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A Dozen Years of Discovery: Insights into the Physiology and Pharmacology of FGF21

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SUMMARY

It has been more than a dozen years since FGF21 burst on the metabolism field in a paper showing that its pharmacologic administration caused weight loss and improved insulin sensitivity and lipoprotein profiles in obese rodents. Since then, FGF21 analogs have advanced all the way to clinical trials, and much progress has been made in understanding FGF21's pharmacology and physiology. In this perspective, we highlight some of the interesting themes that have emerged from this first dozen years of FGF21 research, including its roles in autocrine/paracrine and endocrine responses to metabolic stress.

ETOC Blurb

This Perspective by Kliewer and Mangelsdorf highlights recent concepts that have emerged from contemporary studies on the physiologic and pharmacologic roles of fibroblast growth factor (FGF) 21.

INTRODUCTION

FGF21 was cloned and named based on its membership in the FGF family (Nishimura et al., 2000). While conventional FGFs act in an autocrine or paracrine manner, FGF21 belongs to an atypical FGF subfamily that can in some circumstances circulate as hormones (Beenken and Mohammadi, 2009). This subfamily also includes FGF15/19, which regulates bile acid homeostasis and other aspects of liver metabolism; and FGF23, which regulates phosphate homeostasis. FGF21 is expressed in liver, endocrine and exocrine pancreas, and adipose tissue. However, under normal physiologic conditions, most if not all FGF21 in the blood is derived from the liver (Markan et al., 2014). While the basis for this selective release from

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Declaration of Interests

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liver is not yet understood, FGF21 lacks the canonical heparan-binding domain found in non-endocrine FGFs, which may allow it to escape from the extracellular matrix into the blood.

FGF21 acts on a cell surface receptor complex comprised of two proteins: a conventional tyrosine kinase FGF receptor (FGFR); and a co-receptor protein, named β-Klotho (KLB). FGF21 binds directly to both of these proteins to activate FGFR signaling activity (Kuro, 2018; Lee et al., 2018). In vitro, FGF21 can act through KLB complexed with either the FGFR1c, FGFR2c, or FGFR3c isoforms. However, gene knockout (KO) analyses and studies with activating antibodies specific for either FGFR1 or the FGFR1/KLB complex suggest that FGFR1c may be particularly important for FGF21's actions in vivo (Adams et al., 2012; Foltz et al., 2012; Kolumam et al., 2015; Lan et al., 2017; Wu et al., 2011).

FGF21 PHARMACOLOGY

FGF21 has profound and pleiotropic pharmacologic effects. In obese rodents, it causes weight loss and improves insulin sensitivity without causing hypoglycemia or decreasing food intake (Coskun et al., 2008; Kharitonenkov et al., 2005; Xu et al., 2009). It also decreases triglyceride and cholesterol levels. FGF21 itself or long-acting analogs have similar metabolic effects in monkeys (Adams et al., 2013; Kharitonenkov et al., 2007; Talukdar et al., 2016b; Veniant et al., 2012b). Interestingly, however, FGF21 decreases food intake in obese monkeys (Adams et al., 2013; Talukdar et al., 2016b; Thompson et al., 2016). These studies highlight potential differences in FGF21's mechanism of action across species.

Several human clinical trials have been reported with long-acting FGF21 analogs (Charles et al., 2018; Gaich et al., 2013; Kim et al., 2017; Talukdar et al., 2016b). In two, four-week studies done in obese subjects with type 2 diabetes, FGF21 analogs had favorable effects on body weight and plasma insulin concentrations (Gaich et al., 2013; Talukdar et al., 2016b). Weight loss was not observed in two other trials performed in obese, dyslipidemic people with or without type 2 diabetes (Charles et al., 2018; Kim et al., 2017), which may reflect differences in FGF21 derivatives and dosing regimens. Surprisingly, there was no effect on blood glucose levels in any of these studies. However, FGF21 analogs significantly reduced plasma triglyceride concentrations and increased HDL cholesterol in all studies. In mice, FG21 lowers plasma triglycerides by reducing non-esterified fatty acids and by increasing lipoprotein catabolism in white and brown adipose tissue (Schlein et al., 2016). The molecular basis for the cholesterol lowering effects has yet to be elucidated.

