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T.G.I. FGF21 sobering mice

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Humans and other animals are at risk of excessive exposure to ethanol, which can have harmful effects. In nature, simple sugars in ripening fruits and nectar are a rich source of calories for animals; however, their natural fermentation can lead to alcohol intoxication. Many species have adapted to metabolize alcohol; in humans, the liver hormone FGF21 which is known to regulate carbohydrate and lipid metabolism is strongly increased during alcohol ingestion, and in non-human primates it suppresses alcohol consumption. Now, a study published in *Cell Metabolism* shows this hormone is also important to counteract the effects of alcohol on consciousness and mobility.

It all started after looking at how *Fgf21* knockout (KO) mice respond to a single, high dose of alcohol. "Remarkably, these mice remained unconscious much longer than wild-type mice", say David Mangelsdorf and Steve Kliewer, senior investigators of the study. This observation prompted the two investigators and their team at the University of Texas Southwestern Medical Center to check whether administering FGF21 as a drug would reverse inebriation caused by alcohol in three different KO lines: a global *Fgf21* KO (*Fgf21*$^{-/-}$), a liver-specific *Fgf21* KO (*Fgf21*^{Alb}), and a neuron-specific *Klb* KO (*Klb*^{Camk2a}) which targets β-Klotho (KLB) a protein required for the binding of FGF21 to its receptor. The researchers found that, while all the KO lines took the same time as wild-type mice to lose consciousness, they took much longer to regain it. Supplementing mice with FGF21 awakened the *Fgf21*$^{-/-}$ and *Fgf21*^{Alb} mice, accelerating their recovery, but had no effect on *Klb*^{Camk2a} mice. The team performed additional genetic knockout and pharmacologic inhibition approaches, and altogether the results highlight a close liver-brain relationship, where FGF21 signals from the liver to the locus coeruleus, to activate the noradrenergic system and defend the body against ethanol-induced intoxication. Finally, FGF21 selectively protects from ethanol, given that it did not counteract the loss of consciousness when administered to animals treated with other drugs.

These findings suggest that the liver is not only responsible for metabolizing alcohol but also for sending signals to the nervous system that help to regulate the alert state of mice. Such findings are important as, according to Mangelsdorf and Kliewer: "this work suggests the potential of using FGF21 therapeutically to treat acute alcohol poisoning, which is an important unmet medical need, particularly in hospital ERs".

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