Damage to Brain Area May Immediately Halt Cigarette Addiction

Research Findings
Vol. 22, No. 3 (April 2009)

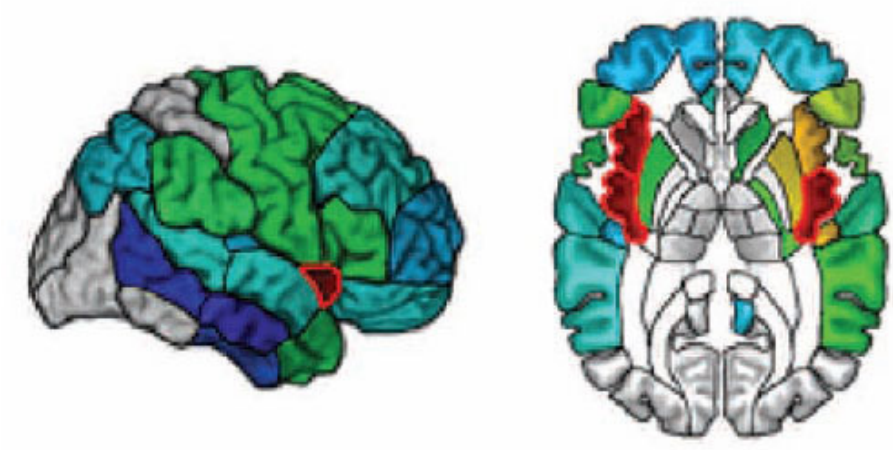
Patients with injury to the insula lost the urge to smoke.

BY LORI WHITTEN, *NIDA Notes* Staff

"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.

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.

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.



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"). 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.

SOURCES

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

Volume 22, Number 3 (April 2009)

Prenatal Nicotine Exposure May Damage Receptors That Influence Auditory Processing

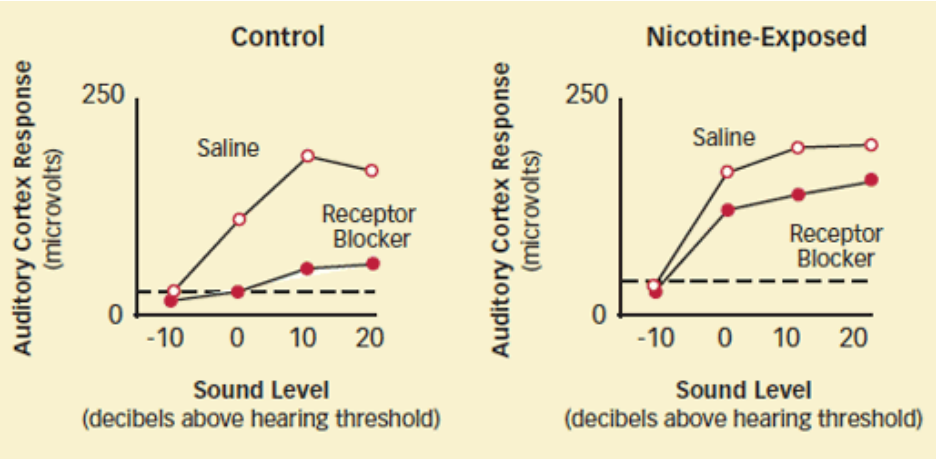
Research Findings
Vol. 22, No. 3 (April 2009)

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."

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. [Abstract]

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. [Abstract]

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. [Abstract]

Volume 22, Number 3 (April 2009)

Imaging Studies Elucidate Neurobiology of Cigarette Craving

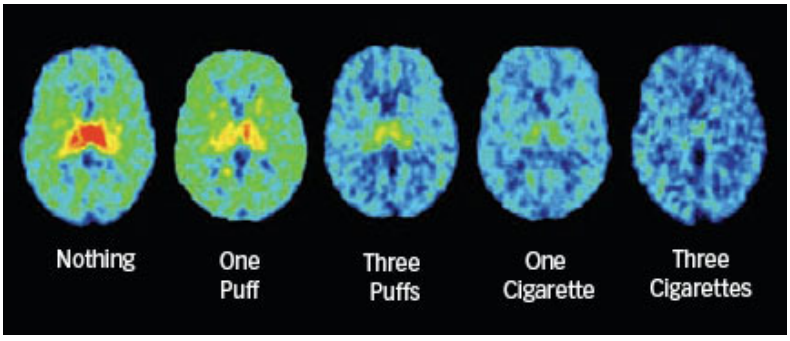
Research Findings
Vol. 22, No. 2 (December 2008)

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 α4β2*-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 cessation 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 α4β2*-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 α4β2*- nACh receptors.

The images revealed that smoking occupied α4β2*-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 α4β2*-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 α4β2*-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. [Abstract]

Brody A.L., et al. Neural substrates of resisting craving during cigarette cue exposure. *Biological Psychiatry* 62(6):642-651, 2007. [Abstract]

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. [Full Text]

Volume 22, Number 2 (December 2008)