Protective Factors May Prevent Alcoholism

Bridget M. Kuehn

Sophisticated brain imaging techniques have helped scientists identify factors that may protect an individual with a genetic predisposition to alcoholism from developing the disorder.

A multi-institution team of scientists has discovered that high levels of certain receptors in the human brain that regulate dopamine, a chemical involved in the brain's reward circuitry, may counteract a genetic predisposition to alcoholism (Volkow ND et al. *Arch Gen Psychiatry*. 2006;63:999-1008). The findings add to a growing body of evidence from human and animal studies that suggest that D_2 dopamine receptors and dopamine play an important role in alcoholism and other addictions. They also suggest that medical or environmental interventions that boost D_2 receptor levels may be potential treatments.

BRAIN CHEMISTRY

Alcoholism has a strong genetic component, accounting for 50% to 60% of the risk of developing the disorder (McGue M. *Curr Dir Psychol Sci*. 1999; 8:109-115). But alcohol dependence also has a strong environmental component. To sort out the relative contributions of these types of risk factors, scientists have focused on how brain chemistry correlates with alcohol use.

Through such studies, researchers have demonstrated that individuals with alcoholism or other addictions have low levels of D_2 dopamine receptors. These findings have led scientists to postulate that low levels of D_2 dopamine receptors could increase an individual's susceptibility to addiction or, conversely, that high levels of D_2 dopamine receptors could have a protective effect.

To test the latter hypothesis, the investigators used positron emission tomographic imaging to measure D_2 dopamine receptor levels in individuals with 3 first- or second-degree relatives with alcoholism (excluding their mother, because of potential effects of maternal drinking during pregnancy) but no personal history of drug abuse or dependence. Compared with controls (study participants with no family or personal history of drug abuse or dependence), these individuals had higher levels of D_2 dopamine receptors.

The team also found a correlation between higher D_2 receptor levels and higher metabolism in the frontal regions of the brain, areas that control inhibitory and emotional responses. These findings suggest that improper regulation of these regions by dopamine in addicted individuals "may underlie their loss of control and compulsive drug intake," the team noted.

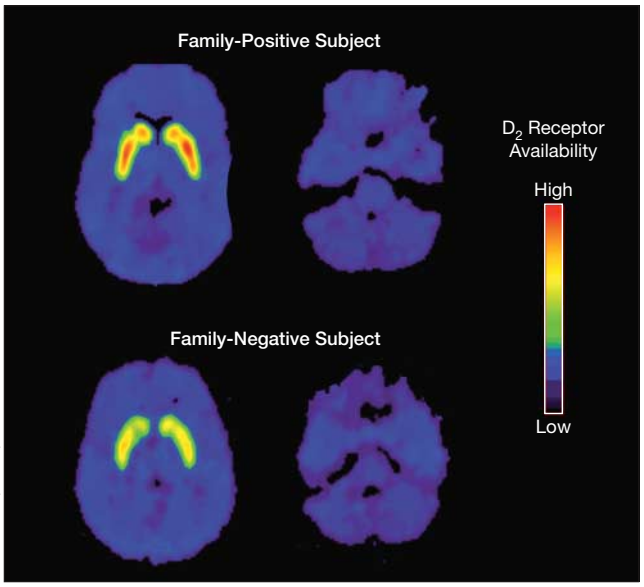
The study did, however, have a few important limitations. First, it did not exclude smokers using less than a pack a day, although the researchers found no significant differences between smokers and nonsmokers in the study. The study also did not verify whether the participants with family histories of alcohol abuse actually inherited a gene or genes that would predispose them to the disorder. Finally, the average age of the individuals in the study was 25 years, so it is possible that some of the study participants could develop the disorder later in life.

Michael A. Nader, PhD, of Wake Forest University in Winston-Salem, NC, said the findings fit very well with much of the previous work done in humans or animals. For instance, rats, even those that have been selectively bred to prefer alcohol, reduced their intake when treated with a gene (delivered by a virus) that boosts the number of D_2 dopamine receptors in their brains (Thanos PK et al. *Alcohol Clin Exp Res*. 2004;28720-728). And humans who have high levels of D_2 dopamine receptors report adverse responses to stimulant drugs (Volkow ND et al. *Synapse*. 2002;46:79-82).

"The interesting thing will be to determine why they have higher levels of D_2 dopamine receptors," Nader said.

