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Tissue-specific Actions of the Metabolic Hormones FGF15/19 and FGF21

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Abstract

Fibroblast growth factors (FGFs) 15/19 and 21 belong to a subfamily of FGFs that function as hormones. Produced in response to specific nutritional cues, they act on overlapping sets of cell surface receptors composed of classic FGF receptors in complex with βKlotho, and regulate metabolism and related processes during periods of fluctuating energy availability. Pharmacologically, both FGF15/19 and FGF21 cause weight loss and improve both insulin sensitivity and lipid parameters, in rodent and primate models of metabolic disease. Recently, FGF21 was shown to have similar effects in obese patients with type 2 diabetes. Here, we discuss emerging concepts in FGF15/19 and FGF21 tissue specific actions and critically assess their putative role as candidate targets for treating metabolic disease.

Keywords

βKlotho; brown adipose tissue; hypothalamus; sympathetic nervous system; arginine vasopressin; corticotropin-releasing factor

Fibroblast growth factors: the basics

The fibroblast growth factors (FGFs; see Glossary) constitute a family of 22 proteins that regulate diverse biological processes such as growth, development, differentiation and wound repair (1). Most FGFs have a high affinity for heparan sulfate in the extracellular matrix and, thus, are restricted to functioning locally as autocrine or paracrine factors. By contrast, the endocrine FGFs, which include FGF15/19, FGF21 and FGF23, have little or no

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affinity for heparan sulfate and can therefore enter the circulation and function as hormones (2). (FGF15 and FGF19 are the mouse and human orthologs, respectively; we refer to them collectively as FGF15/19 unless referring to a specific ortholog.) FGF23 signals from the bone to the kidney to regulate phosphate levels (3). FGF15/19 and FGF21 regulate important aspects of metabolism, and as such, they represent potential pharmaceutical targets for the treatment of obesity, type 2 diabetes and dylipidemia (4). In this review, we will discuss the tissue-specific mechanisms of action of FGF15/19 and FGF21 with a focus on liver, adipose tissue and the nervous system.

Expression and physiological functions

FGF15/19 is expressed in ileal enterocytes of the small intestine, where it is induced by the nuclear receptor farnesoid X receptor (FXR), in response to the postprandial re-uptake of bile acids (Table 1) (5). After entering the portal venous circulation, FGF15/19 acts on the liver to repress bile acid synthesis and gluconeogenesis, and to promote glycogen and protein synthesis (4). FGF15/19 also stimulates gallbladder filling (6). Thus, FGF15/19 regulates diverse aspects of the postprandial response.

Unlike FGF15/19, FGF21 is expressed in multiple tissues including liver, brown adipose tissue (BAT), white adipose tissue (WAT) and pancreas (7). However, under normal physiologic conditions, all circulating FGF21 appears to be derived from liver (8). The molecular basis for this selective secretion of FGF21 from liver is not yet known. In the liver, FGF21 is induced by prolonged fasting by the nuclear receptor, peroxisome proliferator-activated receptor alpha (PPARα) (9–11), and by cyclic AMP responsive element-binding protein H (CREB-H) (12). Gain-of-function experiments show that FGF21 on its own can elicit diverse aspects of this starvation response. Among these, FGF21 stimulates hepatic fatty acid oxidation, ketogenesis and gluconeogenesis, and suppresses lipogenesis, discussed in detail below (9, 10, 13, 14). It blocks ovulation in female mice and suppresses growth (15, 16). In circadian wheel-running experiments, FGF21 reduces overall activity (17). It also sensitizes mice to the hibernation-like state of torpor (10). In complementary loss-of-function studies, FGF21-knockout (KO) mice have impaired ketogenesis and gluconeogenesis, and become prematurely hypoglycemic in response to starvation (13, 18). They also have reduced glucose uptake in BAT in response to refeeding (8).

