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REVIEW

# Fibroblast growth factor 21: a novel metabolic regulator from pharmacology to physiology

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**Abstract** **Fibroblast growth factor 21 (FGF21) is a member of the fibroblast growth factor family. It actually functions as endocrine hormones but does not regulate cell growth and differentiation. It is demonstrated that FGF21 acts on multiple tissue to coordinate carbohydrate and lipid metabolism, including enhancing insulin sensitivity, decreasing triglyceride concentrations, causing weight loss, ameliorating obesity-associated hyperglycemia and hyperlipidemia. Moreover, FGF21 also plays important roles in some physiological processes, such as fasting and feeding, growth hormone axis and thermogenic function of brown adipose tissue. Clinical relevance of FGF21 in humans is still unclear, and the basis and consequences of increased FGF21 in metabolic disease remain to be determined. Both the pharmacological actions and physiological roles make FGF21 attractive drug candidates for treating metabolic disease, but some questions remain to be answered. This article concentrates on recent advances in our understanding of FGF21.**

**Keywords** FGF21; metabolism; pharmacology; physiology; clinical relevance

## Introduction

Fibroblast growth factor 21 (FGF21) was classified as a fibroblast growth factor based on its structure, as it contains a common domain and shares 10%–30% sequence identity with other FGFs [1]. The mammalian fibroblast growth factor family currently consists of 22 members divided into seven subfamilies based on their structural similarities and modes of action [2]. Most FGFs act as paracrine factors regulating cell growth and differentiation [3]. However, members of the FGF21 subfamily, which also includes FGF19 [1] and FGF23 [4–10], differ in two important aspects from all other FGF proteins. First, they have no or very small mitogenic effects. Second, they exert hormone-like effects. Thus, FGF19 (the human ortholog of murine FGF15) [7] is primarily expressed in the intestine but regulates bile acid synthesis in the liver in both rodents [8] and humans [9]. FGF23 is produced in bone tissue and regulates phosphate and vitamin D metabolism via effects on the kidney [10], while FGF21 is predominantly expressed in the liver and has beneficial effects on several metabolic parameters in different animal models of obesity [11].

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## Structure and signaling pathway

The human *FGF21* gene is located on chromosome 19 and encodes a 209-amino acid-long protein with an N-terminal signaling peptide which after cleavage results in a mature protein of 181 amino acids. FGF21 in human and mice share 75% identity at the amino acid level. FGFs mediate their action via a set of membrane-bound FGF receptors (FGFRs) that in turn are expressed in multiple splice variants. FGFR1–4 contain an intracellular tyrosine kinase domain that is activated upon ligand binding. They lead to the activation of a number of downstream signals, including MAPKs, RAF1, AKT1 and STATs [12]. However, FGFs cannot interact with FGFRs directly since they require a co-factor to bind and activate FGFR signaling efficiently. The presence of specific transmembrane protein, β-Klotho, from the Klotho-family involves in the binding and activation of FGFR [13,14]. Several reports suggest that the c-receptor splice isoforms of FGFR1–3 exhibit a particular affinity to β-Klotho and could thus act as endogenous receptors for FGF21 [15–17]. Studies showed that all the effects of FGF21 on growth and metabolism were lost in whole-body β-Klotho-knockout

(KO) mice and the acute insulin-sensitizing effects of FGF21 were lost in adipose tissue-selective β-Klotho-KO mice. β-Klotho is required for FGF21 effects on growth and metabolism [18].

