Brain Scans, Genes Provide Addiction Clues

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SCIENTISTS USING ADVANCED BRAIN imaging and genetic testing to probe the physiological basis of addiction are gleaning new insights into these disorders and how to treat them.

A symposium sponsored by Brookhaven National Laboratory (Upton, NY), held in conjunction with the American Association for the Advancement of Science's annual meeting in San Francisco in February, highlighted several advances in addiction science made over the past year. Researchers presented findings from brain imaging studies revealing the importance of memory and drug-related cues in addiction, the role of monoamine oxidase–inhibiting compounds in cigarette smoking, the damage to inhibitory controls caused by methamphetamine use, as well as results from studies suggesting that genomics could be used to better tailor addiction therapies.

CRAVING KEY

Dopamine, a neurotransmitter associated with pleasurable feelings, plays an important role in reinforcing the use of addictive substances. Many studies have demonstrated that addictive drugs increase endogenous dopamine levels in the nucleus accumbens of the brain. This phenomenon, which also occurs in the brain of someone engaged in eating or other activities necessary for survival, is one of the most powerful mechanisms driving behavior, explained Nora D. Volkow, MD, director of the National Institute on Drug Abuse.

Harder to explain is another key component of addiction: the intense craving or desire that addicted individuals experience when they are exposed to drug-associated cues, such as persons with whom they used the drug, places where they used the drugs, and drug paraphernalia. Now, however, brain imaging techniques are giving scientists a window on what happens in an individual's brain during craving.

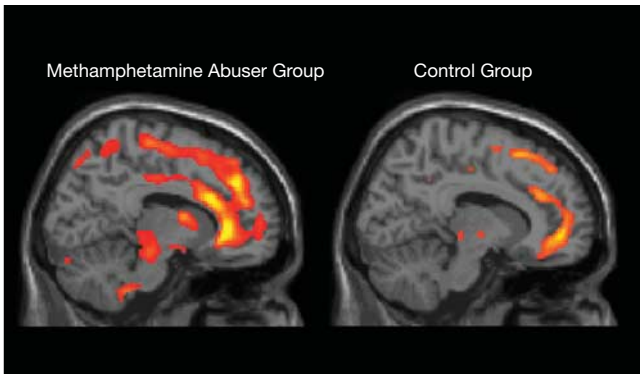
To probe this response, Volkow and her colleagues at Brookhaven National Laboratory used positron emission tomography (PET) scans to obtain an indirect measurement of dopamine levels in the brains of 18 cocaine-addicted individuals under two conditions: while watching videos of people buying and using cocaine and also while watching videos featuring nature scenes (Volkow et al. *J Neurosci*. 2006;26:6583-6588).

To gauge dopamine levels, the scientists injected each individual with a radiotracer that binds dopamine receptors in the brain and used PET to measure the signal produced by the receptor-bound radiotracers. Endogenous dopamine competes with the radiotracer to bind dopamine receptors, so as the brain releases molecules of endogenous dopamine and they bind to receptors, fewer molecules of the radiotracer are able to bind, and the signal weakens.

When the individuals viewed the cocaine-related video, their dopamine levels increased significantly compared with the levels released while they watched nature videos. The scientists noted the effect particularly in the ventral striatum, suggesting this region may play a key role in drug craving. Levels of craving reported by the participants also correlated with the levels of dopamine increase. Similar increases in dopamine levels in the ventral striatum have been documented in individuals exposed to food cues, suggesting that addiction hijacks the same pathways that make eating rewarding.

TARGETED TREATMENTS

New research also suggests that it may soon be possible to use genetics or other factors to target existing treatments to the individuals who may benefit the most from them. One existing drug that may be most effective when used in a targeted fashion is naltrexone.



Positron emission tomography scans reveal that low activity levels in the cerebral cortex, as measured by metabolism of radiolabeled glucose, are positively correlated (yellow areas) with depression in individuals who have abused methamphetamine (*Arch Gen Psych*. 2004;61:73-84).

The US Food and Drug Administration (FDA) approved oral naltrexone for the treatment of heroin addiction in 1984. Naltrexone blocks heroin from binding to opioid receptors and prevents individuals from experiencing the high associated with heroin use. Currently, it is used almost exclusively to treat physicians, nurses, and pharmacists with opioid addictions, said Charles O'Brien, MD, PhD, director of the Center for Studies of Addiction at the University of Pennsylvania in Philadelphia, at the symposium. A variety of factors, such as the need to take a daily pill and occasional adverse effects, such as nausea, have limited its use. In June, the FDA approved a lower-dose monthly injectable form of the drug. This formulation circumvents the liver and prevents nausea, and it also offers the benefit of less frequent administration.

The drug also has been used to treat alcoholism, but studies suggest it is most effective in individuals who have a strong family history of alcoholism, who experience euphoria when using alcohol, and who experience strong cravings (Monterosso JR et al. *Am J Addict*. 2001;10:258-268). These findings suggest that there may be a genetic basis for a patient's response to naltrexone.

