MicroRNA implicated as molecular factor in alcohol tolerance

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In recent years, a class of small molecules known as microRNA have been found to play an important role in regulating gene products in most animal and plant species. A new study now indicates that microRNA may influence the development of alcohol tolerance, a hallmark of alcohol abuse and dependence. Researchers supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) report the findings in the July 31 issue of the journal *Neuron*.

"This is an intriguing contribution to efforts aimed at identifying the molecular bases of alcohol tolerance," noted NIAAA Director Ting-Kai Li, MD.

Tolerance is the decrease in sensitivity to alcohol that develops with repeated exposures to alcohol over time. Individuals who develop high tolerance (low sensitivity) to alcohol are at increased risk for becoming alcohol dependent. Thus, an important research objective has been to identify the adaptations within individual molecules that underlie tolerance.

In previous experiments, Steven N. Treistman, PhD, Professor of Psychiatry at the University of Massachusetts Medical School (UMMS), and colleagues at the university's Brudnick Neurospychiatric Research Institute (BNRI), determined that a brain cell membrane structure known as the BK channel develops tolerance to alcohol, particularly in the supraoptic nucleus and the striatum, two brain regions important in alcohol's effects. In both regions, alcohol tolerance was manifested as

decreased alcohol sensitivity and reduced BK channel density. Previous studies have also shown that there are numerous variants of the BK channel gene.

In the current study, researchers led by Dr. Treistman, who is the director of the BNRI, examined whether microRNA might be involved in the alcohol tolerance observed in the BK channel.

In test tube experiments, the researchers showed that the amount of a specific microRNA molecule known as miR-9 increases in brain cells within minutes of exposure to alcohol. They also found that miR-9 blocks the expression of BK gene variants that contain a specific binding site for the molecule, while sparing those that lack a miR-9 binding site. Remarkably, the BK gene variants were destroyed exhibited high alcohol sensitivity, while those that remained showed significantly lower sensitivity, consistent with the development of tolerance.

"This represents a novel and elegant mechanism by which neurons are able to adapt to alcohol," said Treistman. "Moreover, since adaptation, or tolerance, to the drug likely contributes to alcohol abuse, our findings identify a potential molecular target for therapeutic intervention." Treistman credited his colleagues, especially Andrzej Z. Pietrzykowski, MD, PhD, research assistant professor of psychiatry, for their contributions to this important work.

A widely published expert on the molecular basis of addiction—in particular, the changes in the brain that occur as a function of drug exposure, which may make an individual prone to substance abuse and the compulsive behavior associated with drug addiction—Dr. Treistman noted that the microRNA process observed in this study may represent a general mechanism of neuronal adaptation to alcohol, with miR-9 playing a pivotal role in a complex regulatory network.

"This study demonstrates for the first time that alcohol exposure can cause rapid changes in microRNA levels, altering gene expression and perhaps behavior," said Antonio Noronha, PhD, director of NIAAA's Division of Neuroscience and Behavior. "In future studies, it will be interesting to determine if similar microRNA-based regulatory mechanisms influence alcohol problems in human populations."

Source: University of Massachusetts Medical School