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Metabolic fibroblast growth factors (FGFs): Mediators of energy homeostasis

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Abstract

The metabolic fibroblast growth factors (FGFs), FGF1, FGF15/19, and FGF21 differ from classic FGFs in that they modulate energy homeostasis in response to fluctuating nutrient availability. These unique mediators of metabolism regulate a number of physiological processes which contribute to their potent pharmacological properties. Administration of pharmacological doses of these FGFs causes weight loss, increases energy expenditure, and improves carbohydrate and lipid metabolism in obese animal models. However, many questions remain regarding the precise molecular and physiological mechanisms governing the effects of individual metabolic FGFs. Here we review the metabolic actions of FGF1, FGF15/19, and FGF21 while providing insights into their pharmacological effects by examining known biological functions.

Keywords

FGF21; FGF15; FGF19; FGF1; Obesity; Metabolism

1. Metabolic FGFs

The fibroblast growth factor (FGF) family consists of 22 members involved in a myriad of functions including development, cancer, and metabolism. Classically, FGFs are considered intracrine or paracrine factors. A small subset of FGF members (FGF11-14) function intracellularly while the majority of FGFs are secreted factors [1]. Paracrine FGFs act locally and bind to a cognate FGF receptor, an interaction which is stabilized via heparan sulphate glycosaminoglycan binding. The FGF19 subfamily (FGF15/19, FGF21, FGF23), however, represent an atypical group of FGFs because they lack an affinity for heparan sulfates which allows them to freely diffuse away from their tissue of origin and serve as endocrine molecules [2]. Paracrine and endocrine FGFs signal through cell surface localized FGF receptors (FGFRs) belonging to the tyrosine kinase receptor family [1]. Upon FGF binding, an FGFR dimer forms resulting in receptor transphosphorylation and subsequent activation of downstream signaling cascades initiated through phosphorylation of FRS1/

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PLCγ1 or FRS2α/β [3]. Importantly, members of the FGF19 subfamily require a co-factor to initiate signaling, which in the case of FGF15/19 and FGF21, is a co-factor termed β-klotho [4–7], and in the case of FGF23, is a co-factor termed α-klotho (or Klotho) [8]. In the past decade, it was discovered that several FGFs including FGF1, FGF15/19 and FGF21, possess profound metabolic actions (Fig. 1). This review focuses on the metabolic actions of these FGFs and the development of pharmacological strategies to employ these FGFs in the treatment of metabolic disease.

2. Metabolic actions of FGF21

Multiple studies have demonstrated that extended administration of FGF21 to obese rodent or primate models improves glucose and lipid homeostasis, reduces adiposity, and increases weight loss without decreasing food intake [9–12] (Fig. 1). Remarkably, a single acute injection of FGF21 in either genetic- (i.e., *ob/ob*) or diet-induced obese mice significantly improves glucose homeostasis and insulin sensitivity [13] demonstrating therapeutic efficacy independent of a reduction in body weight. In humans, administration of an FGF21 analog, LY2405319, to obese patients significantly reduced plasma triglycerides, plasma cholesterol, plasma insulin, and body weight [14]. Therefore, FGF21 has profound effects on metabolic homeostasis which may be therapeutically targeted for the treatment of human disease.

FGF21 preferentially signals to tissues through a receptor complex consisting of FGFR1c and β-klotho (Fig. 1). While FGFR1 has a broad tissue distribution, β-klotho is expressed in a limited number of metabolic tissues including adipose tissue, liver, pancreas [15] and specific brain nuclei including the nucleus tractus solitarii (NTS), area postrema (AP), suprachiasmatic nucleus (SCN) [16] and paraventricular nucleus (PVN) [17]. Therefore, the tissue-specific effects of FGF21 are limited to those expressing β-klotho [18,19]. β-klotho functions as a scaffolding molecule forming a ternary complex with FGFR1c [5,7] and the C-terminus of FGF21, thereby allowing FGF21 to interact with FGFR1 and initiate signaling [20–22]. FGF21 activation of FGFR1 results in receptor transphosphorylation and phosphorylation of FRS2α which leads to activation of the MAPK signaling pathway and increased levels of ERK1/2 phosphorylation [4,7]. However, the precise signaling cascade(s) linking FGF21 to its metabolic actions remain unclear.

The expression and metabolic actions of FGF21 are uniquely affected by nutritional status [23] and stress of the organism [24,25]. In addition, FGF21 function is affected by other endocrine signals present in circulation in these contexts. *Fgf21* mRNA expression is detectable in multiple tissues including the liver, white adipose tissue (WAT), brown adipose tissue (BAT), muscle, pancreas, and heart [26]. However, while FGF21 protein has been reported in the media from many of these cell types, circulating levels of FGF21 are derived primarily, if not exclusively, from the liver in vivo as circulating FGF21 levels are completely abolished in liver-specific FGF21 knockout mice [27]. In the following sections, we will review the major metabolic effects of FGF21 and will attempt to incorporate a physiological context for these actions.

