FGF21 is a liver-derived hormone primarily involved in glucose/lipid metabolism. A recent study by Flippo and colleagues\(^1\) demonstrates that administration of FGF21 or an FGF21 analog suppresses alcohol consumption in rodents and non-human primates, likely through an amygdalo-striatal circuit.

Alcohol use disorder (AUD) is a common and debilitating disease associated with negative medical and psychosocial consequences. Currently, there are only a few medications approved for AUD in the U.S. (disulfiram, acamprosate, naltrexone). The small number of medications available, their limited implementation in clinical practice, and the heterogeneity in patients’ responses call for the need to increase the armamentarium of pharmacotherapies for AUD.

Growing evidence indicates that endocrine pathways are involved in alcohol-seeking and consummatory behaviors, suggesting their potential as novel pharmacotherapeutic targets for AUD.\(^2\) Fibroblast growth factor 21 (FGF21) is a 181 amino acid peptide hormone, primarily released by the liver in response to physiological perturbations, with key functions in the homeostatic control of glucose and lipid metabolism.\(^3\) Both preclinical and clinical studies recently found that alcohol consumption increases endogenous FGF21 levels.\(^4,5\) Albeit preliminary, these findings suggest that elevated FGF21 following alcohol use may lead to reduced alcohol intake, potentially through acting on the co-receptor β-klotho (encoded by the KLB gene) expressed in the brain.\(^5\) Therefore, it is possible to hypothesize that a liver-brain axis pathway like FGF21 may serve as a viable target for AUD treatment. However, little work to date has investigated neural mechanisms underlying FGF21’s interplay with alcohol consumption as well as its effects in higher order mammals.

To address these gaps, Flippo and colleagues\(^1\) investigated the effects of FGF21 and a long-acting FGF21 analog (PF-05231023) on alcohol consumption in rodents and non-human primates. They first showed that in mice, alcohol consumption increased circulating FGF21 levels, selective FGF21 deletion from the liver increased alcohol use, and intraperitoneal administration of recombinant human FGF21 dose-dependently reduced alcohol consumption. These findings support the notion that FGF21 may serve as a negative-feedback regulator for alcohol consumption.\(^5\) Systemic PF-05231023 administration was also found to reduce alcohol consumption, both in mice and alcohol-prefering vervet monkeys, the latter being a model closer to harmful drinking in humans. Together, findings across two different species indicate the potential translational utility of FGF21-based pharmacotherapies for AUD.

Next, anterograde tracing of KLB+ neuron projections, patch-clamp experiments, and spontaneous excitatory postsynaptic current recordings revealed that FGF21 administration preferentially amplifies action potential firing of KLB+ neurons from the BLA to nucleus accumbens (NAc) and modulates glutamatergic input onto D2-expressing medium spiny neurons (MSNs) in the NAc. These results should be considered with the finding that administration of recombinant FGF21 is associated with decreased dopamine in the NAc, suggesting that both glutamatergic and dopaminergic systems are involved in FGF21 signaling.\(^7\) Finally, to close the loop, the researchers applied a dual recombinase strategy and showed that FGF21 signaling in KLB\(^{BLA→NAc}\) neurons is necessary and sufficient for suppressing alcohol consumption, by either FGF21 or PF-05231023 administration. This is the first study revealing the existence of an endocrine-sensitive...
subpopulation of amygdalo-striatal projecting neurons that leads to reduced alcohol intake when stimulated by FGF21 or an FGF21 analog. While the present study provided important mechanistic information, more research is needed to understand the bidirectional relationship between FGF21 and alcohol (Figure 1). Previous studies found that acute and chronic alcohol consumption in rodents and humans induce hepatic FGF21 and may be dependent on the carbohydrate response element-binding protein (ChREBP) and/or the peroxisome proliferator-activated receptor (PPARα). While ChREBP and PPARα mediate hepatic FGF21 production under fasting conditions, whether alcohol triggers these specific pathways remains unknown. Future studies should further investigate cellular mechanisms involved in the interplay between FGF21 and alcohol. Hepatocytes secrete FGF21 in response to endoplasmic reticulum stress and oxidative stress and alcohol induces these forms of cellular stress, suggesting that FGF21 may be released as a protective mechanism to safeguard the damaged liver and as a signal to the brain to consume less alcohol. Altogether, the bidirectional relationship between FGF21 and alcohol consumption appears to play an important role in pushing a return from physiological stress toward homeostasis. The dual role of FGF21, both in alcohol-associated liver disease (ALD) and AUD, is of great clinical importance. In fact, alcohol is a leading cause of liver disease, emphasizing the importance of providing integrated treatment for both AUD and ALD. Therefore, a physiological pathway like FGF21 is potentially intriguing in the context of developing treatments for both AUD and ALD.

While substantial evidence points to FGF21 as a promising pharmacotherapeutic target for AUD, clinical research in this field is scarce. Future work should examine, for instance, endogenous FGF21 levels in individuals with AUD and/or in response to alcohol challenges, the effects of FGF21 and/or FGF21 analogs administration together with alcohol, and whether such compounds are safe and effective in individuals with AUD. FGF21 analogs like PF-05231023 have been found to be compounds to alcoholism and craving in humans. Neurepsychol. Rev. 22, 211–228. https://doi.org/10.1007/s11065-012-9209-y.

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