FGF21 is also induced in liver by ketogenic, amino acid-deficient and low protein diets via PPARα and activating transcription factor 4 (ATF4)-dependent mechanisms (9, 19–21), suggesting that it plays a broad role in regulating energy homeostasis in response to nutritional stress. Accordingly, FGF21-KO mice fed a ketogenic diet gained more weight, developed hepatosteatosis and had impaired ketogenesis compared to wild-type mice (22). Interestingly, ketogenic diets do not induce FGF21 in humans (23–25). A plausible explanation for this discrepancy is that ketogenic diets used in rodent studies contain less protein than those used in humans (19). FGF21 is also elevated in serum of obese rodents and humans (24, 26–28), which may be an induced state of FGF21 resistance (28).

In adipose tissue, FGF21 is induced by the nuclear receptor PPARγ (29). In contrast to its regulation in liver, FGF21 in WAT is induced during the transition from the fasted to the fed state as part of a feed-forward regulatory loop that increases fatty acid storage (30). In BAT, FGF21 is induced by cold exposure and β3-adrenergic receptor stimulation by the stress-activated transcription factor, ATF2, and contributes to thermogenesis (31–33). In cold exposure experiments, FGF21-KO mice had lower body temperatures and elevated circulating levels of creatine kinase, consistent with increased shivering (33). The finding that FGF21 is downstream of agonists for both PPARα (in liver) and PPARγ (in adipose) suggests that some of the actions of the lipid-lowering fibrate and insulin-sensitizing thiazolidinedione drugs are due to FGF21. Indeed, FGF21-KO mice were refractory to the insulin-sensitizing actions of the thiazolidinedione, rosiglitazone (30).

In skeletal muscle, FGF21 is induced under conditions of mitochondrial dysfunction by ATF4 (34, 35). FGF21 is also expressed in the α- and β-cells of the endocrine pancreas (36) and in the exocrine pancreas, where its expression is induced by chemically-induced injury (37). While FGF21's physiologic function in pancreas remains to be determined, it increases insulin content and glucose-stimulated insulin secretion and inhibits glucagon secretion in isolated islets (38, 39), and it is protective in a mouse model of pancreatitis (37). Interestingly, PPARα, and ATF4 induce FGF21 in response to amino acid-deficient and low protein diets (9, 19–21). The induction of FGF21 by multiple nutrient-sensing transcription factors (e.g., PPARs, ATFs, and CREB-H) provides a mechanistic explanation for the tissue-specific expression of FGF21 under a range of nutritional contexts (Table 1).

Collectively these data highlight the complex metabolic actions of these hormones.

Pharmacologic effects

FGF15/19 and FGF21 have similar, powerful pharmacologic effects on metabolism (Figure 1). Transgenic overexpression or pharmacological administration of FGF19 or FGF21 to obese rodents increases energy expenditure without decreasing food intake, improves insulin sensitivity, reverses hepatic steatosis and lowers circulating and hepatic triglyceride and cholesterol concentrations (14, 39–42). FGF21 has similar pharmacologic effects in obese, insulin-resistant monkeys (43, 44). Thus, FGF15/19 and FGF21 are promising clinical candidates for treating metabolic disease. Recently, FGF21 was shown to improve metabolic parameters, including body weight and insulin and lipid levels, in obese humans with type 2 diabetes (45). Consistent with its ability to markedly lower insulin and insulin-like growth factor, long-term pharmacologic administration of FGF21 also leads to a profound extension of lifespan in mice (46). One possible adverse side effect of FGF21 is bone loss. In mice, FGF21 inhibits bone formation and stimulates bone resorption (47).

FGF15/19 and FGF21 require βKlotho

FGF receptors (FGFRs) consist of an extracellular ligand-binding domain, a single transmembrane domain and an intracellular tyrosine kinase domain. There are four FGFRs (FGFR1-4), with two splice variants (b and c) existing for FGFR1-3 (1).