## Pharmaceutical actions

The role of FGF21 in regulating metabolism was first reported in 2005 that FGF21 stimulated glucose uptake in mouse 3T3-L1 adipocytes and in primary cultures of human adipocytes [11]. Transgenic mice overexpressing FGF21 in liver had improved insulin sensitivity and glucose clearance, reduced plasma triglyceride concentrations, and were resistant to weight gain when fed a high-fat diet [11]. Administration of recombinant FGF21 to obese, insulin-resistant *ob*/*ob* or *db*/*db* mice or to Zucker diabetic fatty rats caused similar effects, which include reduction in plasma glucose and hepatic triglyceride concentration, increase in energy expenditure and insulin sensitivity [11,19,20]. In similar studies performed with diabetic rhesus monkeys, FGF21 caused significant decreases in fasting plasma glucose, insulin, and triglycerides [21]. Importantly, FGF21 did not cause hypoglycemia either in this primate model or in any of the rodent models. There is evidence that FGF21 exerts some of its effects directly on the endocrine pancreas. Short-term treatment of normal or *db*/*db* mice with FGF21 lowered plasma insulin concentrations [22]. In addition, FGF21 suppressed glucagon secretion from isolated rat islets and reduced plasma glucagon concentrations in mice [11]. Treatment of diet-induced obese mice with FGF21 for longer periods (3–6 weeks) reversed hepatic steatosis, decreased hepatic glucose production, and increased insulin-stimulated glucose uptake in the heart, adipose tissue, and skeletal muscle [20]. Likewise, administration of FGF21 to *ob*/*ob* mice for 8 days improved hepatic insulin sensitivity and also increased liver glycogen content [23]. In summary, FGF21 has profound effects on carbohydrate and lipid metabolism in rodents and primates. An adverse consequence of the effect of FGF21 on adipocytes occurs in bone, where pharmacological levels of FGF21 decrease bone mass. FGF21 causes bone loss in part by enhancing the differentiation of bone marrow mesenchymal stem cells into adipocytes instead of osteoblasts. Bone loss is a potential clinical concern as FGF21 is developed as a drug for treating metabolic disease [24] (Table 1).

**Table 1** Pharmacology and adverse effects of recombinant FGF21

| Pharmaceutical effects |
|---|
| Improve insulin sensitivity |
| Improve dyslipidemia |
| Weight loss |
| Improve hepatic steatosis |
| Increase energy expenditure |
| **Known adverse effect** |
| Bone loss |

## Physiological roles

### FGF21 in fasting and feeding

FGF21 is strongly induced in the mouse liver by fasting [25–27]. Fasting-mediated induction of FGF21 requires the peroxisome proliferator-activated receptor α (PPARα), a nuclear receptor activated by fatty acids and the fibrate class of hypolipidemic drugs [25–27]. PPARα binds directly to the *FGF21* gene promoter to induce its transcription [26]. FGF21 is also strongly induced in the mouse liver by ketogenic diet and by suckling in mouse neonates, i.e., conditions that mimic starvation in forcing the body to burn fatty acids rather than carbohydrates [25,28]. FGF21 has effects in lean mice on metabolism, growth, and the phenomenon of torpor that are all consistent with an important role for FGF21 in coordinating the adaptive starvation response. Fasting is detected by the brain, leading to lipolysis and contributing to other adaptations such as torpor. Fatty acids are released from adipose tissue, taken up by the liver, and either oxidized or converted to ketones. Ketones released by the liver are used as fuel by the brain. Activation of PPARα, presumably via activation by fatty acids, increases transcription of *FGF21*. FGF21 contributes to ketogenesis and gluconeogensis in liver, and adaptation such as torpor by the brain [25,26,29] (Fig. 1A).

Surprisingly, FGF21 is induced in white adipose tissue (WAT) by fasting and refeeding regimens [30]. It was recently showed that the full insulin sensitizing effects of the thiazolidinedione drug (TZD) rosiglitazone, a potent PPARγ agonist, require FGF21 [30]. FGF21-KO mice are refractory to both the beneficial, insulin-sensitizing effects and side effects of TZD such as weight gain and fluid retention. However, unlike the fasting response that elicits FGF21 release from the liver into circulation, feeding and pharmacological induction of FGF21 in WAT do not cause a corresponding increase in circulating levels of FGF21 [30]. These results reveal that FGF21 acts in an autocrine or paracrine fashion in WAT and is a part of feed-forward regulatory pathway that contributes to the fed-state response in WAT (Fig. 1B).

### FGF21 and growth hormone axis

The anabolic actions of growth hormone (GH), including the induction of its downstream effector, insulin-like growth factor 1 (IGF-1), are lost in starving animals [31]. This phenomenon of dissociating the catabolic from the anabolic effects of GH is referred to as "growth hormone resistance." A remarkable phenotype of FGF21 transgenic mice is their diminutive size. FGF21 transgenic mice weigh substantially less than wild-type mice, while retaining their appropriate

