored a symposium on drug discovery, development, and delivery as part of the 2003 Annual Meeting of the Society for Research on Nicotine and Tobacco. More than 300 researchers, treatment providers, and policymakers attended the 1-day meeting on February 9 in New Orleans. The symposium featured discussions of current efforts to discover new targets for potential medications, the development of medications based on existing knowledge of nicotine's effects in the brain, and factors that might speed the delivery of new treatments to smokers who want to quit.



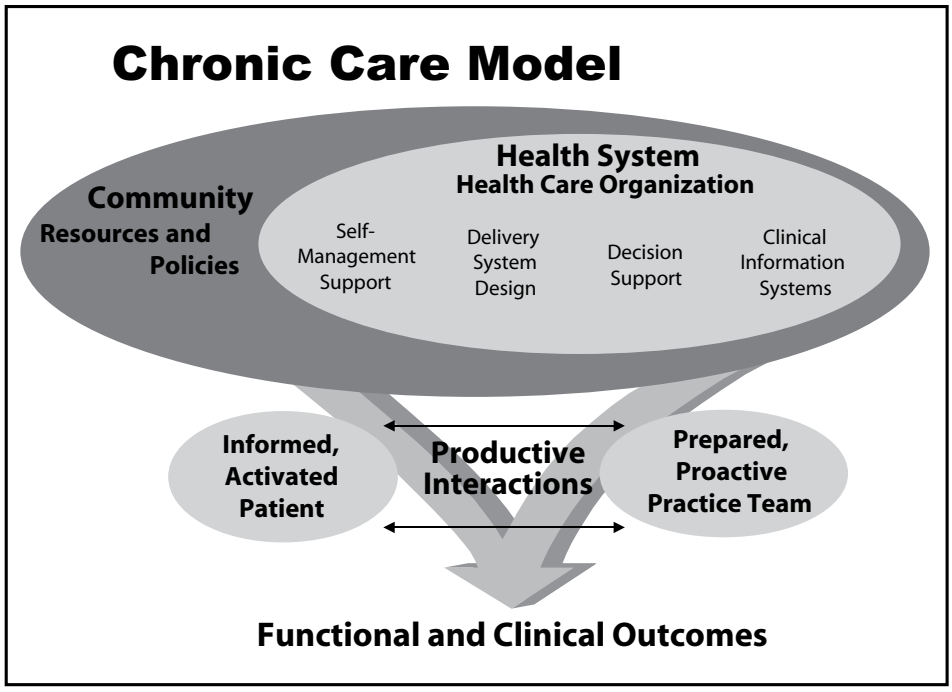
During the discovery section of the program, speakers discussed recent findings in nicotine receptor biology and the role of neurotransmitters, such as gamma-aminobutyric acid (GABA) and glutamate, in nicotine's effects on the brain. The presentations on medication development provided a background on the drug development process; emerging medications, such as antidepressants and nicotine vaccines; and an overview of medications now in development. The delivery portion of the symposium focused on strategies to create widespread medication access and use by individual smokers and within the health care system.

Discovery. Dr. William Corrigall, director of NIDA's Nicotine and Tobacco Addiction Program and symposium moderator, described the neurobiological targets of current research: genes and gene products that play a role in the structure and response of nicotinic receptors and in brain signaling pathways that involve the neurotransmitters dopamine, GABA, serotonin, and glutamate. Dr. Caryn Lerman, of the University of Pennsylvania in Philadelphia, further explored the genetic factor in nicotine research, describing studies on the effect of genetic variations on the activity of enzymes that metabolize nicotine (see "Genetic Variation May Increase Nicotine Craving and Smoking Relapse.")

Dr. Marina Picciotto, of Yale University in New Haven, Connecticut, discussed research that has expanded our understanding of the role of nicotine receptors—the sites at which nicotine attaches to brain cells. This portion of the program also featured discussions of the possibility that neurotransmitters other than dopamine might represent new avenues for pharmacotherapy. For example, Dr. Julie Staley, also of Yale University, described current investigations into the treatment possibilities represented by medications known to act on the serotonin system. The GABA neurotransmitter system, which normally acts to limit dopamine's effect in the brain's pleasure center, might also help in smoking cessation treatment, according to Dr. George McGehee of the University of Chicago. He discussed the mechanism by which nicotine simultaneously stimulates dopamine release and depresses the effect of GABA.

Development. Dr. Frank Vocci, director of NIDA's Division of Treatment Research and Development, described the steps involved in the development of new medications and their approval by the Food and Drug Administration (FDA)—a process that may require a decade of research and testing, at a cost as high as $500 million per medication. Accelerating the process at any stage, from basic research to human clinical trials, will speed the availability of new treatments. Dr. John Hughes, of the University of Vermont in Burlington, suggested that psychiatric medications already approved for treating neurochemical imbalances in the brain might hold clues for developing medications to treat the neurochemical effects of smoking.

Dr. Charles Grudzinskas, of Georgetown University Medical Center in Washington, D.C., summarized potential medications now in FDA Phase I, II, or III trials. These medications include additional nicotine replacement therapies and nicotine vaccines. Dr. Paul Pentel of the Hennepin County Medical Center in Minneapolis, Minnesota, described progress in the development of one type of nicotine vaccine—antibodies that bind to nicotine in the blood, preventing it from crossing the blood-brain barrier and reaching the areas of the brain that underlie addiction. Vaccines may be particularly effective as relapse-prevention medications for smokers who are trying to remain abstinent.



At the 2003 meeting of the Society for Research on Nicotine and Tobacco, Dr. Susan Curry discussed use of a chronic care model to improve the delivery, utilization, and effectiveness of tobacco cessation treatment. This approach draws on the community—of which the health system is a part—to help patients and their practitioners effectively work toward desired health goals.

Delivery. Dr. Scott Leischow, chief of NCI's Tobacco Control Research Branch, discussed barriers to delivery and utilization of current tobacco cessation treatments. These include the high relapse rate associated with current treatments and the cost and "hassle" factor that deter patients from using nicotine replacement therapy, which they contrast to the simplicity of nicotine delivery by cigarettes. To address barriers to use, Dr. Saul Shiffman of the University of Pittsburgh discussed strategies that might increase utilization of existing treatments, including regulatory changes that make cigarettes more expensive and increased advertising and education to encourage more smokers to try to quit.

Providers and insurers also need to address barriers within their control, noted several speakers. Dr. Richard Hurt, of the Mayo Clinic's Nicotine Dependence Center in Minneapolis, Minnesota, discussed the limitations of current clinical treatment. He noted that relatively few medications are available, clinicians are not familiar with them, and patients are reluctant to begin treatment because of embarrassment, inadequate relief from withdrawal, and the difficulty of complying with instructions for use of gum, inhalers, or nasal sprays. Dr. Susan Curry of the University of Illinois at Chicago suggested steps that insurers and health care organizations could take to improve the delivery, utilization, and effectiveness of treatment. For example, she said, health care systems should adopt a chronic disease model to treat smoking, and insurers should include the cost of medications in coverage that provides comprehensive pharmacological and behavioral treatment.

In concluding remarks, Dr. Corrigall noted that the enthusiastic response to the day-long discussion illustrates broad support for steps that will increase and accelerate available treatment options for smokers. "Clinicians and patients need better treatment options, and this symposium represents a significant first step in a collaboration that can help speed the process of getting new and more effective medications to smokers who want to quit." NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

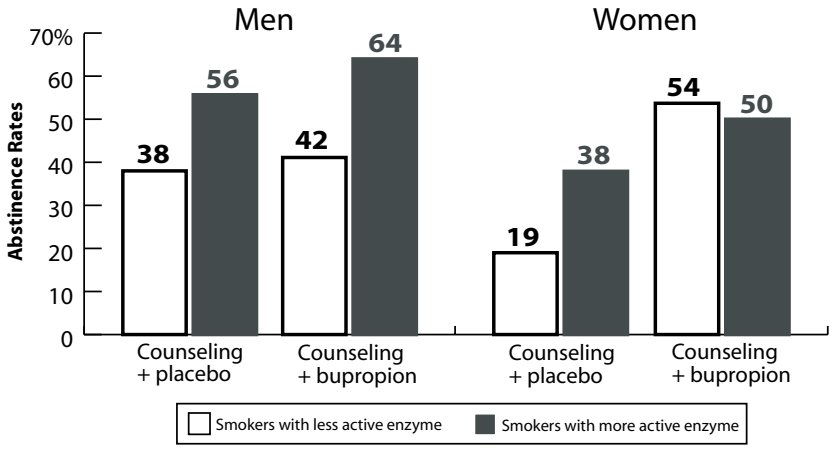
Volume 18, Number 3 (October 2003)

Genetic Variation May Increase Nicotine Craving and Smoking Relapse

By Patrick Zickler, *NIDA NOTES* Staff Writer

Smokers who want to quit can get help with a variety of treatments, including counseling, nicotine replacement therapy (patches, gum, lozenges, or inhalers), and medications. Some smokers use these treatments and succeed; for many, however, the discomfort of withdrawal and craving for nicotine lead to relapse. Recent NIDA-funded research suggests that our genes may partly explain this variable success.

Genetically Determined Enzyme Level Affects Treatment Response



In a study of 426 smokers in a 10-week smoking cessation program, those with a gene form that decreases activity of an enzyme that metabolizes nicotine reported greater craving and were less likely to achieve abstinence during treatment than were participants with the gene form that increases the enzyme's activity. Supplementing counseling with bupropion helped women with the less active enzyme nearly triple their abstinence rate to 54 percent—roughly equal that of women with the more active enzyme.

The research evaluated the effect of an enzyme, designated CYP2B6, on craving and relapse. This enzyme breaks down nicotine in the brain. Some people's genes produce a more active form of the enzyme, while others have a less active form. Dr. Caryn Lerman at the NIDA- and NCI-supported Transdisciplinary Tobacco Use Research Center (TTURC) at the University of Pennsylvania found that among smokers enrolled in a smoking cessation program, those with the genetic variant that decreases activity of CYP2B6 reported greater craving than did those with the more active form of the enzyme. Moreover, those with the less active enzyme were 1.5 times more likely to resume smoking during treatment.

The same enzyme helps break down bupropion, an antidepressant medication that acts on the brain's dopamine system—where nicotine exerts much of its addictive influence—and helps some smokers quit. Dr. Lerman, along with colleagues at Georgetown University in Washington, D.C., the State University of New York at Buffalo, and Brown University in Providence, Rhode Island, also investigated the relationship of CYP2B6 activity with bupropion treatment. They found that bupropion nearly tripled the success rate for women with the less active enzyme.

"These findings provide initial evidence that smokers who have decreased CYP2B6 activity experience greater craving for nicotine than those with the more active form of this enzyme," Dr. Lerman says. "Perhaps of greater interest is the preliminary evidence that, among women, bupropion may overcome the effect this genetic predisposition has on relapse."

Genes, Treatment, and Abstinence

Most people—about 70 percent of the U.S. population—inherit two copies of the "C" variant of the gene that influences CYP2B6 activity. The rest of the population inherits from one or both parents the less common form of the gene—the "T" variant associated with decreased CYP2B6 activity. Among the 426 participants (232 men, 194 women) in the TTURC study, 128 (29.6 percent) had one or two copies of the T form of the gene. All participants received counseling to quit smoking; 229 received bupropion (300 mg/day) and 197 received placebo throughout the 10-week study. The participants provided weekly reports on craving and smoking rates. Abstinence (7 consecutive days without smoking) was

verified with blood tests. At the end of treatment, participants who received counseling and bupropion had higher abstinence rates than those who received counseling and placebo. With one exception, participants with the less active enzyme had lower abstinence rates than those with the more active enzyme. Women with the less active enzyme who received bupropion showed the largest treatment effect, with 54 percent achieving abstinence, up from a 19-percent rate among women in the placebo group, notes Dr. Lerman.

This study suggests that properly selected treatment matched to a patient's characteristics can improve a smoker's chance of quitting.

Theories To Explain Outcomes

The higher abstinence rate with bupropion for women with the lower activity enzyme may be due, in part, to reduced susceptibility to low moods that accompany nicotine withdrawal; overall, women reported more negative feelings than did men when asked to rate their mood during withdrawal. "This rate may reflect better management of the negative moods and craving that abstinence can create. But more study is needed to clarify the mechanisms by which bupropion influences smokers' success in quitting," Dr. Lerman says.

Researchers theorize that the association between the less active enzyme and increased craving could be the result of nicotine's remaining longer in the brains of smokers with the less active enzyme. When nicotine lingers in the brains of these smokers, it may change their brain cells more profoundly than those of smokers with the more active enzyme. If so, the changes might produce more severe addiction marked by more intense craving during abstinence and increased risk of relapse.

"This study offers additional evidence of the important role genes play in smoking and treatment," says Dr. Joni Rutter of NIDA's Division of Neuroscience and Behavioral Research. "While illustrating the increased craving and vulnerability to relapse that may be associated with inherited traits, it also suggests that properly selected treatment matched to a patient's characteristics—in this case, bupropion for some women—can improve a smoker's chance of quitting."

Source

- Lerman, C., et al. Pharmacogenetic investigation of smoking cessation treatment. *Pharmacogenetics* 12(8):627-634, 2002. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 18, Number 2 (August 2003)

Alternative Cigarettes May Deliver More Nicotine Than Conventional Cigarettes

By Susan Farrer, *NIDA NOTES* Contributing Writer

Clove cigarettes, bidis, and additive-free cigarettes deliver at least as much nicotine as conventional cigarettes, suggests recent research conducted by NIDA Intramural Research Program (IRP) investigators in Baltimore. Smokers who choose these cigarettes are as likely to become addicted to nicotine as are other smokers and are exposing themselves to the increased risk of cancers, respiratory disease, and heart disease associated with smoking.

Bidi makers rolling tobacco into tendu leaves, a wrapping that has less porosity than that of conventional cigarettes and that lacks the filter ventilation holes seen in filtered brands. Despite having less nicotine, bidis deliver as much—or more—nicotine as conventional cigarettes.

Dr. Wallace Pickworth and his IRP colleagues conducted two studies comparing the effects of smoking clove cigarettes, bidis, and additive-free cigarettes with the effects of smoking conventional filtered cigarettes as part of an ongoing IRP program that examines nicotine delivery of alternative cigarettes. Their findings refute some consumers' belief that alternative tobacco products—sold on the Internet and at health food stores, ethnic groceries, and drug paraphernalia shops—are safer than conventional cigarettes.

Effects of Smoking Clove Cigarettes

In the clove cigarette study, the IRP investigators analyzed the physical composition of a particular clove cigarette brand and conventional cigarettes and measured the nicotine, tar, and carbon monoxide (CO) delivery of the clove cigarette. They also conducted a small-sample clinical study comparing the nicotine delivery and physiologic and subjective effects of smoking clove cigarettes and conventional cigarettes.

In the nonclinical portion of the study, the investigators removed, weighed, and chemically analyzed the contents of 10 clove cigarettes and 10 each of 4 popular conventional cigarette brands. To measure how much nicotine, tar, and CO the clove cigarette delivered, they used machine-smoking methods based on those developed by the Federal Trade Commission. Analysis showed that the clove cigarette contained less nicotine and tobacco, but the smoking-machine analysis revealed that the clove product delivered more nicotine, tar, and CO than did the conventional cigarettes. The researchers attribute the clove cigarette's higher delivery of toxins to the lower porosity of its paper wrapper and its lack of filter ventilation holes, which are found on most ordinary cigarettes and dilute the smoke inhaled with each puff.

In the clinical part of the study, 10 volunteers (7 men and 3 women) were asked to smoke a clove cigarette and a filtered conventional cigarette of their usual brand. The volunteers, whose mean age was 30.3 years, smoked an average of 21.3 cigarettes a day and had been smoking for an average of 13.4 years. Four of the volunteers had previously smoked clove cigarettes and all had smoked bidis in the past.

After the volunteers smoked the clove or conventional cigarette, the researchers measured their plasma nicotine levels, exhaled CO levels, blood pressure, and heart rates. They also recorded the time and number of puffs taken to smoke each cigarette, and the volunteers rated their satisfaction with smoking each cigarette and its sensory effects.

The researchers found comparable increases in the volunteers' plasma nicotine levels, exhaled CO levels, heart rates, and systolic blood pressure after smoking the clove

and conventional cigarettes. However, the volunteers took longer and more frequent puffs of the clove cigarette than of their own cigarette brands (mean of 549 seconds and 15.1 puffs for the clove cigarette versus 314 seconds and 9.4 puffs for their own brands). This change in smoking behavior increases the amount of nicotine extracted from each cigarette, making it possible for smokers to achieve comparable blood concentrations of nicotine, even though clove cigarettes contain less of the drug per cigarette than do conventional brands.

Effects of Smoking Bidis and Additive-Free Cigarettes

In a related study, Dr. Pickworth and his colleagues compared the clinical effects of smoking bidis, additive-free cigarettes, and conventional cigarettes. As in the clove cigarette study, this research involved 10 volunteers (9 men and 1 woman), all of whom had a history of smoking bidis. However, the volunteers' average age was younger (24.5 years) and they smoked more per day (25 cigarettes) than participants in the clove cigarette study, although they had smoked for fewer years (8.7 years).

In each of four separate sessions, each volunteer smoked a single cigarette: an unfiltered, additive-free cigarette; a strawberry-flavored bidi; an unflavored bidi; and one of the subject's usual, filtered cigarettes. The researchers made the same analytical and physiological measurements and gathered the same behavioral information as they did in the clove cigarette study.

The analysis showed that 2 minutes after smoking, plasma nicotine levels increased the most for participants who had smoked the additive-free brand, followed by levels for smokers of the strawberry bidi, the unflavored bidi, and the conventional cigarette. The volunteers' average heart rate also increased significantly for all of the cigarettes, with the greatest difference (8.5 beats per minute) seen after smoking the additive-free brand and the least difference (2.5 beats per minute) after smoking their own brand. The volunteers spent more time smoking the additive-free cigarette and unflavored bidi (mean of 453 seconds, and 354 seconds, respectively) than the strawberry bidi or their own brands (322 seconds and 297 seconds, respectively). They also took more puffs to smoke any of the bidis and additive-free cigarettes (approximately 14 puffs each) than to smoke their own brand (10 puffs).

Like clove cigarettes, the additive-free cigarette and bidis delivered more nicotine than did conventional cigarettes. Although both the flavored and unflavored bidis are smaller and contain less tobacco than conventional cigarettes, the bidis raised plasma nicotine to levels equal to or greater than the volunteers' own brands. The researchers theorize that like the thicker clove cigarette wrappers, the bidis' nonporous wrappers limit air dilution.

Not Safe Products

The NIDA scientists conclude that clove cigarettes, bidis, and additive-free cigarettes are not safe products and may be as harmful as conventional cigarettes. "Even though the bidis and the clove cigarettes have less nicotine in the cigarette rod—in the case of the bidis about one-third and in the case of the clove cigarettes about one-half or less—people are still able to extract about the same or even more nicotine than they would from a conventional cigarette," says Dr. Pickworth. "When individuals smoke

Alternative Cigarettes and Young Smokers

Clove cigarettes, made in Indonesia and exported worldwide, are composed of 60 to 80 percent tobacco and 20 to 40 percent ground clove buds. They are usually machine rolled, are available with or without filters, and usually are sold in brightly colored packages. Clove cigarettes are sometimes referred to as "trainer cigarettes" and may serve as "gateway" products that introduce young people to smoking. The Monitoring the Future (MTF) survey, conducted by the University of Michigan's Institute for Social Research and funded by NIDA, tracks 8th-, 10th-, and 12th-graders' drug use, including use of tobacco products. In 2002, prevalence of clove cigarette smoking in the past year was 2.6 percent for 8th-graders, 4.9 percent for 10th-graders, and 8.4 percent for 12th-graders.

