FGF21 AND METABOLIC DISEASE IN 2016

A new frontier in FGF21 biology

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In 2016, four studies were published that provided crucial new information on the endocrine actions of the hormone fibroblast growth factor 21 (FGF21). These studies provide a framework for the nutritional stimuli that regulate *FGF21* expression and demonstrate a major role for FGF21 in primates and humans in regulating food intake, macronutrient preference and central reward pathways.

Fibroblast growth factor 21 (FGF21) is an endocrine hormone that regulates energy homeostasis and insulin sensitivity[1]. FGF21 is produced by the liver in response to various nutritional, physiological and pathological stimuli, and signals to multiple tissues including the central nervous system (CNS) and adipose tissues to mediate metabolic effects on carbohydrate and lipid metabolism[1]. Extended pharmacological administration of FGF21 to obese or diabetic rodents increases energy expenditure and browning of adipose tissues, and markedly reduces body weight without significantly affecting food intake[1]. The identification of FGF21, and the subsequent characterization of its function, is a remarkable story that has been full of unexpected twists and turns. Although FGF21 was identified in a screen for factors that induce glucose uptake in white adipocytes *in vitro* through insulin-independent mechanisms, FGF21 was subsequently found to profoundly enhance insulin sensitivity *in vivo*. Notably, despite being identified as a factor that regulates glucose metabolism, the most striking and consistent metabolic effects of FGF21 across species are on lipid metabolism in animal models of obesity and diabetes mellitus[1]. In 2016, a new chapter in the FGF21 story unfolded, as four papers were published that provide novel insights into the production and function of FGF21 in mice, monkeys and humans.

Talukdar and colleagues evaluated the metabolic effects of a long-acting FGF21 analogue, PF-05231023, in monkeys with obesity and humans with obesity and type 2 diabetes mellitus[2]. Consistent with a previous study examining the effects of a different FGF21 analogue in humans[3], Talukdar *et al.* observed marked decreases in body weight in both humans and monkeys with obesity in response to PF-05231023 administration[2]. Surprisingly, in contrast to the metabolic effects of this FGF21 analogue in rodents (that is, increased weight loss without decreased food intake), PF-05231023 reduced body weight in monkeys by decreasing food intake without affecting browning of subcutaneous white adipose tissue. Administration of PF-05231023 to monkeys resulted in a marked decrease in food intake; pair feeding untreated obese monkeys with the same calorie content per day as the 10 mg/kg PF-05231023 treatment group resulted in body weight changes of the same magnitude as obese monkeys administered PF-05231023. Similar metabolic effects were observed in humans following PF-05231023 administration, which included an ~4–5% decrease in body weight after only 25 days[2]; food intake data were not reported. Thus, the effect of FGF21 on body weight that was identified in rodents seems to translate to primates and humans. However, the mechanism underlying this effect might be species-specific, with energy expenditure being the primary mechanism to reduce body weight in rodents and food intake the primary mechanism in primates and humans (FIG. 1).

Although administration or overexpression of FGF21 in rodents does not decrease total caloric intake, von Holstein-Rathlou and colleagues demonstrated that FGF21 regulates macronutrient intake in mice[4]. Previous work in humans identified single-nucleotide polymorphisms (SNPs) near the *FGF21* locus that

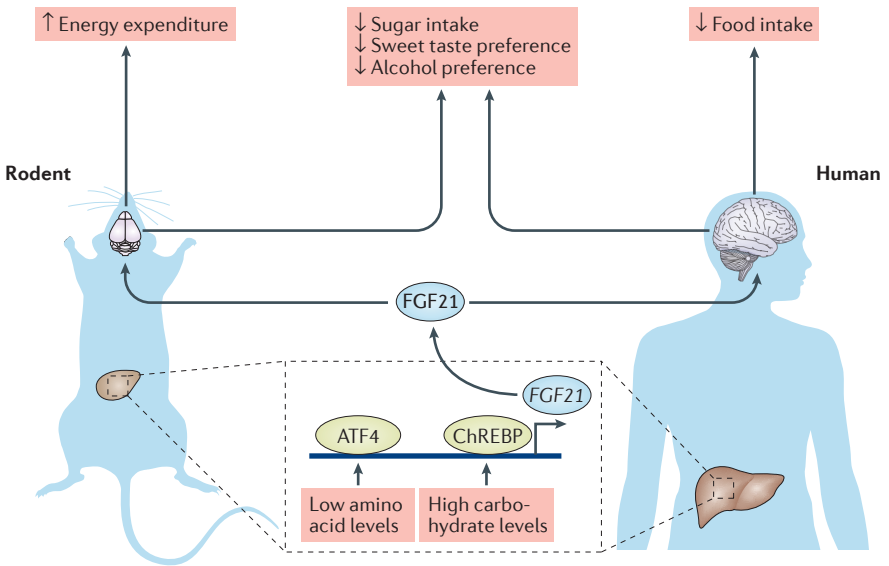

Figure 1 | **Liver-to-brain hormonal axis regulating energy homeostasis.** Production of circulating levels of FGF21 from the liver are induced in response to low protein or high carbohydrate levels in both rodents and humans. The conserved and species-specific effects of FGF21 signalling to the brain are indicated. ATF4, activating transcription factor 4; ChREBP, carbohydrate-responsive element-binding protein; FGF21, fibroblast growth factor 21.