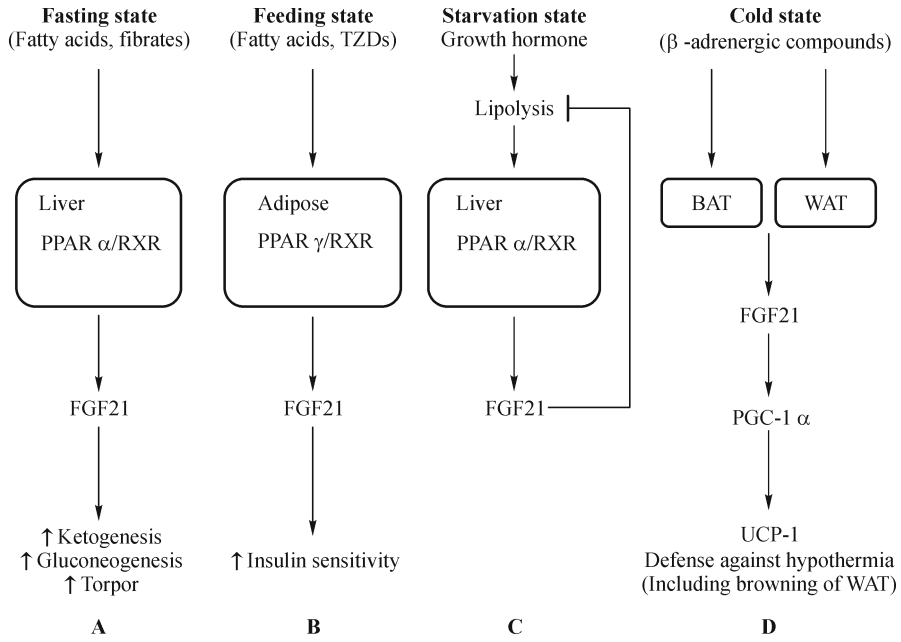


**Fig. 1** Physiological actions of FGF21. (A) In response to fasting or fibrate drugs, FGF21 expression is induced in the liver by the PPARα/RXR heterodimer, and then causes ketogenesis, gluconeogenesis, and torpor; (B) In response to feeding or thiazolidinedione drugs (TZDs), FGF21 expression is induced by the PPARγ/RXR heterodimer in WAT, where FGF21 acts to stimulate PPARγ activity; (C) FGF21 acts as a negative feedback signal to block GH-stimulated lipolysis in adipocytes. FGF21 inhibits growth as part of its broader role in promoting energy conservation during starvation; (D) FGF21 acts to activate and expand the thermogenic machinery to provide the defense against hypothermia.

body proportions [32]. Growth retardation is not due to a decrease in GH concentrations. Rather, basal GH concentrations are modestly increased. Notably, circulating IGF-1 concentrations are reduced in FGF21 transgenic mice, as are hepatic levels of the active form of the transcription factor STAT5, a major regulator of IGF-1 transcription [32]. In addition to an effect on GH signaling, FGF21 can also lead to GH resistance through counteracting the action of GH on lipolysis. It is demonstrated that in FGF21-KO mice, the magnitude of GH-stimulated elevation of circulating glycerol is much higher than that in wild type mice. And FGF21 insufficiency enhances GH-induced lipolysis in mice. These studies suggest that FGF21 acts as a negative feedback signal to block GH-stimulated lipolysis in adipocytes [33]. FGF21 inhibits growth as part of its broader role in promoting energy conservation during starvation (Fig. 1C).

## FGF21 and brown adipose tissue

Some studies showed that FGF21 is induced by cold in brown adipose tissue (BAT) [34,35]. Injection of FGF21 into mice stimulated the expression of thermogenic genes such as uncoupling protein-1 and deiodinase-2 in BAT [19]. However, more recent work has focused on expression and action of FGF21 in BAT itself. Treatment with exogenous FGF21 has been reported to promote thermogenic activity in neonatal BAT and in isolated brown adipocytes [35]. The first report to study cold-induced activation demonstrated that short-term exposure of mice to low ambient temperatures led to a marked induction of FGF21 mRNA levels in BAT [35]. This increase in FGF21 message is specific to BAT as FGF21 was not elevated in liver or WAT in response to cold exposure. It is known that low ambient temperatures activate BAT via the sympathetic nervous system [36]. In particular, β3-adrenergic receptors have been shown to be critical in propagating the thermogenic signal to BAT [37,38]. Selective β3-agonist treatment of WT mice led to a highly significant fold increase in FGF21 mRNA levels in BAT to levels comparable to those observed in WAT and liver. In the same cohort, peroxisome proliferator-activated receptor γ coactivator1α (PGC-1α) mRNA levels were found to be induced by both cold and β3-agonist, while no differences in the expression of PPARα were reported [34]. However, recent research has showed that when exposed to cold or β-adrenergic compounds, certain WAT depots can convert to a "brown-like" state, and FGF21 plays a physiological role in this procedure by regulating PGC-1α. FGF21 acts to activate and expand the thermogenic machinery to provide a robust defense against hypothermia [39] (Fig. 1D).