Bidis are small, brown, hand-rolled cigarettes that are made primarily in India and other South Asian countries. They are available in many flavors, such as chocolate, raspberry, and strawberry, making them appealing to adolescent smokers. The 2002 MTF survey reported that 2.7 percent of 8th-graders had smoked bidis in the past year; figures for 10th- and 12th-graders were 3.1 percent and 5.9 percent, respectively. In some geographic areas, rates are even higher. For example, a 1999 study by the Massachusetts Tobacco Control Program found that 16 percent of students in grades 7 through 12 in one large metropolitan area had smoked bidis in the 30 days prior to the study.

Additive-free cigarettes are made with whole-leaf tobacco and contain no chemical additives, preservatives, or reconstituted tobacco. IRP researchers report that many adolescents—and adults— believe that additive-free cigarettes are less harmful or less addictive than ordinary cigarettes, although scientific evidence contradicts that belief.

these novel cigarettes, they adjust their cigarette smoking behavior to achieve plasma levels of nicotine comparable to those attained by smoking their own brands of cigarette. By that standard, they are at least equally dependence-producing. As a consequence, smokers will increase their smoking as dependence increases, exposing themselves to ever-greater smoking-related health risks."

Sources

- Malson, J.L.; Lee, E.M.; Moolchan, E.T.; and Pickworth, W.B. Nicotine delivery from smoking bidis and an additive-free cigarette. *Nicotine and Tobacco Research* 4(4):485-490, 2002.
- Malson, J.L.; Lee, E.M.; Murty, R.; Moolchan, E.T.; and Pickworth, W.B. Clove cigarette smoking: Biochemical, physiological, and subjective effects. *Pharmacology Biochemistry and Behavior* 74(3):739-745, 2003.
- Malson, J.L.; Sims, K.; Murty, R.; and Pickworth, W.B. Comparison of the nicotine content of tobacco used in bidis and conventional cigarettes. *Tobacco Control* 10(2):181-183, 2001. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

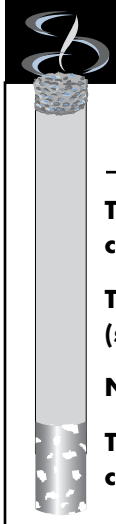
Volume 18, Number 1 (June 2003)

Manipulating Dopamine Levels Changes Smoking Behavior

By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA-supported researchers have demonstrated that lowering and raising the concentration of dopamine in the brain changes smoking behavior and nicotine intake in smokers. After taking a chemical compound that blocks release of dopamine to the brain's pleasure center, smokers lit up sooner and smoked more cigarettes than they did after taking a compound that stimulates dopamine release.

Nicotine triggers the release of dopamine in the brain, and the pleasurable sensations that result are thought to be a driving force in establishing addiction. Animal studies, in which brain cells can be carefully analyzed after nicotine administration, confirm the link between dopamine and addictive behavior. This study demonstrates that in humans, an individual's smoking behavior can be manipulated by stimulating or blocking dopamine release.



Smoking Behavior Changes With Decrease or Increase of Dopamine

	Haloperidol (inhibits dopamine)	Bromocriptine (enhances dopamine)
Total number of cigarettes smoked	**3.0**	**2.3**
Total puffing time (seconds)	**77.6**	**52.0**
Number of puffs taken	**44.8**	**31.1**
Time between cigarettes (minutes)	**32.1**	**41.2**

Smokers who received haloperidol, a dopamine antagonist, smoked more cigarettes during a 5-hour period and took more puffs per cigarette than did smokers who received bromocriptine, which enhances dopamine's effects.

Dr. Nicholas Caskey and his colleagues at the University of California at Los Angeles (UCLA) and the Veterans Affairs West Los Angeles Healthcare Center monitored the smoking behavior of heavy smokers who received oral doses of either haloperidol or bromocriptine.

"Our study was designed to use these compounds to decrease or increase availability of dopamine in a single group of otherwise healthy smokers and evaluate the effect on smoking behavior," explains Dr. Caskey.

Haloperidol is used to treat some psychiatric disorders, and earlier studies found that patients with schizophrenia smoked more during treatment with haloperidol than when they were not taking the antipsychotic medication. Other studies have shown decreased smoking and craving for nicotine among smokers who received bromocriptine (used to treat Parkinson's disease and disorders of the pituitary gland).

Participants in the study (14 men, 6 women, average age 30 years) smoked 15 or more cigarettes per day for at least 2 years. On average, they had been smoking more than 12 years and smoked 20 cigarettes per day at the time of the study. All participants received both haloperidol and bromocriptine over the course of the study, which consisted of two 5-hour sessions spaced roughly a week apart. In their first session, the participants received an oral dose of either 2.0 mg haloperidol or 2.5 mg bromocriptine; in their second session, the participants received the other drug. Over the next 5 hours, the participants were allowed to smoke their preferred brand of cigarettes at will, using a cigarette holder linked to a device that measured characteristics of each puff. They also answered questions about craving and discomfort.

With haloperidol, participants smoked more cigarettes (in total, three cigarettes) per session and smoked them faster (44.8 total puffs, or roughly 15 puffs per cigarette) than they did with bromocriptine (2.3 cigarettes, with 13.5 puffs per cigarette). Participants also reported greater craving with haloperidol (4.5 on a 1-7 scale) than with bromocriptine (3.8). "These results show that smoking behavior can be manipulated within the same subjects by alternately blocking and stimulating dopamine and indicates the importance of dopamine in smoking," Dr. Caskey says.

There currently are no human trials investigating the effectiveness of bromocriptine treatment as part of smoking cessation therapy, but NIDA-supported investigations of selegiline, another medication that acts on the dopamine system, are under way. "There are very few studies that look at the effect of dopamine on smoking in subjects who don't also suffer psychiatric disorders," observes Dr. Allison Chausmer of NIDA's Division of Neuroscience and Behavioral Research. "The findings in this study, particularly the results seen for bromocriptine, offer additional support for investigating potential medications that help control smoking by acting on the dopamine system."

Source

- Caskey, N.H., et al. Modulating tobacco smoking rates by dopaminergic stimulation and blockade. *Nicotine & Tobacco Research* 4(3):259-266, 2002.

NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 6 (March 2003)

Nicotine's Multiple Effects on the Brain's Reward System Drive Addiction

By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA researchers have added another piece to the puzzle of what makes nicotine so addictive. Dr. Daniel McGehee and colleagues at the University of Chicago have shown that along with directly stimulating the brain's reward system, nicotine also stimulates it indirectly by altering the balance of inputs from two types of neurons that help regulate its activity level. This additional stimulation intensifies the pleasure from smoking and makes it last longer.

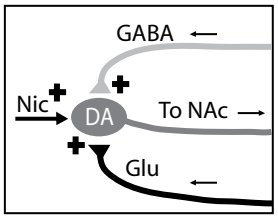
Scientists have long known that nicotine, like other addictive drugs, attaches to the core neurons of the brain's reward system, where beneficial behaviors (such as drinking water when thirsty) are rewarded and reinforced. Situated in a region of the brain called the ventral tegmental area (VTA), these reward-system neurons, called dopaminergic neurons, trigger release of the neurotransmitter dopamine (DA) in a nearby brain region called the nucleus accumbens (NAc). When nicotine attaches to these neurons they increase their activity, flooding the NAc with dopamine, which produces pleasure and a disposition to repeat the behaviors that led to it. That pleasure and disposition drive the process of addiction.

In the new research, Dr. McGehee's team followed up on a clue that nicotine attachment to the DA neurons in the VTA accounts for only part of the drug's pleasure-producing and ultimately addictive effect: Nicotine attachment stimulates the DA neurons for only a few minutes at most, yet dopamine levels in the NAc remain elevated for much longer.

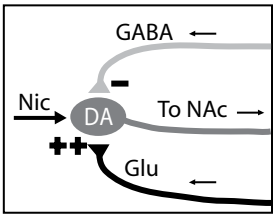
To explain this discrepancy, the researchers studied nicotine's impact on two other types of neurons that affect dopamine levels. These neurons produce neurotransmitters, called glutamate and GABA, that act as fundamental pacemakers throughout the brain. Once released by its producing neuron, glutamate attaches to other neurons, including the DA neurons in the VTA, and stimulates them to speed up their activities. GABA has the opposite effect: It slows neurons down.

The researchers hypothesized that nicotine might act on these pacemaker neurons so as to increase the ratio of glutamate to GABA in the VTA. If the amount of glutamate acting on DA cells were to increase while the amount of GABA remained the same or decreased, the result would favor high levels of dopamine in the NAc. If the glutamate-GABA imbalance were long-lasting, it would explain why dopamine levels in the NAc remain elevated even after nicotine stops directly affecting the dopamine-producing neurons.

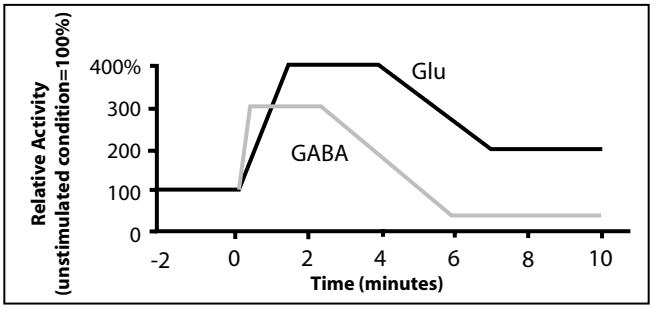
Nicotine's Double Effect on Dopamine Release



Nicotine (Nic) directly stimulates (+) neurons in the ventral tegmental area (VTA) to release dopamine (DA) in the nucleus accumbens (NAc). Nic also stimulates release of glutamate (Glu), triggering additional DA release. VTA cells stimulate release of GABA to moderate DA's effect.



Minutes later, Glu cells continue to stimulate DA release (++), but release of GABA becomes inhibited (-), resulting in sustained high dopamine levels in the NAc.



The increase in the VTA's glutamate-to-GABA ratio lasts for more than 1 hour after a single exposure to nicotine, prolonging and intensifying the drug's pleasurable effects.

Exposure to nicotine has direct and indirect effects on dopamine release in the brain's reward center, the nucleus accumbens.

To test their hypothesis, Dr. McGehee and his colleagues exposed rat VTA cells to nicotine for 10 minutes—roughly the time it takes a person to smoke a single cigarette. By measuring electrical properties of the brain tissue, they found that nicotine affected both pacemaker neurons. In glutamate-producing cells, the brief nicotine application induced a condition known as long-term potentiation, which promotes high-level activity for an extended time. When they evaluated the effect on GABA-producing cells, the researchers found that after an initial increase in GABA transmission lasting only a few minutes, GABA transmission decreased and did not recover fully for more than an hour after nicotine exposure ended. Overall, the result was what the researchers hypothesized: a sustained increase in the VTA's glutamate-to-GABA ratio.

The combination of effects—increasing dopamine release and decreasing the inhibitory [GABA] response—results in an amplification of the rewarding properties of nicotine.

"A brief application of nicotine can induce a lasting effect on excitatory [glutamate] signals to the brain's reward system," summarizes Dr. McGehee. "This suggests that in humans a relatively short nicotine exposure, even for someone who has never smoked before, can cause long-lasting changes in excitatory neurotransmission. It may be an important early step in the process that results in addiction."

"The combination of effects—increasing dopamine release and decreasing the inhibitory [GABA] response—results in an amplification of the rewarding properties of nicotine," explains Dr. McGehee. "It would be difficult to design a better drug to promote addiction."

"Understanding these mechanisms is an important step in explaining how a brief exposure to nicotine results in the long-term excitation of the brain's reward areas," says Dr. William Corrigall, director of NIDA's Nicotine and Tobacco Addiction Program. "It gives us a clearer picture of how smoking can lead so quickly to dependence and addiction, and it also suggests a possible new avenue of investigation for pharmacological treatment."

Sources

- Mansvelder, H.D., and McGehee, D.S. Long-term potentiation of excitatory inputs to brain reward areas by nicotine. *Neuron* 27(2):349-357, 2000.
- Mansvelder, H.D.; Keath, J.R.; and McGehee, D.S. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. *Neuron* 33(6): 905-919, 2002. NN

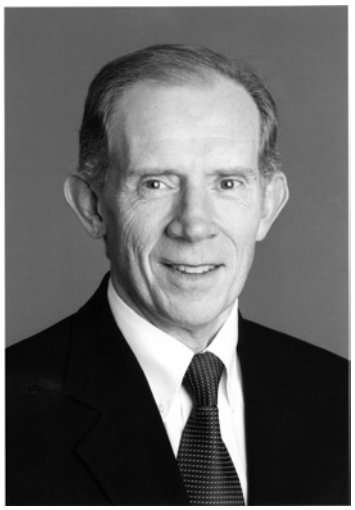
NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 6 (March 2003)

NIDA's Continued Commitment To Nicotine Research

By Glen R. Hanson, Ph.D., D.D.S., NIDA Acting Director



Tobacco use is the Nation's most profound public health problem. Each year, tobacco use accounts for an estimated $50 billion in health care costs, and the human cost is even more staggering. More than 400,000 Americans die annually from tobacco-related diseases. Of course, most smokers want to reduce their risks of heart and lung diseases, cancers, and strokes, but once addicted, smokers and other tobacco users find it very difficult to stop.

NIDA's contribution to the Nation's efforts to reduce tobacco use has been critically important. NIDA-supported research has led the way to development of smoking-cessation medications and has illuminated the causes of addiction. Recent studies have shown how the social and environmental influences that lead people to begin using tobacco conspire with powerful biological effects to quickly produce addiction to nicotine.

NIDA-funded investigations have made major advances in understanding, preventing, and treating tobacco use, but a complete understanding of the complex mechanisms of smoking initiation and nicotine addiction requires a comprehensive and coordinated research effort. NIDA has long recognized the need for an interdisciplinary approach to nicotine research and has forged partnerships with other research institutions in collaborative efforts to reduce nicotine addiction.

In 1998, NIDA cosponsored a groundbreaking conference that brought together leading investigators from throughout the Nation. At this conference, the researchers identified research hypotheses and approaches that have great potential to yield information that will significantly improve our ability to reduce tobacco use and nicotine addiction.

Following up on ideas generated at the conference, NIDA joined with the National Cancer Institute and the Robert Wood Johnson Foundation to establish the Transdisciplinary Tobacco Use Research Centers (TTURCs). These research coalitions have improved our understanding of nicotine addiction at levels from the cellular to the societal, from the role of individual genes to the effects of gender. For example, TTURC researchers have found that genetic influences may help explain why some young people begin smoking while others do not (see "Genetic Variation in Serotonin System May Play Role in Smoking Initiation," *NIDA NOTES,* Vol. 17, No. 2). Other TTURC investigators have helped identify factors that may improve women smokers' chances of successfully quitting (see "Women and Smoking: Sensory Factors, Attitudes About Weight, Phase of Menstrual Cycle All Keys to Quitting," *NIDA NOTES,* Vol. 17, No. 4).

NIDA-supported research has shown how the social and environmental influences that lead people to begin using tobacco conspire with powerful biological effects to quickly produce nicotine addiction.

To amplify the success of these research partnerships, NIDA plans continued support for TTURC researchers and an expanded scope of collaborative efforts. We are joining with the National Institute of Mental Health in a research partnership (RFA MH-03-008) to identify and develop pharmacological compounds that can be used to investigate the roles of specific neurochemical receptors in mood disorders and nicotine addiction. These receptors are important: They are the sites on brain cells where nicotine initiates the cascade of neurochemical activities that contribute to development of dependence and addiction (see "Nicotine's Multiple Effects on the Brain's Reward System Drive Addiction"). This collaboration with NIMH—the National Cooperative Drug Discovery Group Program—will encourage academic and pharmaceutical industry researchers to develop compounds that bind to specific subtypes of nicotine receptors. This will, in turn, make possible the development of specifically

targeted medications for treating nicotine addiction.

Another NIDA initiative—Translating Tobacco Addiction Research to Treatment (RFA DA-03-010)—supports the development of new treatment and prevention options. The initiative encourages researchers from diverse disciplines in their efforts to move beyond animal studies and basic science to clinical applications. Specifically, it will support the use of phase I-style clinical studies or laboratory studies with human volunteers to investigate approaches built upon what we now know about the biological and behavioral mechanisms of nicotine addiction and tobacco use. Behavioral research, for example, demonstrates the important role of environmental cues in drug craving; neurochemical research has identified some of the brain pathways involved in cue-induced craving. Under this new initiative, researchers could investigate the effectiveness of medications that target the neurochemical processes that underlie craving.

A complete understanding of the complex mechanisms of smoking initiation and nicotine addiction requires a comprehensive and coordinated research effort.

NIDA's achievements in nicotine and tobacco research are impressive. NIDA-supported research identified nicotine as the addictive component of tobacco smoke, and NIDA-funded research laid the foundation for the most effective medication now available to treat nicotine addiction—skin patches, gum, and inhalers used to deliver nicotine replacement therapy. But the research, and the results, must continue.

Each day, 3,000 adolescents start smoking; each year more than 30 million smokers try to quit, but most are unsuccessful. NIDA's commitment to new initiatives, as well as continued basic and clinical research, will speed the development of new programs that prevent young people from becoming smokers and will make available new treatments for the millions of Americans who smoke and want to quit. **NN**

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 5 (January 2003)

Youths' Opportunities To Experiment Influence Later Use of Illegal Drugs

By Kimberly R. Martin, *NIDA NOTES* Contributing Writer

NIDA-supported researchers have reported new epidemiological evidence about the associations linking earlier alcohol or tobacco use with later use of marijuana, and the link from earlier marijuana use to later use of other illegal drugs such as cocaine and hallucinogens. This study builds on the many prior NIDA-supported studies of the "gateway" theory of youthful drug involvement: Once use of tobacco or alcohol begins, there is greater likelihood of marijuana use, and once marijuana use begins, there is greater likelihood of other illegal drug use.

"This research increases our understanding of the complex relationship between the different stages of drug use and raises concerns about factors that promote the transition from opportunities to initiate drug use to patterned use," says Dr. Kathleen Etz of NIDA's Division of Epidemiology, Services and Prevention Research. "We know that earlier drug use is associated with later, more advanced use; however, this research identifies a previously overlooked aspect of this transition, opportunities to use."

Prior marijuana use was closely associated with the opportunity to try cocaine and the likelihood of young people's starting to use cocaine once given the opportunity.

Using annual data from the 1991 through 1994 National Household Survey on Drug Abuse (NHSDA), the research team, led by Dr. James C. Anthony from Johns Hopkins University Bloomberg School of Public Health in Baltimore, analyzed the responses of 26,015 individuals aged 12 to 18 who answered questions regarding marijuana use and the responses of 44,624 individuals aged 12 to 25 who answered questions regarding cocaine use. The research focused on a concept called "drug exposure opportunities." This concept takes into account that some young people actively seek out opportunities to try marijuana or cocaine, whereas others are more passive recipients of drug exposure opportunities.