In addition to its use as a potential diabetes and obesity drug, FGF21 has more recently been shown to have a favorable pharmacologic profile in reversing non-alcoholic fatty liver disease and its more severe stage, steatohepatitis (NASH). Several studies in rodents have shown that FGF21 ameliorates many of the sequelae of the disease (Coskun et al., 2008; Fisher et al., 2014; Tanaka et al., 2015; Xu et al., 2009), and FGF21 and its derivatives lower circulating triglycerides and have other favorable effects on lipoprotein profiles in monkeys (Adams et al., 2013; Kharitonenkov et al., 2007; Talukdar et al., 2016b). These promising results have prompted several clinical trials (clinicaltrials.gov), and a recent Phase 2 study

showed significant improvements in liver fat and blood biomarkers of fibrosis in patients with NASH (Sanyal et al., 2019).

Pharmacologic studies have also revealed adverse effects. In rodents, but not monkeys, FGF21 or analogs increased blood pressure and blood corticosterone concentrations (Bookout et al., 2013; Kim et al., 2017; Turner et al., 2018). Whereas one group found that FGF21 caused bone loss in mice (Wei et al., 2012), another did not (Li et al., 2017). In mice, FGF21 also caused anovulation and changed circadian behavior, increasing running wheel activity in the light phase and decreasing it in the dark phase (Bookout et al., 2013; Owen et al., 2013). In human clinical trials, FGF21 analogs increased blood pressure and pulse rate in one study (Kim et al., 2017) but not in another (Talukdar et al., 2016b). FGF21 analogs also increased blood markers of bone loss in two of the human studies (Kim et al., 2017; Talukdar et al., 2016b). It is unknown whether long-term FGF21 exposure causes bone loss in people. The most prevalent adverse event in humans was diarrhea, which has not been reported in either rodents or monkeys (Kim et al., 2017; Talukdar et al., 2016b). These adverse event profiles further highlight the species differences in the FGF21 response and underscore the challenges of using preclinical models to predict FGF21's toxicology in humans.

How does FGF21 mediate its beneficial pharmacologic effects on adiposity, insulin sensitivity and hepatic triglyceride content? In diet-induced obese (DIO) mice, FGF21 induces thermogenesis and energy expenditure by activating brown adipose tissue (BAT) and promoting the browning of white adipose tissue (WAT) (Coskun et al., 2008; Douris et al., 2015; Owen et al., 2014; Xu et al., 2009). FGF21 also stimulates robust glucose uptake into BAT (Ding et al., 2012; Xu et al., 2009) and the secretion of adiponectin from WAT (Holland et al., 2013; Lin et al., 2013). Some of these effects on adipose tissue are direct: KLB and FGFR1c are co-expressed in BAT and WAT, and FGF21's effect on thermogenic gene expression, glucose uptake and adiponectin secretion can be recapitulated in isolated adipocytes in vitro (Holland et al., 2013; Hondares et al., 2010; Kharitonenkov et al., 2005; Lin et al., 2013). Mechanistically, FGF21 induces the phosphorylation and activation of the transcription factor CREB, which regulates thermogenic gene expression (Wu et al., 2011). FGF21 also inhibits the SUMOylation of PPARγ, which increases its insulin sensitizing activity (Dutchak et al., 2012; Katafuchi et al., 2018). Accordingly, selective disruption of KLB in BAT and WAT of DIO mice inhibited FGF21's effects on glucose uptake and insulin sensitivity during the first few hours after administration (BonDurant et al., 2017; Ding et al., 2012; Lan et al., 2017). However, FGF21 treatment for 2 weeks still caused weight loss, improved insulin sensitivity and lowered hepatic triglyceride concentrations in these adipose tissue-specific KLB-KO mice (BonDurant et al., 2017; Lan et al., 2017), demonstrating that FGF21 acts on additional tissues.

