Study identifies genes associated with binge drinking

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University of Maryland School of Medicine researchers have identified two genes associated with binge drinking that may open doors to new, more effective treatments for excessive alcohol drinking. The scientists found that manipulating two receptors in the brain, GABA receptors and toll-like receptor 4 (TLR4), "caused profound reduction" of binge drinking for two weeks in rodents that had been bred and trained to drink excessively. The study was published online the week of Feb. 28 in the journal the *Proceedings of the National Academy of Sciences*.

About 30 percent of Americans who drink do so excessively, and about 75,000 people die each year from the effects of excessive drinking. Current treatments for excessive alcohol drinking include prescription drugs Revia and Campral for controlling cravings. To ease withdrawal symptoms, doctors often prescribe medications such as Valium and Librium that carry their own risks of addiction. Valium and Librium reduce the anxiety alcoholics feel when they stop drinking but do not reduce cravings for alcohol.

The new study found that treatments that manipulate both the GABA receptor and toll-like receptor 4 have the potential to reduce anxiety and control cravings, with little to no risk for addiction, according to lead investigator Harry June, Ph.D., professor of psychiatry and pharmacology and experimental therapeutics at the University of Maryland School of Medicine. The study was funded in part by the National Institute on Alcohol Abuse and Alcoholism, part of the National Institutes of Health.

"Binge drinking — defined as achieving a blood-alcohol content of .08 g percent, the legal limit in many states, in a two-hour period — is a serious form of excessive drinking," says Dr. June. "This is the kind of drinking we see with college students on spring break, and even some adults. It doesn't meet the classic definition of alcoholism, characterized by dependence and a long period of drinking followed by withdrawal. But binge drinking carries the same serious health risks as other types of excessive drinking: Cancer, heart disease and, most notably, the serious public health issue of vehicle accidents."

In the study, Dr. June and senior author Laure Aurelian, Ph.D., professor of pharmacology and experimental therapeutics and microbiology and immunology at the University of Maryland School of Medicine, examined the effect of alcohol on the GABA receptor and TLR4. GABA receptors are a class of receptors in the brain that react to the neurotransmitter GABA and act as inhibitory receptors, calming down or inhibiting the activity of neurons in the brain. GABA receptors react to alcohol, giving drinkers a calm and euphoric feeling and reinforcing excessive drinking behavior. Dr. June has long been interested in the role GABA receptors play in alcoholic drinking. This is the first scientific study to document GABA receptors' key involvement in binge drinking specifically, though scientists already believed that the receptors had a role in excessive drinking in general.

"The University of Maryland School of Medicine employs a dual approach to addiction and substance abuse, providing treatment for those struggling with addiction through its Division of Alcohol and Drug Abuse, as well as invaluable scientific research into the biological roots of addiction and alcoholism," says E. Albert Reece, M.D., Ph.D., M.B.A., vice president for medical affairs for the University of Maryland and the John Z. and Akiko K. Bowers Distinguished Professor and dean of the School of Medicine. "We hope that basic science discoveries such as this one will translate rapidly into better treatments to

improve the lives and health of those struggling with alcohol, and address the serious public health issue of addiction and substance abuse."

One of the study's most novel findings concerns TLR4's important role in binge drinking. Science has traditionally considered TLR4 to be an innate immunity receptor involved with neuroinflammation in the brain. Scientists associated TLR4 with microglia, cells that support inflammatory responses in the brain. "What makes this finding particularly important for the field of neuroscience is that we're showing that TLR4 plays a significant role in neurons, specifically, the neurons that are connected to the GABA receptor," says Dr. June.

To establish the connection between the GABA receptors, TLR4 and alcohol, the scientists manipulated this pathway in the binge drinking rodents. Dr. Aurelian was a pioneer in developing a method to inhibit gene expression, helping scientists to pinpoint the role of individual genes in the body. In this study, she used a herpes viral vector — a deactivated herpes virus — to deliver a gene-modifying agent directly to the neurons in the brain, to target TLR4 and GABA receptors. The scientists found that when they artificially stimulated the GABA receptors and TLR4 in order to simulate the good feelings binge drinkers feel when drinking alcohol, the rats lost interest in alcohol for two weeks after the procedure.

Compounds exist that would stimulate the receptors in the same way the scientists did in the study. "It's very likely that, down the road, these compounds could become new therapies for binge drinking," says Dr. June. "These compounds would act like a substitute for alcohol, much like methadone acts as a substitute for heroin. They would help alcoholics stop drinking, giving them relief from their cravings and from the anxiety that they try to alleviate with drinking."

The next step is to further investigate the newly discovered role that

TLR4 plays in binge drinking. Future treatments could target both GABA receptors and TLR4, or just TLR4, depending on what scientists find, according to Dr. June. More study is needed, says Dr. Aurelian: "The discovery of this involvement of TLR4 in a pathway with GABA is most remarkable. This study provides basically a totally new understanding of what TLR4 and GABA are all about. That's exciting, but there is a lot more to learn about this pathway and where it goes beyond this point. This is a fascinating new paradigm we plan to explore further."

Provided by University of Maryland Medical Center