Brain stress system presents possible treatment

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A brain circuit that underlies feelings of stress and anxiety shows promise as a new therapeutic target for alcoholism, according to new studies by researchers at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), part of the National Institutes of Health (NIH).

In preclinical and clinical studies currently reported online in *Science Express*, NIAAA Clinical Director Markus Heilig, M.D., Ph.D., and colleagues from the NIH, Lilly Research Laboratories, and University College in London found that a brain molecule known as the neurokinin 1 receptor, or NK1R, appears to be a central actor in stress-related drinking.

The researchers first demonstrated that NK1R plays an integral role in alcohol consumption in animals. Mice that were genetically engineered to lack NK1 receptors consumed much less alcohol than did normal mice with fully functional NK1R. Subsequently, in a small clinical study, the researchers showed that an experimental compound designed to block NK1 receptors reduced alcohol craving and improved overall wellbeing among recently detoxified alcohol-dependent individuals who had high levels of anxiety. Using functional brain imaging, the researchers also showed that the exaggerated sensitivity to negative stimuli seen in alcoholics was dampened with the medication, while the lack of responses to pleasurable stimuli was restored.

“This work exemplifies the NIH’s unique capacity for speeding the translation of promising laboratory discoveries into potential new

medical treatments," notes NIH Director Elias Zerhouni, M.D.

"These findings advance our understanding of the link between stress and alcohol dependence and raise the prospect of a new class of medications for treating alcoholism," adds NIAAA Director Ting-Kai Li, M.D.

Relapse to uncontrolled drinking after periods of sobriety is a defining characteristic of alcoholism and is often triggered by stress.

"The driving force behind dependent individuals' alcohol use transitions from what we call reward craving to relief craving," explains Dr. Heilig. "By the time people seek treatment for alcoholism, the pleasurable or rewarding effects of the drug are gone for most patients. Instead, alcohol-dependent individuals often feel low, anxious and are sensitive to stress, and they use alcohol to relieve these bad feelings."

Previous studies have shown that a brain chemical known as Substance P (SP) is released in response to stress, produces symptoms of anxiety, and binds preferentially to NK1R. SP and NK1R are highly expressed in brain areas involved in stress responses and drug reward. Studies have also shown that anxiety and stress responses can be reduced in both animals and humans by inactivating NK1R. Such studies suggest that interfering with NK1R function could possibly subvert any role it might play in stress-related alcohol consumption.

Dr. Heilig and his colleagues conclude that if further studies establish activation of the SP-NK1R system as a consistent feature of alcohol dependence, compounds that block NK1R may have considerable potential for treating alcoholism, and potentially other addictions.

Source: National Institute on Alcohol Abuse and Alcoholism