2.1. Glucose metabolism

2.1.1. Acute FGF21 administration—A single injection of recombinant FGF21 significantly lowers plasma glucose levels in genetically obese (*ob/ob*) and diet-induced obese (DIO) mice without inducing hypoglycemia [13]. This acute effect is dramatic, lowering plasma glucose levels by over 50% in obese mice, an effect which lasts up to 6 h [13]. Several studies have demonstrated an important role for adipose tissues in mediating the acute metabolic effects of FGF21. Mice lacking either β-klotho [19] or FGFR1 in adipose tissue [28] do not respond to acute FGF21 administration. However, it is currently unclear which type(s) of adipocytes (i.e., white, brown, or brite/beige) FGF21 signals to in order to mediate its glucose lowering effects. Moreover, the molecular signaling mechanisms for this effect have not been completely determined. At the systems level, the acute glucose lowering effects of FGF21 are primarily due to enhanced glucose disposal and whole body glycolysis, and to a lesser extent, suppression of endogenous glucose production [13]. Using hyperinsulinemic-euglycemic clamps and radioactive 2-deoxyglucose uptake, two groups independently demonstrated that acute administration of FGF21 to DIO mice increased whole-body glucose uptake, markedly increased glucose infusion rate, and trended to decrease endogenous glucose production [13,19]. Consistent with these results, acute administration of a pegylated form of FGF21 to DIO mice significantly increased the rate of glucose disposal without effecting endogenous glucose production [29]. Assessment of the relative tissue-specific uptake of glucose at the end of the clamps differed between the studies, with one group observing increased glucose uptake only in brown adipose tissue (BAT) [19], and the other group reporting increased glucose uptake in multiple tissues including white and brown adipose tissue, heart, and skeletal muscle of DIO mice treated with FGF21 [13]. Yet, both studies clearly demonstrate that brown adipose tissue, and potentially other tissues, facilitate the ability of FGF21 to acutely and potently enhance insulin sensitivity. Interestingly, FGF21 acutely enhances insulin stimulated glucose uptake in primary brown adipocytes, but not primary white adipocytes [27], suggesting direct effects. Collectively, these studies suggest that the acute insulin-sensitizing effects of FGF21 are mediated by direct FGF21 signaling to adipose tissue and may involve both non-cell autonomous and cell autonomous mechanisms to regulate glucose homeostasis.

Two recent studies reported that adiponectin levels are induced in response to FGF21 administration, and that adiponectin is critical for the acute insulin-sensitizing effects of FGF21 [30,31]. However, a more recent study did not detect any changes in adiponectin levels either in vivo or in vitro in response to FGF21 [32]. In addition, circulating adiponectin levels are not altered under physiological conditions when circulating FGF21 levels are induced [27]. And finally, administration of a bispecific antibody agonist for the FGFR1/β-klotho complex acutely increased insulin sensitivity in diet-induced obese mice lacking adiponectin [33]. It is important to note that while FGF21 primarily functions to enhance peripheral glucose disposal [13,19,29], adiponectin functions to suppress hepatic glucose production [34,35]. Therefore, the modest decrease in endogenous glucose production following acute FGF21 administration is likely attributable to adiponectin, whereas the FGF21-mediated effects on peripheral glucose disposal are adiponectin-independent and function through enhanced insulin-stimulated glucose uptake.

Physiologically, FGF21 has multiple functions, one of which is to enhance insulin sensitivity. FGF21 is induced during fasting, refeeding, and overfeeding [23,27]. The function of FGF21 during these metabolically distinct conditions is impacted by the presence or absence of other endocrine signals. During fasting when insulin is absent or reduced, elevated circulating FGF21 regulates hepatic gluconeogenesis, beta-oxidation [36] and adipose tissue lipolysis [37]. However, during refeeding when both insulin and FGF21 levels are increased in circulation, FGF21 functions to maximize nutrient uptake by enhancing insulin-stimulated glucose uptake [27] (Fig. 2). During this time, FGF21 likely serves as a metabolic switch facilitating the transition from prolonged fasting into a refed state. By enhancing insulin-stimulated nutrient uptake while still acutely regulating aspects of the fasting response, FGF21 mediates energy homeostasis when nutrient availability is fluctuating [27].

In addition to refeeding, circulating FGF21 levels are elevated by overfeeding and insulin resistance [23] (Fig. 2). During overfeeding, as the nutrient load reaches excess, FGF21 may act in a compensatory manner to mitigate decreasing insulin sensitivity and facilitate insulin-stimulated disposal of excess glucose to brown adipose tissue [27] (Fig. 3). Although the transcriptional mechanisms responsible for hepatic FGF21 induction during overfeeding have not been clearly defined, the presence of the glucose activated transcription factor, ChREBP, binding element in the FGF21 promoter could function to induce both hepatic and plasma FGF21 protein levels when plasma glucose levels are abnormally elevated [38,39]. At some point, however, tissues may become “FGF21 resistant” [40], resulting in the gradual increase in plasma FGF21 levels observed with extended high fat diet feeding without an improvement of metabolic function. Importantly, while tissues of obese animals may have impaired signaling in response to physiological levels of FGF21, tissues are not completely resistant to FGF21 function. Compared to wild-type DIO mice that have impaired FGF21 signaling, DIO mice lacking circulating FGF21 have worsened glucose and insulin tolerance and increased hepatic steatosis [27] which demonstrates that FGF21 still provides some protective metabolic function under these conditions. In addition, obese animal models are still responsive to pharmacological levels of exogenous FGF21, much like insulin administration during insulin resistance. Indeed, the ED_{50} value for the glucose lowering effects of FGF21 in insulin resistant (and perhaps FGF21 resistant) mice, are well above physiological levels [41].

2.1.2. Chronic FGF21 administration—Extended administration of FGF21 increases energy expenditure and weight loss which also leads to increases in insulin sensitivity and glucose uptake [10,11] (Fig. 3). These effects on energy expenditure and weight loss are more pronounced in diet-induced models of obesity compared to genetic, leptin-deficient models (i.e., *ob/ob*). For example, pharmacological administration of FGF21 to DIO mice reduced body weight by ~20% when administered for 10 days, whereas *ob/ob* mice receiving the same dose of FGF21 for 22 days had an ~5% increase in body weight compared to 10% increase by controls [41]. Thus, in leptin-deficient mice, FGF21 reduces weight gain compared to increasing weight loss in DIO mice. It is unclear if these effects are due to loss of leptin in *ob/ob* mice or the gain of specific fuels/calories by high fat diet. It will be interesting to determine whether FGF21 signaling impacts leptin’s ability to increase

energy expenditure [42] similar to FGF21 enhancing insulin action to mediate the acute glucose lowering effects (Fig. 3). Notably, obese humans receiving the FGF21 analog LY2405319 for 28 days had an approximate 2% decrease in body weight [14], which demonstrates that the metabolic effects of FGF21 are therapeutically applicable to human disease. While the reduction in plasma glucose levels in this human study trended lower and did not achieve statistical significance, insulin levels significantly decreased, suggesting improved insulin sensitivity [14]. Glucose tolerance, however, was not assessed in these patients.