## Clinical relevance of FGF21 in humans

Circulating FGF21 levels are induced by fibrates and other PPARα agonists in humans [40,41]. Circulating FGF21

concentrations are also increased in obese individuals fed a very low-calorie diet for 3 weeks [40]. While these data suggest similarities in the way that FGF21 is regulated across species, the magnitude of FGF21 induction by PPARα agonists and fasting is modest in humans compared with mice. Notably, circulating FGF21 levels are not increased in humans by either shorter-term fasts or ketogenic diets [40–42] or in subjects with anorexia nervosa [43,44], suggesting that there may be important differences in the regulation and function of FGF21 between rodents and humans. Interestingly, circulating FGF21 concentrations are increased in human subjects who either are overweight or have type 2 diabetes, impaired glucose tolerance, or nonalcoholic fatty liver disease [45–52]. It seems likely that this circulating FGF21 is derived from the liver, perhaps due to the induction of FGF21 by elevated hepatic lipid and carbohydrate levels. While the human findings appear to be at odds with the insulin-sensitizing actions of FGF21 in rodents and monkeys, hepatic FGF21 mRNA levels and plasma FGF21 concentrations are similarly increased in diet-induced and genetically obese mice [53,54]. Importantly, these mice still respond to pharmacological doses of FGF21 with improved insulin sensitivity. One possibility is that obesity and insulin resistance cause "FGF21 resistance" in rodents and humans. While a study from one group supports this hypothesis [54], another study does not [55]. The basis and consequences of increased FGF21 in metabolic disease remain to be determined.

## Conclusions and perspectives

The understanding of FGF21 as a major metabolic regulator is rapidly evolving. In spite of this accelerated pace of investigation, the scientific appreciation of FGF21 biology is still fragmented and controversial, and these knowledge gaps are yet to be filled through prioritized research focused on the most fundamental questions. With the therapeutic relevance of FGF21 pathway in humans being the primary inquiry, FGF21 has remarkable pharmacological effects on carbohydrate and lipid metabolism, particularly in the context of obese animals. The pharmacological actions of FGF21 make it attractive as future drugs for treating metabolic disease. Indeed, FGF21 is already in clinical trials. However, an adverse consequence of the effect of FGF21 on adipocytes occurs in bone, where pharmacological levels of FGF21 decrease bone mass [24]. Even though FGF21 resistance has been demonstrated in rodents, this does not preclude FGF21 inducing a robust pharmacological response in these species [23,54]. Thus, it seems plausible that chronically delivered pharmacological doses of more potent FGF21 agonists will be capable of overcoming FGF21 resistance in humans, if this is indeed the case. Anyway, based on their profound pharmacological and physiological effects on metabolism, future studies in humans should explore the therapeutic potential of FGF21 and provide a better understanding of its mechanism of action.

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## References

1. Nishimura T, Nakatake Y, Konishi M, Itoh N. Identification of a novel FGF, FGF-21, preferentially expressed in the liver. Biochim Biophys Acta 2000; 1492(1): 203–206
2. Presta M, Dell'Era P, Mitola S, Moroni E, Ronca R, Rusnati M. Fibroblast growth factor/fibroblast growth factor receptor system in angiogenesis. Cytokine Growth Factor Rev 2005; 16(2): 159–178
3. Itoh N, Ornitz DM. Evolution of the *Fgf* and *Fgfr* gene families. Trends Genet 2004; 20(11): 563–569
4. White KE, Evans WE, O'Riordan JLH, Speer MC, Econs MJ, Lorenz-Depiereux B, Grabowski M, Meitinger T, Strom TM. Autosomal dominant hypophosphataemic rickets is associated with mutations in *FGF23*. Nat Genet 2000; 26(3): 345–348
5. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, Takeuchi Y, Fujita T, Fukumoto S, Yamashita T. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci USA 2001; 98(11): 6500–6505
6. Yamashita T, Yoshioka M, Itoh N. Identification of a novel fibroblast growth factor, FGF-23, preferentially expressed in the ventrolateral thalamic nucleus of the brain. Biochem Biophys Res Commun 2000; 277(2): 494–498
7. Nishimura T, Utsunomiya Y, Hoshikawa M, Ohuchi H, Itoh N. Structure and expression of a novel human FGF, FGF-19, expressed in the fetal brain. Biochim Biophys Acta 1999; 1444 (1): 148–151
8. Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG, Luo G, Jones SA, Goodwin B, Richardson JA, Gerard RD, Repa JJ, Mangelsdorf DJ, Kliewer SA. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. Cell Metab 2005; 2(4): 217–225
9. Lundåsen T, Gälman C, Angelin B, Rudling M. Circulating intestinal fibroblast growth factor 19 has a pronounced diurnal variation and modulates hepatic bile acid synthesis in man. J Intern Med 2006; 260(6): 530–536
10. Fukumoto S, Yamashita T. FGF23 is a hormone-regulating phosphate metabolism—unique biological characteristics of FGF23. Bone 2007; 40(5): 1190–1195
11. Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, Sandusky GE, Hammond LJ, Moyers JS, Owens RA, Gromada J, Brozinick JT, Hawkins ED, Wroblewski VJ, Li DS,