KLB and FGFR1c are co-expressed in discrete regions of the brain, including the suprachiasmatic nucleus and paraventricular nucleus (PVN) in the hypothalamus and the area postrema and nucleus of the solitary tract in the hindbrain (Bookout et al., 2013; Liang et al., 2014). Notably, direct infusion of FGF21 into the brains of DIO rats increased energy expenditure and insulin sensitivity (Sarruf et al., 2010). Conversely, selective disruption of KLB in neurons eliminated the long-term beneficial effects of either FGF21 or an FGFR1/

KLB-specific activating antibody on body weight, glycemia and hepatic triglyceride concentrations in DIO mice (Bookout et al., 2013; Lan et al., 2017; Owen et al., 2014). Knockout of KLB in neurons also eliminated FGF21's effects on circadian behavior, glucocorticoid concentrations and ovulation (Bookout et al., 2013; Owen et al., 2013). Thus, many—if not most—of FGF21's pharmacologic actions require that it act directly on neurons.

In DIO mice, FGF21 increases energy expenditure by activating the sympathetic nervous system (SNS). FGF21 injection either peripherally or directly into the brain activated sympathetic nerve activity in BAT through an indirect mechanism involving induction of corticotropin-releasing hormone (Liang et al., 2014; Owen et al., 2014). Likewise, central administration of FGF21 increased norepinephrine turnover in BAT and WAT and the browning of WAT (Douris et al., 2015). These effects were inhibited by administering a β-adrenergic receptor antagonist, and FGF21's browning activity was eliminated in β-adrenergic receptor-KO mice. Thus, FGF21 signals in the brain to activate the SNS and induce β-adrenergic receptor-mediated thermogenesis in adipose tissue.

Three studies have used uncoupling protein 1 (UCP1)-KO mice to investigate whether the UCP1-mediated futile cycle is required for FGF21's metabolic actions (Kwon et al., 2015; Samms et al., 2015; Veniant et al., 2015). All three studies demonstrated that FGF21 can cause weight loss in mice lacking UCP1, suggesting the existence of alternative and/or compensatory mechanisms. However, here the findings diverge. Whereas Veniant et al. reported that FGF21-mediated induction of energy expenditure was mostly intact in UCP1-KO mice, Samms et al. showed that nearly all of FGF21's weight loss effect in UCP1-KO mice was due to reduced food consumption rather than increased energy expenditure. While both groups concluded that UCP1 is not required for FGF21's long-term beneficial effect on glucose homeostasis, a third group showed that FGF21-mediated stimulation of bolus glucose clearance is lost in UCP1-KO mice (Kwon et al., 2015). The reasons for these seemingly contradictory findings are not yet known, but it is interesting to speculate that they might be due to differences in ambient temperatures. Nevertheless, when taken together, the studies suggest that FGF21 exerts its broad metabolic actions through both UCP1-dependent and UCP1-independent mechanisms.

We conclude that FGF21 mediates its beneficial pharmacologic effects by acting through both peripheral and neural mechanisms (Figure 1). In the DIO mouse model, only direct effects on the nervous system are essential for FGF21's chronic effects on body weight, insulin sensitivity and hepatic triglyceride content, but this probably reflects the importance of weight loss in driving the other metabolic improvements in this particular model. Precisely where in the nervous system FGF21 is acting to mediate its diverse effects remains an open question. The FGF21 receptor complex is expressed both inside (hypothalamus) and outside (hindbrain) the blood-brain barrier (Bookout et al., 2013). While FGF21 can cross the blood-brain-barrier, it does so with only low efficiency (Hsuchou et al., 2007). The finding that direct intracerebroventricular injection of FGF21 into the brain stimulates sympathetic outflow to BAT more quickly than intravenous injection suggests that FGF21 may need to cross the blood-brain barrier (Owen et al., 2014). Likewise, the onset of metabolic effects of an FGFR1/KLB-activating antibody, which crosses the blood-brain

barrier only very poorly, is much slower than for native FGF21 (Lan et al., 2017). However, additional studies will be needed to elucidate whether FGF21 is working through central or peripheral neurons or both. An additional key question is whether the preclinical animal model findings will translate to humans. While most adult humans have at least some BAT (Nedergaard et al., 2007), it is unclear whether FGF21 causes weight loss via UCP1-mediated thermogenesis. As discussed above, FGF21 analogs reduce food intake in obese monkeys, suggesting that other mechanisms may also come into play in humans. Additional, long-term clinical studies will be required to assess FGF21's efficacy— both with respect to its beneficial and adverse effects—and its mechanisms of action in people.