Further evidence that some patients are predisposed to respond to naltrexone treatment came from a 2003 study of 141 patients randomly assigned to receive naltrexone (n=82) or placebo (n=59). The study found that patients with a variant of the gene encoding the μ-opioid receptor were more likely to benefit from the drug (Oslin DW et al. *Neuropsychopharmacology*. 2003;28:1546-1552). During 12 weeks of treatment, patients with 1 or 2 copies of the *Asp40* allele who were treated with naltrexone had a significantly lower rate of relapse or stayed abstinent longer if they did relapse than did those with 2 copies of the *Asn40* allele. A second group of scientists reported at the American College of Neuropsychopharmacology meeting in December that they had replicated these findings in patients participating in the Combining Medications and Behavioral Interventions (COMBINE) trial, O'Brien said.

The findings may have broader implications for physicians trying to select the best treatments for their patients. "Once we begin to correlate genotype with medication response, then physicians will be able to do a much better job of selecting the right medication from the beginning," O'Brien said.

MOOD-BOOSTING CIGARETTES

While much research on smoking has focused on the effects of nicotine, cigarette smoke contains 4000 chemical compounds, some of which also reinforce smoking behavior. This may explain why nicotine replacement therapies are often ineffective alone. In particular, some chemicals in cigarette smoke inhibit monoamine oxidase (MAO), an enzyme that breaks down neurotransmitters. Such inhibition may produce antidepressant effects, as MAO inhibitors are used to treat depression, said Joanna Fowler, PhD, director of the Center for Translational Neuroimaging at Brookhaven National Laboratory.

Using PET, Fowler and colleagues found that compared with controls, smokers have 40% lower levels of MAO in their brains and 35% to 45% lower levels in other organs, such as the heart, lungs, kidney, and spleen (Fowler JS et al. *Nature*. 1996;379:733-736, Fowler JS et al. *Proc Natl Acad Sci U S A*. 2003; 100:11600-11605). "We don't know the physiological implications, but we think it may account for the increased rate of smoking in diseases like depression," Fowler said.

The lower MAO levels also may account for smokers' lower risk for Parkinson disease. Fowler explained that when MAO breaks down neurotransmitters, it creates hydrogen peroxide, a source of damaging free radicals that may contribute to Parkinson disease; smokers with lower levels of MAO may thus have lower levels of free radicals.

Other groups are conducting clinical trials to determine whether certain MAO inhibitors may be useful in smoking cessation. A preliminary 8-week randomized placebo-controlled trial of selegiline hydrochloride showed promising results (George TP et al. *Biol Psychiatry*. 2003;53:136-143). Nine of 20 patients randomly assigned to receive selegiline hydrochloride were abstinent at 1 week vs only 3 of 20 patients given placebo, and 6 of the patients taking the drug were abstinent during the last 4 weeks of the trial compared with 1 patient in the placebo group. The scientists are currently conducting a larger trial, Fowler said.

Scientists have also recently isolated MAO-inhibiting chemicals in tobacco smoke (Khalil AA et al. *Bioorg Med Chem*. 2006;14:3392-3398). In this and previous studies, the scientists identified MAO-inhibiting effects of terpene *trans-trans*-farnesol in the rat brain and in human, baboon, monkey, dog, rat, and mouse livers. Such studies may lead to the development of smoking cessation treatments or neuroprotective agents.

BOOSTING INHIBITION

Brain imaging studies also are providing evidence that methamphetamine use may cause functional and structural deficits that interfere with users' ability to control negative emotions.

Edythe D. London, PhD, of the Semel Institute of Neuroscience and Biobehavioral Science at the University of California in Los Angeles, and colleagues have used PET scans and radiolabeled glucose to monitor and compare brain activity in methamphetamine-addicted individuals who have abstained from the drug for 4 to 11 days with that of controls (London ED et al. *Arch Gen Psychiatry*. 2004;61:73-84). They found abnormally low levels of activity (as measured by glucose metabolism) in the cerebral cortex that was related to symptoms of depression.

More recent findings by researchers from the University of California in Los Angeles provide more evidence that individuals who use methamphetamine lose the ability to control their negative

emotional responses. Using functional magnetic resonance imaging, the scientists measured brain activity in methamphetamine-dependent individuals and controls as they viewed emotionally charged images. The methamphetamine-dependent individuals reported a weaker emotional response to the images than did controls, but their scans revealed more activity in the amygdala, a region involved in regulating emotion. When asked to suppress their emotional response to the images, healthy individuals showed activity in part of the prefrontal cortex, but methamphetamine-dependent individuals did not.

London said the findings suggest that methamphetamine use leads to a loss of function in parts of the brain that control emotion. This, she said, may explain why methamphetamine users often are involved with serious crimes and violence and why they have difficulty abstaining. "It could be that they misinterpret environmental stimuli and react in a strong way," she said.

She and her colleagues are now studying whether modafinil, a drug used to treat narcolepsy, might help in treating methamphetamine dependence. The drug has been shown to improve inhibitory control in healthy individuals and in those with attention-deficit/hyperactivity disorder. Such a means to control a problematic symptom of methamphetamine abuse may improve the effectiveness of existing therapies, such as behavioral therapy. □

Whatever practical people may say, this world is, after all, absolutely governed by ideas, and very often by the wildest and most hypothetical ideas.
—Thomas Henry Huxley (1825-1895)