The researchers found that alcohol and tobacco users were more likely than nonusers to have an opportunity to try marijuana and were also more likely to try the drug when the opportunity arose. About 75 percent of alcohol or tobacco users reported an opportunity to try marijuana by age 18, and more than 85 percent of them made the transition to marijuana use. Only about 25 percent of nonsmokers and nondrinkers were given an opportunity to try marijuana by the same age. Of these, fewer than 25 percent began smoking marijuana within 6 years after they were first given the opportunity. Overall, alcohol or tobacco users were seven times more likely to start using marijuana than individuals who had used neither alcohol nor tobacco.

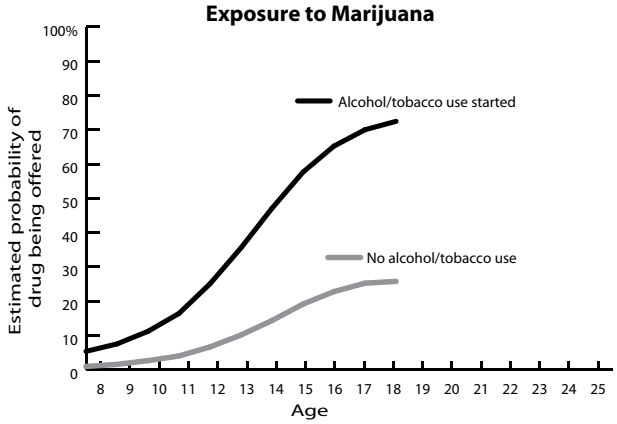
Prior marijuana use was closely associated with the opportunity to try cocaine and the likelihood of young people's starting to use cocaine once given the opportunity. Among the young people who were given the chance to try cocaine, those who were already using marijuana were 15 times more likely to use cocaine than those who did not use marijuana. About 50 percent of marijuana users used cocaine within 2 years of their first opportunity to do so. However, among young people who never used marijuana, fewer than 10 percent initiated cocaine use.

In a separate but related study, the researchers analyzed data from 41,271 young people who participated in the 1991 through 1994 NHSDA, investigating the relationship between the use of marijuana and use of hallucinogens. The results showed that marijuana users are more likely than nonusers to be offered an opportunity to use LSD, mescaline, mixed stimulant-hallucinogens, and PCP and more likely than nonusers to try these hallucinogenic drugs when they're offered. By age 21, nearly one-half of the teenagers who had smoked marijuana were presented with the opportunity to try hallucinogens, compared to only one-sixteenth of those who had not used marijuana. Once given the opportunity to use hallucinogens, marijuana smokers were about 12 times more likely to use hallucinogens than those who did not use marijuana.

"These studies are the first to support the idea of two separate mechanisms linking the use of alcohol, tobacco, marijuana, cocaine, and hallucinogens—one mechanism

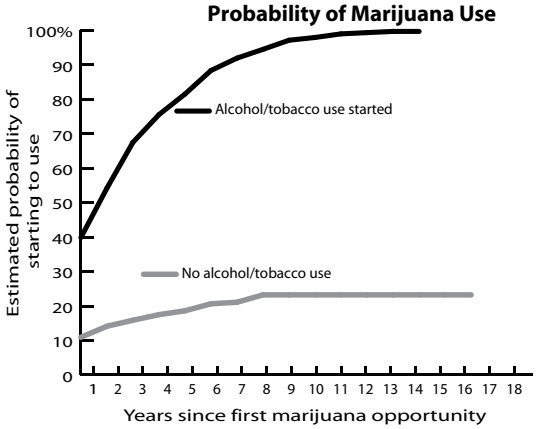
Drug Use Associated With More Opportunities To Use, Higher Rates of Acceptance

Exposure to Marijuana



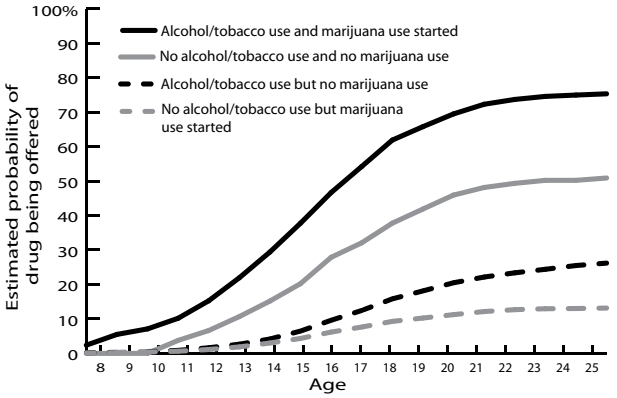
The likelihood that a nonsmoking, nondrinking 14-year old will be exposed to marijuana is only 14 percent, but the odds jump to 47 percent for a user of alcohol or tobacco.

Probability of Marijuana Use



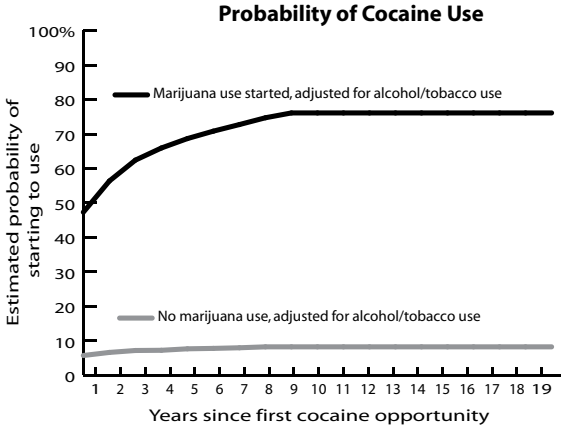
Among nonsmoking, nondrinking youth, 11 percent will be marijuana users 1 year after their first exposure to marijuana, compared to 40 percent of alcohol/tobacco users. Over time, the likelihood of marijuana use for the alcohol/tobacco users climbs to greater than 95 percent.

Exposure to Cocaine



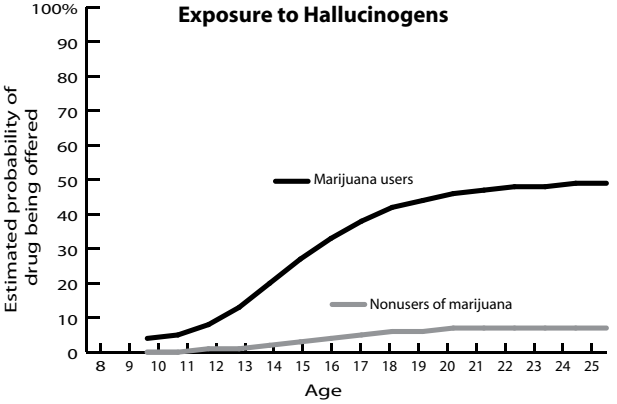
A 14-year-old user of tobacco or alcohol and marijuana is 10 times more likely to be exposed to cocaine than a nonsmoking nondrinker.

Probability of Cocaine Use



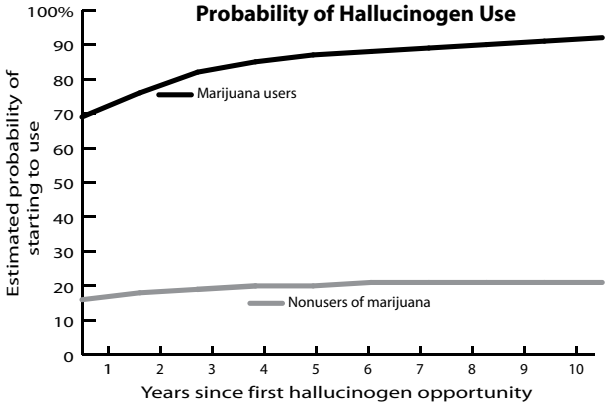
Having been exposed to cocaine, fewer than 1 in 10 nonusers of marijuana will use cocaine, compared to 50 to 75 percent for marijuana users.

Exposure to Hallucinogens



Although fewer that 5 percent of nonusers of marijuana are exposed to hallucinogens, the likelihood jumps to nearly 50 percent for marijuana users over time.

Probability of Hallucinogen Use



Fewer than one in five nonusers of marijuana who are exposed to hallucinogens will use hallucinogens, but 70 to 90 percent of marijuana users will try hallucinogens.

Sources: Wagner and Anthony, *American Journal of Epidemiology,* 2001; Wilcox et al., *Drug and Alcohol Dependence,* 2002.

involving increased drug exposure opportunity, and a separate mechanism involving increased likelihood to use once the opportunity occurs," says Dr. Anthony. "Even if there is an underlying common vulnerability or predisposition that accounts for the observed sequencing of drug exposure opportunities and actual drug use, these observations may have implications for the design and evaluation of drug prevention activities. Drug users often are members of social circles where drug use and experimentation are more common and friends are likely to share drugs. In addition to trying to persuade young people not to use drugs, it may be worthwhile for us to persuade users not to share their drugs with friends." Previous research has also shown that although males are more likely than females to have opportunities to use drugs, both are equally likely to make a transition into drug use once an opportunity to try a drug has occurred. Dr. Anthony and his colleague, Dr. Fernando Wagner, also from Johns Hopkins University Bloomberg School of Public Health, have made similar observations in ongoing research studies.

Dr. Anthony believes that his research carries a strong message for parents and pediatricians, who often neglect the opportunity to ask children and adolescents about whether they have had chances to try illegal drugs. As Dr. Anthony notes, "Kids will talk to us about their chances to try illegal drugs even when they are unwilling to talk about actual drug use. Once the chance to try marijuana or cocaine occurs, it is a red flag, and we need to be paying close attention to what happens next."

"Future research in this area will be a great asset to the development of effective drug prevention programs," says Dr. Etz. "It will assist us in understanding the process through which the use of one drug is related to use of another and help us to target prevention programs to individuals more likely to progress to advanced substance use."

Sources

- Wagner, F.A., and Anthony, J.C. Into the world of illegal drug use: Exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. *American Journal of Epidemiology* 155(10):918-925, 2001.
- Wilcox, H.C.; Wagner, F.A.; and Anthony, J.C. Exposure opportunity as a mechanism linking youth marijuana use to hallucinogen use. *Drug and Alcohol Dependence* 66(2):127-135, 2002. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 4 (November 2002)

Women and Smoking: Sensory Factors, Attitudes About Weight, Phase of Menstrual Cycle All Key To Quitting

By Jill S. Williams, *NIDA NOTES* Contributing Writer

NIDA-funded researchers are studying gender differences in smoking behavior and working to develop treatment plans that will help more women end their nicotine addiction. Three recent studies headed by Dr. Kenneth Perkins of the University of Pittsburgh add to this knowledge and test new treatment approaches for women.

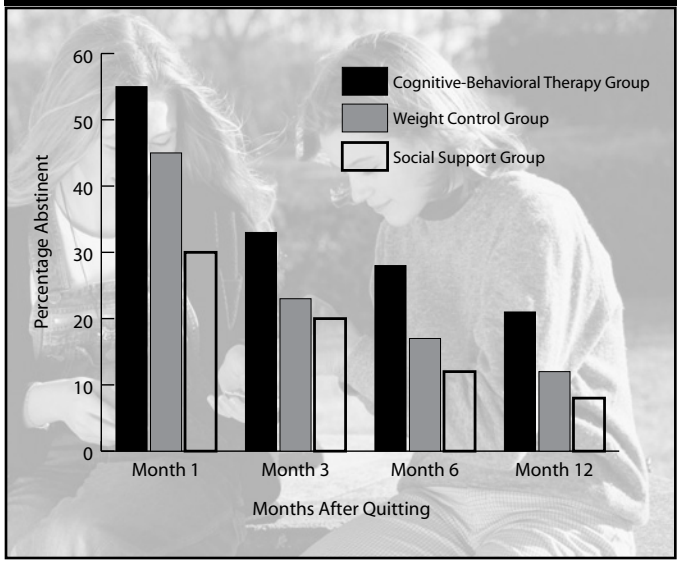
In one set of studies, Dr. Perkins has found that the smell and taste of cigarettes play a greater role in women's smoking behavior than in that of men. Another study found that cognitive-behavioral therapy aimed at changing attitudes about weight promotes smoking cessation by women. Additionally, Dr. Perkins found that menstrual cycle phase has an effect on both mood and tobacco withdrawal symptoms for women trying to quit smoking—a finding that suggests that women could improve their success rate simply by starting their quit attempt during certain days of their cycle.

Sensory Factors in Smoking

Dr. Perkins and his colleagues used a set of laboratory studies to examine the effects of sensory cues—seeing a lit cigarette and smelling and tasting smoke—on smoking behavior of women versus men. In one of the studies, researchers recruited 51 young smokers (21 men, 30 women) from the nearby community for what subjects were told was a test of different kinds of cigarettes. The smokers wore opaque goggles or swimmers' noseclips while smoking to test the roles that visual and olfactory cues—that is, cues related to seeing and smelling—play in smoking pleasure and reinforcement. Researchers measured smoking reinforcement—the number of puffs taken in different situations—and pleasure—using subjective measures such as the Rose Sensory Questionnaire—to assess the extent that sensory cues reinforce smoking.

They found that blocking olfactory stimuli made a greater difference to women than to men. While pleasure in smoking was reduced for both women and men when visual and olfactory cues were blocked, women found significantly less pleasure in smoking and also smoked less than men under the blockade conditions. This study shows that sensory cues play a larger role in smoking for women than for men and further demonstrates that the olfactory cues, not the visual, were the cause of the difference.

Weight Control Methods Impact Smoking Abstinence



Women who participated in cognitive-behavioral therapy, learning to accept a modest weight gain while trying to quit smoking, achieved greater abstinence levels than those in the weight control group, who were given daily calorie goals, or the social support group, who received counseling that did not focus on weight issues.

Dr. Perkins has recently tested the effects of nicotine "dose" in cigarettes on smoking pleasure and reinforcement in 30 men and women smokers. The smokers sampled, rated, and then smoked their regular brand of cigarette or an ultra-low-nicotine cigarette, both of which were presented with brand markings concealed. The nicotine dose of cigarettes had less effect on self-reported pleasure and reinforcement in women compared to men, consistent with the notion that nicotine may be a less important influence on smoking behavior in women than in men.

"Because women pay more attention to cues related to smell than do men," says Dr. Perkins, "they could benefit from counseling to avoid those cues and could learn cognitive coping strategies to reduce the urge to smoke." Such behavioral counseling is not now used widely or effectively, he says. He suggests that future research could

focus on other conditioned reinforcers of smoking, such as brand markings, "hand-mouth" activity, environmental contexts, and consumption of other drugs (such as caffeine or alcohol), with the goal of finding ways to extinguish the reinforcing effects of these stimuli or finding sensory substitutes.

Dr. Cora Lee Wetherington, NIDA's Women and Gender Research Coordinator, points out that this study is consistent with other research showing that women may benefit less from the nicotine patch or gum but more from the nicotine inhaler than do men. "Women lose both the sensory cues and the nicotine when they quit smoking," she says. "Therefore, replacing those cues—something the inhaler can do, but not the patch or gum—and learning ways to avoid or cope with those cues may help more women succeed in quitting."

Attitudes About Weight Gain

Previous smoking cessation trials have found that more than half of women smokers have a hard time quitting, at least partly because of concerns about weight gain. The average postquit weight gain of 10 pounds sabotages many attempts to quit smoking early on and causes some women to resist even trying to quit, to drop out of treatment, or to relapse after quitting. Research has found that dieting to prevent this weight gain is ineffective and may actually interfere with quit efforts. Now, a new study has shown that cognitive-behavioral therapy (CBT) aimed at reducing dietary restraint and changing attitudes about weight proved more successful at both controlling weight gain and promoting smoking cessation.

Dr. Perkins and his colleagues studied 219 women between the ages of 18 and 65 who wanted to quit smoking but were significantly concerned about gaining weight, as determined by telephone interviews during subject recruitment. The women, divided into three treatment groups, all received standard smoking cessation counseling. Each group also received either behavioral weight-control counseling, CBT to reduce weight concerns, or social support not focused on weight issues.

Members of the weight-control group were given daily calorie goals and instructed to track food intake in a diary, with the goal of reducing between-meal snacking (the primary source of excess calorie intake after quitting smoking). These women successfully prevented any weight gain in the month after quitting, as expected.

The CBT group received therapy to help them accept a modest weight gain in light of the benefits of quitting smoking. In putting together a CBT approach for smokers, Dr. Perkins turned to his colleague Dr. Marsha Marcus, who is an expert on eating disorders. "We wanted to help women accept the likelihood that they may gain 5 to 10 pounds, and we used CBT to modify their attitude toward that weight gain," she says. "We identified unrealistic thoughts or beliefs about weight gain and smoking, and we developed cognitive approaches to counteract those thoughts. Our key message was, 'adopt moderation in eating, reduce stress levels, and exercise more during an attempt to quit smoking.'"

At 1-year followup, 21 percent of the CBT group had successfully quit smoking, compared with 13 percent of the weight-control group and 9 percent of the social support group. Weight gain for those continuously abstinent at 1 year averaged 6 pounds for the CBT group, 12 pounds for the weight-control group, and 17 pounds for the social support group.

"Health care providers and smokers should be aware that the CBT approach has more promise than the diet approach," says Dr. Perkins. He suggests that future research can distill the key elements of the CBT intervention so it can be delivered concisely and test a combination of CBT with medication to further improve outcomes.

Today, researchers are paying more attention to the possibility of sex differences and analyzing those differences in their own data. "Both women and health care providers should recognize the obstacles women face and consider how to approach them to maximize their chances of success at quitting smoking," says Dr. Perkins.

Dr. Wetherington sees great value in this type of research: "Because of the gender-based approach Dr. Perkins has taken, we are beginning to see that what works best for males may not work best for females, and vice versa. We are beginning to develop better treatment strategies.

Sources

- Perkins, K.A.; Jacobs, L.; Sanders, M.; and Caggiula, A.R. Sex differences in the subjective and reinforcing effects of cigarette nicotine dose. *Psychopharmacology* 163(2):194-201, 2002.
- Perkins, K.A., et al. Sex differences in the influence of nicotine dose instructions on the reinforcing and self-reported rewarding effects of smoking. *Psychopharmacology* 184(3-4):600-607, 2006.
- Perkins, K.A., et al. Cognitive-behavioral therapy to reduce weight concerns improves smoking cessation outcome in weight-concerned women. *Journal of Consulting and Clinical Psychology* 69(4):604-613, 2001.
- Perkins, K.A.; Levine, M.; and Marcus, M. Tobacco withdrawal in women and menstrual cycle phase. *Journal of Consulting and Clinical Psychology* 68(1): 176-180, 2000.
- Perkins, K.A. Smoking cessation in women: Special considerations. *CNS Drugs* 15(5):391-411, 2001. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

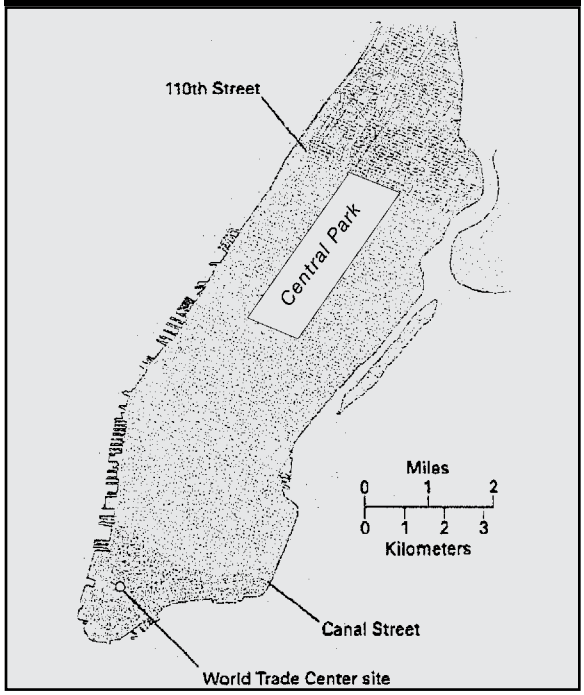
Volume 17, Number 4 (November 2002)

Depression, PTSD, Substance Abuse Increase in Wake of September 11 Attacks

By Jill S. Williams, *NIDA NOTES* Contributing Writer

A survey of New York City residents in the wake of the September 11, 2001, terrorist attacks found high levels of both depression and posttraumatic stress disorder (PTSD) among respondents and documented an increase in substance abuse. The survey, conducted by NIDA-funded researchers Dr. David Vlahov and his colleagues at the New York Academy of Medicine 5 to 8 weeks after the terrorist attacks, quantifies the relationships among stress, depression, and substance abuse. The results provide insight into public health service delivery needs as well as clues to effective treatment strategies to help individuals cope with traumatic events.