An important caveat with FGF21-based pharmacology is that the composition, potency and duration of action of these drugs differ greatly from endogenous FGF21. Even in studies using native, recombinant FGF21, the typical pharmacologic dose (typically 100–1000 ng/ml) far exceeds the endogenous circulating concentrations that have been observed in either animal models or humans (maximum levels of less than 30 ng/ml). These differences in concentration and exposure may explain why FGF21 and its analogs elicit pharmacologic effects that are not always consistent with its physiologic actions, which are described next.

FGF21 PHYSIOLOGY

FGF21 expression is induced by a variety of stresses in different tissues, including liver, adipose tissue and pancreas. FGF21 in turn acts to alleviate these stresses. Here, we break down FGF21's physiology into its autocrine/paracrine and endocrine actions.

Autocrine/paracrine actions

FGF21 expression is regulated by various physiologic stresses in tissues where it is not released into the blood but rather acts in an autocrine/paracrine manner like conventional fibroblast growth factors. Tissues where this has been studied include WAT, BAT and exocrine pancreas.

FGF21 is induced in WAT by fasting/refeeding (Dutchak et al., 2012). However, DIO mice selectively lacking FGF21 in adipose tissue showed only a trend toward decreased adiposity but normal insulin sensitivity (Markan et al., 2014), suggesting that FGF21 has little impact on basal adipose tissue physiology. In contrast, the autocrine action of FGF21 in adipose tissue appears to play a prominent role in cold-induced thermogenesis. Cold exposure markedly elevated FGF21 expression in WAT and to a lesser extent in BAT (Chartoumpekis et al., 2011; Fisher et al., 2012; Hondares et al., 2011). FGF21 knockout in mice decreased cold-induced thermogenic gene expression in WAT but not BAT and compromised the adaptive thermogenic response (Fisher et al., 2012). Mechanistically, this autocrine action of FGF21 has been attributed to the induced expression of the coactivator PGC-1α (Fisher et al., 2012) and to the induction and secretion of the cytokine, CCL11 (Huang et al., 2017), both of which are potent drivers of adipocyte browning.

Acinar cells in the exocrine pancreas synthesize and secrete more protein than any other cell type in the body. They therefore must have mechanisms to minimize proteotoxic stress. FGF21 plays a unique role in this process by acting as a potent secretagogue (Coate et al.,

2017). FGF21 is expressed at high levels in acinar cells, and this level is increased further in response to feeding to keep pace with postprandial digestive enzyme synthesis (Coate et al., 2017; Johnson et al., 2009; Singhal et al., 2016). Notably, acinar cells secrete all of their FGF21 into the pancreatic ducts, where it acts on acinar cells in an autocrine/paracrine fashion to stimulate digestive enzyme secretion and thereby prevent protein overload. The physiologic importance of this pathway was demonstrated in mice lacking FGF21 or KLB, which accumulate zymogen granules, have increased ER stress, and are susceptible to cerulein-induced pancreatitis (Coate et al., 2017; Johnson et al., 2009). Conversely, pharmacologic administration or transgenic overexpression of FGF21 protected the pancreas against ER-stress, inflammation and injury in mouse models of pancreatitis (Coate et al., 2017; Johnson et al., 2014; Johnson et al., 2009). In humans, the resolution of acute pancreatitis is correlated with increasing levels of circulating FGF21, further suggesting FGF21 plays a protective role (Shenoy et al., 2016). These studies suggest a potential pharmacologic role for FGF21 in preventing and treating pancreatitis.