Mehrbod F, Jaskunas SR, Shanafelt AB. FGF-21 as a novel metabolic regulator. J Clin Invest 2005; 115(6): 1627–1635

12. Kharitonenkov A, Shanafelt AB. Fibroblast growth factor-21 as a therapeutic agent for metabolic diseases. BioDrugs 2008; 22(1): 37–44
13. Kurosu H, Ogawa Y, Miyoshi M, Yamamoto M, Nandi A, Rosenblatt KP, Baum MG, Schiavi S, Hu MC, Moe OW, Kuro-o M. Regulation of fibroblast growth factor-23 signaling by klotho. J Biol Chem 2006; 281(10): 6120–6123
14. Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, Fujita T, Fukumoto S, Yamashita T. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature 2006; 444 (7120): 770–774
15. Kurosu H, Choi M, Ogawa Y, Dickson AS, Goetz R, Eliseenkova AV, Mohammadi M, Rosenblatt KP, Kliewer SA, Kuro-o M. Tissue-specific expression of betaKlotho and fibroblast growth factor (FGF) receptor isoforms determines metabolic activity of FGF19 and FGF21. J Biol Chem 2007; 282(37): 26687–26695
16. Ogawa Y, Kurosu H, Yamamoto M, Nandi A, Rosenblatt KP, Goetz R, Eliseenkova AV, Mohammadi M, Kuro-o M. BetaKlotho is required for metabolic activity of fibroblast growth factor 21. Proc Natl Acad Sci USA 2007; 104(18): 7432–7437
17. Kharitonenkov A, Dunbar JD, Bina HA, Bright S, Moyers JS, Zhang C, Ding L, Micanovic R, Mehrbod SF, Knierman MD, Hale JE, Coskun T, Shanafelt AB. FGF-21/FGF-21 receptor interaction and activation is determined by betaKlotho. J Cell Physiol 2008; 215(1): 1–7
18. Ding X, Boney-Montoya J, Owen BM, Bookout AL, Coate KC, Mangelsdorf DJ, Kliewer SA. βKlotho is required for fibroblast growth factor 21 effects on growth and metabolism. Cell Metab 2012; 16(3): 387–393
19. Coskun T, Bina HA, Schneider MA, Dunbar JD, Hu CC, Chen Y, Moller DE, Kharitonenkov A. Fibroblast growth factor 21 corrects obesity in mice. Endocrinology 2008; 149(12): 6018–6027
20. Xu J, Lloyd DJ, Hale C, Stanislaus S, Chen M, Sivits G, Vonderfecht S, Hecht R, Li YS, Lindberg RA, Chen JL, Jung DY, Zhang Z, Ko HJ, Kim JK, Véniant MM. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. Diabetes 2009; 58 (1): 250–259
21. Kharitonenkov A, Wroblewski VJ, Koester A, Chen YF, Clutinger CK, Tigno XT, Hansen BC, Shanafelt AB, Etgen GJ. The metabolic state of diabetic monkeys is regulated by fibroblast growth factor-21. Endocrinology 2007; 148(2): 774–781
22. Wente W, Efanov AM, Brenner M, Kharitonenkov A, Köster A, Sandusky GE, Sewing S, Treinies I, Zitzer H, Gromada J. Fibroblast growth factor-21 improves pancreatic beta-cell function and survival by activation of extracellular signal-regulated kinase 1/2 and Akt signaling pathways. Diabetes 2006; 55(9): 2470–2478
23. Berglund ED, Li CY, Bina HA, Lynes SE, Michael MD, Shanafelt AB, Kharitonenkov A, Wasserman DH. Fibroblast growth factor 21 controls glycemia via regulation of hepatic glucose flux and insulin sensitivity. Endocrinology 2009; 150(9): 4084–4093
24. Wei W, Dutchak PA, Wang X, Ding X, Wang X, Bookout AL, Goetz R, Mohammadi M, Gerard RD, Dechow PC, Mangelsdorf DJ, Kliewer SA, Wan Y. Fibroblast growth factor 21 promotes bone loss by potentiating the effects of peroxisome proliferator-activated receptor γ. Proc Natl Acad Sci USA 2012; 109(8): 3143–3148
25. Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E. Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. Cell Metab 2007; 5(6): 426–437
26. Inagaki T, Dutchak P, Zhao G, Ding X, Gautron L, Parameswara V, Li Y, Goetz R, Mohammadi M, Esser V, Elmquist JK, Gerard RD, Burgess SC, Hammer RE, Mangelsdorf DJ, Kliewer SA. Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. Cell Metab 2007; 5(6): 415–425
27. Lundåsen T, Hunt MC, Nilsson LM, Sanyal S, Angelin B, Alexson SE, Rudling M. PPARalpha is a key regulator of hepatic FGF21. Biochem Biophys Res Commun 2007; 360(2): 437–440
28. Hondares E, Rosell M, Gonzalez FJ, Giralt M, Iglesias R, Villarroya F. Hepatic FGF21 expression is induced at birth via PPARalpha in response to milk intake and contributes to thermogenic activation of neonatal brown fat. Cell Metab 2010; 11(3): 206–212
29. Reitman ML. FGF21: a missing link in the biology of fasting. Cell Metab 2007; 5(6): 405–407
30. Dutchak PA, Katafuchi T, Bookout AL, Choi JH, Yu RT, Mangelsdorf DJ, Kliewer SA. Fibroblast growth factor-21 regulates PPARγ activity and the antidiabetic actions of thiazolidinediones. Cell 2012; 148(3): 556–567
31. Thissen JP, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. Endocr Rev 1994; 15(1): 80–101
32. Inagaki T, Lin VY, Goetz R, Mohammadi M, Mangelsdorf DJ, Kliewer SA. Inhibition of growth hormone signaling by the fasting-induced hormone FGF21. Cell Metab 2008; 8(1): 77–83
33. Chen W, Hoo RL, Konishi M, Itoh N, Lee PC, Ye HY, Lam KS, Xu A. Growth hormone induces hepatic production of fibroblast growth factor 21 through a mechanism dependent on lipolysis in adipocytes. J Biol Chem 2011; 286(40): 34559–34566
34. Chartoumpekis DV, Habeos IG, Ziros PG, Psyrogiannis AI, Kyriazopoulou VE, Papavassiliou AG. Brown adipose tissue responds to cold and adrenergic stimulation by induction of FGF21. Mol Med 2011; 17(7–8): 736–740
35. Hondares E, Iglesias R, Giralt A, Gonzalez FJ, Giralt M, Mampel T, Villarroya F. Thermogenic activation induces FGF21 expression and release in brown adipose tissue. J Biol Chem 2011; 286(15): 12983–12990
36. Klingenspor M. Cold-induced recruitment of brown adipose tissue thermogenesis. Exp Physiol 2003; 88(1): 141–148
37. Scarpace PJ, Tse C, Matheny M. Thermoregulation with age: restoration of beta(3)-adrenergic responsiveness in brown adipose tissue by cold exposure. Proc Soc Exp Biol Med 1996; 211(4): 374–380
38. Takahashi A, Shimazu T, Maruyama Y. Importance of sympathetic nerves for the stimulatory effect of cold exposure on glucose utilization in brown adipose tissue. Jpn J Physiol 1992; 42(4): 653–664
39. Fisher FM, Kleiner S, Douris N, Fox EC, Mepani RJ, Verdeguer F, Wu J, Kharitonenkov A, Flier JS, Maratos-Flier E, Spiegelman BM. FGF21 regulates PGC-1α and browning of white adipose tissues in adaptive thermogenesis. Genes Dev 2012; 26(3): 271–281
40. Gälman C, Lundåsen T, Kharitonenkov A, Bina HA, Eriksson M, Hafström I, Dahlin M, Amark P, Angelin B, Rudling M. The

circulating metabolic regulator FGF21 is induced by prolonged fasting and PPARalpha activation in man. Cell Metab 2008; 8(2): 169–174