Signaling by the endocrine FGFs requires a co-receptor from the Klotho family of single transmembrane proteins. While FGF23 signaling requires αKlotho, both FGF15/19 and FGF21 require βKlotho to bind to their FGF receptors (48). This then activates extracellular signal-regulated kinases 1 and 2 (ERK1/2) and other downstream kinases. Studies with global βKlotho-KO mice show that βKlotho is essential for most, if not all, of the physiological and pharmacological functions of FGF15/19 and FGF21 (49–51). FGF15/19 binds to βKlotho in complex with FGFR1c, 2c, 3c and 4. FGF21 also binds to βKlotho in complex with FGFR1c, 2c or 3c but, notably, not FGFR4 (48). Knockout studies in mice suggest that the FGFR1c isoform is particularly important for the in vivo actions of FGF21 (52, 53). Interestingly, many of the metabolic actions of both FGF19 and FGF21, in particular the weight loss and insulin-sensitizing effects, are recapitulated by activating antibodies directed against either FGFR1c or the FGFR1c/βKlotho heteromer (53, 54).

While the FGFRs are broadly expressed across tissues, βKlotho has a more restricted expression pattern (7). This distribution along with the availability of tissue-specific βKlotho-KO mice (17, 49) has facilitated studies into the tissue-specific actions of FGF15/19 and FGF21.

FGF15/19 and FGF21 actions on liver

Both βKlotho and FGFR4 are abundantly expressed in liver, where FGF15/19 suppresses bile acid synthesis and gluconeogenesis (5, 55–57). These effects can be recapitulated in primary cultures of hepatocytes (55, 57), demonstrating that FGF15/19 acts directly on the liver. FGF15/19 inhibits bile acid synthesis by repressing the transcription of the gene encoding cholesterol 7α-hydroxylase (CYP7A1), the enzyme that catalyzes the first and rate-limiting step in bile synthesis (55, 57). Elimination of either βKlotho or FGFR4 in mice (5, 50) or chemical inhibition of ERK1/2 in primary human hepatocytes (58) blocks this inhibition of *CYP7A1* by FGF15/19. As mentioned above, FGF15/19 also has a number of effects in hepatocytes that are similar to insulin, including stimulation of protein and glycogen synthesis and suppression of gluconeogenic gene expression (56, 57). Notably, however, an important difference to insulin is that FGF15/19 inhibits rather than stimulates fatty acid synthesis (59). In addition to its beneficial effects on liver metabolism, FGF15/19 also stimulates hepatocyte proliferation through an FGFR4-dependent mechanism (60, 61). Chronic exposure of mice to FGF19 resulted in hepatocellular carcinomas, and this effect was lost in FGFR4-KO mice (60, 62).

As noted above, FGF21 has dramatic effects on liver metabolism that include the induction of fatty acid oxidation, ketogenesis and gluconeogenesis and the suppression of lipogenesis (9, 10, 13, 14, 40). FGF21 has coordinate effects on hepatic gene expression that are consistent with these metabolic effects. However, in contrast to FGF15/19, these in vivo effects were not recapitulated in either isolated, perfused livers or primary rodent hepatocytes treated with FGF21 (13, 63). Moreover, tissue-specific knock out of βKlotho in nervous system (64) or FGFR1 in adipose tissue (52) eliminated most of FGF21's effect on hepatic gene expression. Thus, many of the effects of FGF21 on liver appear to be indirect. Consistent with this possibility, there is virtually no FGFR1 expression in liver and little or no FGFR2 and FGFR3 (7). However, FGF21 injection in mice was shown to induce

ERK1/2 phosphorylation and immediate early gene expression in liver (65), suggesting at least some direct effects may occur at pharmacologic concentrations. Further studies with liver-specific βKlotho-KO mice are needed to determine precisely how much of the effect of FGF21 on liver metabolism is direct.

FGF15/19 and FGF21 actions on adipose tissue

Both WAT and BAT express βKlotho and FGFR1c at high levels (7), indicating that they are likely to be target tissues for FGF15/19 and FGF21. A role for FGF21 in regulating metabolism was first suggested by in vitro experiments in which it increased glucose uptake in murine 3T3-L1 and primary human adipocytes (39). Additional studies showed that FGF21 induces ERK1/2 phosphorylation and genes involved in glucose uptake, lipogenesis, lipolysis and other aspects of lipid metabolism in white adipocytes in vitro and in vivo (14, 39, 63). Among the genes induced by FGF21 in white adipocytes was uncoupling protein 1 (*Ucp1*) (33), which is typically found in brown adipocytes, where it causes uncoupled respiration and thermogenesis. This so-called “browning” of white adipocytes occurs in subcutaneous WAT depots that are innervated by the sympathetic nervous system and likely contributes to FGF21's thermogenic effects (33). The expression and secretion of adiponectin, a hormone that regulates glucose and fatty acid homeostasis was also induced by FGF21 in white adipocytes both in vitro and in vivo (66, 67). Adiponectin is required for the full metabolic efficacy of FGF21 in vivo (66, 67).

