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Controversial drug shown to act on brain protein to cut alcohol use

A naturally occurring hallucinogen advocated by some clinicians as a potent anti-addiction drug has been rigorously studied for the first time, confirming its ability to block alcohol craving in rodents, and clarifying how it works in the brain. The new research findings about the drug Ibogaine open the way for development of other drugs to reverse addiction without Ibogaine's side effects, potentially adding to the small arsenal of drugs that effectively combat addiction.

Derived from a West African shrub, Ibogaine has been championed for years by a cadre of clinicians and drug treatment advocates impressed with its ability to reverse withdrawal symptoms and craving for alcohol and various drugs of abuse. It has been used outside of the U.S. to treat addiction by American and other clinicians. But its side effects, including hallucinations, which made it popular in the 1960s drug culture, and evidence of toxicity to certain nerve cells in rodent studies have discouraged careful studies of its clinical potential against drug and alcohol addiction. The FDA has not approved use of Ibogaine in the U.S.

Scientists at UCSF's Ernest Gallo Clinic and Research Center have now shown definitively in experiments with mice and rats that Ibogaine does reduce alcohol consumption, and they have determined that it does so by increasing the level of a brain protein known as glial cell line-derived neurotrophic factor, or GDNF. In a separate study, they demonstrated that GDNF by itself decreases alcohol consumption.

The research is being published in the January 19 issue of The Journal of Neuroscience.

"By identifying the brain protein that Ibogaine regulates to reduce alcohol consumption in rats, we have established a link between GDNF and reversal of addiction -- knowledge of a molecular mechanism that should allow development of a new class of drugs to treat addiction without Ibogaine's side effects," said Dorit Ron, PhD, UCSF associate professor of neurology and also principal investigator at the Gallo Center. Ron is co-senior author of the paper with Patricia Janak, PhD, UCSF assistant professor of neurology and also principal investigator at the Gallo Center.

In their research, the scientists first carried out classic behavioral studies showing that Ibogaine reduced alcohol consumption. They induced the rats to consume alcohol in daily drinking sessions and then demonstrated that their drinking declined precipitously when they received Ibogaine. The drug was administered either by injection or directly into the same brain region where GDNF levels were shown to increase.

The research also showed that Ibogaine was quite effective in preventing relapse, or "falling off the wagon" -- the vulnerability of recovered alcoholics or addicts to return to uncontrolled drinking or drug use when exposed to the drug of abuse months or even years after breaking the habit.

In this analysis, the researchers provided alcohol to rats until they had become "experienced" daily drinkers. They then withheld alcohol for two weeks, which normally leads to greatly increased drinking when when alcohol is again available. When they administered Ibogaine, they found that the heightened craving and consumption was significantly reduced.

"The discovery that Ibogaine reduced binge drinking after a period of abstinence was an exciting finding for us because this is the type of behavior in alcoholics for which very few effective drugs exist," Janak said.

The scientists confirmed in a cell model that Ibogaine stimulated GDNF activity. Finally, they showed that a known inhibitor of GDNF blocked Ibogaine's ability to decrease alcohol craving in the rats, suggesting a direct link between Ibogaine's desirable actions and GDNF.

"If we can alter the GDNF pathway, we may well have a new treatment against alcohol and drug addiction without the unwanted side effects of Ibogaine," Ron said.

Colleagues in the research and coauthors on the paper are postdoctoral fellows Dao-Yao He, PhD, Nancy N.H. McGough, PhHD; Ajay Ravindranathan, PhD; Jerome Jeanblanc, PhD; Marian Logrip, BA, UCSF neurology graduate student; and Khanhky Phamluong, BA, research associate, all at the Gallo Center.

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