Map of Study Area Relative to World Trade Center



Manhattan residents living closest to the World Trade Center, south of Canal Street, were three times more likely than residents from Canal to 110th Street to suffer symptoms of posttraumatic stress disorder.

Stress has long been recognized as one of the most powerful triggers for drug craving and relapse to drug abuse. Research has shown that survivors of disasters are prone to stress-related problems such as PTSD and depression. People who experience major trauma and those with PTSD or depression may self-medicate with drugs or alcohol to relax, cope with stress, or relieve symptoms. "This study is one of the first to capture data on the effects of traumatic events on substance abuse patterns," says Dr. Jacques Normand of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. "The increase in substance abuse found here was of significant magnitude. This study reminds counselors and treatment providers to be alert to increased use of alcohol, tobacco, and marijuana in the wake of such events."

Survey respondents reported post-attack rates of depression and PTSD that were approximately twice the baseline levels previously documented in a 1999 benchmark national study. Some 9.7 percent had symptoms of depression, and 7.5 percent qualified for a diagnosis of PTSD compared to baseline levels of 4.9 percent for depression and 3.6 percent for PTSD.

In looking at rates of new substance use among respondents, the researchers found that, of respondents who did not use these substances during the week before September 11, 3.3 percent started smoking cigarettes after September 11; 19.3 percent started drinking alcohol; and 2.5 percent began using marijuana. Overall, the percentages of respondents who smoked, consumed alcohol, and used marijuana increased 9.7 percent, 24.6 percent, and 3.2 percent, respectively, after the attacks.

Almost 29 percent of respondents reported that they were smoking more cigarettes and/or marijuana and/or drinking more alcohol. Among those who were already using these substances before September 11, 41.2 percent smoked more cigarettes and 41.7 percent drank more alcohol after the attacks. Among smokers, 8.2 percent smoked at least one additional pack of cigarettes a week; 20.8 percent of drinkers had at least one additional drink a day.

"The survey results are significant for the sheer numbers of people revealed to be affected by the disaster, the scope of the problem on a citywide scale, and challenges to the delivery of services," says Dr. Vlahov. He estimates that of the approximately 911,000 people in the area of New York under study, 67,000 had PTSD and approximately 87,000 had depression at the time of the study. Likewise, he estimates that 265,000 people increased their use of any of the substances in question: 89,000 smoked more cigarettes, 226,000 consumed more alcohol, and 29,000 used more marijuana. "This survey demonstrated that

whole populations are affected by such disasters," says Dr. Vlahov. "The increases in use of cigarettes, alcohol, and marijuana across the population are large, making this a broad public health issue."

While the initial survey goal was to perform a public health assessment to document the scope of the problems and to help authorities apply for appropriate aid, Dr. Vlahov says that other questions also drove the research. "From a scientific perspective, we knew that attention typically focuses on victims, rescue workers, and their families. But here was an event that affected everyone in a major way. We asked, how do people cope with the stress of a disaster? Do they turn to cigarettes, alcohol, or marijuana? What are the implications for public health planning and delivery?"

Association Between Respondents' 9/11 Experiences and Current Posttraumatic Stress Disorder and Depression

Characteristics	Number of Respondents	PTSD[a] Odds Ratio (95% C.I.)	Depression[a] Odds Ratio (95% C.I.)
Had symptoms of a panic attack during or soon after the events of 9/11/01	124	7.6 (4.2-13.7)	2.6 (1.3-4.9)
Lost possessions	36	5.6 (2.5-12.4)	NS[b]
Lost job because of the attacks	64	NS[b]	2.8 (1.2-6.3)
Friend or relative killed	108	NS[b]	2.3 (1.1-4.6)
Two or more life stressors in the previous 12 months	183	5.5 (2.6-11.6)	3.4 (1.8-6.6)
Low social support in previous 6 months	358	NS[b]	2.4 (1.2-4.8)
Residence south of Canal Street	50	2.9 (1.3-6.8)	NS[b]
Hispanic ethnicity	114	2.6 (1.3-5.5)	3.2 (1.7-6.3)

[a] *Current PTSD and depression defined as symptoms consistent with the diagnosis within 30 days before the interview.*
[b] *Not a significant association.*

Certain characteristics of survey respondents were found to significantly elevate the odds that they would report symptoms consistent with a diagnosis of PTSD or depression. For example, respondents who reported symptoms of a panic attack during or soon after the terrorist attacks were 7.6 times more likely to suffer from PTSD and 2.6 times more likely to suffer depression than respondents who did not report panic attack symptoms.

Survey Methodology

Researchers randomly selected 1,008 adults living south of 110th Street in Manhattan, the area closest to the World Trade Center, to take part in the telephone survey. A 35-minute questionnaire was used to assess respondents' exposure to the September 11 events, psychological symptoms after the attacks, changes in substance abuse patterns, and other factors such as demographics, levels of social support, and previous life stressors. Surveyors referred respondents for counseling services as appropriate. The overall cooperation rate for the survey was 64.3 percent; 52 percent of respondents were women, and 71.6 percent were white. The mean age of respondents was 42 years.

Surveyors used a series of questions based on accepted psychological tests to diagnose both depression and PTSD. To determine levels of pre- and post-September 11 substance abuse, surveyors asked respondents to estimate how many times they had used cigarettes, alcohol, and marijuana during the week before September 11, and then asked about the number of times they had used each substance during the week before the survey was conducted.

Analyses revealed that those who were most directly exposed to events were more likely to suffer PTSD; those who experienced loss—of jobs, possessions, friends or family members—were more likely to suffer from depression. Dr. Vlahov says that the key demographic, event experience, and other characteristics most closely related to diagnosis of either PTSD or depression provide important clues to immediate crisis intervention: "Clinicians can learn that getting a history of an individual's exposure to events can help focus or target issues and clarify how he or she may be reacting."

The survey data revealed associations between specific psychological diagnoses and drug use patterns. Survey respondents diagnosed with PTSD were approximately five times

For More Information

Help for those struggling with stress and substance abuse issues is available in two recent NIDA publications:

- "Stress and Substance Abuse: A Special Report" is a research summary that can be downloaded from NIDA's Web site. Go to *www.drugabuse.gov/stressanddrugabuse.html*.
- *Community Drug Alert Bulletin: Stress and Substance Abuse* is available from NIDA. Order publication #PHD914 by phone (877-643-2644; 240-645-0228 for the deaf) or at the NIDA Web site, *www.drugabuse.gov*.

as likely as other respondents to increase their use of cigarettes or marijuana. Survey respondents who were diagnosed with depression were much more likely to increase use of all three substances than were those who were not depressed. Again, Dr. Vlahov suggests that these data may be important to clinicians. "Increased use of cigarettes, alcohol, and marijuana may be an indicator of underlying psychological response issues. Clinicians should look for links between PTSD, depression, and increased use of cigarettes, alcohol, or marijuana."

Followup studies will assess outcomes at 4 months, 6 to 8 months, and 12 months after the attacks. "We need a better understanding of the extent to which substance abuse complicates psychological problems," says Dr. Vlahov. "Longitudinal studies will help us determine whether increased use of substances leads to dependence, and to identify predictors of drug dependence that will help us guide intervention planning."

Sources

- Galea, S.; Ahern, J.; Resnick, H.; Kilpatrick, D.; Bucuvalas, M.; Gold, J.; and Vlahov, D. Psychological sequelae of the September 11 terrorist attacks in New York City. *New England Journal of Medicine* 346(13):982-987, 2002.
- Vlahov, D., et al. Increased use of cigarettes, alcohol, and marijuana among Manhattan, New York, residents after the September 11th terrorist attacks. *American Journal of Epidemiology* 155(11):988-996, 2002. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 17, Number 2 (May 2002)

Genetic Variation in Serotonin System May Play Role in Smoking Initiation

By Patrick Zickler, *NIDA NOTES* Staff Writer

Each day more than 3,000 young people smoke their first cigarette, and the likelihood of becoming addicted to nicotine is higher for these young smokers than for those who begin later in life. A number of biological, social, and environmental factors combine to influence smoking initiation, and NIDA-supported research suggests that genetic factors play a role in determining a smoker's susceptibility to nicotine addiction. (See "Evidence Builds That Genes Influence Cigarette Smoking," *NIDA NOTES,* Vol. 15, No. 2.) Now, researchers at the University of Pennsylvania in Philadelphia and Virginia Commonwealth University in Richmond have found an association between smoking initiation and variations in a gene related to the brain's serotonin system, which is involved in mood v and behavior.

Variation in Gene May Affect Likelihood of Smoking at Early Age

	Allele Combination		
	A/A	A/C	C/C
Distribution among smokers	18%	51%	31%
Age at smoking initiation (yr)	15.6	17.1	17.5

Researchers at the University of Pennsylvania have found that women and men who inherit the "A" form (allele) of the tryptophan hydroxylase gene from both parents and who become smokers are likely to begin smoking at an earlier age than women and men who inherit the "C" allele.

At the NIDA-supported Transdisciplinary Tobacco Use Research Center at the University of Pennsylvania, Dr. Caryn Lerman and her colleagues investigated the possible relationship between smoking behavior and different forms (alleles)—designated 779A and 779C—of a gene that regulates tryptophan hydroxylase (TPH), an enzyme involved in the synthesis of serotonin. "There is evidence from previous studies linking the less common 779A allele with behaviors related to poor impulse control," Dr. Lerman says. "Because of the association of tobacco and other substance use with poor impulse control, we speculated that the TPH gene may play a role in smoking initiation as well."

To investigate this possibility, the researchers recruited 249 smokers (smoked at least 5 cigarettes per day for the past year) and 202 nonsmokers (smoked fewer than 100 cigarettes in their lifetime). All the participants were white; their average age was 44 years, and slightly more than half (56 percent) were women. All participants completed written questionnaires that provided information on their age, education, marital status, and certain psychological traits. Smokers provided smoking histories, including the age when they started smoking at least one cigarette per day.

The researchers tested samples of the participants' blood to determine whether they had the 779A or 779C alleles for the TPH gene. The overall allele frequency was 42 percent for the THP 779A allele and 58 percent for the 779C allele. There was no significant association of the presence or absence of the 779A allele with becoming a regular smoker, Dr. Lerman says. But among participants who did become smokers, the 779A allele was associated with the age at which they began smoking. Those who inherited copies of 779A from both parents started smoking at age 15.6 years, those with one A and one C allele began smoking at 17.1, and those with two copies of 779C began smoking at 17.3 years.

"In light of other findings that 779A is associated with poor impulse control, one interpretation of this study is that individuals with that allele may be prone to engage in risky behavior such as smoking initiation at an earlier age," Dr. Lerman says.

Dr. Lerman discussed her research results with Dr. Patrick Sullivan at Virginia Commonwealth University. Dr. Sullivan and his colleagues then developed a study to look for possible associations between the TPH 779A allele and smoking initiation in a group of 740 participants who had previously been enrolled in research dealing with genetic influences on a range of behaviors, including drug abuse and addiction. As part of the earlier study, the participants

had completed extensive questionnaires that included information about smoking, including age at which smoking began, age at which smokers first became dependent on nicotine (suffered withdrawal if they tried to quit), and the severity of their dependence—measured by a standard tool called the Fagerstrom Tolerance Questionnaire (FTQ). For the TPH study, the participants were divided into three categories: those who had never smoked, regular smokers who had a low degree of dependence (scores of 0 to 3 on the 11-point FTQ), and regular smokers with a high degree of dependence (FTQ scores of 7 or higher). Dr. Sullivan and his colleagues analyzed the participants' TPH genes and found that the 779A allele was strongly associated with whether participants initiated smoking, but, unlike the University of Pennsylvania study, not strongly associated with an early age of smoking initiation.

"The fact that there is not complete agreement is not surprising," Dr. Sullivan says. "The two studies used different populations of subjects and were not designed to test the same hypothesis. Nonetheless, the two studies appear to have captured a similar influence that plays a role in the web of factors that underlies smoking initiation."

"It is rare to find confirmation of a candidate gene related to addiction, and these studies make a good case for an association between the TPH gene variant and smoking initiation," says Dr. Rebekah Rasooly of NIDA's Division of Neuroscience and Behavioral Research. "This kind of association helps us to better understand the factors that influence young potential smokers. They are the most vulnerable to becoming regular smokers and need to clearly understand all the risks associated with smoking that first cigarette."

Sources

- Lerman, C., et al. Tryptophan hydroxylase gene variant and smoking behavior. *American Journal of Medical Genetics* 105(6):518-520, 2001.
- Sullivan, P.F., et al. Association of the tryptophan hydroxylase gene with smoking initiation but not progression to nicotine dependence. *American Journal of Medical Genetics* 105(5):479-484, 2001. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 3 (August 2001)

Nicotine Disrupts Brain Development in Rats

By Patrick Zickler, *NIDA NOTES* Staff Writer

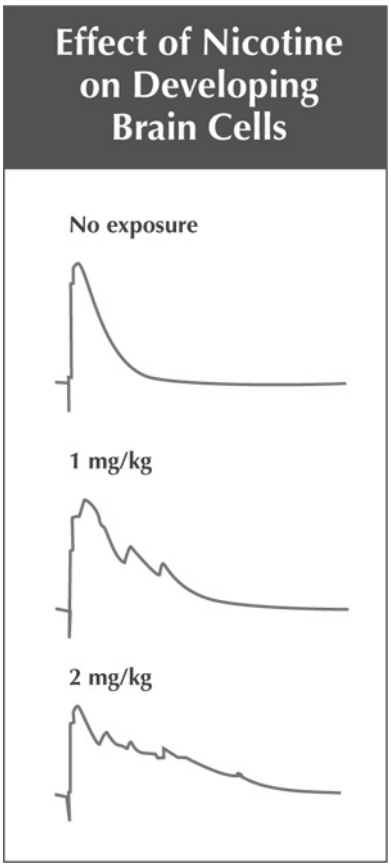
Exposure to nicotine during a brief but crucial stage of brain development in rats appears to cause long-lasting disruption of some brain functions. NIDA-supported researchers Dr. Frances Leslie, Dr. Raju Metherate, and colleagues at the University of California, Irvine, found that nicotine injected into rats throughout the second postnatal week affected development of an area of the brain that is concerned with the interpretation of sounds, and that the effects persisted for at least 10 days after nicotine injections were discontinued.

"There are critical periods during which nicotine exposure can produce profound changes in brain function," Dr. Leslie says. "Our study suggests that the nicotine content of tobacco triggers responses in developing brains that are strikingly different from those in an adult brain."

In rats, there is a dramatic increase during the second postnatal week in the number of nicotinic acetylcholine receptors—brain cell structures that are sensitive to nicotine and help regulate the action of the chemical messenger acetylcholine. Developments in the rat brain during this period correspond to changes that take place in human fetuses during the last weeks of gestation.

To evaluate the effect of nicotine during this period of brain development, the researchers injected rat pups twice each day with saline or with nicotine (1 or 2 mg per kilogram of body weight-levels typically used by researchers to simulate exposure levels thought to occur in human fetuses due to maternal smoking) for 1 week (postnatal days 8 through 14). Two other groups of rats received injections (2 mg/kg) on postnatal days 1 through 8 and on postnatal days 20 through 25, respectively. The researchers then measured electrical properties of brain cells in the auditory cortex to determine the cells' ability to properly process electrical signals involved in hearing. They found that cells from animals exposed to nicotine—at doses of 1 or 2 mg/kg—during the second postnatal week had significant impairment while those exposed to the higher dose earlier or later did not.

"Together, these findings indicate that chronic nicotine exposure during week 2, but not before or after, alters development in the auditory cortex of rats," Dr. Leslie says. The resulting defects do not impair the animals' ability to distinguish sounds—they are not hard of hearing—but the defects make the rats less able to associate sounds, such as the yips of littermates, with specific activities such as feeding, according to the researchers. "In humans, maternal smoking has been associated with cognitive deficits in infants, and particularly with auditory-related cognitive impairments such as reduced ability to orient toward clearly heard sounds. This animal study suggests a mechanism that might underlie these impairments," Dr. Leslie says.



To determine the effect of nicotine on developing brains in the auditory cortex (the part of the brain where sounds are associated with meanings), researchers measured an electrical property (excitatory postsynaptic potential or EPSP) that influences the transmission of signals from one nerve cell to another. In animals not exposed to nicotine (top), neurons exhibited smooth short-duration EPSPs. Nerve cells from animals exposed daily to nicotine at doses of 1 mg/kg (middle) and 2 mg/kg (bottom) during the second week after birth exhibited longer duration EPSPs marked by frequent spikes, which interfere with effective transmission.

Source

- Aramakis, V.B.; Hsieh, C.Y.; Leslie, F.M; and Metherate, R. A critical period for nicotine-induced disruption of synaptic development in rat auditory cortex. *Journal of Neuroscience* 20(16):6106-6116, 2000. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 2 (May 2001)

Adolescents, Women, and Whites More Vulnerable Than Others to Becoming Nicotine Dependent

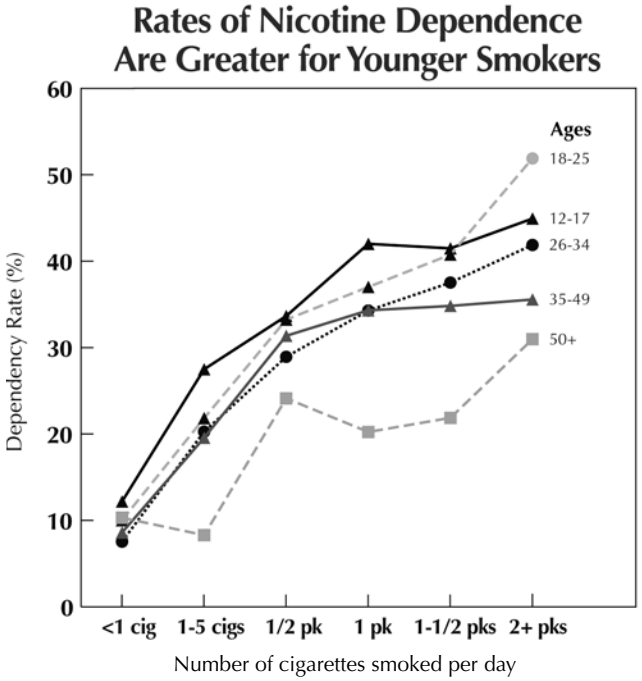
By Patrick Zickler, *NIDA NOTES* Staff Writer

Rates of drug dependence—the percentage of users who experience symptoms that reinforce their drug use and have trouble quitting—are higher for nicotine than for marijuana, cocaine, or alcohol. Rates of dependence also vary among different groups of smokers, according to NIDA-supported research. A new study suggests that differences in sensitivity to nicotine make some smokers more likely than others to develop nicotine dependence. Age, sex, and race all appear to make a difference.