As in white adipocytes, FGF21 stimulates glucose uptake and thermogenic gene expression in brown adipocytes both in vitro and in vivo (32, 33, 40, 49, 68). In terms of molecular mechanism, FGF21 increased the phosphorylation of the transcription factor cAMP response element-binding protein (CREB), which directly regulates *Ucp1* gene transcription (54). FGF21 also increased the phosphorylation of a second transcription factor, STAT3, which regulates mitochondrial respiration (54). Taken together, these findings highlight an important role for FGF21 in promoting thermogenesis by acting directly on BAT.

Two different loss-of-function approaches have been used to evaluate the importance of FGF21 acting on adipose tissue in vivo. First, FGF21 has been tested in aP2-SREBP-1c transgenic mice, which lack WAT and have dysfunctional BAT. These lipodystrophic mice were refractory to FGF21's beneficial effects on body weight, plasma insulin and glucose tolerance (54, 69). Second, the consequence of eliminating either βKlotho or FGFR1 selectively in adipose tissue in mice was examined using the aP2-Cre transgene, which disrupts floxed (fl) gene alleles in both WAT and BAT. The acute effects of FGF21 on insulin sensitivity and glucose uptake in BAT were lost in diet-induced obese mice with adipose tissue-selective βKlotho ($\beta Klotho^{fl/fl}$;aP2-Cre) deletion (49). Similarly, the effects of FGF21 on body weight as well as plasma glucose, insulin, triglycerides and adiponectin were lost in diet-induced obese mice with FGFR1 selective deletion in adipose tissue ($FGFR1^{fl/fl}$;aP2-Cre) (52). However, since the aP2-Cre transgene is also expressed in the nervous system (70), including sites where βKlotho is expressed (see below), additional studies are required with adipose-specific Cre drivers to clarify the relative importance of adipose tissue in the FGF21 response.

FGF19 administration also induces ERK1/2 phosphorylation in WAT (63). A recent study compared the pharmacologic effects of FGF19 and FGF21 in diet-induced obese $FGFR1^{fl/fl}$;aP2-Cre mice (52). The weight loss effects of both FGF19 and FGF21 were compromised in these KO mice, suggesting a common mechanism. However, while the beneficial glycemic actions of FGF21 were lost in $FGFR1^{fl/fl}$;aP2-Cre mice, those of FGF19 were not. These data highlight important differences in the target tissues and/or target receptor complexes of FGF15/19 and FGF21.

FGF15/19 and FGF21 actions on the nervous system

While all four FGFRs are broadly expressed throughout the nervous system, βKlotho has a much more restricted expression pattern (7). In the hypothalamus, βKlotho is expressed in the suprachiasmatic nucleus (SCN) (17), which regulates circadian rhythm, and in the paraventricular nucleus (PVN) (18), which is activated in response to various physiological stresses. βKlotho is also expressed in the area postrema and solitary nucleus in the hindbrain and in the nodose ganglia of the periphery (17). Together these nuclei comprise the dorsal-vagal complex, which serves as a major integrative center for the autonomic nervous system.