Taken together, the autocrine/paracrine actions of FGF21 highlight its important role in metabolic stress responses.

Endocrine actions

An oddity of FGF21 as a fibroblast growth factor is its ability to circulate in the blood and function as a hormone. A study using hepatocyte-specific KO mice showed that liver is the major source of circulating FGF21 under physiologic conditions (Markan et al., 2014). Under certain pathophysiologic conditions, FGF21 is also ectopically expressed and released from nonhepatic tissues such as muscle (Izumiya et al., 2008; Kim et al., 2013) and BAT (Ruan et al., 2018). The molecular basis of the tissue-specific secretion of FGF21 has not been resolved.

FGF21 is induced at the transcriptional level and released from murine liver in response to a remarkable diversity of nutritional stresses including starvation, amino acid restriction, ketogenic and high fat diets, simple sugars and ethanol (BonDurant and Potthoff, 2018; Fisher and Maratos-Flier, 2016). Among the transcription factors involved in FGF21 induction are PPARα, which induces FGF21 in response to starvation and ketogenic diet (Badman et al., 2007; Inagaki et al., 2007), and ChREBP, which induces FGF21 in response to simple sugars (Fisher et al., 2017; Iroz et al., 2017). The mechanism through which FGF21 is induced by alcohol has not been explained. In humans, FGF21 blood levels are rapidly and robustly induced by ethanol, with weaker responses elicited by simple sugars, long-term fasting and obesity (Desai et al., 2017; Soberg et al., 2018; Song et al., 2018). FGF21-KO mice are susceptible to steatosis and other harmful liver effects caused by alcohol, fructose and ketogenic diet, revealing a protective role for FGF21 against these nutrient stressors (Badman et al., 2009; Desai et al., 2017; Fisher et al., 2017; Liu et al., 2016; Zhu et al., 2014). It remains to be determined whether these hepatoprotective effects occur by FGF21 acting through autocrine/paracrine or endocrine mechanisms.

Among its established endocrine actions in mice, FGF21 signals from liver to BAT to stimulate glucose uptake in response to prolonged consumption of a high fat diet, presumably to mitigate peripheral insulin resistance (Markan et al., 2014). FGF21 appears to

play an analogous role as an endocrine signal during the transition from the fasted to the fed state: although FGF21 enters the circulation during fasting, it remains in the blood during the early stages of refeeding, when it stimulates glucose disposal (Markan et al., 2014). Endocrine FGF21 is also contributory, but not essential, for various aspects of the adaptive response to starvation, including ketogenesis and the inhibition of female fertility (Badman et al., 2009; Badman et al., 2007; Bookout et al., 2013; Hotta et al., 2009; Inagaki et al., 2007; Owen et al., 2013; Potthoff et al., 2009). The ability of FGF21 to function through both autocrine/paracrine and endocrine mechanisms helps explain some of its seemingly contradictory regulatory patterns across tissues. For example, feeding induces FGF21 in pancreas but suppresses it in liver. However, FGF21 is limited to acting only locally when made by the pancreas.

In 2013, the FGF21 field took an unexpected turn with the publication of two human GWAS studies showing associations between SNPs in and around the FGF21 gene and macronutrient preference (Chu et al., 2013; Tanaka et al., 2013). More specifically, these SNPs were linked to increased carbohydrate consumption and decreased protein and fat consumption. Subsequent GWAS studies showed associations between SNPs in FGF21 and KLB with alcohol consumption (Clarke et al., 2017; Schumann et al., 2016; Soberg et al., 2017). These findings together with the FGF21 induction data suggested the existence of endocrine feedback loops wherein FGF21 suppresses the overconsumption of simple sugars and alcohol.