41. Christodoulides C, Dyson P, Sprecher D, Tsintzas K, Karpe F. Circulating fibroblast growth factor 21 is induced by peroxisome proliferator-activated receptor agonists but not ketosis in man. J Clin Endocrinol Metab 2009; 94(9): 3594–3601
42. Dushay J, Chui PC, Gopalakrishnan GS, Varela-Rey M, Crawley M, Fisher FM, Badman MK, Martinez-Chantar ML, Maratos-Flier E. Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. Gastroenterology 2010; 139(2): 456–463
43. Dostálová I, Kaválková P, Haluzíková D, Lacinová Z, Mráz M, Papezová H, Haluzík M. Plasma concentrations of fibroblast growth factors 19 and 21 in patients with anorexia nervosa. J Clin Endocrinol Metab 2008; 93(9): 3627–3632
44. Fazeli PK, Misra M, Goldstein M, Miller KK, Klibanski A. Fibroblast growth factor-21 may mediate growth hormone resistance in anorexia nervosa. J Clin Endocrinol Metab 2010; 95(1): 369–374
45. Chen WW, Li L, Yang GY, Li K, Qi XY, Zhu W, Tang Y, Liu H, Boden G. Circulating FGF-21 levels in normal subjects and in newly diagnose patients with Type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes 2008; 116(1): 65–68
46. Chavez AO, Molina-Carrion M, Abdul-Ghani MA, Folli F, Defronzo RA, Tripathy D. Circulating fibroblast growth factor-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. Diabetes Care 2009; 32(8): 1542–1546
47. Mraz M, Bartlova M, Lacinova Z, Michalsky D, Kasalicky M, Haluzikova D, Matoulek M, Dostalova I, Humenanska V, Haluzik M. Serum concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor-21 in patients with type 2 diabetes and obesity. Clin Endocrinol (Oxf) 2009; 71(3): 369–375
48. Cuevas-Ramos D, Almeda-Valdes P, Gómez-Pérez FJ, Meza-Arana CE, Cruz-Bautista I, Arellano-Campos O, Navarrete-López M, Aguilar-Salinas CA. Daily physical activity, fasting glucose, uric acid, and body mass index are independent factors associated with serum fibroblast growth factor 21 levels. Eur J Endocrinol 2010; 163 (3): 469–477
49. Li H, Bao Y, Xu A, Pan X, Lu J, Wu H, Lu H, Xiang K, Jia W. Serum fibroblast growth factor 21 is associated with adverse lipid profiles and gamma-glutamyltransferase but not insulin sensitivity in Chinese subjects. J Clin Endocrinol Metab 2009; 94(6): 2151–2156
50. Li H, Fang Q, Gao F, Fan J, Zhou J, Wang X, Zhang H, Pan X, Bao Y, Xiang K, Xu A, Jia W. Fibroblast growth factor 21 levels are increased in nonalcoholic fatty liver disease patients and are correlated with hepatic triglyceride. J Hepatol 2010; 53(5): 934–940
51. Matuszek B, Lenart-Lipińska M, Duma D, Solski J, Nowakowski A. Evaluation of concentrations of FGF-21 — a new adipocytokine in type 2 diabetes. Endokrynol Pol 2010; 61(1): 50–54
52. Yilmaz Y, Eren F, Yonal O, Kurt R, Aktas B, Celikel CA, Ozdogan O, Imeryuz N, Kalayci C, A*vs*ar E. Increased serum FGF21 levels in patients with nonalcoholic fatty liver disease. Eur J Clin Invest 2010; 40(10): 887–892
53. Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG, Liu F, Wong RL, Chow WS, Tso AW, Lam KS, Xu A. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes 2008; 57(5): 1246–1253
54. Fisher FM, Chui PC, Antonellis PJ, Bina HA, Kharitonenkov A, Flier JS, Maratos-Flier E. Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. Diabetes 2010; 59(11): 2781–2789
55. Hale C, Chen MM, Stanislaus S, Chinookoswong N, Hager T, Wang M, Véniant MM, Xu J. Lack of overt FGF21 resistance in two mouse models of obesity and insulin resistance. Endocrinology 2012; 153(1): 69–80