Neither FGF15/19 nor FGF21 are expressed in the adult brain (7), although FGF15/19 is expressed in the nervous system during development (71, 72). FGF21 crosses the blood-brain barrier by simple diffusion (73) and is present in human cerebrospinal fluid (74) and in the hypothalamus of fasted mice (18), where it induces ERK1/2 phosphorylation (75). Intracerebroventricular (i.c.v) injection of FGF21 increases energy expenditure and insulin sensitivity in diet-induced obese rats (76), and central administration of FGF21 is sufficient to promote hepatic gluconeogenesis in lean mice (18), demonstrating that FGF21 can act directly on the brain. Likewise, i.c.v. injection of FGF19 improved glucose tolerance and increased metabolic rate in ob/ob mice through an insulin-independent mechanism (41, 77). In rats, i.c.v. injection of FGF19 improved glucose tolerance, decreased food intake and caused weight loss (78). However, FGF19 crosses the blood-brain barrier less efficiently than FGF21 (79). Whether this difference in brain permeability has physiologic or pharmacologic consequences remains to be determined.

Recent work has shown that βKlotho expression in the nervous system is required for many of the chronic actions of FGF21 in lean mice, including its effects on ketogenesis, growth, circadian behavior and female reproduction (16, 17). Likewise, in diet-induced obese mice, the beneficial metabolic effects of FGF21 on body weight and insulin sensitivity were absent in mice lacking βKlotho in the nervous system as were its effects on metabolic gene expression in WAT, BAT and liver (64). These studies further showed that FGF21 acts on the nervous system to stimulate sympathetic nerve outflow to BAT, which induces fatty acid oxidation and thermogenesis. All of these effects require that FGF21 acts on the hypothalamus, since the phenotypes were maintained in mice lacking βKlotho in the dorsal-vagal complex but were lost in mice lacking βKlotho in both the hypothalamus and the dorsal-vagal complex (64). FGF21 may also stimulate sympathetic outflow to WAT to induce both the browning of white adipocytes and the lipolysis required for hepatic ketogenesis. This would explain why these effects of FGF21 are lost in mice lacking βKlotho in the nervous system (17, 64).

In the hypothalamus, FGF21 affects the expression of two key neuropeptides: arginine vasopressin (AVP) and corticotropin-releasing factor (CRF) (16–18, 64). In lean mice, chronic administration of FGF21 dampens *Avp* expression in the SCN (16). Conversely, *Avp* mRNA levels were elevated in the hypothalamus of fasted, nervous system-specific βKlotho-KO mice. In female mice, reduced AVP levels cause lower levels of luteinizing hormone, which is secreted from the pituitary to induce ovulation. Accordingly, FGF21 administration blocked the estrous cycle. This anovulatory effect of FGF21 was overcome by i.c.v. administration of AVP (16).

In addition to suppressing AVP, FGF21 administration induces *Crf* expression in the hypothalamus (17, 18, 64). CRF in turn increases adrenocorticotropic hormone secretion from the pituitary, which stimulates adrenal glucocorticoid secretion and hepatic gluconeogenesis. Accordingly, FGF21 administration increased circulating corticosterone levels and gluconeogenesis in mice (13, 17). Conversely, the induction of *Crf* and gluconeogenesis by starvation was attenuated in FGF21-KO mice (13, 18). CRF also activates sympathetic nerve activity to BAT (80). Notably, FGF21's induction of sympathetic nerve activity to BAT was completely blocked by a CRF receptor antagonist (64). Thus, induction of CRF represents a common mechanism whereby FGF21 induces glucocorticoids/gluconeogenesis and thermogenesis/weight loss. CRF also inhibits growth and female reproduction (81, 82), and thus may contribute to FGF21's effects on these processes as well.

It remains to be determined precisely where in the hypothalamus FGF21 acts to induce *Crf* expression. βKlotho and CRF are most highly expressed in the SCN and PVN, respectively. Since SCN-mediated regulation of CRF is the basis for daily fluctuations in glucocorticoid concentrations (83), FGF21 may regulate CRF expression in the PVN indirectly by acting on the SCN. However, a recent report showed that βKlotho is also expressed in CRF neurons in the PVN, where FGF21 induces *Crf* gene expression by activating the transcription factor CREB (18), much like FGF21 induces *Ucp1* in BAT (54). Thus, FGF21 could induce *Crf* in the PVN through either direct or indirect actions.