Compared to the hyperinsulinemic-euglycemic clamp studies in rodents following acute FGF21 administration, clamp studies in DIO mice treated with recombinant FGF21 for three weeks revealed an increased glucose infusion rate, decreased basal and clamp hepatic glucose production, and increased glucose turn-over and glycogen synthesis, demonstrating enhanced insulin sensitivity and overall improved glucose handling compared to vehicle treated controls [10]. Enhanced glucose uptake determined by 2-deoxyglucose tracing at the end of these clamp studies also revealed enhanced FGF21-mediated glucose uptake into multiple tissues including white and brown adipose tissues, heart and skeletal muscle [10]. Similar clamp data pertaining to glucose flux and glucose uptake were reported for lean and DIO mice infused with recombinant FGF21 for seven days [43]. In addition to clamp studies, assessment of tissue-specific glucose uptake by [^{18}F]-FDG/PET imaging in DIO mice revealed that brown adipose tissue, but not muscle, is a major site of glucose disposal following FGF21 administration for 2 weeks [44].

To determine which tissue(s) FGF21 directly signals upon to mediate its metabolic actions, two independent groups utilized tissue-specific FGF21 receptor knockout mice. The first group used β-klotho conditional knockout mice to remove β-klotho from the nervous system (β-klotho$^{fl/fl}$;Camk2a-Cre), and found that the effects of FGF21 on body weight and insulin sensitivity were lost in DIO β-klotho$^{fl/fl}$;Camk2a-Cre mice [45]. This study also demonstrated that administration of FGF21 directly into the brain via intracerebroventricular (ICV) injection increased sympathetic nerve activity, which functions to increase thermogenesis in adipose tissues [45]. Consistent with FGF21 acting on the nervous system, previous studies in rats demonstrated that ICV administration of FGF21 increases energy expenditure [46]. In contrast, however, a second group generated adipose-specific FGFR1 knockout mice (FGFR1$^{fl/fl}$;aP2-Cre) and determined that DIO FGFR1$^{fl/fl}$; aP2-Cre mice were refractory to the effects of FGF21 on energy expenditure and lowering of plasma insulin, glucose, and triglycerides [28]. In addition, the authors state, but do not show, that ablation of FGFR1 from neurons (using a Nestin-Cre) did not impair the metabolic actions of FGF21 [28]. Consistent with FGF21 acting directly on adipose tissue, FGF21 administration to lipodystrophic mice (aP2-SREBP-1c transgenic) lacking mature adipocytes did not affect body weight or glucose homeostasis [47,48]. Therefore, both adipose tissue and the central nervous system have been implicated as direct target tissues mediating the effects of FGF21 on energy expenditure (Fig. 3), but additional studies are necessary to delineate the cellular target(s) of FGF21 action.

The molecular mechanism(s) underlying the metabolic effects of extended FGF21 administration are also unclear although significant insight has been provided by a number

of recent studies. The glucose lowering effect of extended FGF21 administration is independent of hepatic glucose production or improved hepatic insulin sensitivity. FGF21 effectively lowered plasma glucose levels in lean and diet-induced obese liver insulin receptor knockout mice which maintain elevated hepatic glucose production [49]. Alternatively, a number of studies have reported that extended administration of FGF21 induces a thermogenic gene expression profile in both white and brown adipose tissue [23,50] including induction of uncoupling protein 1 (UCP1), a specialized inner mitochondrial membrane protein which dissipates chemical energy as heat. These effects on gene expression also occur in vitro in differentiated brown and white adipocytes treated with FGF21 [51,52], suggesting FGF21 signals directly to these tissues to mediate a thermogenic response. The energy expending effects of FGF21, therefore, have been proposed to be mediated by adipose tissue thermogenesis. While the exact physiological context for these thermogenic effects are unclear, FGF21 has been shown to increase adipose thermogenic gene expression by increased hepatic production in neonates in response to milk [53], and being produced from adipose tissue in response to cold [52,54–56]. In addition, it was also recently determined that FGF21 is induced in rodents and humans in response to dietary protein restriction [57]. Protein restriction increases energy expenditure and decreases adiposity [57,58], both effects which require FGF21 [57].

While adipose-tissue thermogenesis has been proposed to mediate the energy expending effects of FGF21, two recent studies demonstrated that UCP1 is not required for the effects of FGF21 on energy expenditure in vivo [59,60]. In addition, the importance of brown adipose tissue in mediating the effects of FGF21 has been questioned due to maintenance of FGF21 efficacy in mice following the surgical excision of intrascapular brown adipose tissue [43,44] Together, these recent data suggest that adipose-mediated thermogenesis may not be responsible for the energy expending effects of FGF21. However, UCP1 KO mice have compensatory mechanisms of thermogenesis [61], and it is possible that FGF21-mediated increases in energy expenditure involve both UCP1-dependent and -independent mechanisms within adipose tissue. In addition, the studies involving surgical removal of intrascapular brown adipose tissue do not demonstrate elimination of all brown adipose tissue, making it premature to conclude that FGF21 efficacy does not require brown adipose tissue. Finally, inducible brown adipocytes (i.e., beige/brite cells) in subcutaneous fat have high thermogenic capacity [62] and are also activated by FGF21 [23]. Therefore, additional studies are necessary to determine the mechanism(s) for the energy expending effects of FGF21.

