Potential new drug for alcohol dependence

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(Medical Xpress) -- Research from Karolinska Institutet has identified a monoamine stabiliser as a potential new drug for the treatment of alcohol dependence. Tested on rats, whose reward system is gradually blunted by long-term alcohol abuse, the compound OSU6162 balances dopamine levels in the brain. This serves to reduce the craving for more alcohol to maintain normal feelings of wellbeing while removing the pleasure from drinking.

Alcohol is the world's third largest risk factor for disease burden, and the socioeconomic costs related to alcohol are enormous. Despite the severity of the disease, there are only three FDA-approved medications for alcohol dependence. The prescription rates are low, possibly due to varying clinical efficacy. Consequently, more effective medications are crucial.

The drug candidate OSU6162 has been studied for the treatment of alcohol dependence by researchers at Karolinska Institutet and the University of Gothenburg based on the knowledge of how the brain's reward system works to encourage us to behave in ways that promote survival. Eating delicious food, exercising and having sex all trigger the release of the chemical messenger dopamine in the brain reward system. Dopamine generates a feeling of wellbeing, and a memory between the specific action and the feeling is created so that we will repeat it.

When we drink alcohol, the brain's reward system releases more dopamine than during natural stimulation such as food, exercise, or sex. This results in a highly pleasurable - euphoric - feeling. But frequent

alcohol drinking gradually blunts the system and the quantity of dopamine released drops. Over time, larger amounts of alcohol are needed to generate euphoria and ultimately one has to drink alcohol to prevent dysphoria or depression. The established memory between alcohol and well-being amplifies this effect and creates a strong craving for alcohol. Even after a long period of sobriety it can take as little as walking past the local bar to trigger a relapse.

"OSU6162 has the unique ability to stabilize the brain's dopamine levels by raising low and decreasing high levels, which makes it particularly attractive for the treatment of alcohol dependence," says Pia Steensland, associate professor at the Department of Clinical Neuroscience at Karolinska Institutet, who led the study. "We tested OSU6162 on rats that had consumed alcohol for a long time because their brain reward system works in much the same way as ours."

All of the rats in the study had free access to both alcohol and water. After a few months, some of the rats voluntarily consumed excessive amounts of alcohol while others preferred water. All were then treated with OSU6162, after which the high consumers drastically reduced their alcohol intake. Following the treatment they preferred drinking water, just like the rats consuming low amounts of alcohol. The use of special chambers with pedals that trigger light, sound and scent signals showed that OSU6162 also reduced the rats' desire to work hard to gain access to alcohol and prevented relapse to drinking after a long period of abstinence.

OSU6162 is currently being successfully tested at the University of Gothenburg for mental fatigue following head trauma in humans. The next step is to investigate whether OSU6162 is equally efficient when treating alcohol-dependent humans. The researchers will be recruiting participants for this study during the autumn of 2012.

"Our results suggest that OSU6162 blocks the increase in dopamine levels, and thereby prevents the rewarding effects of alcohol," says Steensland. "The dopamine levels decrease in the reward system decrease after long-term alcohol abuse. Our rats' lack of interest in alcohol after treatment with OSU6162 would suggest that the compound can stabilise or normalise the disrupted dopamine levels induced by long term alcohol consumption."

The rights to OSU6162 are held by Nobel Prize laureate Arvid Carlsson, who together with his team in Gothenburg has developed the compound. He is also one of the study's co-authors. The research has been funded by a number of parties, including the Swedish Research Council, the National Board of Health and Welfare, the Swedish Brain Foundation, the Eva and Oscar Ahrén Foundation, the Olle Engkvist Foundation and the Swedish Alcohol Retailing Monopoly (SRA). OSU6162 was generously donated to Arvid Carlsson by Pfizer Pharmaceuticals, Inc.

More information: Pia Steensland, Ida Fredriksson, Sarah Holst, Kristin Feltmann, Johan Franck, Björn Schilström and Arvid Carlsson, The monoamine stabilizer (-)-OSU6162 attenuates voluntary ethanol intake and ethanol-induced dopamine output in N.Accumbens, *Biological Psychiatry*, online 18 Juli 2012. www.biologicalpsychiatryjournal.com/

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