Concluding remarks and future perspectives

Since their cloning at the turn of the millennium, the characterization of FGF15/19 and FGF21 has been replete with interesting twists and turns, from the finding that both can act as hormones to the discovery of their striking and diverse biological actions (Table 1). Although tremendous progress has been made in understanding the physiologic and pharmacologic actions of these two hormones, much remains to be learned regarding their mechanisms of action. For example, while this review is focused on liver, adipose tissue and brain (summarized in Figure 1), βKlotho and the FGF receptors are expressed in other key metabolic tissues such as endocrine and exocrine pancreas (37, 38), where its contribution to the whole-body actions of FGF15/19 and FGF21 remains largely unexplored. In addition, while the requirement of βKlotho is well established, further studies using tissue-specific knockouts of the various FGFR genes are needed to establish their definitive involvement in mediating many of the effects of FGF15/19 and FGF21.

FGF21 mediates many of its pharmacologic effects by acting directly on the nervous system and adipose tissue. One outstanding question is why knocking out either βKlotho in the nervous system or FGFR1 in adipose tissue has a similar disruptive effect on FGF21 action. One possibility is that FGF21 acts on adipose tissue and brain simultaneously to provide both the fuel and the fire to drive weight loss. In this regard, efficient BAT-mediated thermogenesis requires both the mobilization of oxidative substrate and the induction of sympathetic outflow (84). FGF21 regulates both processes in BAT and presumably browned WAT, which likely accounts for its efficacy in causing weight loss in the context of obesity. The finding that FGF21-mediated induction of thermogenesis requires a state of energy excess (64) explains why FGF21 does not increase energy expenditure in lean mice. While at least some humans have metabolically-active BAT and the capacity to brown WAT (85), it remains to be determined if FGF21 acts through the same mechanism in people. It also remains to be seen whether FGF21 activates sympathetic outflow to tissues other than BAT such as the heart and vasculature. If so, FGF21 may have effects on heart rate and blood pressure.

As noted above, activating antibodies against either FGFR1c or the FGFR1c/βKlotho heteromer can recapitulate many of the pharmacologic effects of both FGF19 and FGF21 (53, 54). Given that the SCN and PVN are protected by the blood-brain barrier, which is generally considered impervious to antibodies, how can these findings be reconciled with a requirement for FGF21 to act on the nervous system? We suggest two possibilities. First, assuming that there is cooperativity between FGFR1c/βKlotho complexes in the nervous system and adipose tissue, efficacious activation of receptors in the adipose tissue alone may elicit a response in the context of some minimal degree of endogenous FGF21 activity in the brain. A second, trivial explanation is suggested by evidence that at least some antibodies, including one against FGFR1 (86), can cross the blood-brain barrier, albeit inefficiently. Thus, even low levels of high-affinity antibodies might be sufficient to elicit the response.

While FGF15/19 shares many of FGF21's pharmacologic effects, less is known about its target tissues. Because FGF15/19 acts on the FGFR4/βKlotho complex, it has strong effects in liver that are not shared by FGF21. In addition to its requisite role in bile acid homeostasis, FGF15/19 suppresses hepatic gluconeogenesis and induces glycogen synthesis (56, 57, 87), which could contribute to its beneficial glycemic profile. However, the finding that FGF19 derivatives with little or no FGFR4 activity retain their glycemic activity in ob/ob mice (88, 89) suggests that FGF19 exerts a major part of its metabolic effect through direct actions on tissues other than liver.

In closing, FGF15/19 and FGF21 are both exciting candidates for treating metabolic disease, and derivatives of both are currently in clinical trials. In addition, FGF15/19 may have utility in treating bile acid-related diseases such as primary biliary cirrhosis and bile acid diarrhea. However, both hormones have potential side effects, including liver mitogenicity for FGF15/19 (60) and bone loss for FGF21 (47). Whether these side effects are manifest in patients remains to be seen. Notably, it may be possible to engineer derivatives that minimize or lack these side effects. Already, FGF15/19 derivatives have been reported that lack the liver mitogenicity while retaining its beneficial metabolic or bile acid effects (89,

90). Clearly, future studies into understanding the mechanisms of action of FGF15/19 and FGF21 are the key to unlocking their full pharmaceutical potential.