2.2. Lipid metabolism

Administration of FGF21 to DIO mice dramatically improves hepatic and peripheral lipid metabolism including reversing hepatic steatosis, reducing adiposity, lowering plasma triglycerides, non-esterified fatty acids and cholesterol while increasing plasma β-hydroxybutarate levels [9–11] (Fig. 1). In two separate human studies, FGF21 analogs significantly improved lipid levels in patients. In the first study, the FGF21 analog LY2405319 significantly reduced plasma triglycerides, plasma LDL, and increased HDL in a dose dependent fashion [14]. The second study using a different FGF21 analog, PF-05231023, for a shorter duration of just 14 days, also possessed marked lipid lowering

effects including significantly decreased triglycerides, total cholesterol and LDL cholesterol, and increased HDL cholesterol [63]. Physiologically, plasma FGF21 levels are induced and produced from the liver during fasting [27] in response to fatty acid-mediated activation of the nuclear hormone receptor peroxisome proliferator-activated receptor α (PPARα) [37,64]. Consistent with a role during fasting, FGF21 is sufficient to increase hepatic gluconeogenesis, beta-oxidation, and ketogenesis in chow fed lean mice, whereas loss of FGF21 impairs these hepatic processes during fasting [36]. This ability of FGF21 to stimulate hepatic lipid oxidation increases hepatic insulin sensitivity in obese animal models by decreasing both hepatic diacylglycerol [43] and ceramide [30] levels.

FGF21 enhances insulin action, and in models of hyperinsulinemia, FGF21 functions to enhance insulin-stimulated suppression of lipolysis [65] and hepatic gluconeogenesis [10]. Gene profiling of obese mice treated with FGF21 revealed reduced hepatic lipogenic and gluconeogenic gene expression while also reducing active levels of SREBP-1c and target genes involved in hepatic glycolysis, de novo fatty acid synthesis and triglyceride synthesis [10,11]. Therefore, the pharmacological properties of FGF21 on lipid metabolism are likely comprised of its physiological actions during fasting, refeeding and overfeeding, and may explain why humans treated with the FGF21 analog, LY2405319, showed characteristics of improved insulin sensitivity yet had elevated ketones and non-significant changes in plasma glucose levels [14].

The effect of FGF21 on hepatic metabolism, however, does not appear to be due to direct action on the liver since FGFR1 is not expressed in hepatocytes [15] and treatment of hepatocytes [17,36] or isolated perfused livers with FGF21 [36] does not recapitulate the effects observed in vivo. Instead, extrahepatic mechanisms regulate the effects on hepatic metabolism including a liver-brain axis for increasing gluconeogenesis [17], decreasing cholesterol and triglycerides [16], and a liver-to-adipose axis for regulating cholesterol levels [28] and suppressing hepatic glucose production [30,31]. In addition, it is likely that the improvements in dyslipidemia due to FGF21 treatment occurs secondary to its enhancement of insulin sensitivity and energy expenditure.

2.3. Caveats of FGF21 therapy

In contrast to the beneficial effects of exogenous FGF21, pharmacological administration or overexpression of FGF21 have been reported to cause detrimental effects including bone loss [66], impaired fertility in females [67], and altered circadian rhythm [16]. In addition, overexpression of FGF21 inhibits growth [68]. However, unlike other FGFs, FGF21 is not mitogenic [9]. Since the effects of FGF21 on fertility and circadian rhythm requires central signaling [16,67], these safety concerns may be eliminated by developing FGF21-based therapies that do not cross the blood-brain barrier. Importantly, the metabolic effects of FGF21 are retained in animal models of metabolic disease using modified variants of FGF21 that are not expected to cross the blood brain barrier [29,69,70]. However, as central FGF21 signaling is also implicated in the therapeutic effects of FGF21 [45], long-term safety studies need to be conducted with these FGF21 variants.

3. Metabolic actions of FGF15/19

FGF15 and FGF19 are mouse–human orthologues which share ~50% amino acid identity [71]. Despite this low homology, both FGF15 and FGF19 are produced from the ileum of the small intestine, enter circulation to regulate metabolism [72,73], and both similarly regulate hepatic gene expression in mice [74,75]. Therefore, FGF15 and FGF19 (FGF15/19) will be referred to interchangeably unless referring to a particular species. Unlike FGF21 which preferentially signals through FGFR1, FGF19 interacts with and activates both FGFR4 and FGFR1 in vitro and in vivo [4,6], and in both cases, requires β-klotho to mediate metabolic effects [72,76] (Fig. 1). FGF15/19 levels are induced post-prandially in epithelial cells of the small intestine [74] and are then released into portal circulation to regulate bile acid, carbohydrate and lipid metabolism (Fig. 1). The following sections will examine the multiple roles of FGF15/19 in metabolism and disease.

3.1. Bile acid metabolism

A major physiological role for FGF15/19 is the regulation of bile acid metabolism. Bile acids are synthesized from cholesterol in the liver and stored in the gall bladder [77]. Following a meal, bile acids are released from the gall bladder into the intestine where they function to emulsify lipid for absorption. Bile acid production in the liver and their reabsorption in the small intestine are crucial due to their high energetic cost of generation and their toxicity as detergents. Activation of the nuclear hormone receptor farnesoid X receptor (FXR) in the ileum by bile acids results in the transcription and production of FGF15/19 from the intestine into hepatic portal circulation [74] (Fig. 4). In mice, ileal *Fgf15* mRNA levels are maximally induced 1 hour post-prandially [75], and in humans, serum FGF19 levels are increased 2–3 hours following a meal [73]. FGF15/19 subsequently binds and signals through the hepatic FGFR4/β-klotho receptor complex to suppress further production of bile acids by decreasing expression of CYP7A1, the rate-limiting enzyme regulating bile acid production [74]. Treatment of hepatocytes with FGF15/19 represses *Cyp7a1* mRNA expression [74], and the effects of FGF15 on bile acid metabolism are lost in liver-specific β-klotho knockout mice [72], which demonstrate direct actions on the liver. Bile acid pools are regulated by circadian rhythm [73], and plasma FGF15 and hepatic CYP7A1 levels are negatively correlated throughout the day [72,78]. Recently the transcription factor Kruppel-like factor 15 (KLF15) was found to repress *Fgf15* mRNA expression in intestinal epithelial cells thus regulating circadian expression of FGF15 and consequently CYP7A1 (Fig. 4) [78]. This study provides mechanistic insight into the regulation of FGF15 expression and the factors contributing to the changes in bile acid production throughout the day. In humans, FGF19 expression is increased by oral administration of bile acids [73] and is suppressed by bile acid sequestration [79] which demonstrates the conservation of this pathway in humans. Thus, this intestine-to-liver hormonal axis mediated by FGF15/19 serves as an important negative feedback loop to regulate bile acid homeostasis.

