MedicalXpress

Protein controls both alcohol craving and organ damage

February 11 2015

What if there was a drug that could simultaneously curb a person's craving for alcohol while also protecting their heart and liver from alcohol's damaging effects? While an actual pill that can do this might be a ways off, the results of a new study from researchers at the University of Iowa suggest that it might be potentially possible.

The team led by Rory Fisher, Ph.D., professor of pharmacology in the UI Carver College of Medicine, has identified a protein called RGS6 (regulator of G protein signaling 6) that acts through two separate mechanisms to control alcohol-seeking behavior and alcohol-induced cell death in heart, liver, and other organs.

"Given the prevalence of alcohol abuse worldwide there is a clear need for more effective therapeutics," Fisher says. "We propose that inhibiting this RGS6 protein could represent a new approach to counteract alcohol dependence and at the same time protect against the cell-killing actions of alcohol in the heart and liver."

In the U.S., alcohol abuse or dependence affects 20 percent of women and 40 percent of men in their lifetimes. In addition to the social costs of alcohol misuse, including traffic accidents and violent crime, chronic alcohol use also takes a heavy toll on an individual's health, causing lasting and sometimes irreversible damage to the heart and liver as well as other organs.

Previous work from Fisher's lab had suggested that RGS6 might be

important in signaling pathways in the brain that appear to be involved in addiction and alcohol dependence. In addition, their studies also had implicated the protein in pathways that controlled cell death in heart muscle.

In the new study published Feb. 2 in the online Early Edition of the *Proceedings of the National Academy of Sciences* (*PNAS*), the UI team, including first author Adele Stewart, Ph.D., used mice lacking RGS6 to probe the protein's roles in both alcohol craving and organ damage. The researchers found that mice without the RGS6 protein consumed less alcohol than wild-type mice when given free access. The mice without RGS6 also were less susceptible to alcohol-induced reward and had less severe and shorter-lived alcohol withdrawal symptoms.

At the same time, when mice that lacked the RGS6 protein were treated chronically with alcohol, they experienced less damage to heart and liver as well as the lining of the gut compared to mice with the protein.

"To our knowledge RGS6 is the only gene with a demonstrated ability to promote alcohol-seeking behaviors while simultaneously worsening the damaging effects of alcohol consumption on the heart, stomach, intestine and liver," Fisher says.

The study showed although the same protein is involved in these two different effects, the biological mechanisms that produce the effects are different. In the brain, RSG6 is involved in alcohol craving by controlling levels of dopamine, a neurotransmitter associated with addiction and reward-seeking behavior. In the heart and liver, RSG6's effect is based on its role in a pathway that causes cell death through production of damaging compounds called reactive oxygen species.

There currently are only a few drugs that purport to treat alcohol dependence and none that treat the damaging effects alcohol has on

various organs. The UI study suggests that targeting the actions of RGS6 might accomplish both aims. However, given that the protein works its dual effect through very different biological pathways, separate drugs may be required to treat the two health problems.

In addition to Fisher and Stewart, the research team included Biswanath Maity, Simon Anderegg, Chantal Allamargot, and Jianqi Yang.

Provided by University of Iowa