Team reports hormone disorder drug could help drinkers stay sober

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A drug prescribed for male and female infertility and menstrual disorders could hold the key to a more effective treatment for alcoholism, according to a study by researchers at the UCSF-affiliated Ernest Gallo Clinic and Research Center.

The study showed that "alcoholic" rodents, when injected with the drug cabergoline, decreased their alcohol consumption and alcohol-seeking behavior and were less likely to relapse.

Cabergoline, which is marketed under the trade name Dostinex, is approved by the Food and Drug Administration in pill form to treat conditions caused by excess of the hormone prolactin.

The study, led by Dorit Ron, PhD, a principal investigator at the Gallo Center and associate professor of neurology at UCSF, is now on line (February 20, 2009), in the journal "Biological Psychiatry."

Notably, cabergoline did not impact the rats' consumption of sucrose and, in a subgroup of binge-drinking mice, the drug did not appear to significantly affect intake of water or saccharin.

"This is encouraging," says Ron, "because it demonstrates that cabergoline is specific for alcohol, but does not affect general reward or pleasure. One of the problems with some existing drugs to treat alcoholism is a side effect that decreases pleasure, making compliance an obstacle to sobriety."

The research builds on an earlier, provocative finding by Ron and her colleagues regarding the protein GDNF (glial cell line-derived neurotrophic factor), which they had injected into rats' VTA (ventral tegmental area) brain region, associated with drug-seeking behavior.

In this earlier study, the scientists had trained rats to consume alcohol. Some, like humans, drank in moderation, while others binged. But when GDNF was administered, both heavy and light drinkers lost at least some of their craving for alcohol. This effect became apparent within 10 minutes and lasted at least 24 hours, the scientists discovered. Importantly, administration of GDNF into the brain prevented the rats from relapsing after a period of abstinence.

While the discovery broke new ground, the scientists knew that GDNF could not be used to treat alcoholic humans because its molecule is too large to cross the blood-brain barrier. So, in the present study, Ron and her colleagues looked at cabergoline, a compound that has been shown in cells to increase the expression of GDNF.

After establishing that cabergoline treatment resulted in an increase of the level of GDNF and activation of the GDNF pathway in the rats' VTA, the researchers sought to test its impact on rodents' drinking habits.

Rats underwent a two-month training program in which they learned to press a lever to obtain alcohol. Researchers found that when rats were injected with cabergoline, they were less likely to press the lever. The higher the dose of cabergoline, the lower the number of lever presses reported. The researchers also found that binge-drinking mice consumed less alcohol after cabergoline administration.

In further study, the researchers found that cabergoline was effective in reducing both craving for alcohol and relapse to drinking. Relapse is a

critical issue for alcoholic patients trying to stay abstinent.

As further evidence of the interplay between cabergoline and GDNF, alcohol intake was tested on mice that had been genetically engineered to have a single copy of the GDNF gene, and therefore less GDNF in the brain. As expected, the scientists found that the drinking habits of these genetically modified mice were not affected by cabergoline.

Although the results of the study offer fresh hope to problem drinkers, Ron cautions that human clinical trials are needed before cabergoline can be safely prescribed. Higher doses of cabergoline have been used to treat Parkinson's disease and have been linked to heart valve problems.

"However," notes Ron, "we show that in mice and rats, a low dose of the drug is enough to reduce excessive alcohol consumption, alcohol seeking and relapse. The dose is similar to what is given to humans for the treatment of hyperprolactinemia."

Cabergoline may eventually be prescribed for other addictions. A pilot study conducted on cocaine addicts, cited in Ron's paper, reported a substantial reduction in cocaine use.

In the United States, 17.6 million people -- approximately one in every 12 adults -- abuses alcohol or is alcohol-dependent, according to the National Institutes of Health. But there are just three medications approved to treat alcohol dependence -- disulfiram (Antabuse), naltrexone (Depade, ReVia), and acamprosate (Campral).

Source: University of California - San Francisco