3.2. Glucose and lipid metabolism

The effects of FGF19 on carbohydrate and lipid metabolism were first identified in mice constitutively overexpressing FGF19 [80]. These mice displayed decreased adiposity,

increased energy expenditure, and improved plasma metabolite profiles [80]. Consistent with this study, peripheral administration (i.e., intraperitoneal (i.p.) or subcutaneous (s.c.) injection) of FGF19 to genetic or diet-induced obese animal models decreases body weight and adiposity while lowering circulating glucose and lipid levels [81–84]. However, unlike the effects on bile acid metabolism, the pharmacological effects of FGF19 are mediated through FGFR4-independent mechanisms in vivo [84] (Fig. 1). The ability of FGF19 to improve glucose homeostasis was retained in FGFR4 knockout mice [84], and wild-type mice receiving a mutant FGF19 variant, which specifically activated FGFR4, did not improve glucose metabolism in obese mice [85]. Since the metabolic FGFs signal through a common FGF receptor (i.e., FGFR1) [48] and since FGF19 and FGF21 both require the co-receptor β-klotho, it is plausible that the pharmacological effects of FGF19 may not represent FGF15/19 biology, but instead arise from a mimetic function of other FGFs. Interestingly, a comparison of the pharmacological effects of FGF19 and FGF21 revealed that while FGF21 mediates its effects on body weight and glucose homeostasis through FGFR1 in adipose tissue, FGF19 mediates it effects on body weight, but not glycemia, through FGFR1 in adipose tissue [28]. These data identify similarities and differences in the pharmacological mechanism of action for FGF19 and FGF21, and demonstrate the importance of adipose tissues in facilitating metabolic FGF function.

The adipose-independent effects of FGF19 on glycemia may be mediated through actions on the central nervous system (CNS). FGF15 is expressed in and functions throughout the nervous system during mouse embryogenesis [86,87]. However, *Fgf15* mRNA is not detected in the adult CNS, but instead is localized to the ileum [15]. Several reports indicate a central action of FGF19 in mediating beneficial effects on metabolism. FGF19 is capable of crossing the blood brain barrier [88] and ICV injection of FGF19 into DIO rats reduced body weight, food intake, and improved glucose homeostasis; all effects which were reversible by ICV administration of a FGF-inhibitor [89]. Central FGF19 signaling reduces plasma glucose levels by regulating hepatic insulin-independent glucose disposal, a process referred to as glucose effectiveness (GE) [90]. This effect of FGF19 is mediated through suppression of AGRP/NPY neuronal activity in the arcuate nucleus [91] (Fig. 4). Additionally, FGF19 suppresses the hypothalamic-pituitary-adrenal (HPA) axis to decrease plasma ACTH and corticosterone levels to suppress hepatic glucose production and whole body lipolysis [92] (Fig. 4). Therefore, FGF19 signals to the CNS to regulate glucose homeostasis through insulin-independent glucose disposal and suppression of hepatic glucose production.

To gain insight into the physiological role of FGF15/19 in metabolism, the phenotypes of FGF15 and FGFR4 total knockout mice and liver-specific β-klotho knockout mice were examined. Similar to bile acid metabolism, the liver is an important target for the physiological effects of FGF15/19 on glucose metabolism. FGF15/19 increases hepatic protein and glycogen synthesis [93], and FGF15/19 functions to suppress hepatic gluconeogenesis through the repression of the transcriptional co-activator PGC-1α [75]. Notably, FGF15 KO mice have abnormal glucose homeostasis including elevated gluconeogenesis in the fed state [75], and both FGF15 KO [93] and liver-specific β-klotho knockout mice have elevated postprandial hepatic glycogen levels [72]. These effects of FGF15/19 are mediated independent of insulin [93] and demonstrate that FGF15/19, in

addition to its pharmacological actions, functions physiologically to regulate hepatic lipid and glucose metabolism (Fig. 4).

3.3. Caveats of FGF19 therapy

While overexpression or administration of FGF19 improves metabolic homeostasis, it also causes hepatocellular proliferation (Fig. 1). FGF19 transgenic mice have increased hepatocyte proliferation as early as 2 months of age and develop hepatocellular carcinoma and die within 12 months of age [94]. Hepatocyte proliferation is also seen in wild-type mice injected with FGF19 for six days [94] which is mediated through a FGFR4-dependent pathway [82]. Therefore, identification of FGF19 variants which lack mitogenic activity and retain metabolic activity could be therapeutically advantageous. Indeed, a variant of FGF19 has been generated which specifically activates the FGFR1c/β-klotho complex to improve metabolic homeostasis without increasing hepatocellular proliferation like native FGF19 [95]. In addition, engineered forms of FGF19 which retain the ability to regulate bile acid metabolism but lack tumorigenicity have been reported [96,97]. However, induction of FGF19 has also been associated with the development and aggressiveness of other types of cancer including prostate [98,99] and colon cancer [100]. Therapeutic strategies to inhibit FGF19 function to reduce cancer progression have been proposed and should also be carefully evaluated. Inhibition of FGF19 in monkeys with an anti-FGF19 antibody resulted in liver toxicity and diarrhea due to impaired bile acid homeostasis [101]. Therefore, additional studies are necessary to determine whether FGF19 variants that affect metabolism also affect the progression or development of other types of cancer and vice versa.

