A synthetic derivative of the kudzu vine can reduce drinking and prevent relapse

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Kudzu extracts have been used in Chinese folk medicine to treat alcoholism for about 1,000 years. Daidzin is an anti-drinking substance in kudzu. A synthetic form of daidzin, called CVT-10216, can successfully reduce drinking and prevent relapse in preclinical rodent models.

Kudzu and its extracts and flowers have been used in traditional Chinese folk medicine to treat alcoholism for about 1,000 years. Kudzu contains daidzin, an anti-drinking substance. Daidzin inhibits human aldehyde dehydrogenase 2 (ALDH-2), which metabolizes alcohol into acetaldehyde. Inhibiting ALDH-2 promotes the accumulation of acetaldehyde, which has aversive effects. A recent test of a synthetic ALDH-2 inhibitor (CVT-10216) on rodents shows that it reduces drinking and prevents relapse by increasing acetaldehyde while drinking and later decreasing dopamine in the brain region that controls relapse during abstinence.

Results will be published in the November issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"I think the over-arching issue here is medical treatment," said Ivan Diamond, vice president of neuroscience at Gilead Science, Professor Emeritus of neurology, cellular and molecular pharmacology and neuroscience at the University of California, San Francisco, and corresponding author for the study.

"Alcoholism is a medical disorder, not just a problem of will power," he said. "Physicians treat medical disorders in order to prevent harm, while not necessarily curing the disease being treated - for example, drug treatment of hypertension, statins for high cholesterol, insulin for diabetes - and the same will become true for treating alcoholism. Heavy drinking causes harm. We need to prevent heavy drinking in order to prevent harm."

Diamond added that relapse may be the biggest problem facing physicians today. "We are talking about a patient who has the motivation to undergo a very unpleasant detoxification to try to stop drinking, and then gets into trouble afterward," he said. "Nearly 80 percent of abstinent alcoholics or addicts relapse within a year. Current therapies for alcoholism help, but we can do much better."

"Extracts of various parts of the kudzu vine have been used in many Chinese herbal medicine formulas and are said to be helpful in treating a variety of maladies, including alcoholism and intoxication," said Ting-Kai Li, a professor in the department of psychiatry at Duke University Medical Center, and former director of the National Institute on Alcohol Abuse and Alcoholism. "Recent research has found that several compounds of the isoflavone family - puerarin, daidzin, daidzein - in the kudzu extract decrease alcohol intake in experimental animals."

"Drs. Wing Ming Keung and Bert Vallee at Harvard were the first to confirm kudzu's effects and isolate daidzin as the most potent of the isoflavones in kudzu," added Diamond. "They went further by searching for the basis of daidzin's anti-drinking properties, discovering that daidzin was a selective inhibitor of ALDH-2. Based on x-ray crystallographic studies of daidzin binding to ALDH-2, our team set out to design a compound that would interact more efficiently with ALDH-2, finally choosing CVT-10216 as our best candidate to date."

Diamond and his colleagues administered CVT-10216 to groups of rats bred for moderate and high levels of drinking, after having exposed them to various scenarios of alcohol administration: two-bottle choice, deprivation-induced drinking, operant self-administration, and cue-induced reinstatement. The researchers then tested for blood acetaldehyde levels, alcohol-induced dopamine release in the nucleus accumbens, and effects of the inhibitor on drinking behavior and relapse.

"We had several key findings," said Diamond. "We found that, one, CVT-10216 is a highly selective reversible inhibitor of ALDH2 without apparent toxicity. This means that it does not cause serious damage to other proteins and functions. Two, treatment with our ALDH-2 inhibitor increases acetaldehyde in the test tube and in living animals." Acetaldehyde's aversive effects can include a flushing reaction and feeling ill, which tend to reduce drinking. "And three, we found that our ALDH-2 inhibitor suppresses drinking in a variety of rodent drinking models."

But that's not the whole story, Diamond added. "Most importantly, we also found that CVT-10216 prevents the usual increase in drinking (binge drinking) that occurs after five days of abstinence, and also prevents relapse to drink, even when alcohol is not present. This means that something else besides acetaldehyde helps to suppress craving for, and prevent relapse to, drinking alcohol. We believe that 'something else' is dopamine." He said that current concepts suggest that increased dopamine in the nucleus accumbens drives craving and relapse into drinking.

"Alcohol-induced increases in dopamine in the nucleus accumbens are prevented by CVT-10216 in a dose-dependent manner," said Diamond. "This means the drug has a therapeutic effect in the brain, probably on the desire to drink. Importantly, CVT-10216 does not reduce basal

dopamine levels when there is no stimulation to increase dopamine levels. This is consistent with our findings that CVT-10216 does not appear to affect moderate drinking, and does not have adverse side effects at the therapeutic doses used."

"The findings show promise that CVT-10216 might be better tolerated than Antabuse™," said Li. "How this happens is yet unknown, but suggests that the compound may be useful in treating alcohol relapse and perhaps for other psychoactive, potentially addictive compounds."

Diamond agreed: "Disulfiram or Antabuse™ has been around for 50 years," he explained. "It is called an ALDH-2 inhibitor, but it actually inhibits far more than that. Most believe that disulfiram would not be approved today as a new drug for alcoholism because of its many toxicities. Instead, we have developed CVT-10216, a reversible inhibitor with a very favorable profile, so far." Diamond hopes this novel compound will become an effective therapeutic agent for alcoholism.

"The goal of medicine is harm reduction," emphasized Diamond. "Excessive drinking causes harm while moderate drinking appears to be safe. Increasing numbers of doctors believe abstinence is an unrealistic goal. It sounds like heresy, but it isn't. Therefore, an ideal drug might be able to prevent uncontrolled relapse, convert heavy drinkers into moderate drinkers, and avoid the harmful consequences of excessive alcohol intake. If our compound works and is safe to use, then I think most physicians would not hesitate to prescribe a new drug to prevent relapse and reduce heavy drinking. My goal is to make this happen."

Source: Alcoholism: Clinical & Experimental Research