Role of Environment in Addiction Probed

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IT MAY NOT BE EASY AT THE TOP, BUT life at the bottom of the social hierarchy may make individuals more vulnerable to addiction, according to animal research that is helping to elucidate the role of environmental factors in addiction.

In fact, having a less stressful, more privileged environment may provide a degree of protection from addiction or relapse during recovery, according to a recent review of the role of environment in addiction (Nader and Czoty. *Am J Psychiatry*. 2005;162:1473-1482). Using advanced brain imaging techniques, scientists have shown that environmental factors have lasting effects on brain receptors known to be altered by drug abuse, providing a possible molecular basis for the chronic relapsing nature of addiction and suggesting possible targets for treatment.

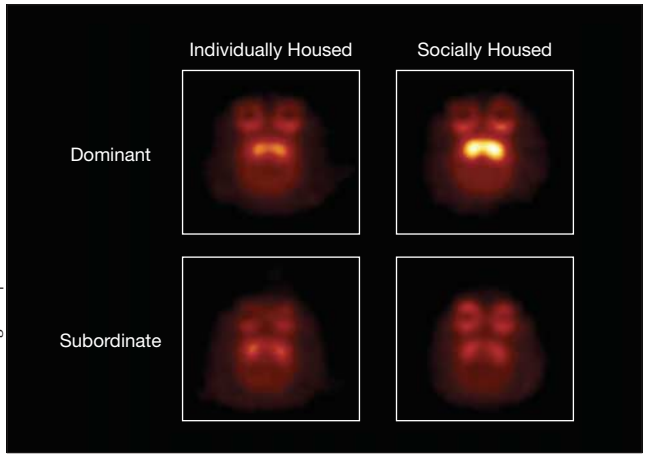
A MONKEY MODEL

Because ethical and practical considerations make it difficult to sort out the interactions between environmental factors and addiction in humans, scientists have turned to animal models to search for clues. One such model, developed by Michael A. Nader, PhD, of Wake Forest University, in Winston-Salem, NC, and colleagues, involves studying the interactions between cocaine use by cynomolgus monkeys and the stressors the animals encounter living in a hierarchical social group. The arrangement allows researchers to first measure baseline levels of D_2 dopamine receptors (in drug-naive, individually housed animals) and then monitor changes that occur in levels of these receptors when each monkey is introduced to a group-living situation and takes its place in the social hierarchy. Receptor levels are also measured while an animal self-administers the drug by pressing a lever to release an intravenous dose of cocaine, as well as during abstinence and relapse.

Using this model, Nader and his colleagues found that subordinate monkeys were more likely than dominant monkeys to use cocaine and use it in higher quantities, although prolonged exposure to the drug seems to erase this difference. Imaging studies revealed these effects were directly correlated with D_2 dopamine receptor levels in the animals' brain. Monkeys that become dominant in the social hierarchy develop more D_2 receptors, while subordinate monkeys maintain the number of D_2 receptors they had at baseline.

Over time, as the monkeys abuse cocaine, both groups lose D_2 receptors. After several months of abstinence, the numbers of D_2 receptors in the dominant monkeys, but not the subordinate monkeys, begin to rebound.

Nader hypothesizes that the dominant monkeys' enriched lifestyle—more treats, more freedom to move about the pen, and more grooming from subordinate monkeys—boosts the number of dopamine receptors in the brain. He suggests that the increase in dopamine receptors makes the animals less vulnerable to the reinforcing effects of cocaine, which could translate to reduced likelihood of relapse. In tests meant to mimic relapse, abstinent monkeys that are administered cocaine by researchers resume cocaine-seeking activities they had stopped during abstinence. And in tests in which "relapsed" monkeys given high doses of cocaine are given choices between food reinforcement and cocaine-seeking activity that does not produce a dose of cocaine, the subordinate monkeys were more likely than the dominant monkeys to choose cocaine-seeking behavior. Although this is a widely used model of relapse in animals, its ability to predict human outcomes is unknown. Nader and colleagues are also exploring whether drug



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The environment may alter cocaine's reinforcing effects by dysregulation of the dopaminergic system. An imaging study of dominant and subordinate monkeys housed alone or together shows effects of environment on levels of dopamine D_2 receptors (Morgan et al. *Nat Neurosci*. 2002;5:169-174).

treatment or manipulating environmental variables can boost the subordinate monkeys' D_2 receptor levels.

"It's basically telling us that the brain is plastic; it changes in response to environment and it changes in response to chronic exposure to drugs like cocaine," said David Shurtleff, PhD, director of the division of basic neuroscience and behavioral research at the National Institute on Drug Abuse, in Bethesda, Md.

Human studies also have linked the number of D_2 receptors an individual has with his or her vulnerability to the reinforcing effects of a drug. In one such study, individuals who reported they experienced pleasurable feelings after taking a dose of methylphenidate (a stimulant used to treat attention-deficit/hyperactivity disorder) had significantly fewer D_2 receptors than individuals who reported unpleasant feelings after taking a dose (Volkow et al. *Am J Psychiatry*. 1999;156:1440-1443).

TREATMENT STRATEGIES

Such findings suggest the possibility that pharmaceutical or behavioral therapies that increase the brain's D_2 receptors may be an effective treatment for drug abuse, Shurtleff said. A recent study by Panayotis K. Thanos, PhD, a neuroscientist at Brookhaven National Laboratory, in Upton, NY, provides some support for this hypothesis (Thanos et al. *Life Sci*. 2005;77:130-139). He used a genetically modified adenoviral vector to deliver into alcohol-using mice a rat gene that codes for D_2 dopamine receptor. Mice treated in this manner reduced their alcohol intake.

While the findings provide some intriguing insights, many questions remain to be answered before they can be translated into effective clinical interventions, Shurtleff said. Does the brain completely recover from chronic cocaine use? If so, how long does it take? And are there ways to facilitate a return to normal function or accelerate the process? "We're really at an early stage in understanding how the brain is changed by drugs of abuse," he said.

The findings do, however, emphasize the importance of long-term abstinence in recovery.

"To recover from drug abuse can take an extremely long period of time," Shurtleff said, pointing out that even after 7 months of abstinence, the monkeys' brain levels of D_2 receptors have not returned to normal.

Although the dopamine system plays an important role in addiction, other factors, such as the glutamate and γ-aminobutyric acid receptors, are likely to be involved as well, Shurtleff said. It is important for scientists to understand how these systems interact with each other and the environment to contribute to drug addiction. "We need to broaden our research—and we are—to get a complete picture of the disease," he said. □