Dr. Denise Kandel and Dr. Kevin Chen of Columbia University in New York City analyzed data collected between 1991 and 1993 as part of the National Household Survey of Drug Abuse, which surveys a representative sample of the U.S. population 12 years and older. In examining data from 22,292 respondents who had smoked cigarettes during the preceding month, Dr. Kandel and her colleagues determined rates of nicotine dependence symptoms based on respondents' reports of tolerance (needing to smoke more to feel the effects), withdrawal symptoms, smoking more than intended, failed efforts to cut down, negative social and job-related consequences, and persistent health problems.

The researchers found that among persons who smoke one-half pack of cigarettes each day, nicotine dependence rates are higher among females than males (31.6 percent compared with 27.4 percent) and higher among whites (31.3 percent) than among blacks (25 percent) and Hispanics (27.6 percent). Adolescents smoke fewer cigarettes than adults but experience significantly higher rates of dependence than adults at the same level of use. Dependence rates are lowest among adults older than 50. Overall, the researchers say, dependence rates increase sharply as consumption moves up to 10 cigarettes per day. The rates level off with higher consumption, although dependent smokers need to smoke more to feel the physical effects of nicotine.

"Understanding the differences among groups in their vulnerability to developing nicotine dependence will be valuable in developing targeted strategies for prevention," Dr. Kandel says. "The higher rates at which adolescent, women, and white smokers develop symptoms of nicotine dependence given the same quantity smoked daily seem to reflect differences in sensitivity to nicotine. Increased sensitivity may also account for the fact that adolescents develop symptoms of dependence at lower doses of nicotine than adults."



Data from the National Household Survey on Drug Abuse show that the rate of nicotine dependence is higher in people younger than 25 than in other age groups and that the dependence develops with less exposure to nicotine.

Adolescents appear to be particularly vulnerable to becoming nicotine dependent, especially at low levels of cigarette consumption and when they continue to smoke on a regular daily basis, according to the researchers. Adolescents' nicotine dependence rates were associated with the length of time that they had been daily smokers, in contrast with adults, in whom dependence rates were associated with the amount of tobacco smoked. "Once regular smoking has been established, quantity smoked may become a

more important determinant of dependence than duration of daily smoking," Dr. Kandel says. "This possible connection suggests that with adolescents we should focus not only on preventing the uptake of smoking but on shortening smoking careers as soon as possible."

Source

- Kandel, D.B., and Chen, K. Extent of smoking and nicotine dependence in the United States: 1991-1993. *Nicotine and Tobacco Research* 2(3):263-274, 2000. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 1 (March 2001)

Maternal Smoking During Pregnancy Associated With Negative Toddler Behavior and Early Smoking Experimentation

By Josephine Thomas, *NIDA NOTES* Contributing Writer

NIDA-funded researchers have added to the accumulating scientific evidence that women's smoking during pregnancy adversely affects their children's health and development. Two new studies have linked prenatal tobacco exposure to negative behavior in toddlers and smoking experimentation by pre-adolescents. In a study conducted by Dr. Judith Brook, Dr. David Brook, and Dr. Martin Whiteman of the Mount Sinai School of Medicine in New York City, mothers who smoked during pregnancy indicated that their toddlers exhibited more negative behaviors—impulsiveness, risk-taking, and rebelliousness—than mothers who did not smoke during pregnancy reported among their children.

A study conducted by NIDA-funded researchers Dr. Marie Cornelius and Dr. Nancy Day demonstrates that, even more than growing up in a home where the mother smokes, prenatal exposure to smoke may predispose children to early smoking experimentation. Dr. Cornelius, Dr. Day, and their colleagues at the University of Pittsburgh School of Medicine found that not only does such exposure to maternal smoking predict early experimentation, it also appears linked to child anxiety, depression, and behaviors such as hitting and biting others.

Previous studies have supported a link between prenatal smoking exposure and behavioral problems in later childhood and adolescence (see "Drug Abuse and Conduct Disorder Linked to Maternal Smoking During Pregnancy," *NIDA NOTES,* Vol. 15, No. 5). Combined with earlier results, the new studies suggest that prenatal smoking contributes to a train of developmental difficulties and health risks that begin at an early age.

Toddler Negativity

The Mount Sinai study included 99 mothers who smoked and their 2-year-old children. The mothers are participants in a large community study that Dr. Judith Brook has been conducting with Dr. Patricia Cohen of Columbia University in New York City for the past 25 years. In the new study, the mothers answered a questionnaire that elicited information about their children's behaviors and their own smoking histories, alcohol and drug use, personalities and attitudes, styles of child-rearing, and socioeconomic characteristics.

Fifty-two of the women reported that they had smoked while pregnant, and 47 said they either stopped smoking during pregnancy or did not begin to smoke until after they had given birth. The mothers who smoked during pregnancy scored their children higher on the questions that measured toddler negativity. The mother's disciplinary style also was strongly linked to a toddler's negative behavior. However, when the researchers adjusted for this factor in the analysis, they determined that a mother's smoking during pregnancy independently increased the estimated risk of negativity at age 2 by fourfold.

"We found three major maternal risk factors related to toddler negativity," says Dr. Brook. "They are maternal smoking during pregnancy, conflicts between the mother and child, and the mother's use of power-assertive discipline, such as hitting the child. We can speculate that maternal smoking during pregnancy causes disturbances in the neurophysiological functioning of the fetus," says Dr. Brook. "This, in turn, could precipitate the toddler's negative behavior."

The potential implications of these findings reach beyond early childhood. Previous studies have demonstrated that toddlers who display negative behaviors are more likely to use drugs, exhibit delinquent behaviors, and achieve less as adolescents and to develop severe mental health problems later in life.

Early Experimentation With Tobacco

Although the effects of maternal smoking on childhood behaviors have been studied, few studies have investigated the connection between maternal smoking and childhood experimentation with tobacco. The connection is important because the earlier a person starts smoking, the more

likely he or she is to become a regular smoker, become addicted, and suffer the long-term adverse health effects of smoking.

Dr. Cornelius and her colleagues interviewed 589 10-year-olds. Six percent of the children said they had tried cigarettes, smokeless tobacco, or both. Most of the reported tobacco use was experimental; only a few children had used tobacco more than a few times.

In this prospective study, begun by Dr. Day in 1982, the children's mothers have been providing researchers with information about themselves, and they reported on their smoking at the time they were pregnant with the children who are now 10. Putting data from the children together with those reports, the researchers estimated that maternal smoking of at least a half-pack of cigarettes per day during pregnancy increased by fivefold the likelihood that a child would have tried tobacco by age 10. The only factor that produced a greater risk of early experimentation was exposure to smoking within the child's peer group.

It is not yet clear exactly why these factors are related to early experimentation. "Perhaps the nervous system damage caused by maternal smoking may later be expressed as impulsivity, inattention, aggression, depression, and/or anxiety and may create a vulnerability in the child that could contribute to poorer adjustment and an increased likelihood of early initiation of tobacco use," Dr. Cornelius says.

Dr. Cornelius notes that in her study, the 10-year-olds who were exposed prenatally to tobacco were more likely to have experimented than those whose mothers were current smokers. This finding reinforces the hypothesis that a physiological effect of prenatal exposure to smoking, rather than a genetic vulnerability affecting both mother and child, may be an important link between mothers' smoking during pregnancy and early childhood experimentation.

Sources

- Brook, J.S.; Brook, D.W.; and Whiteman, M. The influence of maternal smoking during pregnancy on the toddler's negativity. *Archives of Pediatric and Adolescent Medicine* 154(4):381-385, 2000.
- Cornelius, M.D.; Leech, S.L.; Goldschmidt, L.; and Day, N.L. Prenatal tobacco exposure: Is it a risk factor for early tobacco experimentation? *Nicotine & Tobacco Research* 2:45-52, 2000. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 1 (March 2001)

Smoking May Lead to Anxiety Disorders in Adolescents and Young Adults

Using a wealth of data obtained through a 25-year longitudinal study, NIDA-funded researcher Dr. Judith Brook of the Mount Sinai School of Medicine in New York, Dr. Patricia Cohen of Columbia University in New York, and their colleagues have documented adverse effects of smoking in several critical areas of functioning during young adulthood. Most recently, the team has reported a connection between tobacco use by adolescents and young adults and the likelihood that they will develop agoraphobia (fear of leaving home or of the outdoors), generalized anxiety disorder, or panic disorder. Analyzing data from their Children in the Community study, funded by NIDA and the National Institute of Mental Health, the researchers were able to separate the effects of smoking from the effects of age, gender, childhood temperament, alcohol and other drug abuse, and depression among the adolescents, as well as parents' smoking, education, and behavioral and/or mental health problems.

The researchers interviewed 688 youths and their mothers in 1983, between 1985 and 1986, and again between 1991 and 1993. A total of 69 of the youths smoked heavily—at least 20 cigarettes every day—and experienced an anxiety disorder during adolescence, early adulthood, or both. Of these 69 youths, 29 (42 percent) began smoking before they were diagnosed with an anxiety disorder. The remaining 40 youths were split between those who were diagnosed with anxiety disorders before they reported heavy smoking (13, or 19 percent) and those who reported smoking and were diagnosed with anxiety disorders at the same interview session (27, or 39 percent).

Adolescents who smoked heavily were 6.8 times more likely to develop agoraphobia, 5.5 times more likely to develop generalized anxiety disorder, and 15.6 times more likely to develop a panic disorder as young adults than were their counterparts who smoked fewer than 20 cigarettes a day or not at all. The investigators speculate that impaired respiration and the potentially damaging effects of nicotine on blood vessels to the brain may help explain why the adolescents who smoked heavily were at increased risk of developing anxiety disorders.

The long-held notion that depression causes some adolescents to smoke may be true. But Dr. Brook's study suggests the opposite may also be true—that smoking increases the risk of depression in this population. Dr. Brook and her team recommend that future research examine further the possible relationships between various anxiety disorders and smoking.

Source

- Johnson, J.G.; Cohen, P.; Pine, D.S.; Klein, D.F.; Kasen, S.; and Brook, J.S. The association between cigarette smoking and anxiety disorders during adolescence and early adulthood. *Journal of the American Medical Association* 284(18):2348-2351, 2000. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

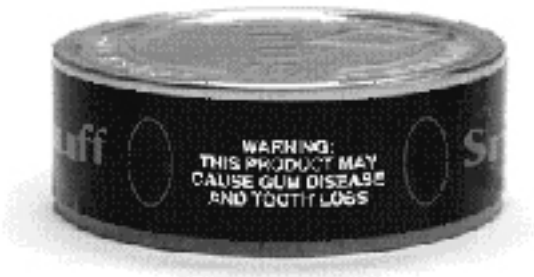
Research Findings

Volume 16, Number 1 (March 2001)

Nicotine Patch Helps Smokeless Tobacco Users Quit, But Maintaining Abstinence May Require Additional Treatment

By Robert Mathias, *NIDA NOTES* Staff Writer

An estimated 9.6 million people in the United States used smokeless tobacco products—moist snuff and chewing tobacco—during 1998, according to the National Household Survey on Drug Abuse. More than 70 percent of these individuals had used smokeless tobacco during the month before they were surveyed.



People who are trying to quit using smokeless tobacco may benefit from a transdermal nicotine patch during the first critical months after stopping use, a NIDA-supported study suggests. Study participants treated with the nicotine patch experienced less severe withdrawal symptoms and lower levels of craving for nicotine and were significantly more likely to maintain short-term abstinence than users in a control group who were treated with an inactive patch. Treatment with nicotine-free mint snuff also reduced withdrawal symptoms and craving but had no effect on abstinence rates.

"These findings suggest that the nicotine patch can reduce the discomfort that people experience when quitting smokeless tobacco," says Dr. Dorothy Hatsukami of the University of Minnesota School of Medicine, who conducted the study. "Knowing that withdrawal symptoms can be minimized may encourage more people to try to quit," she says. While the study suggests that the nicotine patch may help patients achieve initial abstinence from smokeless tobacco, it remains unclear how the patch and other treatments should be used to sustain abstinence over the long term, she says.

Most tobacco-related research has focused on cigarette smoking with its more extensive range of harmful consequences, Dr. Hatsukami says. "However, we also need to study smokeless tobacco use because it is not an insignificant problem by any means," she says. Regular use of smokeless tobacco products may cause such problems as receding gums, tooth decay, mouth sores, precancerous lesions, and cancers of the mouth and throat. Smokeless tobacco users also may be at increased risk of heart disease and smoking cigarettes. Undesirable social consequences include bad breath, tobacco-stained teeth, and the need to spit tobacco juice.

Many individuals use smokeless tobacco despite its obvious drawbacks because they are hooked on nicotine, a highly addictive drug. As with cigarettes, smokeless tobacco products deliver substantial doses of nicotine along with powerful cancer-causing chemicals. Users of moist snuff—which consists of finely ground tobacco—place a pinch, or dip, of snuff between their cheek and gum and hold it there. Users of chewing tobacco—which comes in leaf and plug forms—place a wad, or chew, in their cheek pouch and chew it. Because nicotine from smokeless tobacco is absorbed through the mouth, the drug takes longer to produce its rewarding effect in the brain than it does when it is absorbed through the lungs during cigarette smoking. The amount of nicotine obtained from smokeless tobacco is comparable to that of cigarettes, and once smokeless tobacco users become addicted they find it just as difficult as cigarette smokers do to quit, Dr. Hatsukami says. She notes that more than 90 percent of the smokeless tobacco users in her study had tried unsuccessfully to quit on their own at least once. Nearly 25 percent of the study's participants had made more than 6 unsuccessful quit attempts, and nearly 10 percent had tried to quit more than 10 times.

In her study, Dr. Hatsukami randomly assigned a total of 402 smokeless tobacco users to one of 4 treatments: active nicotine patch, inactive patch, a combination of

active patch and a non-nicotine mint snuff, or a combination of inactive patch and mint snuff. All participants received initial counseling on smokeless tobacco cessation methods and a self-help manual to take home prior to beginning treatment. On their quit date, patients began using their assigned treatments and continued for 10 weeks. During treatment, participants met weekly with counselors for brief support sessions. Results were assessed 15, 25, 36, and 62 weeks after participants stopped using smokeless tobacco. The study found that both the active patch and mint snuff reduced craving and withdrawal symptoms, such as irritability, frustration, anger, anxiety, and depressed mood. Withdrawal symptoms generally peaked during the first week after use was stopped. Only the active patch improved rates of continuous abstinence at 10 and 15 weeks following cessation. By the 23rd week, the differences in abstinence rates among all treatments had become marginal, although active patch users were still slightly more likely to be abstinent. At 62 weeks following cessation, no significant differences in abstinence were observed for any of the treatment conditions.

Many individuals use smokeless tobacco despite its obvious drawbacks because they are hooked on nicotine, a highly addictive drug.

"A number of studies have shown that the nicotine patch is more effective than a placebo patch in sustaining long-term abstinence from cigarette smoking, but the patch appeared to be effective with smokeless tobacco users only during the period of actual patch use and shortly thereafter," notes Dr. Hatsukami. "We don't know if this means we need to use the patch for longer periods of time with smokeless tobacco users or if sensory or behavioral aspects of smokeless tobacco use, such as putting something in one's mouth, may be as important as the nicotine in sustaining use," she says. The fact that a nicotine-free mint snuff also reduced withdrawal symptoms illustrates the potential importance of the sensory aspects of smokeless tobacco in sustaining its use, she says. Previous research does suggest that intensive, multicomponent, behavioral treatment may help smokeless tobacco users to sustain abstinence over the longer term, she says.

"Many questions about smokeless tobacco use and its treatment remain unanswered," Dr. Hatsukami says. "We really need to learn more about all the dimensions of smokeless tobacco use to develop effective treatments that are better tailored to this underserved population," she says.

Sources

- Hatsukami, D.K., et al. Treatment of spit tobacco users with transdermal nicotine system and mint snuff. *Journal of Consulting and Clinical Psychology* 68(2):241-249, 2000.
- Hatsukami, D.K., and Severson, H. Oral spit tobacco: addiction, prevention and treatment. *Nicotine and Tobacco Research* 1(1):21-44, 1999. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 1 (March 2001)

Women and Smokeless Tobacco Use

Although more than 90 percent of smokeless tobacco users in the United States are male, a substantial number of women also use smokeless tobacco products. In 1998, 0.5 percent of females over the age of 12, about 573,000, were current users of smokeless tobacco products, according to the National Household Survey on Drug Abuse.

The comparatively small percentage of women who use smokeless tobacco accounts in part for the lack of research on the patterns of smokeless tobacco use among women, says Dr. Dorothy Hatsukami of the University of Minnesota School of Medicine. In addition, "women rarely respond to our advertisements to participate in smokeless tobacco treatment studies," she says. For example, Dr. Hatsukami recently reported that 99.8 percent of 402 people who responded to advertisements for participation in a smokeless tobacco treatment study with the nicotine patch were male. (See "Nicotine Patch Helps Smokeless Tobacco Users Quit, But Maintaining Abstinence May Require Additional Treatment.")

"Women may be embarrassed about admitting smokeless tobacco use because the general perception is that smokeless tobacco use is socially undesirable, and women don't use it," Dr. Hatsukami speculates. Among the unattractive features of smokeless tobacco use is the need to spit tobacco juice from time to time and dislodge particles of loose tobacco that get trapped between the teeth. This disadvantage of smokeless tobacco use was the one most frequently cited by women who participated in a study of female smokeless tobacco users who weren't seeking treatment, conducted by Dr. Hatsukami and her colleagues.

In the study, 20 female smokeless tobacco users from the upper Midwest completed a questionnaire and brief interview. The study revealed some similarities between females' smokeless tobacco use and what research has shown about males' smokeless tobacco use. For example, on average, both sexes began using smokeless tobacco between 16 and 18, and friends played a major role in their initiating use. About 25 percent of men and women also indicated they used smokeless tobacco to help them stop smoking.

The study also revealed some differences in patterns of smokeless tobacco use by females and the patterns of use reported in a previous study that assessed features of smokeless tobacco use among males who weren't seeking treatment. For example, on average, the women said they used 3.6 dips of moist snuff daily, compared to the 6.3 dips reported by males, and women held the tobacco in their mouths about 22.5 minutes, compared to 39.9 minutes for men. A tin of snuff lasted women anywhere from 2 days to 3 months with a median duration of 6 days per tin. In contrast, men used approximately 2.8 tins per week.

The women in this study may have used less smokeless tobacco than men because they had used smokeless tobacco for less than 4 years, Dr. Hatsukami says. This contrasts with the men, who averaged more than 5 years of smokeless tobacco use. Perceived social disapproval of women using smokeless tobacco also may contribute to lower patterns of use in women. In fact, 38 percent of the women in Dr. Hatsukami's study said they could not use smokeless tobacco in the presence of certain people, and another 25 percent cited social disapproval as a drawback to smokeless tobacco use. These social concerns may reduce opportunities for women to use smokeless tobacco and lead to lower levels of use, Dr. Hatsukami says. In spite of these drawbacks, a significant percentage of women in the study said the relaxing and calming effects and pleasure they associate with smokeless tobacco use are advantages of using these products.