ENVIRONMENTAL INFLUENCE

Evidence from animal studies suggests that environmental factors may upregulate D_2 receptor levels in the brain and reduce the abuse of drugs. Nader and colleagues have demonstrated that achieving high social status and having a lifestyle with low stress can increase D_2 receptor levels and reduce drug use in cynomolgus monkeys (Nader MA and



Arch Gen Psychiatry. 2006;63:999-1008

New research has revealed that individuals who have a family history of alcoholism but do not develop the disorder (family-positive) themselves have higher levels of dopamine D2 receptors available than do normal (family-negative) controls. This finding suggests these receptors may have a protective effect.

Czoty PW. *Am J Psychiatry*. 2005;162:1473-1482). Monkeys that have been trained to self administer an intravenous dose of cocaine by pressing a lever are more likely to administer the drug if they are lower in the social hierarchy. Moreover, although prolonged drug use reduces D_2 receptor levels in both dominant and subordinate monkeys, D_2 levels in dominant animals begin to rebound after several months of abstinence while those of subordinate monkeys do not.

This growing body of evidence suggests that interventions that boost D_2 dopamine receptors, whether drugs or other therapies, may help treat alcoholism or other addictions or may help protect individuals who have a genetic predisposition from developing these disorders.

Drug interventions may be problematic because of the complexity of the dopamine system, said Gene-Jack Wang, MD, of the Brookhaven National Laboratory in Upton, NY, and a member of the research team. However, environmental interventions have shown promise. For instance, exercise has been shown to boost D_2 dopamine receptor levels, Wang said. And, as Nader's studies suggest, boosting an individual's positive social interactions might be another approach.

Perhaps the most important finding of the study is the hopeful message it sends individuals with a family history of alcoholism.

"This study helps us understand the fundamental nature of the behavior of alcoholism," Wang said. "Just because a person is born with a genetic predisposition to alcoholism doesn't mean that's it. There are things that can help them." □

Guidelines: Community Support Vital to Promote Cancer-Preventing Lifestyle

Bridget M. Kuehn

THE AMERICAN CANCER SOCIETY has released five new guidelines for cancer prevention that emphasize the importance of maintaining a healthy weight, boosting physical activity levels, and implementing community-based interventions that promote healthy lifestyles. The guidelines were produced by a national panel of experts who reviewed the scientific evidence to date (Kushi LH et al. *CA Cancer J Clin*. 2006;56:254-281).

To stay current, the guidelines are revised every 5 years. This year's guidelines call for a higher level of physical activity than has been recommended previously and continue to emphasize weight control, a healthy diet, and community support.

Lifestyle factors have a significant influence on cancer risk. One third of the more than 500 000 cancer deaths that occur in the United States each year can be attributed to exposure to tobacco products, according to the panel's report. Another third of the cancer deaths is attributable to diet and physical activity habits. In light of these data, the first four guidelines outline specific lifestyle actions individuals can take to reduce their cancer risk. These include

- Maintaining a healthy weight throughout life by balancing caloric intake with physical activity
- Adopting a physically active lifestyle
- Consuming a healthy diet emphasizing plant-based foods
- Limiting consumption of alcoholic beverages to no more than 1 drink per day for women and 2 drinks per day for men.

This year's guidelines boost the recommended physical activity levels to at least 30 minutes of moderate to vigorous physical activity above and beyond normal daily activities on 5 or more days per week. Previous recommendations included normal daily activities in the 30-minute window; however, typical daily activities are often of low intensity and may not provide enough benefit, according to the panel. In fact, the new recommendation states that lengthening the time engaged in moderate to vigorous physical activity to between 45 and 60 minutes per day may offer even greater benefits.

The fifth guideline recognizes that some factors are outside of an individual's control and require community interventions. For instance, longer workdays and more households with two wage earners reduces time for food preparation and increases families' reliance on convenience foods that may be less nutritious than homemade foods. Additionally, physical activity can be hampered by a lack of neighborhood sidewalks and recreation areas. To address these factors, the guidelines encourage public, private, and community organizations to increase the availability of healthy foods in schools, workplaces, and communities and provide safe, enjoyable, and accessible places for physical activity.

"For years, we've told people what habits to adopt to lower their cancer risk, but it has become increasingly clear we need to create environments that make it easier to make healthy choices," said Colleen Doyle, MS, RD, director of nutrition and physical activity for the American Cancer Society and a member of the panel. "These guidelines underscore what communities can and should be doing to make those healthy habits achievable." □