4. Metabolic actions of FGF1

FGF1 along with FGF2 comprise the FGF1 subfamily. FGF1 signals in an autocrine/paracrine manner through interactions with FGF receptors and heparan sulfate (Fig. 1). FGF1 does not possess an N-terminal signal peptide and is therefore not classically secreted [102]. Instead, FGF1 is released from cells through mechanisms independent of the endoplasmic reticulum and Golgi processing pathways [102]. FGF1 was initially identified from pituitary and brain extracts and was identified as a mitogen for cultured fibro-blasts [102]. *Fgf1* mRNA is expressed at high levels in the CNS, liver, lung and kidney [15]. Contrary to the binding properties of most FGFs, FGF1 is capable of binding both the ‘b’ and ‘c’ isoforms of FGFR1-3 and FGFR4 [1,103].

4.1. Glucose and lipid metabolism

Recent studies have identified the metabolic actions of FGF1 and proposed its therapeutic potential for treating metabolic disease. Parental delivery of recombinant FGF1 lowered blood glucose in *ob/ob* and DIO mice without causing hypoglycemia or effecting insulin secretion or production. Interestingly, administration of FGF1 to STZ-treated mice failed to lower plasma glucose levels, suggesting these effects are mediated through insulin sensitization. DIO wild-type mice treated with FGF1 for 3 weeks demonstrated significantly increased glucose infusion rate, enhanced insulin-stimulated glucose disposal and decreased hepatic glucose production during hyperinsulinemic-euglycemic clamps without altering circulating levels of adiponectin [104]. In vitro, however, FGF1 has mitogenic effects. To

circumvent this issue, a FGF1 variant was generated which lacks mitogenic activity. This FGF1 variant lacking the first 24 amino acids on the N-terminus, termed rFGF1$^{\Delta NT}$, retained some binding affinity for FGFR1c and FGFR2c but not for the other FGFRs [104]. Parental delivery of rFGF1$^{\Delta NT}$ lowered circulating glucose in *ob/ob* and DIO mice through FGFR1 signaling in adipose tissue as the metabolic effects were lost in DIO adipose-specific FGFR1 KO mice (FGFR1$^{fl/fl}$;aP2-Cre) [104]. These effects of FGF1 are consistent with those observed following FGF19 or FGF21 administration [28]. However, unlike FGF19 and FGF21, FGF1 does not bind to nor require β-klotho for signaling [105].

Loss of function studies using FGF1 knockout mice revealed an important physiological role of FGF1 in metabolism. FGF1 null mice lack obvious abnormalities [106] despite the reported role of FGF1 as a regulator of human adipogenesis [107–110] and adipose tissue remodeling [111]. However, endogenous levels of FGF1 are induced in white adipose tissue during caloric excess and loss of FGF1 results in increased insulin resistance under conditions of high fat diet feeding [111]. Collectively, these data demonstrate that FGF1 functions physiologically to maintain metabolic homeostasis.

4.2. Caveats of FGF1 therapy

FGF1 possesses angiogenic and anti-apoptotic effects which has led to trials investigating its therapeutic potential in cases of cardiac ischemia and nerve injury [1]. Although these biological actions endow FGF1 with therapeutic potential, significant concerns remain regarding its oncogenic properties. For example, increased FGF1 expression has been detected in ovarian cancer and associated with poor survival [112] and also associated with prostate and breast cancers [113,114]. Long term studies with rFGF1$^{\Delta NT}$ are necessary to determine its safety as a therapeutic for metabolic disease.

5. Summary/conclusions

In a manner atypical of classic FGFs, FGF15/19 and FGF21 are secreted into circulation as endocrine hormones, whereas FGF1 functions as a classical FGF in an autocrine/paracrine manner. Physiologically, each of these FGFs signals through a cognate receptor to elicit specific metabolic responses. In models of metabolic disease, administration of pharmacological doses of metabolic FGFs improves energy homeostasis through a common FGFR1 dependent pathway (Fig. 1). Importantly, the metabolic FGFs have overlapping yet distinct functions on energy homeostasis. Despite the recent explosion in studies examining the mechanisms of the pharmacological effects of metabolic FGFs, several key questions remain. For example, what is the mechanism for the energy expending effects of metabolic FGFs? In addition, which cell type(s) are directly targeted to mediate these effects? The discovery that UCP1 is not required for the effects of FGF21 on energy expenditure raises new questions about the importance of adipose tissue thermogenesis in mediating FGF21 function [59,60]. Answers to these questions and other mysteries of metabolic FGF biology will likely uncover novel therapeutic strategies for the treatment of metabolic disease.