Identifying factors associated with smokeless tobacco use by women and their current patterns of use could generate ways to prevent and treat smokeless tobacco use among women, Dr. Hatsukami says. "The data from this research could help target some of the educational and prevention messages that we should be giving to women," she says. "However, first we have to make women smokeless tobacco users aware that other women use smokeless tobacco products and that they are not abnormal, so they are willing to seek help," she says.

Sources

- Boyle, R.G.; Gerend, M.A.; Peterson, C.B.; and Hatsukami, D.K. Use of smokeless tobacco by young adult females. *Journal of Substance Abuse* 10:19-25, 1998.
- Hatsukami, D.K.; Keenan, R.M.; and Anton, D.J. Topographical features of smokeless tobacco use. *Psychopharmacology* 96:428-429, 1988. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 5 (October 2000)

Nicotine Vaccine Moves Toward Clinical Trials

By Barbara Shine, *NIDA NOTES* Staff Writer

A new vaccine that prevents nicotine from reaching the brains of rats may offer hope for smokers trying to break their addiction. The compound, called NicVAX, may even prove useful as an inoculation against nicotine addiction, much like those that protect children from tetanus, measles, and polio.

Dr. Ali Fattom (left) and Dr. Sham Shirali of Nabi examine a flask of the nicotine preparation used to produce NicVAX. Photo by Jane Barrett, Nabi, Rockville, Maryland.

"Some form of vaccination against nicotine would be highly useful because vaccinated individuals would not be able to get a 'kick' from the nicotine in tobacco smoke or chewing tobacco," says NIDA Director Dr. Alan I. Leshner. "If people found tobacco less rewarding, they would be less likely to continue using it. Ultimately, however, our best treatment for nicotine addiction is prevention."

NicVAX is manufactured by Nabi, a Florida-based pharmaceutical company that has NIDA grant support to conduct preclinical studies to determine whether the vaccine is toxic to animals and, then, if the compound is proven safe, clinical trials to evaluate its safety and efficacy in humans. The 4-year project begins this fall, and clinical trials are planned for 2002. Primary coinvestigators include Dr. Ali Fattom and other Nabi scientists in Rockville, Maryland, as well as the Minnesota- and Texas-based researchers who conducted the early animal studies.

Paul Pentel and his colleagues at the Minneapolis Research Foundation and Hennepin County Research Center in Minneapolis and Dr. David Malin at the University of Houston at Clear Lake tested NicVAX with rats. Injection of NicVAX stimulated antibodies to neutralize nicotine in the blood, reducing by 65 percent the amount of nicotine that reached the animals' brains. The nicotine-specific antibodies produced by NicVAX also reduced the effects of nicotine on blood pressure and the heart.

Now NicVAX is proposed as a therapy that can enhance current treatments for nicotine addiction by helping quitting smokers resist the urge to light up. The hypothesis is that the vaccine may inhibit nicotine's "priming effect"—the phenomenon in which a formerly addicted individual experiences an increased desire to use a drug after a single exposure, which contributes to relapse. A treatment program built around NicVAX might also include supportive counseling and a medication such as bupropion (Zyban) to reduce withdrawal symptoms.

The animal studies suggest the vaccine's potential for preventing addiction in new tobacco users as well. When rats were injected simultaneously with a nicotine solution and the vaccine, the antibodies that reduced nicotine levels in the rat brains also reduced nicotine dependence. When the nicotine dosing was stopped, the control group, rats injected with nicotine and a placebo solution, showed significantly greater levels of dependence—measured by abstinence signs such as teeth chattering and tremors—than did the rats treated with NicVAX. Rats were exposed to nicotine at levels comparable to 10 packs of cigarettes daily for a week.

Continuing doses of nicotine do not interfere with the vaccine's ability to induce antibodies in the rats. Animals immunized with NicVAX while they were being injected with nicotine still produced nicotine-specific antibodies. Thus it may be possible to vaccinate a smoker while he or she is still using tobacco so that adequate antibodies will be in place at smoking cessation. The vaccine will continue to work during any relapse, inhibiting the pleasurable response that nicotine would otherwise cause. Further, the vaccine never enters the brain and is therefore unlikely to produce neurological side effects.

Sources

- Pentel, P.R.; Malin, D.H.; Ennifar, S.; et al. A nicotine conjugate vaccine reduces nicotine distribution to brain and attenuates its behavioral and cardiovascular effects in rats. *Pharmacology Biochemistry and Behavior* 65(1):191-198, 1999.
- Hieda, Y.; Keyler, D.E.; VanDeVoort, J.T.; et al. Immunization of rats reduces nicotine distribution to brain. *Psychopharmacology* 143(2):150-157, 1999. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 5 (October 2000)

NIDA's Nicotine Research Provides Scientific Approaches To Combat a Deadly Addiction

By NIDA Director Dr. Alan I. Leshner

Nicotine addiction takes a terrible toll on American health. More than 430,000 people die in this country each year from smoking-related causes, and the annual cost of these preventable illnesses—in health care expenditures and lost productivity—is more than $97 billion. Despite growing public awareness of the deadly dangers of tobacco, nearly 3,000 people younger than 18 become smokers every day and, once addicted, find it very difficult to stop.

Over the past decade, NIDA's nicotine-related research has provided crucial insights into the neurobiological and behavioral aspects of nicotine addiction, and this research has led the way to important advances in treating nicotine addiction. For example, NIDA-supported basic science research and clinical pharmacological studies played a major role in the development of nicotine replacement therapy—a skin patch or chewing gum that reduces the physical discomfort of nicotine withdrawal. Our behavioral science research has contributed to the development, testing, and validation of new behavioral therapies to help smokers resist the craving that often defeats the most determined efforts to stop smoking.

Over the past decade, NIDA's nicotine-related research has provided crucial insights into the neurobiological and behavioral aspects of nicotine addiction, and this research has led the way to important advances in treating nicotine addiction.

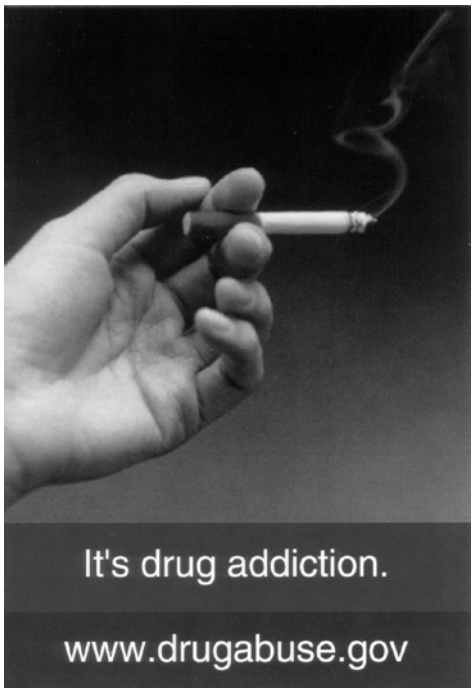
Many of the accomplishments of NIDA's nicotine research effort have been incorporated into a new set of recommendations for primary care practitioners, "Treating Tobacco Use and Dependence: A Clinical Practice Guideline." The recommendations, which were released by U.S. Surgeon General Dr. David Satcher in June, are based on an evaluation of nearly 6,000 peer-reviewed research studies. They endorse pharmacotherapies—sustained release bupropion or nicotine replacement therapy by patch, gum, inhaler, or nasal spray—as well as behavioral therapy, counseling, and support programs to help patients overcome their addiction to nicotine. NIDA—along with the National Cancer Institute; the National Heart, Lung, and Blood Institute; the Centers for Disease Control and Prevention; the Agency for Healthcare Research and Quality; The Robert Wood Johnson Foundation; and the University of Wisconsin Medical School's Center for Tobacco Research and Intervention—sponsored development of the guidelines.

The dividends from NIDA's ongoing investment in nicotine research are increasing. For example, investigators at the Minneapolis Medical Research Foundation have developed a vaccine that, in rats, produces nicotine-specific antibodies that reduce by as much as 65 percent the amount of nicotine that passes from the blood to the brain. The vaccine also prevents some of nicotine's cardiovascular effects and reduces the development of nicotine dependence. This research is a promising first step toward development of a medication that could limit the movement of nicotine from the blood to the brain, reducing the "rush" that addicted smokers experience when they light up and making it easier for them to quit (for more detailed information on this research, see "Nicotine Vaccine Moves Toward Clinical Trials"). Other NIDA-supported researchers have demonstrated important connections between addictions to nicotine and other addictive drugs. This knowledge can help us develop better therapies for patients with multiple addictions (see "Nicotine Craving and Heavy Smoking May Contribute to Increased Use of Cocaine and Heroin," *NIDA NOTES*, Vol. 15, No. 5). NIDA's program of research into genetic factors that influence nicotine addiction has identified a genetically determined variation in liver metabolism that significantly decreases the rate at which the body breaks down and eliminates nicotine from the blood. Individuals with this genetic trait are less likely to become addicted to nicotine and more likely to be able to quit if they do become addicted. NIDA-supported

researchers have found a medication—methoxsalen—that inhibits nicotine metabolism in the same way as the genetic variation. Their studies of the effects of methoxsalen in humans suggest the possibility of developing an entirely new approach to pharmacological treatment of nicotine addiction (see "NIDA-Funded Researchers Identify Compound That Inhibits Nicotine Metabolism, Decreases Urge to Smoke").

Earlier this year, NIDA announced a new research program designed to expand our understanding of the basic science that influences neurobiological and behavioral effects of nicotine and other tobacco chemicals. This program will support investigations that further explain the connections between nicotine and regional brain metabolism, the roles of nicotinic receptors and endocrine regulation, genetic contributions to variations in susceptibility to nicotine addiction, and the neurobiological and behavioral components of nicotine craving.

NIDA's scientific inquiries have provided critical insights into numerous discrete features of nicotine addiction. But tobacco use and nicotine addiction are complex subjects that can only be truly understood as a dynamic interaction of genetic, environmental, neurophysiological, and behavioral effects. To give us the broad perspective we need to fully understand this interaction, last year NIDA joined with the National Cancer Institute and The Robert Wood Johnson Foundation to create seven Transdisciplinary Tobacco Use Research Centers (TTURCs) devoted to investigating new ways to combat tobacco use and nicotine addiction. The TTURCs represent an important new approach to research. They bring together collaborators who will have the freedom to investigate broad aspects of nicotine addiction, from factors that influence smoking initiation to the function of specific neurochemicals, and to study the issues at levels ranging from molecular genetics to peer interactions.



An important part of NIDA's mission is dissemination of the knowledge gained through research. NIDA's newest "art card" describes the similarity between nicotine's addictive properties and those of other addictive drugs. The colorful postcards are distributed at restaurants, bookstores, and coffee shops.

The deadly effects of nicotine reach from the individual cell to our national health. NIDA is committed to continuing and expanding a program of scientific research that provides comprehensive and detailed knowledge that can be transformed into effective tools to prevent and treat the chronic and catastrophic effects of nicotine addiction. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 5 (October 2000)

Drug Abuse and Conduct Disorder Linked to Maternal Smoking During Pregnancy

By Raymond Varisco, *NIDA NOTES* Contributing Writer

Researchers at Columbia University in New York City have found new evidence that children whose mothers smoke during pregnancy are at much greater risk than other children for drug abuse and conduct disorder. The findings reinforce those of other studies spanning more than 25 years that have shown similar problems associated with prenatal exposure to smoke in children ranging from toddlers through teens. The study also revealed marked gender differences, with girls at significantly increased risk for drug abuse and boys at significantly increased risk for conduct disorder.

The investigators interviewed 147 mother-child pairs 3 times over 10 years, with the children ranging from ages 6 to 23 at the start of the study. Both mothers and children were interviewed on entry into the study, again 2 years after the initial interview, and, finally, about 10 years after the initial interview. Because the researchers followed the children through either adolescence or young adulthood—something few studies have done before—they were able to collect data about whether and when the children began to abuse drugs, says Dr. Myrna Weissman, the study's principal investigator.

Data were gathered on psychiatric and substance abuse disorders of parents; family environmental factors, such as divorce and family discord; and maternal factors, such as alcohol and coffee consumption and postnatal smoking, to rule out other explanations for the presence of drug abuse and conduct disorder.

The researchers found that maternal smoking during pregnancy has long-term effects on children's behavior and health that cannot be explained by any other factor included in the study. Risk for adolescent drug abuse in girls was more than 5-fold higher if their mothers smoked more than 10 cigarettes a day during pregnancy. Among boys whose mothers smoked more than 10 cigarettes a day, risk for the onset of conduct disorder was greater than 4-fold that of boys whose mothers did not smoke, with the increase appearing in boys younger than 13. The drug most frequently abused by both boys and girls was marijuana, and the most frequent combination of drugs abused was marijuana and cocaine. Of the females who abused drugs, 70 percent abused more than one.

Why boys exposed to smoking before birth should be at risk for conduct disorder and girls at risk for drug abuse remains to be understood, Dr. Weissman says. She speculates that the differences may be related to sex differences in prenatal brain development.

Many of the findings of this study are consistent with those of related studies, she notes. Researchers at the University of Chicago also have found a link between maternal smoking during pregnancy and conduct disorder in boys, she says. Likewise, a 1994 study conducted by Dr. Weissman's coinvestigator Dr. Denise Kandel found that maternal smoking during pregnancy increases risk for adolescent-onset smoking in girls. Studies also have found other behavioral problems in children exposed prenatally to smoke. For example, scientists at Massachusetts General Hospital found an association between prenatal exposure to smoke and attention deficit hyperactivity disorder. Similarly, a recent study by Dr. Judith Brook and her colleagues at Mount Sinai School of Medicine in New York City has found negative behavior in 2-year-olds of mothers who smoked during pregnancy.

Sources

- Brook, J.S.; Brook, D.W.; and Whiteman, M. The influence of maternal smoking during pregnancy on the toddler's negativity. *Archives of Pediatrics and Adolescent Medicine* 154:381-385, 2000.
- Kandel, D.B.; Wu, P.; and Davies, M. Maternal smoking during pregnancy and smoking by adolescent daughters. *American Journal of Public Health* 84:1407-1413, 1994.
- Wakschlag, L.S; Lahey, B.B.; Loeber, R.; Green, S.M.; Gordon, R.A.; and Leventhal, B.L. Maternal smoking during pregnancy and the risk of conduct disorder in boys. *Archives of General Psychiatry* 54:670-676, 1997.
- Weissman, M.M.; Warner, V.; Wickramaratne, P.J.; and Kandel, D.B. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry* 38:7, 1999. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 5 (October 2000)

NIDA-Funded Researchers Identify Compound That Inhibits Nicotine Metabolism, Decreases Urge to Smoke

By Patrick Zickler, *NIDA NOTES* Staff Writer

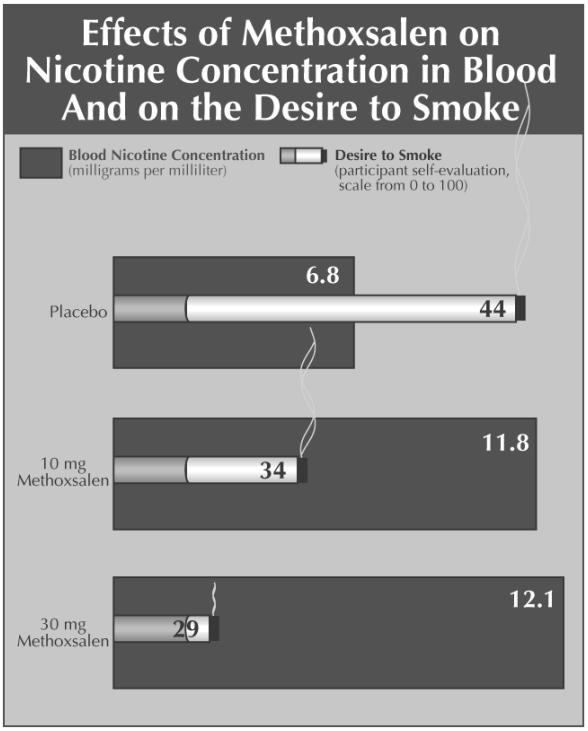
In 1998, NIDA-supported investigators identified a genetic variation that makes some individuals less liable to become addicted to nicotine and, if addicted, more likely to smoke fewer cigarettes and have an easier time quitting than do individuals without the variation. Now the researchers have found that methoxsalen, a medication that mimics the effect of the genetic variation by partially blocking the body's ability to break down nicotine, significantly improves the effectiveness of oral nicotine replacement in reducing a smoker's urge for nicotine. And, according to Dr. Edward Sellers and his colleagues at the University of Toronto, when smokers who receive methoxsalen do light a cigarette, they take fewer and shorter puffs, thereby reducing their exposure to tobacco smoke's carcinogenic components.

"These results suggest that methoxsalen, or other medications that act at the primary site of nicotine metabolism, may represent part of a potent new treatment for nicotine addiction," Dr. Sellers says. "Methoxsalen therapy could reduce smokers' exposure to the harmful constituents of tobacco smoke while serving as part of a step-by-step program of smoking reduction leading to cessation."

Addicted smokers maintain the nicotine in their blood at a concentration that prevents the physical discomfort of withdrawal. They light up a cigarette when that concentration falls. Many smokers who are trying to quit rely on nicotine replacement by transdermal patch or nicotine chewing gum to maintain nicotine levels without smoking. Regardless of the nicotine's source, the drug's blood level falls as it is metabolized by an enzyme produced in the liver, cytochrome P450 2A6 (or CYP2A6).

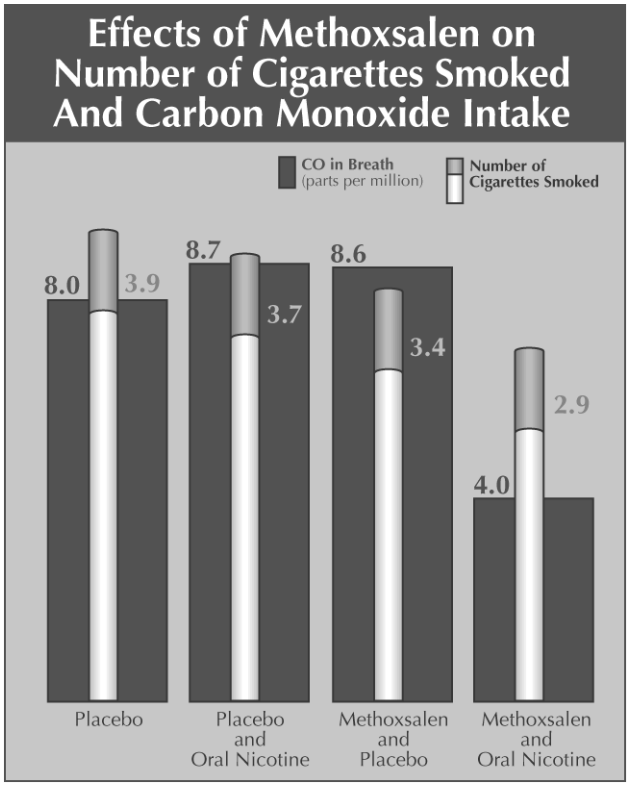
Dr. Sellers and his colleagues tested more than 200 medications to find compounds that decreased CYP2A6 activity. They found that methoxsalen, which currently is used in treatment regimens for severe psoriasis, reduces the activity of CYP2A6 and makes more nicotine—whether from a cigarette or nicotine replacement—available in the blood for longer. "We found that methoxsalen is a potent CYP2A6 inhibitor," Dr. Sellers says.

