The Mosaic of Addiction

The articles by Petrakis et al. and Heinz et al. in this issue add to our understanding of the mechanisms by which genes and the environment interact to produce alcoholism and other forms of drug addiction. Petrakis et al. report that the *N*-methyl-D-aspartic acid receptor antagonist ketamine causes less dysphoria and somewhat more euphoric responses in healthy young people with a family history of alcoholism than in subjects from families with no alcoholism. This is an important clue in the search for biological factors that increase the vulnerability for alcoholism. Previous studies have reported other biological differences between comparison subjects and individuals with a family history of alcoholism, who are, of course, at high risk for the development of alcoholism. One of these differences with therapeutic implications is the response of the endogenous opioid system to alcohol (1). Compared with those with negative family histories, the relatives of alcoholics have a lower baseline plasma β-endorphin level and a much larger endorphin response to test doses of alcohol. While the plasma endorphin response is not a measure of CNS activation of the endogenous opioid system, we know from animal data that alcohol activates the endogenous opioid system centrally. Animal models of excessive drinking, which have been predictive of clinical response, have shown that alcohol, like other drugs of abuse, stimulates the release of dopamine in the ventral striatum. This alcohol-dopamine activation is believed to involve the endogenous opioid system because it is specifically blocked by pretreatment with an opiate receptor antagonist (2). Blocking opiate receptors has also been reported to block the stimulation or euphoria produced by alcohol in volunteers with a family history of alcoholism (3) and to reduce the "high" produced by alcohol in patients who "slip up" during clinical trials for the treatment of alcoholism (4).

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The report by Heinz et al. describes reduced dopamine D_2 receptor availability in recently detoxified alcoholics. While the authors consider the possibility that this is an adaptive down-regulation produced as a response to prior high dopamine levels triggered by repeated alcohol ingestion, it is also possible that this is a preexisting (inherited) difference. Low D_2 availability would be consistent with the report that methylphenidate, which increases synaptic dopamine by blocking the reuptake transporter, produces more enjoyment of the drug and increased dopamine release in nonaddicted comparison subjects with low D_2 receptor availability (5). Thus, the difference reported by Heinz et al. could make individuals with a family history of alcoholism more sensitive to alcohol reward and more vulnerable to the development of alcoholism. Cocaine addicts, too, have low D_2 receptor availability, which, like the findings reported in alcoholics, could be a reaction to high dopamine or a vulnerability factor that increases euphoria and the risk of developing addiction to the drug. Of those exposed to alcohol, only 10%–15% become dependent. For cocaine, the risk is 16% (6). Thus, only a minority of those exposed to drugs become dependent, and one of the many variables influencing the progression toward addiction may be the inherited availability of D_2 receptors.

The finding by Heinz and colleagues of an inverse correlation between the severity of cue-stimulated alcohol craving and D_2 receptor availability in the ventral striatum is consistent with both animal models and previous human studies aimed at elucidating the mechanisms of alcohol dependence. In rodent models of alcohol drinking, rein-

statement of the behavior after abstinence is provoked by cues previously associated with alcohol availability. This cue-induced reinstatement (arguably a model of craving) involves the endogenous opioid-dopamine system because it is blocked by naltrexone (7). Furthermore, in human alcoholics exposed to alcohol cues, the craving response is significantly reduced by naltrexone (8). Thus, there is remarkable consistency among animal models, human laboratory studies, and data from clinical trials.

Alcoholism is such a complex disorder involving multiple environmental, familial, and biological factors that it is a source of wonderment that a simplistic animal model could predict success in the clinic. However, two effective medications have developed from these models: naltrexone and acamprosate. Acamprosate, although available in Europe for more than a decade, was just approved in the United States, and naltrexone, although approved for alcoholism since 1995, is grossly underused. Many clinicians probably are not aware that the majority of double-blind clinical trials show a significant advantage for this medication in preventing relapse. Unlike antidepressants, in which there is a commercial reason for selective publication of positive studies, naltrexone is generic and not highly profitable. Thus, negative trials of naltrexone for this complex disorder are just as likely to be published as are positive studies. Perhaps one of the reasons that medications are not routinely used to prevent alcohol relapse lies in the notion that total abstinence is the only desirable goal and a medication that blocks some of the rewarding properties of alcohol is dismissed as a "crutch." Given the devastation produced by repeated relapses and the accumulating evidence of a biological basis for many—if not most—forms of alcoholism, perhaps a crutch is medically and morally justified.

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