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Glossary Box

Arginine vasopressin (AVP)	Neuropeptide that regulates many physiologic processes, including water retention and vasoconstriction. Among its actions, AVP secreted from the SCN inhibits the hypothalamic-pituitary-adrenal axis and glucocorticoid secretion
Brown adipose tissue (BAT)	Type of adipose tissue that is specialized to dissipate the mitochondrial proton gradient as heat
Corticotropin-releasing factor (CRF)	Neuropeptide that regulates many stress-related processes. Among its actions, CRF secreted from the PVN activates the hypothalamic-pituitary-adrenal axis to stimulate glucocorticoid secretion
Cytochrome P450 7A1 (CYP7A1)	Enzyme that catalyzes the first and rate-limiting step in the classic bile acid synthetic pathway
Extracellular signal-regulated kinases 1 and 2 (ERK1/2)	Intracellular protein kinases activated by diverse extracellular stimuli, including FGFs
Fibroblast growth factors (FGFs)	Family of secreted proteins that regulate diverse biological processes, including growth, development, differentiation and metabolism
FGF receptors (FGFRs)	Transmembrane proteins with an intracellular tyrosine kinase domain that is activated by the binding of an FGF to an extracellular domain. In mammals, there are four genes encoding FGFRs
Intracerebroventricular (i.c.v.)	Direct introduction of drugs or chemicals into the ventricles of the brain
Paraventricular nucleus (PVN)	Region of the hypothalamus in brain activated by various stress conditions. It secretes the neuropeptide CRF
Suprachiasmatic nucleus (SCN)	Region of hypothalamus in brain that controls circadian behavior
Uncoupling protein-1 (UCP1)	Protein present on inner mitochondrial membrane that disrupts the respiratory proton gradient, resulting in

	the generation of heat. Present in BAT and induced by cold and other stress condition in WAT
White adipose tissue (WAT)	Type of adipose tissue that is specialized to synthesize and store fatty acids as triglyceride

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- FGF15/19 and FGF21 have beneficial effects on body weight and insulin sensitivity.
- FGF15/19 acts on the liver to regulate bile acid homeostasis.
- FGF21 acts on adipose tissue and the brain to exert many of its metabolic effects.
- FGF21 activates the sympathetic nervous system.

Outstanding Questions Box

- Do FGF15/19 and FGF21 exert their beneficial effects on body weight, insulin sensitivity and dyslipidemia through the same mechanism?
- Do activating antibodies against either FGFR1c or the FGFR1c/βKlotho heteromer exert their metabolic effects through the same pathways as FGF15/19 and FGF21?
- Why does elimination of the FGFR1c/βKlotho receptor complex in either adipose tissue or brain disrupt FGF21's weight loss and insulin sensitizing actions?
- How much of the effect of FGF15/19 and FGF21 on hepatic metabolism is mediated directly on the liver?
- Does FGF21 activate sympathetic outflow to tissues other than BAT such as WAT, adrenal, heart and the vasculature?
- What are the functions of βKlotho in the endocrine and exocrine pancreas?

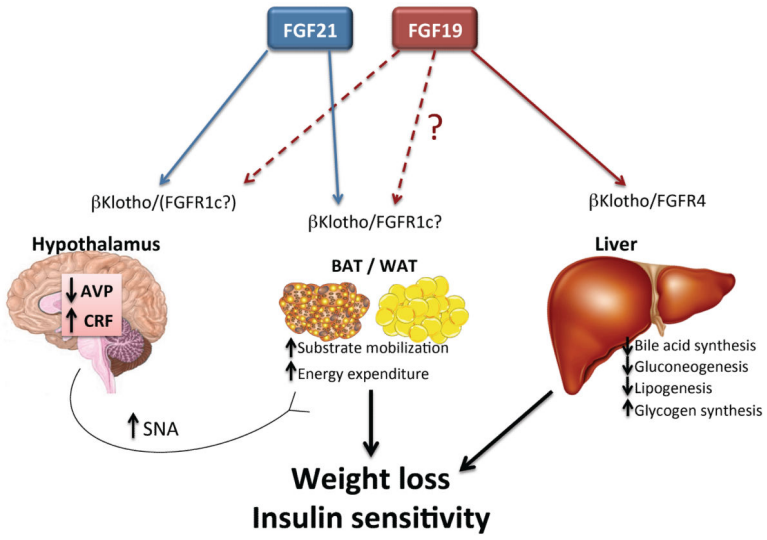

Figure 1. Schematic representation of the beneficial pharmacological actions of FGF19 and FGF21