The researchers conducted two studies of methoxsalen's effect on nicotine metabolism and craving for nicotine in smokers with normal CYP2A6 metabolism who were not trying to quit smoking. In one study, 17 smokers (8 men and 9 women) received methoxsalen or placebo in combination with oral nicotine replacement. Blood levels of nicotine were measured in samples taken at 30-minute intervals for 3 hours. Participants who received either 10 or 30 milligrams of methoxsalen had mean nicotine levels roughly twice as high as those given placebo. The participants also were asked at hourly intervals to rate their urge to smoke. Those who received methoxsalen reported far less desire to smoke.



Methoxsalen inhibits the normal liver metabolism of nicotine, and the resulting higher concentration of nicotine in the blood reduces a smoker's desire to smoke. Horizontal bars indicate average blood nicotine concentrations measured 5 times during 3 hours following the administration of oral nicotine combined with placebo or methoxsalen. Cigarettes indicate the participants' desire to smoke, rated from 0 (none) to 100 (strongest).

In a second study, 11 participants (5 men and 6 women, all of whom had participated in the first study) received either methoxsalen or placebo in combination with nicotine or placebo. Following a 60-minute abstinence, the participants were allowed to smoke at will for 90 minutes.



Participants were allowed to smoke at will for 90 minutes following the administration of combinations of placebo, oral nicotine, and 30 milligrams of methoxsalen. Participants who received methoxsalen and nicotine had significant reductions in the number of cigarettes smoked and carbon monoxide—one of tobacco smoke's most harmful components—measured in breath.

Smokers who had received methoxsalen plus nicotine smoked fewer cigarettes, had longer intervals between cigarettes, and took fewer puffs on each cigarette.

The doses of methoxsalen used in the studies are lower than the dose approved for human use in treating psoriasis, Dr. Sellers says, but the medication has not been proven safe for long-term use in humans. "We need to establish methoxsalen's safety and efficacy in chronic use before it could be used as part of any smoking cessation treatment," he says.

Methoxsalen offers several advantages as a part of treatment for smoking cessation, Dr. Sellers says. For example, it would make possible the use of a pill, rather than a patch or gum, for nicotine replacement. "Most patients prefer taking an oral medication, and there are places where gum is not appropriate," he says. And, because methoxsalen eliminates almost completely the activity of CYP2A6, which varies from person to person, its use with a nicotine pill could result in more predictable response to nicotine replacement than is possible with either patch or gum, Dr. Sellers says.

Source

- Sellers, E.M.; Kaplan, H.L.; Tyndale, R.F. Inhibition of cytochrome P450 2A6 increases nicotine's bioavailability and decreases smoking. *Clinical Pharmacology and Therapeutics* 68(1):35-43, 2000. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 4 (September 2000)

Gender Differences in Drug Abuse Risks and Treatment

By Patrick Zickler, *NIDA NOTES* Staff Writer

Over the past few years NIDA has made a major research commitment to identifying and understanding differences in the ways that women and men—or girls and boys—are first exposed to drugs, in their risks of abuse and addiction, and in the effectiveness of drug treatment. Understanding these differences, and incorporating that understanding into drug abuse prevention and treatment, can reduce the dangers and improve outcomes. NIDA-supported research has shown that gender differences play a role from the very earliest opportunity to use drugs, that women and men tend to abuse different drugs, that the effects of drugs are different for women and men, and that some approaches to treatment are more successful for women than for men.

Are Women Less Likely Than Men to Abuse Drugs?

Men are more likely than women to have opportunities to use drugs, but men and women given an opportunity to use drugs for the first time are equally likely to do so and to progress from initial use to addiction. However, women and men appear to differ in their vulnerability to some drugs. Both are equally likely to become addicted to or dependent on cocaine, heroin, hallucinogens, tobacco, and inhalants. Women are more likely than men to become addicted to or dependent on sedatives and drugs designed to treat anxiety or sleeplessness, and less likely than men to abuse alcohol and marijuana. There are also differences between men and women who seek treatment for drug abuse. Women in treatment programs are less likely than men to have graduated from high school and to be employed and are more likely than men to have other health problems, to have sought previous drug treatment, to have attempted suicide, and to have suffered sexual abuse or other physical abuse.

Are There Gender Differences In the Biological Effects of Drugs?

Animal research and human studies have revealed that males and females may differ in their biological responses to drugs. In studies of animals given the opportunity to self-administer intravenous doses of cocaine or heroin, females began self-administration sooner than males and administered larger amounts of the drugs. Women may be more sensitive than men to the cardiovascular effects of cocaine. In human studies, women and men given equal doses of cocaine experienced the same cardiovascular response despite the fact that blood concentrations of cocaine did not rise as high in women as in men. In studies involving long-term cocaine users, women and men showed similar impairment in tests of concentration, memory, and academic achievement following sustained abstinence, even though women in the study had substantially greater exposure to cocaine. Women cocaine users also were less likely than men to exhibit abnormalities of blood flow in the brain's frontal lobes. These findings suggest a sex-related mechanism that may protect women from some of the damage cocaine inflicts on the brain.

Does Gender Play a Role in Nicotine Addiction?

Women and men are equally likely to become addicted to nicotine, yet women typically smoke cigarettes with lower nicotine content than those smoked by men, smoke fewer cigarettes per day, and inhale less deeply than men. Overall, however, women are less successful than men in quitting smoking and have higher relapse rates after they do quit. Treatment involving nicotine replacement therapy—nicotine gum or patch—works better for men than for women.

What Are Women's Risks for HIV/AIDS?

Research suggests that there are sex-related differences in some fundamental aspects of the HIV/AIDS disease process. For example, an HIV-infected woman with half the amount of virus circulating in the bloodstream as an infected man will progress to a diagnosis of AIDS in about the same time. And, according to the Centers for Disease Control and Prevention, among cases that progress to a diagnosis of AIDS, drug abuse accounts for a greater percentage of cases among women than among men. Nearly half (47 percent) of all women diagnosed with AIDS are injecting drug users (IDUs), whereas among men, IDUs account for 32 percent of AIDS cases. An additional 19 percent of women, compared with 2 percent of men, with AIDS report having sex with users who inject drugs. In all, drug abuse is nearly twice as likely to be directly or indirectly associated with AIDS in women (66 percent) as in men (34 percent).

For More Information

NIDA's gender-related research is discussed in *Drug Addiction Research and the Health of Women,* available on NIDA's home page on the World Wide Web: *www.drugabuse.gov* or from the *DrugPubs* Research Dissemination Center, by phone: 877-643-2644 (TTY/TDD: 240-645-0228), or e-mail: *drugpubs@nida.nih.gov.*

NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

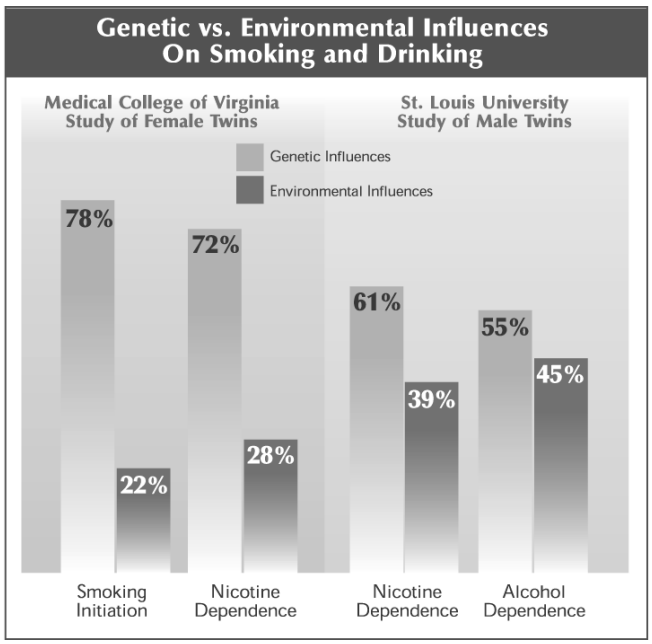
Research Findings

Volume 15, Number 2 (August 2000)

Evidence Builds That Genes Influence Cigarette Smoking

By Patrick Zickler, *NIDA NOTES* Staff Writer

More than one in four Americans older than 17 regularly smokes cigarettes despite increasing public awareness of tobacco's severe health risks. Some start younger than others and, among those who try to quit, some are more successful than others. NIDA-supported scientists are finding increasing evidence that these differences may be due in part to an inherited vulnerability to nicotine addiction.



A Medical College of Virginia study involving 949 female twin pairs found genetic factors to be more influential than environmental factors in smoking initiation and nicotine dependence. Likewise, a St. Louis University study of 3,356 male twin pairs found genetic factors to be more influential for dependence on nicotine and alcohol.

At the St. Louis University Health Sciences Center, Dr. William True and Dr. Hong Xian interviewed male twin pairs to assess genetic influences on smoking. In twin studies, researchers compare patterns of tobacco use in fraternal and identical twin pairs, who typically are exposed to common environmental influences. If genes play a role in determining tobacco use, identical twins—who share the same genes—will be more similar in their use of tobacco than fraternal twins, who share roughly half of their genes. The St. Louis University researchers found that among the 3,356 twin pairs studied, genetic factors make a stronger contribution to nicotine dependence (61 percent) than do environmental factors (39 percent) and also play a more prominent role (55 percent) than environmental factors (45 percent) in alcohol dependence. In another study, Dr. Kenneth Kendler and his colleagues at the Medical College of Virginia in Richmond interviewed 949 female twin pairs and found that genetic factors play a more important role (78 percent) than do environmental factors (22 percent) in smoking initiation and in nicotine dependence (72 percent vs. 28 percent).

"These studies emphasize the importance of understanding the role of genetic influences in smoking," says Dr. Jaylan Turkkan, chief of NIDA's Behavioral Sciences Research Branch. "The more we understand about vulnerabilities, risks, and possible protective factors, the better able we will be to tailor treatments that help people stop smoking."

Other NIDA-supported scientists are studying genes that are polymorphic—that is, in different individuals the same gene has slight variations called alleles—and have found that individuals with one type of allele are more likely to begin smoking or to have greater success quitting than are individuals with another type. For example, researchers at the University of Toronto have found that different alleles in a gene that helps regulate nicotine metabolism may protect some smokers from becoming dependent on nicotine (see "Study Shows How Genes Can Help Protect from Addiction," *NIDA NOTES,* V13-6, 1998).

Dr. Caryn Lerman, principal investigator of the NIDA-supported Transdisciplinary Tobacco Use Research Center at Georgetown University in Washington, D.C., and her colleagues studied two genes, designated SLC6A3 and DRD2, that may influence smoking behavior by affecting the action of the brain chemical dopamine. In a study involving 289 smokers and 233 nonsmokers (42 percent male, 58 percent female, average age 43), the researchers found that smokers were less likely to have an allele designated SLC6A3-9 (46.7 percent) than were nonsmokers (55.8 percent). The likelihood of smoking was even lower if the individual had both the SLC6A3-9 allele and the

DRD2-A2 allele. In addition, Dr. Lerman observed that smokers with the SLC6A3-9 allele were more likely to have started smoking later and to have had longer periods of smoking cessation than those without the allele. These findings imply that the allele may impart a protective effect. Therefore, Dr. Lerman suggests, smokers without the SLC6A3-9 allele may be better able to quit smoking if their treatment incorporates a medication such as bupropion that acts on the brain's dopamine pathway. This hypothesis is currently being tested in a randomized trial.

"The more we understand about vulnerabilities, risks, and protective factors, the better able we will be to help people stop smoking."

Dr. Lerman and her colleagues also studied a polymorphism in a gene, designated 5-HTTLPR, that helps regulate the brain chemical serotonin to determine the gene's possible role in smoking. The polymorphism has two alleles, one designated the short, or *S,* allele, the other the long, or *L* allele. In previous studies the *S* allele has been linked to neuroticism—an anxiety-related personality trait. Dr. Lerman and her colleagues studied 185 smokers (46 percent male, 54 percent female, and average age 45) to investigate the possible relationship between genetically influenced neuroticism and smoking behavior. They found that neuroticism was associated with increased nicotine dependence, smoking for stimulation, and smoking to relieve negative mood in the group of smokers who had the *S* allele. Among smokers with the *L* allele, neuroticism was not associated with these smoking patterns. "Anxious persons tend to smoke more and have more difficulty quitting," Dr. Lerman says. The new findings suggest that among smokers with neuroticism, determining the 5-HTTLPR genotype may help identify who will be more responsive to a particular type of treatment. "Once validated, these results may lead to targeted pharmacotherapy for smoking cessation," says Dr. Lerman.

"This area of research represents our first small steps along a very complicated path to understanding the role that genes play in drug abuse," notes Dr. Harold Gordon of NIDA's Clinical Neurobiology Branch. "Many genes interact with each other and with other biological and environmental factors. Defining these interactions and understanding their influence on nicotine addiction will be crucial to development of treatments for smoking and for other addictions."

Sources

- Kendler, K., et al. A population-based twin study in women of smoking initiation and nicotine dependence. *Psychological Medicine* 29(2):299-308, 1999.
- Lerman, C., et al. Evidence suggesting the role of specific genetic factors in cigarette smoking. *Health Psychology* 18(1):14-20, 1999.
- Lerman, C., et al. Interacting effects of the serotonin transporter gene and the neuroticism in smoking practices and nicotine dependence. *Molecular Psychiatry* 5(2):189-192, 2000.
- True, W.R., et al. Common genetic vulnerability for nicotine and alcohol dependence in men. *Archives of General Psychiatry* 56(7):655-661, 1999. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

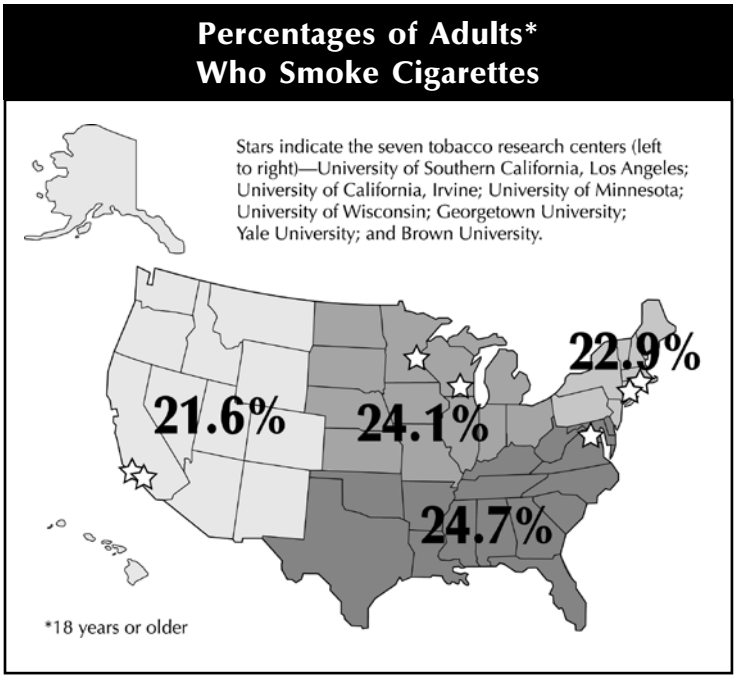
Research Findings

Volume 15, Number 1 (March 2000)

NIDA Joins NCI, Robert Wood Johnson Foundation To Launch Tobacco Research Centers

By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA, the National Cancer Institute (NCI), and The Robert Wood Johnson Foundation (RWJF) have awarded grants to seven academic research institutions to establish Transdisciplinary Tobacco Use Research Centers (TTURCs) devoted to investigating new ways to combat tobacco use and nicotine addiction. The institutions will receive $70 million from NIDA and NCI for the project. RWJF will provide an additional $14 million over 5 years to support improved communications and policy development at the TTURCs.



Although the prevalence of adult cigarette smokers is high, the numbers reflect only one piece of the problem. NIDA's new research centers will seek ways to combat all types of tobacco use among all population segments, adults and children alike. Statistics from Centers for Disease Control and Prevention in Atlanta.

In the past, research grants typically have focused on single components of tobacco use and nicotine addiction, treatment, or prevention, notes Dr. Jaylan Turkkan, chief of NIDA's Behavioral Sciences Research Branch and coordinator of NIDA's TTURC efforts. "The transdisciplinary approach will bring together collaborators who will have the freedom to investigate wider aspects of nicotine addiction, such as factors that influence smoking initiation, and to study the issues at levels ranging from genetics to peer interactions," Dr. Turkkan says.

"The transdisciplinary centers represent an important new approach to research," says NIDA Director Dr. Alan I. Leshner. "Tobacco use and nicotine addiction are incredibly complex subjects, and transdisciplinary investigation can give us the broad perspective we need to understand the etiology of this addiction. This approach will lead to the development of new interventions that will help prevent tobacco use, particularly among teens and younger children."

The TTURC concept evolved from informal conversations among researchers and policymakers at a July 1998 conference—"Addicted to Nicotine"—cosponsored by NIDA, RWJF, NCI, and the Centers for Disease Control and Prevention. Several months later, NCI's Tobacco Research Implementation Group recommended transdisciplinary centers as its highest tobacco use research priority. Within a year, NIDA and NCI jointly issued a Request for Applications from academic centers interested in developing such centers. The first TTURC awards were announced in October 1999. The centers, principal investigators, and research areas are:

- Brown University Center for Behavioral and Preventive Medicine at the Miriam Hospital, Providence, Rhode Island; *Principal Investigator* Dr. David Abrams; *Research Area* Identification of early childhood and lifetime psychiatric factors that determine smoking initiation, dependence, use patterns, cessation, and response to cessation treatment.
- University of California, Irvine; *Principal Investigator* Dr. Frances Leslie; *Research Area* Identification of predictors of nicotine addiction in animals and tobacco susceptibility and use in humans;
- University of Southern California, Los Angeles; *Principal Investigator* Dr. C. Anderson Johnson; *Research Area* Preventing tobacco use among youth of diverse cultures.

- Georgetown University, Washington, D.C.; *Principal Investigator* Dr. Caryn Lerman; *Research Area* Identification of biobehavioral basis of smoking initiation, smoking treatment, and harm from tobacco exposure.
- University of Minnesota, Minneapolis; *Principal Investigator* Dr. Dorothy Hatsukami; *Research Area* Treating smokers who have been resistant to conventional methods of intervention or who have not been previously targeted.
- University of Wisconsin Medical School, Madison; *Principal Investigator* Dr. Michael Fiore; *Research Area* Relapse to tobacco use.
- Yale University, New Haven, Connecticut; *Principal Investigator;* Dr. Stephanie O'Malley; *Research Area* Treatment of tobacco addiction. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 14, Number 4 (November 1999)

New NIDA Clinic Tests Therapies to Help Teens Quit Smoking

By Steven Stocker, *NIDA NOTES* Contributing Writer

NIDA's Intramural Research Program (IRP) recently opened a new Teen Tobacco Addiction Treatment Research Clinic at the Bayview Medical Center in Baltimore. At the clinic, researchers will evaluate promising therapies for adolescent nicotine addiction.

One of the clinic's first research projects will be a pilot study of smoking cessation treatments for 13- to 17-year-old cigarette smokers. "More than one-third of 17-year-olds who smoke say they are interested in some form of treatment to help them quit," says IRP's Dr. Eric Moolchan, director of the new clinic and leader of the smoking cessation study.

Cutting the ribbon to dedicate NIDA's new Teen Tobacco Addiction Treatment Research Clinic (TTATRC) in Baltimore are, from left, Dr. Jean Lud Cadet, clinical director, NIDA's Intramural Research Program (IRP); NIDA Director Dr. Alan I. Leshner; Dr. Barry Hoffer, director of NIDA's IRP; Dr. Eric Moolchan, director of TTATRC; and Dr. Monique Ernst, IRP researcher.