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Abbreviations

DIO	diet induced obesity
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
UCP1	uncoupling protein 1
KO	knockout
CNS	central nervous system
SNA	sympathetic nerve activity
ICV	intracerebroventricular
ChREBP	carbohydrate response element binding protein
FDG/PET	fludeoxyglucose/positron emission tomography
GE	glucose effectiveness
BAT	brown adipose tissue
WAT	white adipose tissue
ob*/*ob	leptin deficient mice

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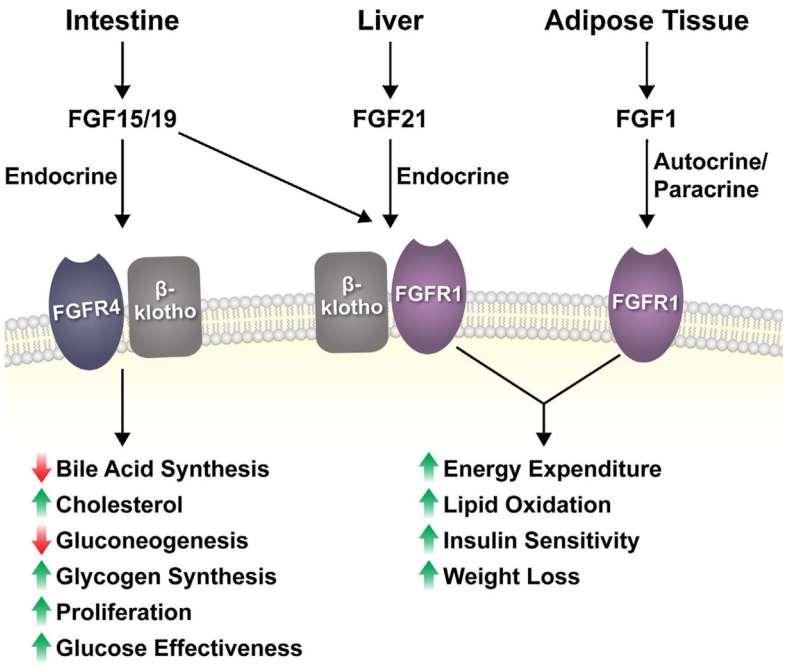

Fig. 1.

Summary of metabolic FGFs. The metabolic FGFs are produced by specific tissues and signal in either an endocrine or autocrine/paracrine fashion to target cells through FGFR4 or FGFR1, complexed with or without β-klotho, to regulate metabolism. FGF15/19 signaling through hepatic FGFR4/β-klotho regulates the indicated hepatic processes (except glucose effectiveness which occurs through central effects), while the direct cellular targets of FGF21 through FGFR1/β-klotho signaling remain unclear. Endogenous FGF1 acts in an autocrine/paracrine manner to signal through FGFR1 independent of β-klotho. Although the metabolic FGFs possess different physiological functions, they produce similar pharmacological actions in models of metabolic disease through a common FGFR1-mediated pathway.

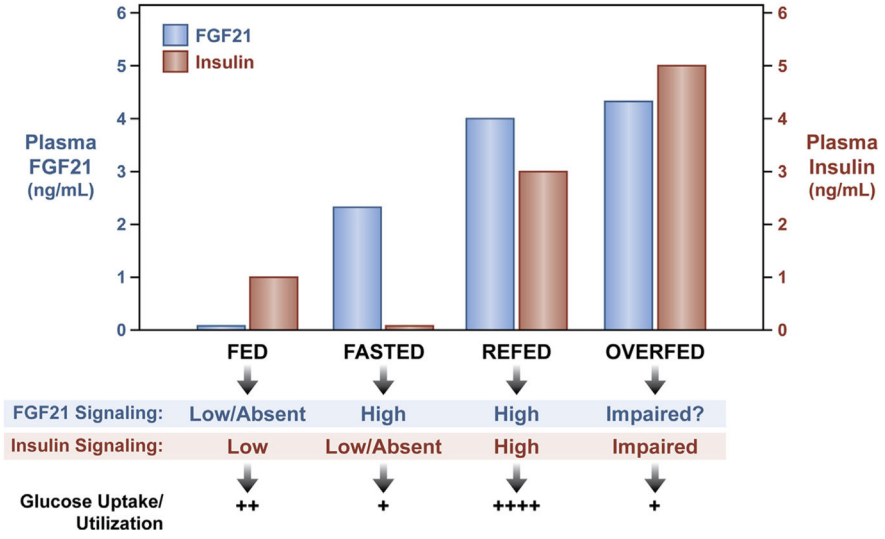

Fig. 2.

FGF21 function is altered by nutritional status. FGF21 expression is regulated by nutritional status and it may mediate its functions through signaling crosstalk with other endocrine factors like insulin. Endogenous plasma FGF21 and insulin levels under various physiological conditions are presented relative to their respective level of signaling and functional effect on glucose uptake and utilization.

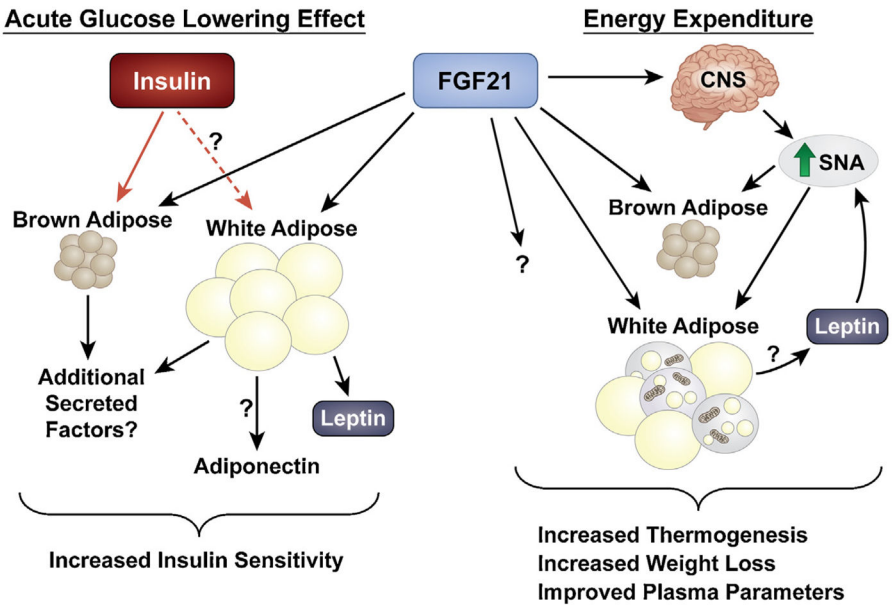

Fig. 3.

