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NEUROENDOCRINOLOGY

FGF21 influences a 'sweet tooth' in mice

Liver-derived fibroblast growth factor 21 (FGF21) is involved in energy homeostasis, but its mechanistic role in macronutrient intake has been unclear. In two papers, both published in *Cell Metabolism*, investigators have now identified a hepatic FGF21-dependent mechanism that regulates a preference for sweet-tasting foodstuffs and alcohol intake, which is mediated by neuronal circuits in the brain.

In one study, the investigators, led by Matthew Gillum and Matthew Potthoff, used *Fgf21* knockout mice to show that loss of this growth factor leads to increased consumption of a high-sucrose diet, glucose and fructose compared with wild-type littermates. Interestingly, the *Fgf21* knockout mice did not increase their intake of saccharin, which suggests that FGF21 regulates macronutrient intake. Moreover, transgenic mice that overexpress FGF21 prefer normal chow over a high-sucrose feed.

The high-sucrose diet increased plasma levels of FGF21, which was abolished in a liver-specific FGF21 knockout mouse. Similarly, mice lacking the transcription factor ChREBP, which mediates FGF21 levels in response to carbohydrates, did not experience an increase in plasma levels of this growth factor.

Given that the FGF21 receptor, FGFR1c, and co-receptor β-klotho are not expressed in the taste bud epithelium, the team hypothesized that FGF21 regulates taste preference via the central nervous system. Indeed, wild-type mice injected with recombinant FGF21 directly into the brain had reduced preference for the high-sucrose diet. Paraventricular nucleus-specific knockout of β-klotho in the hypothalamus eliminated this action of FGF21, an effect not seen when β-klotho was eliminated in other regions of the brain.

"Our study identifies a novel liver-to-brain hormonal axis that represents a feedback loop to regulate carbohydrate intake," says Potthoff. "The hope is that these experiments will clarify both the physiological involvement of FGF21 in human sweet preference, as well as establish whether manipulating FGF21 levels is likely to have health benefits in humans by improving diet," adds Gillum.

In the second study, the investigators also showed that FGF21 transgenic mice had reduced preference for sucrose and that a central nervous system-specific knock-out of β-klotho abolished this effect. The taste preference was specific to sweetness as no changes were observed in preference for fatty acids or bitter tastes. Furthermore, using a long-acting FGF21 analogue, the team found that in take of saccharin was also reduced in a primate model of obesity.

As dopamine regulates reward behaviours, the team investigated whether FGF21 can regulate signalling by this neurotransmitter in the brain. After confirming in mice that β-klotho was expressed in the nucleus accumbens (a region of the brain that integrates reward behaviour), the investigators analysed levels of dopamine in response to FGF21. After 2 weeks of FGF21 treatment, levels of dopamine and its metabolites were significantly decreased in the nucleus accumbens.

Finally, as dopamine also regulates alcohol intake, the group assessed FGF21 transgenic mice for their preference for ethanol. These mice had reduced preference for all ethanol concentrations tested compared with wild-type controls. Plasma levels of ethanol were similar between the two groups of mice, which suggests that the ethanol seeking behaviour had changed as opposed to a simple modulation of alcohol bioavailability.

"Previous work had shown that FGF21 expression in liver is markedly increased by eating a high-carbohydrate diet and by consuming alcohol," explain David Mangelsdorf and Steven Kliewer, who led the study. "Our work provides a plausible physiologic basis for these prior findings."

"FGF21 is probably part of a feedback hepatic-neuroendocrine circuit that curtails the desire to overload on sweet foods," highlight Mangelsdorf and Kliewer, who conclude that, "one intriguing hypothesis is that FGF21 might have evolved to temper the intake of too much alcohol, which is often found in foods that are high in sugar."

Tim Geach

ORIGINAL ARTICLES von Holstein-Rathlou, S. *et al.* FGF21 mediates endocrine control of simple sugar intake and sweet taste preferences by the liver. *Cell Metab.* http://dx.doi.org/101016/j.cmet.2015.12.003 | Talukdar, S. *et al.* FGF21 regulates sweet and alcohol preference. *Cell Metab.* http://dx.doi.org/101016/j.cmet.2015.12.008

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