In two bottle preference experiments, in which mice were given the choice between drinking either pure water or water sweetened with various natural sugars or artificial sweeteners, FGF21 administration markedly decreased sweet intake (Talukdar et al., 2016a; von Holstein-Rathlou et al., 2016). An FGF21 analog also suppressed sweet preference in monkeys (Talukdar et al., 2016a). FGF21-KO mice consumed more glucose, sucrose and fructose than WT mice, and FGF21's effect on sweet preference was lost in mice selectively lacking KLB in the PVN (von Holstein-Rathlou et al., 2016). Similarly, FGF21 acting on neurons reduced alcohol preference, and neuron-specific KLB-KO mice consumed more alcohol than WT mice at high alcohol concentrations (Schumann et al., 2016; Talukdar et al., 2016a; von Holstein-Rathlou et al., 2016). Thus, FGF21 signals from the liver to the brain to limit sugar and alcohol intake. Among its effects in the brain, FGF21 reduced the concentration of the neurotransmitter dopamine in the nucleus accumbens, a region that coordinates reward behaviors, suggesting a possible mechanism of action (Talukdar et al., 2016a).

In addition to decreasing sweet and alcohol preference, FGF21 stimulates water intake in mice and rats. In mice, pharmacologic FGF21 increased water consumption within two hours of administration (Song et al., 2018). Water restriction studies showed that this effect was due to thirst and not secondary to diuresis. The short time required for FGF21 to act and the fact that the effects on water drinking occurred in lean mice, where FGF21 does not induce energy expenditure or weight loss, indicate that the thirst response is not secondary to thermogenesis. Studies performed with FGF21-KO mice showed that FGF21 is essential for increased water intake caused by a ketogenic diet and is contributory to alcohol-induced thirst (Song et al., 2018).

FGF21 does not appear to stimulate thirst through the classical renin-angiotensin-aldosterone or arginine vasopressin (AVP) pathways. This is particularly interesting in the context of alcohol, which had been thought to cause thirst primarily by inhibiting AVP release from the pituitary, thereby stimulating diuresis. FGF21's effect on thirst is eliminated in neuron-specific KLB-KO mice and partially inhibited by either knocking out KLB in the PVN or co-administering β-adrenergic receptor antagonists (Song et al., 2018). Interestingly, a previous study showed that norepinephrine injection into the PVN stimulates thirst in rats (Leibowitz, 1978). Our findings suggest that FGF21 may act through this pathway.

While an FGF21 analog also stimulated water consumption in rats, albeit only weakly compared to mice, a different conclusion was reached regarding it mechanism of action (Turner et al., 2018). In kinetic studies, the FGF21 analog increased urine output before water intake, indicating diuresis as its primary effect. However, the FGF21 analog had no diuretic effect in a water restriction study, which is the gold standard clinical method for distinguishing primary polyuria. It remains to be determined whether FGF21 induces water consumption through different mechanisms in rats and mice.

Taken together, the thirst and preference findings suggest a prominent, pre-emptive role for endocrine FGF21 in maintaining water balance in the face of dehydrating nutritional conditions (Figure 2). FGF21 is strongly induced in liver by dehydrating nutrients, most notably alcohol, in both rodents and humans. In mice, FGF21's subsequent actions are two-fold: First, it stimulates thirst and water intake. Second, it promotes the drinking of pure water in order to optimize hydration. FGF21 mediates both these effects by signaling to the nervous system. The GWAS studies strongly suggest that FGF21's effect on preference is conserved in humans. Whether its effect on thirst is also conserved awaits further studies.

OUTSTANDING QUESTIONS

The physiologic and pharmacologic actions of FGF21 present an interesting conundrum: Why would a hormone that protects against nutritional stressors drive energy expenditure when administered pharmacologically to obese animals? The answer may lie in part in FGF21's activation of the SNS, which has obvious implications for energy expenditure. However, FGF21-mediated activation of the SNS may also be important for maintaining blood pressure in the face of dehydration and possibly starvation. In support of this hypothesis, FGF21-KO mice had reduced blood pressure when fed a ketogenic diet (Song et al., 2018). Conversely, pharmacologic FGF21 increased blood pressure in both rodents and humans (Kim et al., 2017; Turner et al., 2018). Thus, we speculate FGF21 evolved as an endocrine factor to stimulate sympathetic tone in the vasculature. Why FGF21 does not induce thermogenesis in the context of either dehydration or starvation is another outstanding question. Presumably, there are mechanisms to ensure that thermogenesis occurs only in the context of energy surfeit. Leptin is a candidate mediator of this role (Veniant et al., 2012a). Conversely, why aren't physiologic concentrations of FGF21 protective against obesity? Is there an FGF21 resistance? And on which neurons does FGF21 act to elicit its array of effects?

