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Are you thirsty? FGF21 might be involved in that too

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New research by David Mangelsdorf, Steven Kliewer and colleagues shows that fibroblast growth factor 21 (FGF21) stimulates water-drinking behaviour in mice. The findings not only provide a mechanistic link between the physiological effects of FGF21, but also describe a novel and unexpected way in which the body regulates thirst.

FGF21 is a weight-loss-promoting hepatokine that regulates energy homeostasis and insulin sensitivity. The hormone, which signals to multiple tissues, including the central nervous system and adipose tissues, is produced in response to the ingestion of nutritional stimuli, such as low-protein diets, high-fat and low-carbohydrate ketogenic diets, simple sugars and alcohol. Numerous studies have detailed the different physiological responses of FGF21, but researchers are still unsure of what links these responses together.

“The first clue to the question of what links the effects of FGF21 came when we noticed that when given pharmacologically, FGF21 greatly stimulates animals to drink water,” explains Mangelsdorf. “Remarkably, intake of many of the known inducers of FGF21, such as the ketogenic diet and alcohol, also promote thirst and water-drinking behaviour — this prompted us to explore whether the thirst response to alcohol and the ketogenic diet were dependent on FGF21.”

Credit: George Diebold/Getty

To investigate the role of FGF21 in the thirst response, the team conducted a gain-of-function study where they gave recombinant FGF21 to mice and measured their drinking behaviour. They followed these experiments with a loss-of-function study, where they monitored the drinking behaviour of control mice and mice that had a genetic deletion of FGF21 or its receptor, after receiving a ketogenic diet or alcohol. Mangelsdorf, Kliewer and their team also measured the time it took for FGF21 to induce the thirst response using a gustometer, which measures the number of times a mouse licks its water bottle.

“Using these approaches we were able to show that the thirst response following ingestion of alcohol or while on a ketogenic diet is dependent on FGF21 action,” notes Mangelsdorf. By genetically deleting the FGF21 receptor in the brain, the investigators were also able to show that FGF21 receptor expression in the hypothalamus is required for the effect of FGF21 on drinking behaviour in mice. “Finally, we found that levels of FGF21 in the blood of humans are substantially increased in response to alcohol consumption, which confirms findings from another recent study and suggests that this thirst response is also relevant in humans,” adds Mangelsdorf.

These findings reveal the existence of an intricate sensing pathway that regulates water balance in response to nutrient stress in the form of a ketogenic diet or alcohol. “In this pathway, the liver, which is the first responder to a nutrient stress, secretes FGF21,” explains Mangelsdorf. “FGF21 then signals to the brain to do two things: one is to suppress the desire to further consume the stressing agent; the second is to consume more water to prevent dehydration.” One of the most intriguing aspects of this work is that hydration can affect thermogenesis, body weight and other metabolic parameters. The authors therefore speculate that many of the previously reported beneficial pharmacological properties of FGF21 on these parameters might be secondary to its effects on water balance.

Mangelsdorf, Kliewer and colleagues are now focused on further dissecting the exact neural circuitry that is involved in mediating the effects of FGF21. They would also like to test the prediction that FGF21 stimulates thirst in humans.

“Taken together with our previous work showing FGF21 suppresses the desire to drink alcohol and consume sweets, these findings imply that FGF21 could potentially be used as a therapeutic to quell these desires,” concludes Mangelsdorf.

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