NEUROENDOCRINOLOGY

Mechanism for the effects of FGF21

Fibroblast growth factor 21 (FGF21) has a well-established role in modulating macronutrient uptake; it is produced by the liver in response

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to high-carbohydrate ingestion to signal to the brain to reduce carbohydrate intake and also has a role in modulating the preference for sweet-tasting foods and drinks. However, the neural pathways underlying these effects have been unclear. New work published in *Cell Metabolism* offers a potential mechanism for the effects of FGF21.

"In this work, we generated novel reporter mice, which allows us to identify all cells that FGF21 is capable of signalling to (β -Klotho (KLB)-Cre mice)," explains author Matthew Potthoff. "Using these mice, we performed single-cell RNA sequencing to identify these cells specifically in the brain, and then made a series of mutant mice in which we deleted the required FGF21 co-receptor (KLB) from specific types of neurons." The researchers were able to demonstrate that FGF21 signalling to glutamatergic neurons in the hypothalamus is required to elicit a reduction in sugar intake in mice, and to alter their sweet taste preferences.

"Interestingly, we found that FGF21 signals to specific neurons in the hypothalamus to lower sugar intake by enhancing their sensitivity to glucose," says Potthoff. Here, the researchers demonstrated that FGF21 has a direct effect on the ventromedial hypothalamus, which alters sugar intake but not sweet preference or energy expenditure. Wild-type mice were administered with either FGF21 or vehicle directly to the ventromedial hypothalamus. Only the mice that received FGF21 exhibited a significant reduction in sugar intake. The researchers also investigated whether FGF21 signalling in the ventromedial hypothalamus was important for energy homeostasis and weight loss by administering FGF21 to diet-induced obese wild-type mice and diet-induced obese KLB SF1-knockout mice (which have an impaired response to FGF21 in the hypothalamus). Similar effects were seen in both groups of mice, including reduced circulating levels of triglycerides, weight loss and improved insulin sensitivity. This finding indicates that FGF21 signalling in the ventromedial hypothalamus is not required to improve metabolic parameters or to induce weight loss.

"Going forward, we are particularly interested in identifying other brain regions that FGF21 acts on to regulate body weight (through increases in energy expenditure) and how FGF21 alters membrane excitability to achieve such potent and sustained effects on body weight regulation," concludes Potthoff.

Claire Greenhill

ORIGINAL ARTICLE Jensen-Cody, S. O. et al. FGF21 signals to glutamatergic neurons in the ventromedial hypothalamus to suppress carbohydrate intake. *Cell Metab.* <https://doi.org/10.1016/j.cmet.2020.06.008> (2020)

AGEING

Age-related muscle loss — novel target identified

Ageing is associated with a decline in brown adipose tissue (BAT) function, as well as sarcopenia. Sarcopenic obesity is a major public health concern, but to date no targeted treatment strategies have been identified. Now, Thorsten Gnad, Alexander Pfeifer and colleagues have reported that a synthetic molecule can restore the function of muscle and BAT in aged and obese mice to the levels of young, lean mice.

"To combat the obesity pandemic, we have been looking for novel targets that regulate whole body energy expenditure," says Pfeifer. "Our focus was on two major energy consuming tissues, BAT and skeletal muscle." The authors screened for G protein-coupled receptors that activate cAMP production and thereby stimulate energy consumption. The team found that the adenosine receptor A2B was highly

expressed in both BAT and skeletal muscle, which is interesting considering the team have previously shown that adenosine activates human and murine BAT.

The investigators used a combination of pharmacological and genetic tools to investigate the role of A2B in metabolism and muscle physiology in both in vitro and in vivo models. The team first showed that the pharmacological stimulation of A2B markedly increased whole-body energy expenditure in mice. In addition to this finding, and somewhat surprisingly, the authors found that high-fat diet-fed mice that were treated with an A2B agonist had increased skeletal muscle mass.

"The story took another unexpected turn when we found that loss of A2B results in enhanced loss of muscle in aged mice," adds Pfeifer. "Excitingly, mice deficient for A2B

EXERCISE

Exercise adaptations to milk confer benefits in offspring

Maternal exercise before and during pregnancy in animal models confers benefits in offspring, including improvements in glucose metabolism, adiposity and cardiac function, via unclear mechanisms. A study in *Nature Metabolism* now shows that the benefits of exercise training are mediated by an oligosaccharide present in breast milk.

The researchers exposed wild-type (WT) female mice to running exercise before and during pregnancy. A second group of WT mice were sedentary, and all mice were fed a high-fat diet (HFD). "We took offspring from exercise-trained dams and had them drink milk from sedentary dams, and offspring from sedentary dams and had them drink milk from exercise-trained dams," explains corresponding author Kristin Stanford. Strikingly, adult offspring that had consumed milk as neonates from exercise-trained dams showed improved glucose

metabolism, reduced adipose tissue mass and reduced body weight, compared with offspring that had drunk milk from sedentary dams.

Next, the researchers examined the activity levels of 139 pregnant women and the concentrations of human breast milk oligosaccharides at 2 months postpartum. The levels of 3'-sialyllactose (3'-SL) correlated with activity levels and negatively correlated with BMI. Exercised female mice also showed increased levels of 3'-SL in milk.

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