In closing, we raise a final, fundamental question: why isn't FGF21 mitogenic like conventional FGFs, especially since it acts on FGFR1, which is known to drive proliferation? Does KLB alter the signaling pathways downstream of the FGFRs? Given all these questions and many more, we anticipate that the next dozen years of FGF21 research will be as productive and interesting as the last.

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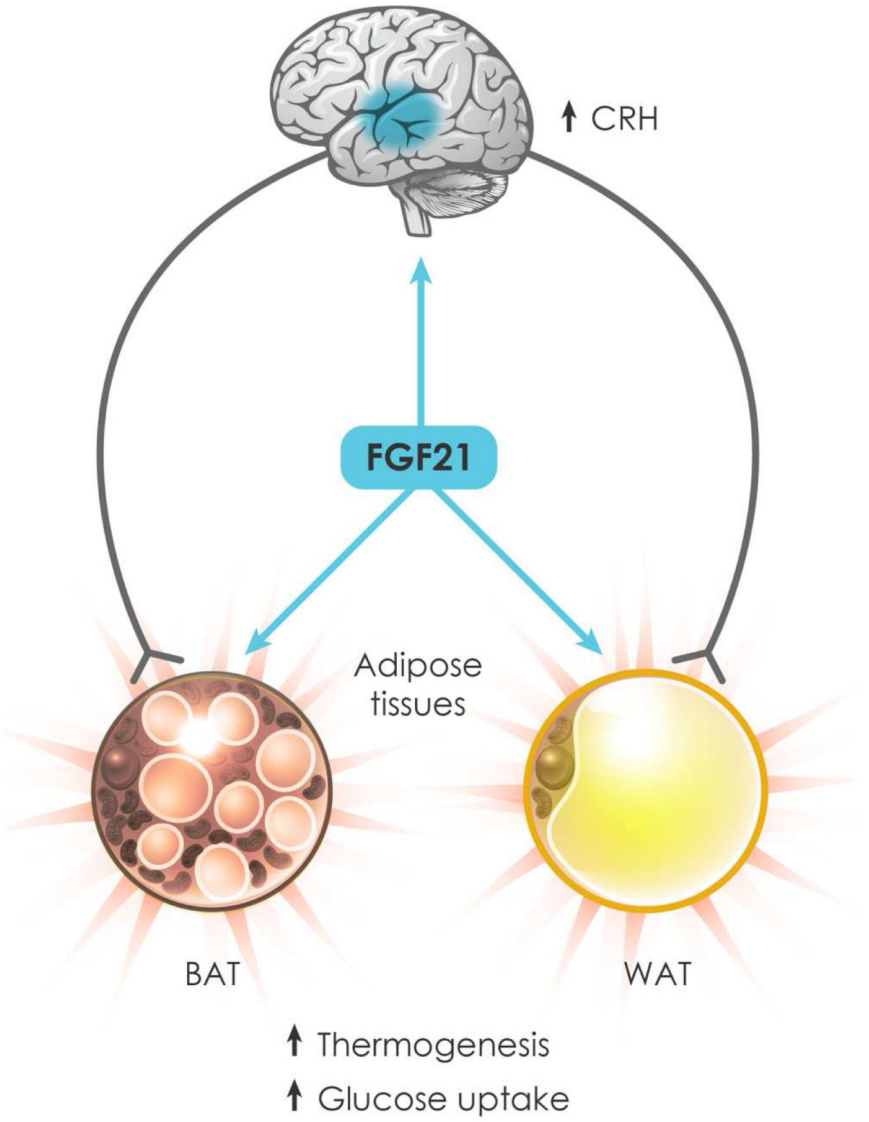

Figure 1.