In obese animals, pharmacologic administration of FGF19 and FGF21 causes weight loss and increases insulin sensitivity. FGF21 increases thermogenic energy expenditure through its coordinate action on adipose tissue and the hypothalamus to mobilize glucose and lipids, and to stimulate sympathetic nerve activity via AVP and CRF. These effects of FGF21 require signalling through βKlotho and one of the FGFRs (likely FGFR1c). In this way, FGF21 provides both the fuel (oxidative substrate) and the fire (beta adrenergic signaling) to drive heat production in the obese state. FGF19 works directly on liver through βKlotho and FGFR4 to decrease bile acid synthesis and provide beneficial effects on cholestatic diseases. In addition, FGF19 suppress hepatic glucose and lipid production, but may also improve metabolic parameters by activating similar processes to FGF21 in adipose and the CNS.

Table 1

Summary of FGF15/19 and FGF21 actions in different biological contexts

Hormone	Stimulus (transcriptional inducer)	Tissue source of FGF	Target Tissue	Effect	References
FGF15/19	Postprandial bile acids (FXR)	Small intestine	Liver	↓ Bile acid synthesis	(5)
				↓ Gluconeogenesis	(56)
				↑ Glycogen synthesis	(87)
				↑ Protein synthesis	(87)
	Pharmacology		Liver CNS BAT WAT	Beneficial	
				↓ Bile acid synthesis	(5)
				↓ Gluconeogenesis	(56)
				↑ Glycogen synthesis	(87)
				↑ Thermogenesis and weight loss	(41, 42)
				↑ Insulin sensitivity	(41, 42)
				↓ Blood triglyceride levels	(41, 42)
				↓ Blood cholesterol levels	(41, 42)
				Adverse	
				↑ Liver cell growth, neoplasia	(60)
FGF21	Starvation (PPARα,CREB-H)	Liver	CNS	↑ Hepatic fatty acid oxidation, ketogenesis and gluconeogenesis	(9, 10, 13)
				↑ Growth hormone resistance	(15)
				↓ Ovulation	(16)
				↓ Wheel-running activity	(17)
	Fasting/refeeding, overfeeding (PPARα, PPARγ)	Liver WAT	BAT WAT	↑ Glucose uptake and fatty acid storage	(8, 30)
	Cold (ATF2)	BAT WAT	BAT WAT	↑ Thermogenesis	(31–33)
				↑ Browning of WAT	(33)
	Ketogenic, low amino acid/protein diets (PPARα, ATF4)	Liver	CNS BAT	↑ Hepatic fatty acid oxidation and ketogenesis	(9, 22, 91)
				↑ Thermogenesis and weigh↑ loss	(19, 22)
	Mitochondrial dysfunction, pancreatitis (ATF4)	Skeletal muscle Pancreas	N/K	N/K	(35, 37, 92)
	Pharmacology		CNS BAT WAT	Beneficial	
				↑ Thermogenesis and weigh↑ loss	(14, 39, 40)
				↑ Browning of WAT	(33)
				↑ Glucose uptake	(40, 49)

Hormone	Stimulus (transcriptional inducer)	Tissue source of FGF	Target Tissue	Effect	References
				↑ Insulin sensitivity	(40, 93)
				↓ Blood triglyceride levels	(39, 43)
				↓ Blood cholesterol levels	(9, 10, 43)
				↑ Lifespan	(46)
				Adverse	
				↑ Bone loss	(47)
				↑ Glucocorticoids	(17, 64)

N/K, not known.