The research project will test the combination of nicotine replacement therapy (NRT) and group counseling for treating nicotine addiction in adolescents. NRT helps smokers learn to abstain from smoking by replacing the nicotine that they previously obtained from cigarettes, thereby preventing withdrawal symptoms and craving for nicotine. NRT forms currently available include the nicotine patch and gum.

Dr. Moolchan says that many health care providers are reluctant to prescribe nicotine patches or gum for adolescents because of a lack of studies showing that these products are safe and effective in this age group. The IRP pilot study will help determine whether adolescents can use the nicotine patch and gum safely, whether they can tolerate the same nicotine doses in the patch and gum as adults, and whether they will follow the instructions on how to use these products. Later studies will focus more on the effectiveness of the patch and gum in helping adolescents quit smoking.

"It's important that we develop effective treatments for young people to try to get them to quit smoking as early as possible," says IRP Director Dr. Barry Hoffer. "Research shows that 90 percent of people who die prematurely of a cigarette-related disease started smoking when they were adolescents. If we can help adolescents quit smoking, we should be able to prevent many of these premature deaths."

The IRP study will have 3 groups, each with 18 adolescents. The first group will receive active patches containing nicotine and placebo gum without nicotine, the second group will receive placebo patches and active gum, and the third group will receive placebo patches and placebo gum. Participants will not be told whether the products they receive are active or placebo.

All three groups will also participate in group counseling sessions because studies with adult smokers have indicated that smoking cessation programs that combine behavioral therapy with medications produce the highest abstinence rates. In the counseling sessions, a mental health professional and Dr. Moolchan, who is a pediatrician, will discuss various topics involving smoking and health and will teach the adolescents how to modify their behavior to deal with situations that might cause them to smoke.

Even though smoking is the primary focus of the sessions, other topics—such as peer relations, school, and dating—will be discussed. "Addressing these other issues is important because adolescent smokers often think that smoking helps them in their social relations," says Dr. Moolchan. "Furthermore, problems concerning social relations can negatively affect mood, and smokers often regulate their mood with nicotine."

The IRP project also will examine other aspects of adolescent smoking. One study will analyze how adolescents smoke cigarettes—for example, how deeply they inhale or how many puffs they take per cigarette. IRP researchers will also study whether nicotine withdrawal causes

adolescents to experience problems with concentration and short-term memory and whether nicotine-replacement treatments can reverse these deficits. Another project will measure chemical evidence of cigarette consumption in saliva to determine whether adolescents metabolize the components of cigarette smoke in the same way that adults do.

"More than one-third of 17-year-olds who smoke say they are interested in some form of treatment to help them quit."

The researchers will recruit adolescents from the Baltimore area through referrals from healthcare providers, schools, churches, and youth centers. Dr. Moolchan hopes that this study will establish contacts in the community that can be used to recruit adolescents for future studies. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 14, Number 2 (August 1999)

New Tracers Will Help Researchers Track Nicotine in the Brain

Dr. Edythe D. London and her colleagues at the Brain Imaging Center of NIDA's Intramural Research Program in Baltimore have developed a new class of radio-labeled chemicals capable of binding tightly to nicotinic acetylcholine receptors, the molecules in the brain where nicotine acts. These probes will enable scientists to monitor nicotinic pathways in the brain by external imaging. Because these radiotracers attach themselves with more selectivity and less toxicity than currently available nicotinic radiotracers, researchers believe they may be ideal for both positron emission tomography (PET) and single photon emission computed tomography (SPECT), two common brain imaging technologies.

Testing in primates has led scientists to conclude that this new class of radiotracers will be practical for studying the underlying mechanisms of nicotine dependence in humans and will be useful for developing and testing therapies for nicotine addiction. These radiotracers may also benefit the study of Alzheimer's disease, Parkinson's disease, and Tourette's syndrome, which scientists believe are conditions characterized at least in part by abnormalities in nicotinic receptors. The Brain Imaging Center is now seeking FDA approval to use the new radiotracers in studies with human volunteers. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 13, Number 5 (February 1999)

Nicotine Conference Highlights Research Accomplishments And Challenges

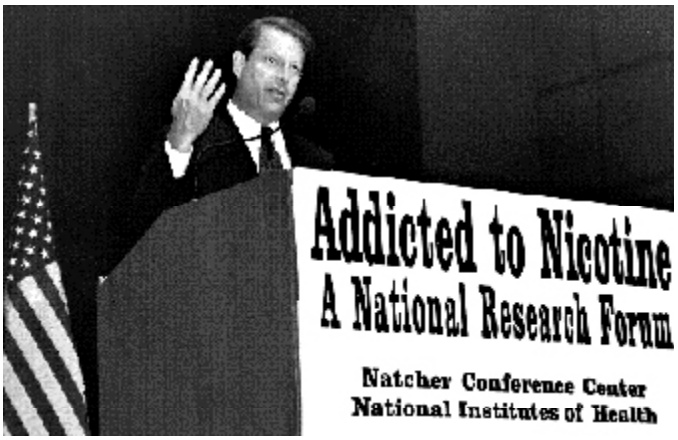
By Barbara Cire, *NIDA NOTES* Associate Editor

Provocative new research findings about the nicotine addiction process, how nicotine addiction drives tobacco use, and nicotine addiction treatment were the focus of "Addicted to Nicotine: A National Research Forum," held in Bethesda, Maryland in July. The meeting was sponsored by NIDA and The Robert Wood Johnson Foundation and cosponsored by the National Cancer Institute and the Office on Smoking and Health of the Centers for Disease Control and Prevention. NIDA Associate Director Dr. Timothy P. Condon and Dr. Jaylan Turkkan, Chief of NIDA's Behavioral Sciences Research Branch, served as cochairs of the conference planning committee.

Keynote speaker Vice President Al Gore noted that the conference had drawn some of the world's best researchers "to reinforce that nicotine is a drug—a dangerous, highly addictive drug, and we should treat it as a drug." He cited recent research findings indicating that while the overall incidence of smoking has decreased, the number of adolescents starting to smoke has increased. "If children don't start smoking by age 19, they are unlikely to start," he said. "But, if they do start, it's hard to stop. Seventy percent of current smokers say they want to stop smoking, but can't. That's because nicotine is a highly addictive drug—as addictive as heroin or cocaine."

"We are here to apply the power of science to this problem," said NIDA Director Dr. Alan I. Leshner. He challenged the approximately 600 participants to highlight what is known about nicotine addiction and tobacco use and to "tell us what else we need to know to set the research agenda for the next decade." More than 40 scientists from the United States, Canada, and Sweden presented research results in four topic areas: the pharmacology of nicotine; individual and environmental risk factors for smoking initiation and nicotine intake; the biology of nicotine addiction; and treatment of nicotine addiction.

Dr. Jack Henningfield of The Johns Hopkins University School of Medicine in Baltimore said that, since the beginning of the 20th century, scientists have known that nicotine is a potent substance that affects the nervous system and stimulates heart rate and muscular activity, that nicotine's effects depend on the amount administered, and that responsiveness to nicotine diminishes with repeated use. NIDA-supported research has demonstrated conclusively that nicotine meets all the criteria of an addictive drug, he stressed.



In his keynote address at NIDA's nicotine conference, Vice President Al Gore tells participants that 3,000 young people start smoking each day, ultimately resulting in death for one-third of them.

Nicotine is now understood to affect the structure and function of the nervous system, Dr. Henningfield said.

Chronic nicotine exposure and withdrawal produce changes in brain function, including cerebral metabolism and hormone levels, he added.

Dr. Rachel Tyndale of the University of Toronto presented information about a gene variant for an enzyme called CYP2A6 that may protect some individuals from becoming addicted to nicotine. In humans, 60 to 80 percent of nicotine is metabolized by the CYP2A6 enzyme. Individuals with a defective version of the gene for CYP2A6 metabolize nicotine slowly and inefficiently. When people start to smoke, they often experience dizziness or nausea; when nicotine metabolism is slowed, these unpleasant effects may last longer, Dr. Tyndale explained. Thus, people with a defective version of this gene are less likely to continue smoking and, if they do smoke, are more likely to smoke less than people with a fully functioning version of this gene.

"This genetic defect protects approximately 7 million North Americans from smoking," said Dr. Tyndale. "Inhibiting the CYP2A6 enzyme may provide new therapeutic approaches to the prevention and treatment

of smoking. The manipulation of CYP2A6 must be explored."

Dr. Marina Picciotto of Yale Medical School in New Haven, Connecticut, discussed a particular protein that she and her colleagues in France, Sweden, and Switzerland have identified as essential to the nicotine addiction process. Using sophisticated bioengineering tools, the researchers produced a strain of mice that lack this protein. They found that the genetically altered mice did not experience the normal rewarding and reinforcing aspects of nicotine that typically lead to addiction.

"The majority of smokers try to quit on their own without seeking help. The quit rate for this group is 5 percent or less," said Dr. Maxine Stitzer of The Johns Hopkins University School of Medicine, summarizing treatment research that compared the effectiveness of nicotine replacement therapy and behavioral therapy separately and combined. Because these treatments operate by different mechanisms, complementary and potentially additive effects may be expected when they are used in combination, she said.

"Typical long-term abstinence rates of 6 to 12 months for one type of therapy alone are about 20 percent," Dr. Stitzer said. "Combining therapies can produce long-term abstinence rates as high as 35 to 40 percent. We need to know how to improve access, affordability, and acceptability of both pharmacologic and behavioral therapies to take better advantage of existing treatments such as over-the-counter nicotine-replacement products. We must also learn how to strengthen the linkage between the two therapy types."

Dr. Marina Picciotto of Yale Medical School discusses a recently identified protein that is involved in the reinforcing and rewarding aspects of nicotine addiction.

For More Information

Additional information about nicotine and its addictive properties can be obtained by calling NIDA Infofax at 1-888-NIH-NIDA (644-6432) or by accessing NIDA's home page on the World Wide Web at *www.nida.nih.gov* and going to the "Addicted to Nicotine" conference information. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 13, Number 3 (July 1998)

Like Other Drugs of Abuse, Nicotine Disrupts the Brain's Pleasure Circuit

By Neil Swan, *NIDA NOTES* Staff Writer

All drugs of abuse disrupt the normal flow of the neurotransmitter dopamine, stimulating its release and increasing its brain levels. This action is believed to be significantly involved in producing drug-induced feelings of pleasure and reward and, over time, addiction and vulnerability to withdrawal symptoms. Drugs of abuse begin this action by chemically binding to specific molecular sites called receptors, some of which are found on dopamine nerve cells.

Recent findings from several NIDA-funded researchers confirm not only that nicotine is highly addictive but that it affects the same brain mechanism as other drugs of abuse and increases brain levels of dopamine. The findings also suggest how nicotine abstinence and withdrawal activate the body's stress systems. Two research teams have spotlighted how nicotine, just like heroin or cocaine, activates dopamine-containing nerve cells in the brain's mesolimbic system, which is involved in emotion and behavior. Another group has shown that some brain changes during withdrawal from chronic nicotine use are similar to those that occur during withdrawal from other drugs of abuse.

Dr. John A. Dani of Baylor College of Medicine in Houston and his colleagues have shown that nicotine binds at multiple receptors on dopamine nerve cells, or neurons, to activate the neurons. Theoretically, this activation of dopamine neurons by nicotine begins the response that leads to feelings of pleasure and reward, and then addiction. The researchers examined dopamine nerve cells from the brains of rats that had been exposed to nicotine for prolonged periods. They found that nicotine at levels comparable to those found in human smokers first activates or sensitizes these neurons but then quickly desensitizes them.

The researchers believe nicotine-induced desensitization of dopamine cells may explain why smokers report that they rapidly become tolerant to the effects of smoking during the day. The tolerance fades overnight so that by the next morning the dopamine cells are resensitized to nicotine, the researchers theorize.

"This finding suggests a cellular explanation for smokers' reports that their first cigarette of the day is the most pleasurable," while the pleasurable effect of cigarettes smoked later in the day is greatly reduced, says Dr. Dani. "It's a biophysical extrapolation to explain how the cellular response to nicotine ultimately affects behavior," he explains. The results further support the theory that nicotine acts through the same cellular mechanism as other addictive drugs and that this mechanism—dopamine activity in the mesolimbic system—is implicated in various ways in the cellular and behavioral effects of addictive drugs, he says.

Dr. Marina Picciotto of Yale Medical School in New Haven, Connecticut, and her colleagues in France, Sweden, and Switzerland have gone a step further and have pinpointed the specific protein to which nicotine binds on a particular nicotinic receptor on a dopamine cell.

The researchers used a strain of mouse developed by Dr. Picciotto in which the gene that encodes this protein is eliminated or "knocked out." The researchers found that these knockout mice did not self-administer nicotine as their normal sisters did. The finding suggests that the mice without the protein, called the beta 2 subunit, did not experience the normal reinforcing, or rewarding, effects of nicotine. But the mice did self-administer cocaine, an indication that knocking out the beta 2 subunit affected only their response to nicotine, not to other drugs.

The experiment tested the behavioral response of the mice. But what about their physiological response? If the knockout mice were injected with nicotine, would the nicotine increase dopamine levels? No. In a followup experiment, nicotine injections did not boost dopamine levels in the brains of knockout mice. This finding provided further evidence of the influential role of the beta 2 subunit in the nicotine addiction process. The study findings are consistent with the theory that the dopamine brain circuit is the reward pathway used by all drugs of addiction but that different drugs activate this pathway through different molecular gateways.

"In our altered mice, we've shown that if you take away one subunit of the nicotinic receptor, you take away the ability of nicotine to stimulate dopamine release," explains Dr. Picciotto.

"To actually pinpoint a particular protein shown to be critical to nicotine addiction is a major discovery," says

NIDA Director Dr. Alan I. Leshner. Future medications for nicotine addiction might target that specific protein, he says.

Dr. Picciotto is now studying how this nicotinic receptor and its subunits affect the rewarding properties of other drugs such as morphine, cocaine, and alcohol. "People who abuse other drugs are also likely to be smokers, and we would like to know more about interactions between the different systems that mediate the rewarding effects of these different drugs," she says.

Another NIDA-funded study shows that the severity of changes that occur in the brain's pleasure circuits during withdrawal from chronic nicotine use rivals that experienced during withdrawal from other abused drugs such as cocaine, amphetamine, morphine, and alcohol.

The study found dramatically decreased sensitivity to pleasurable electrical stimulation in the brains of rats after nicotine administration was stopped. The decreased sensitivity, which lasted several days, may correspond to the depression experienced by humans who quit smoking "cold turkey."

"Understanding these decreases in the brain's sensitivity to pleasurable stimulation during nicotine abstinence helps explain why it's so hard for people to stop smoking and may help develop better treatments for nicotine withdrawal symptoms such as depression, anxiety, irritability, and craving for a cigarette," says Dr. Leshner. "The brain-change similarities to other drugs of abuse emphasize that there are common characteristics to withdrawal from all addictive substances, one of which is decreased sensitivity to pleasure," he says.

Dr. Athina Markou and her colleagues at The Scripps Research Institute in La Jolla, California, measured the effects of nicotine abstinence on the brain's sensitivity to pleasure-inducing electric pulses. They taught rats to self-administer brief electrical pulses in the lateral hypothalamus, part of the brain's reward circuitry, and then monitored the level of pleasure, or reward, experienced by the animals.

Reward sensitivity measures were taken during and after administration of nicotine. For a week the rats were infused with a steady dose of nicotine to produce nicotine blood levels equivalent to those of a human smoking 30 cigarettes a day.

While nicotine was administered, the animals' sensitivity to brain reward remained stable, as shown by the fact that they self-administered pleasure-inducing pulses at the same level as before nicotine was introduced. When the rats' nicotine was cut off, however, the scientists had to increase the intensity of electrical current by more than 40 percent before the rats showed through their behavior that electrical pulses to the brain were again pleasurable.

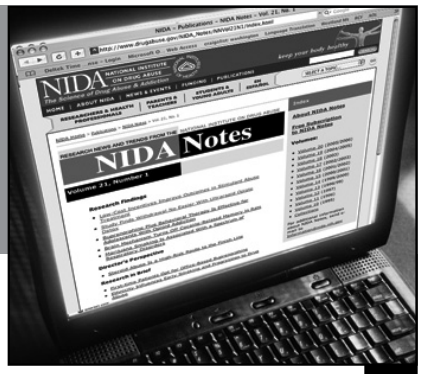
"These results are comparable to the altered brain reward sensitivity found during withdrawal from many other addictive drugs," says Dr. Markou. The experiment provides a valid animal model for studying the function of brain reward circuits involved in nicotine withdrawal and to help develop treatments for nicotine addiction, she adds.

Sources

- Epping-Jordan, M.P.; Watkins, S.S.; Koob, G.F.; and Markou, A. Dramatic decreases in brain reward function during nicotine withdrawal. *Nature* 393:76, 1998.
- Picciotto, M.R., et al. Acetylcholine receptors containing the β2 subunit are involved in the reinforcing properties of nicotine. *Nature* 391:173-177, 1998.
- Pidoplichko, V.I.; DeBiasi, M.; Williams, J.T.; and Dani, J.A. Nicotine activates and desensitizes midbrain dopamine neurons. *Nature* 390:401-404, 1997. NN

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Keeping up with Drug Abuse Research has never been easier!



Subscribe FREE to NIDA Notes, now available in **two no-cost** options—traditional print or an e-mail version with links to our Web site. This bimonthly publication of the National Institute on Drug Abuse offers the latest research findings in **drug abuse and addiction**. Topics include:

- *Costs to Society*
- *Health Consequences, including HIV/AIDS*
- *Origins and Causes*
- *Pharmacology*
- *Prevention*
- *Short- and Long-Term Effects*
- *Treatment*
- *Trends and Patterns*
- *And More*

NIDA, one of the National Institutes of Health, supports most of the world's research on the health aspects of drug abuse and addiction...and **NIDA Notes** tells you all about it!

Please enter my **NO-COST** subscription to **NIDA Notes**. (Type or print clearly.)

Select delivery method: ❑ Print ❑ E-mail ❑ Both

Circle one: Mr. Ms. Dr.

Name _____

Organization _____

Address _____

City _____ State _____ Zip _____

Country _____

E-mail _____

MAIL TO: NIDA Notes Subscription Department
MasiMax Resources, Inc.
1375 Piccard Drive, Suite 175
Rockville, MD 20850

FAX TO: (240) 632–0519

Subscriptions are also available online at **www.drugabuse.gov**.

Questions? E-mail us at nidanotes@masimax.com.

Check the one category that best describes your field:

❑ Drug Abuse Treatment
❑ Medical Practice
❑ Research
❑ Policy/Advocacy
❑ Library Science
❑ Drug Abuse Prevention
❑ Educator
❑ Media
❑ Criminal Justice
❑ Other_____
Please specify.

Check all the areas of interest that apply to you:

❑ HIV/AIDS Epidemiology
❑ HIV/AIDS Prevention
❑ HIV/AIDS Treatment
❑ Children and Adolescents
❑ Criminal Justice
❑ Drug Abuse Epidemiology
❑ Drug Abuse Prevention
❑ Drug Abuse Treatment
❑ Education
❑ Health Services
❑ Neuroscience
❑ Pharmacology
❑ Other _____
Please specify.

Revised July 2009
Revised April 2008
Revised June 2005
Printed September 2002