FGF21 mediates its pharmacologic effects by acting directly on neurons and adipocytes. In the hypothalamus, FGF21 induces corticotropin-releasing hormone (CRH), resulting in sympathetic outflow to brown and white adipose tissue (BAT and WAT, respectively). FGF21 also acts directly on BAT and WAT to stimulate thermogenic gene expression and glucose uptake. The net effect is energy expenditure and weight loss in obese animals.

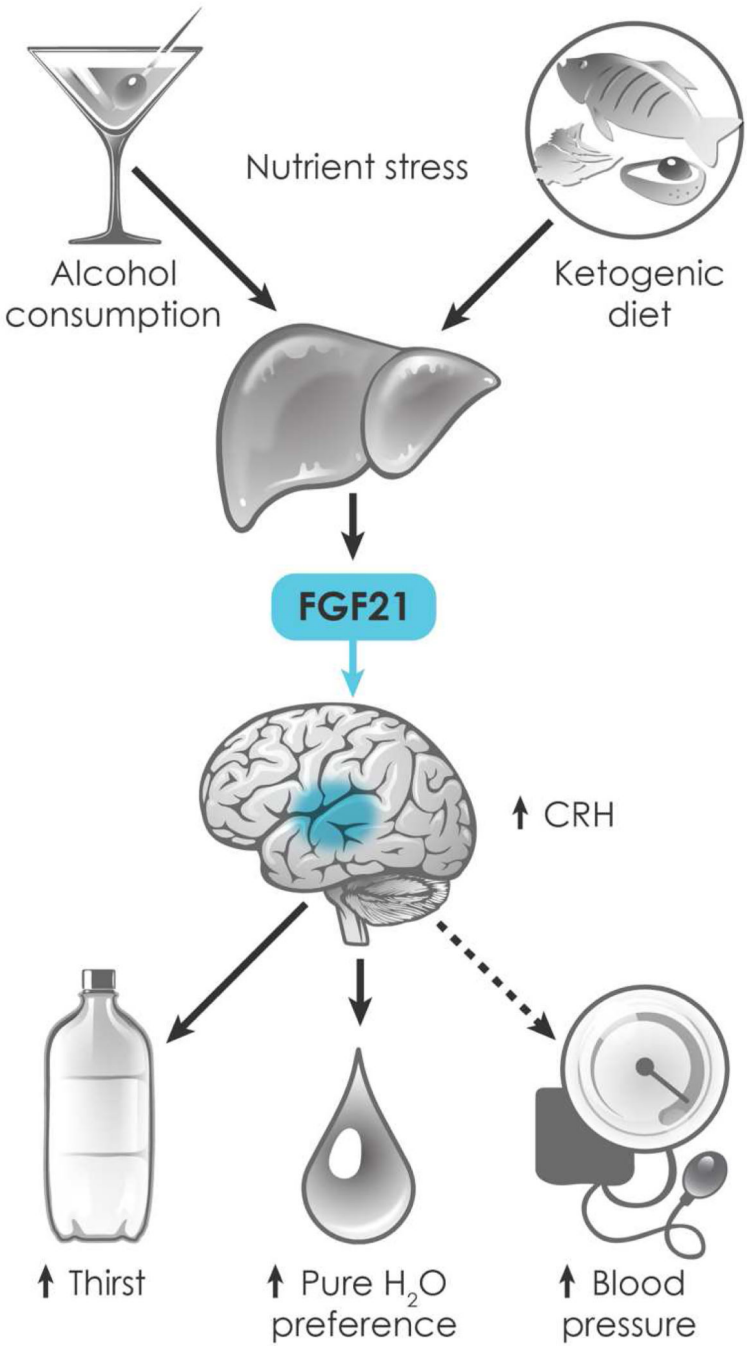

Figure 2.

Among its physiologic endocrine actions, FGF21 regulates hydration. FGF21 is induced in liver by dehydrating metabolic stresses, including alcohol and ketogenic diet, and circulates to the nervous system, where it stimulates thirst and drinking of pure water. FGF21 also stimulates blood pressure, possibly as a mechanism to prevent dehydration-associated hypotension.