Liver hormone reduces preference for sweets, alcohol, via brain's reward pathway

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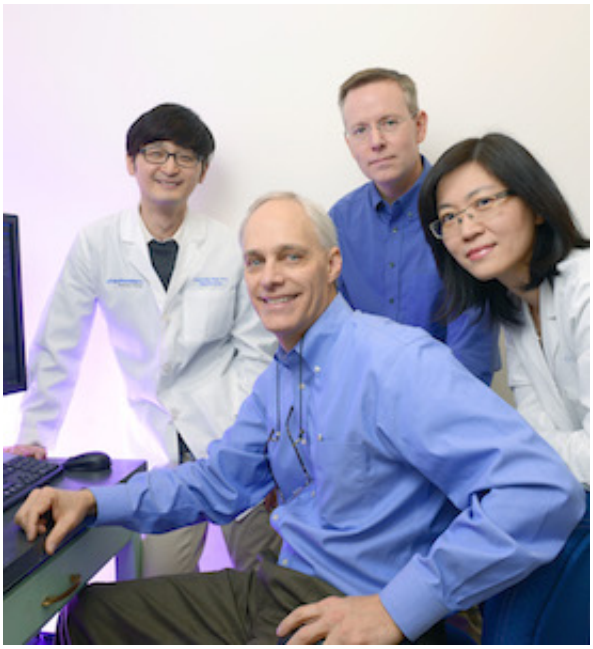

(L-r) Dr. Parkyong Song, Dr. David Mangelsdorf, Dr. Steven Kliewer, and Dr. Yuan Zhang. Members of the UTSW research team found the hormone FGF21 reduced cravings for sweets and alcohol. Credit: UT Southwestern

A liver hormone works via the brain's reward pathway to reduce cravings for sweets and alcohol in mammals, UT Southwestern Medical Center researchers have found.

"This is the first time a hormone made in the liver has been shown to affect sugar and alcohol preference in mammals," said Dr. Steven

Kliewer, Professor of Molecular Biology and Pharmacology at UT Southwestern and co-senior author of the study, published online today in *Cell Metabolism*.

The hormone - fibroblast growth factor 21, or FGF21 - is associated with environmental stress such as extreme dietary changes or cold temperature exposure. It is also produced when mammals consume carbohydrates. Because of FGF21's unique effects, forms of the protein are being evaluated as drugs for the treatment of obesity and type 2 diabetes.

"Our findings raise the possibility that FGF21 administration could affect nutrient preference and other reward behaviors in humans, and that the hormone could potentially be used to treat alcoholism," said Dr. Kliewer, who holds the Nancy B. and Jake L. Hamon Distinguished Chair in Basic Cancer Research.

The researchers report that mice with elevated levels of FGF21 showed reduced preference for sweetener- and alcohol-laced water as well as a marked decrease in levels of dopamine, a neurotransmitter that plays a central role in reward behavior.

"We found that FGF21 administration markedly reduces sweet and alcohol preference in mice, and sweet preference in larger animal models," said co-senior author Dr. David Mangelsdorf, Chair of the Department of Pharmacology and a Howard Hughes Medical Institute Investigator, who runs a joint laboratory with Dr. Kliewer. Dr. Mangelsdorf holds the Alfred G. Gilman Distinguished Chair in Pharmacology, and the Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology in Honor of Harold B. Crasilneck, Ph.D.

To confirm that FGF21 acts via a brain pathway, the researchers took

advantage of the fact that FGF21 requires the co-receptor β-Klotho in order to function. When FGF21 levels were increased in mice genetically unable to make β-Klotho in the central nervous system, the effect on taste preference disappeared.

This marks the fourth study from the Mangelsdorf-Kliewer laboratory to show that FGF21 directly affects the central nervous system. First, in two studies in Nature Medicine in 2013, they reported on FGF21's ability to regulate metabolism, circadian (body clock) behavior, and female reproduction. In 2014, they reported in *Cell Metabolism* that FGF21 acts on the brain to cause weight loss.

"The finding that FGF21 acts via the brain was completely unexpected when we started down this path of investigation a dozen years ago," Dr. Kliewer said. "These findings suggest that additional studies are warranted to assess the effects of FGF21 on sweet and alcohol preference and other reward behavior in humans."

More information: *Cell Metabolism*, Talukdar and Owen et al: "FGF21 Regulates Sweet and Alcohol Preference" dx.doi.org/10.1016/j.cmet.2015.12.008

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