Model for the pharmacological effects of FGF21. Acute pharmacological administration of FGF21 to models of metabolic disease increases insulin sensitivity whereas chronic administration increases energy expenditure, weight loss and insulin sensitivity. The acute insulin sensitizing effects of FGF21 requires functional adipose tissue(s). FGF21 enhances insulin action to increase peripheral glucose disposal, and functions to promote the secretion of adipokines including adiponectin and leptin. Extended administration of FGF21 increases energy expenditure through actions on the central nervous system (CNS) and adipose tissues. FGF21 increases sympathetic nerve activity (SNA) which stimulates brown adipose tissue thermogenesis and “browning” of white adipose tissue. Leptin also increases sympathetic nerve activity and leptin may be important for the effects of FGF21 on energy expenditure. FGF21 may also affect energy expenditure through a yet unidentified pathway. FGF21-mediated increases in energy expenditure increases weight loss and disposes of excess nutrients to improve metabolic profiles.

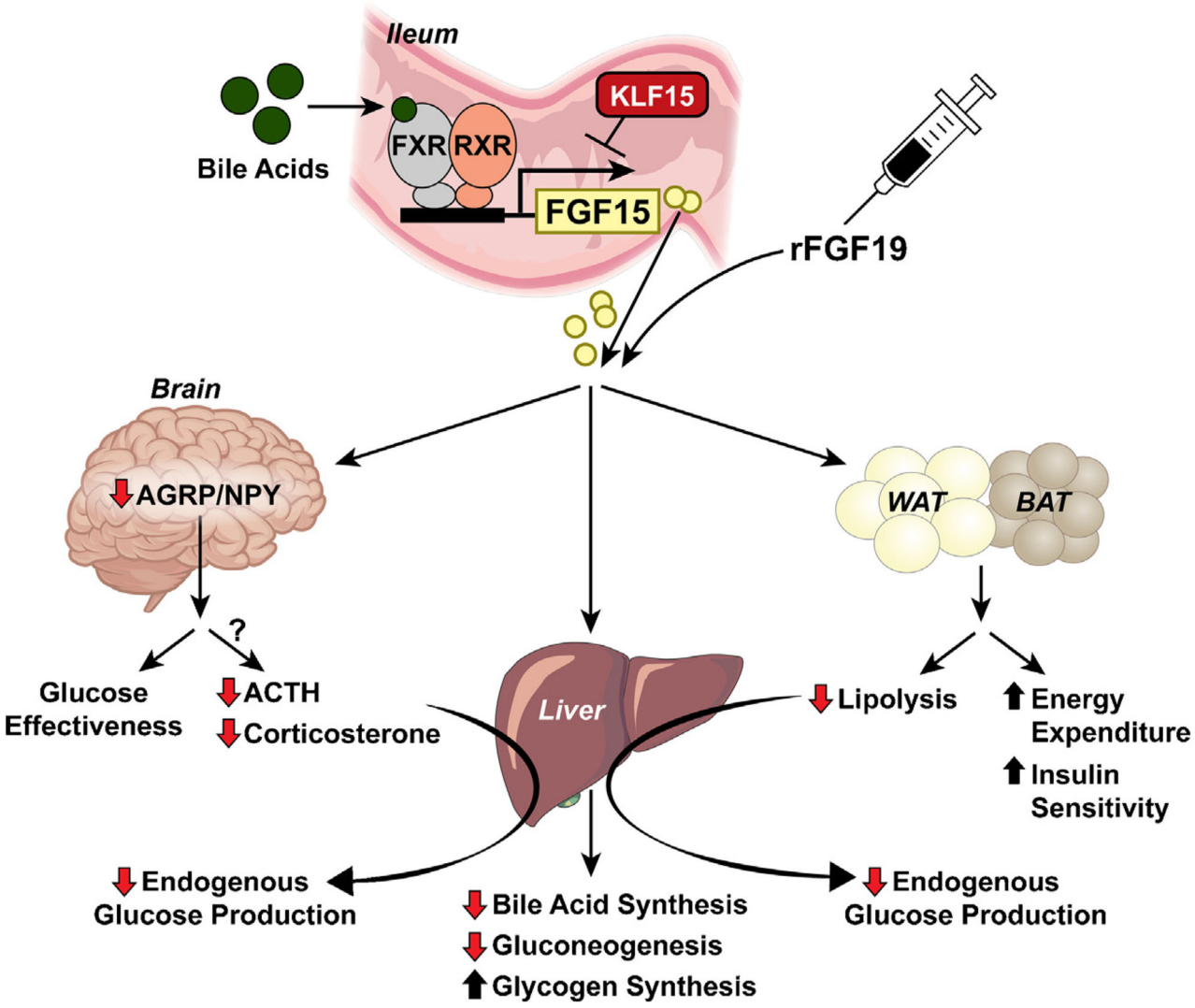

Fig. 4.

Model for the physiological and pharmacological actions of FGF15/19. FGF15 is produced from the ileum of the small intestine in response to bile acid mediated activation of FXR, whereas FGF15 expression is repressed by KLF15. Once released into circulation, or administered pharmacologically, FGF15/19 acts on multiple tissues including the liver, adipose tissues and central nervous system to elicit specific metabolic effects. FGF15/19 can act directly on the liver to decrease bile acid synthesis, decrease hepatic gluconeogenesis and increase glycogen synthesis. FGF15/19 also signals to the brain to decrease AGRP/NPY neuron activity which increases glucose effectiveness. In addition, FGF15/19 signaling in the CNS suppresses the HPA axis (decreases ACTH and corticosterone), which reduces hepatic glucose production through decreased corticosterone levels and whole body lipolysis. FGF15/19 action on white and brown adipose tissues (WAT and BAT, respectively) increases energy expenditure and insulin sensitivity.