Key advances

- Administration of an FGF21 analogue to primates markedly decreases body weight and food intake but does not increase browning of adipose tissues[2]
- FGF21 mRNA and protein expression is induced in the liver, and the protein enters the circulation in response to low levels of protein and high levels of carbohydrate[4,9]
- Elevated levels of FGF21 signal to the brain to suppress sugar intake and sweet taste preference[4,7]
- FGF21 decreases central reward and reduces alcohol preference[7]

are associated with changes in macronutrient intake, including increased carbohydrate intake and decreased fat intake[5,6]. Using both gain-of-function and loss-of-function animal models, von Holstein-Rathlou *et al.* discovered that FGF21 regulates simple sugar intake and preference but not the intake of lipids or protein[4]. Mice lacking FGF21 exhibited increased simple sugar intake, whereas mice overexpressing FGF21 had markedly reduced sugar consumption, without decreased total caloric intake. Acute administration of recombinant FGF21 protein to wild-type mice rapidly and significantly suppressed simple sugar intake. Interestingly, exogenous FGF21 administration also suppressed the intake of the non-caloric sweetener sucralose. von Holstein-Rathlou and colleagues found that FGF21 production by the liver is increased by high carbohydrate levels through activation of the transcription factor ChREBP. FGF21 then enters the circulation and signals to paraventricular neurons in the hypothalamus to reduce sugar intake. These effects of FGF21 were not mediated by taste sensing but, rather, through taste processing[4]. Together, these data reveal that FGF21 functions as a key mediator of a novel liver-to-brain hormonal axis that regulates macronutrient preference by acting as a sugar satiety signal (FIG. 1).

Consistent with the role of FGF21 in regulating sugar intake, a second study by Talukdar and colleagues also found that FGF21 suppresses sweet taste preference by signalling to the CNS[7]. However, in contrast to the study of von Holstein-Rathlou and colleagues, Talukdar *et al.* extended their studies to monkeys and found that administration of the long-acting FGF21 analogue, PF-05231023, potently inhibited sweet taste preference[7]. Interestingly, Talukdar *et al.* also discovered that overexpression of FGF21 in mice reduced alcohol preference, which suggests that FGF21 affects central reward. Indeed, long-term administration of FGF21 in mice decreased levels of dopamine in the nucleus accumbens and the ventral tegmental area, key brain regions that regulate central reward[7]. Importantly, this role of central FGF21 signalling in the regulation of alcohol consumption seems to translate to humans, as a SNP in *KLB* (encoding the FGF21 obligate co-receptor β-klotho) is associated with alcohol consumption[8]. Increased levels of this liver-derived hormone might thus be produced in response to excess levels of carbohydrate and/or alcohol to suppress reward and prevent alcohol-induced and non-alcohol-induced liver injury (FIG. 1).

Although FGF21 gene and protein expression is induced by high levels of carbohydrate to regulate nutrient metabolism[4], FGF21 is also induced during a number of different physiological conditions (including fasting and overfeeding) and in response to other diets (such as ketogenic diets, low-protein diets and high-fat diets)[1,9]. Explaining this paradoxical elevation of FGF21 levels has been difficult. To identify the nutritional and metabolic context for FGF21 induction, Solon-Biet and colleagues used the geometric framework, a multidimensional framework of 25 diets varying in macronutrient (protein, carbohydrate and fat) and total-energy density, to assess the contribution of macronutrient intake and energy intake to hepatic and circulating levels of FGF21 in mice[9]. This comprehensive analysis revealed that maximal FGF21 induction was associated with a combination of low protein and high carbohydrate intake. Interestingly, FGF21 expression was not significantly altered by fat intake or total energy intake. Consistent with the *in vivo* data, incubation of human HepG2 liver cells with glucose increased FGF21 protein expression, and maximal levels were observed under conditions of high glucose levels and low branched-chain amino acid levels[9] (FIG. 1). These data are thus consistent with the observation that low protein[10] and high carbohydrate[4] levels induce FGF21 expression in humans and align with the model of von Holstein-Rathlou *et al.*, which proposed that FGF21 functions as a negative-feedback satiety signal to maintain macronutrient balance through suppression of simple sugar intake[4].

In summary, four important studies published in 2016 have shifted our understanding of the major physiological mechanisms controlling FGF21 expression and the physiological and pharmacological consequences of FGF21 signalling to the CNS. Additional studies are necessary to determine how the effects of FGF21 on macronutrient intake are retained across species despite species-specific differences in total caloric intake and energy expenditure (FIG. 1). Future studies elucidating the central pathways mediating FGF21 functions might yield important therapeutic targets to treat metabolic disease and drug addiction.

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Competing interests statement
The author declares no competing interests.