INTRODUCTION

Hormones such as insulin and glucagon have well-established roles in controlling substrate utilization and energy balance in response to nutritional status. In recent years, additional metabolic hormones, which include fibroblast growth factor 21 (FGF21), have been identified. FGF21 is a member of a family of atypical fibroblast growth factors (FGFs), which include FGF15/19 (FGF15 and FGF19 are mouse and human orthologs, respectively) and FGF23, which lack the conventional FGF heparin-binding domain (1, 2). As a consequence, these FGFs can diffuse away from their tissues of origin and function as hormones. FGF15/19 and FGF23 play prominent roles in regulating bile acid and phosphate homeostasis, respectively (3, 4).

FGF21 is abundantly expressed in liver, pancreas, and white adipose tissue (WAT) (5, 6). FGF21 signals through cell-surface receptors composed of the classic FGF receptors, which are tyrosine kinases, complexed with β-Klotho, a recently characterized single-pass membrane-spanning protein with 2 glycoside domains (7–10). In vitro studies indicate that FGF21 prefers the FGFR1c/β-Klotho complex over those containing other FGFR isotypes (9, 10). Nevertheless, there is evidence that FGF21 can act through all 4 FGFR isotypes. Whereas the FGFRs are broadly expressed, β-Klotho is expressed in a more select set of tissues that include liver, WAT, pancreas, and testes (10, 11). It is anticipated that these will be important sites of FGF21 action.

FGF21 PHARMACOLOGY: EFFECTS ON METABOLISM

The role of FGF21 in regulating metabolism was first described by Kharitonenkov et al (12), who reported that FGF21 stimulated glucose uptake in mouse 3T3-L1 adipocytes and in primary cultures of human adipocytes. They further showed that FGF21 has remarkable in vivo effects. 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 (12). 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 reductions in plasma glucose and insulin concentrations. Subsequent studies by this group and others showed that administration of FGF21 to high-fat-diet–induced obese mice increased fat utilization and energy expenditure and reduced plasma glucose, insulin, and lipid concentrations and hepatic triglyceride concentrations (12–14). FGF21 also improved hepatic and peripheral insulin sensitivity in both high-fat-diet–induced obese and lean mice. In one study, it was shown that the decrease in hepatic triglyceride concentrations was accompanied by a decrease in lipogenic gene expression (14).

In similar studies performed with diabetic rhesus monkeys, FGF21 caused significant decreases in fasting plasma glucose, insulin, and triglycerides (15). FGF21 also lowered LDL cholesterol, increased HDL cholesterol, and caused modest weight loss. 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 (16). Immunostaining of pancreases from db/db mice showed increases in both the number of islets and the amount of insulin...
per islet in FGF21-treated animals. However, FGF21 did not affect islet cell proliferation (16). In in vitro studies, FGF21 increased insulin mRNA and protein amounts in islets isolated from healthy rats and protected them from glucolipotoxicity and cytokine-induced apoptosis (16). In addition to its effects on insulin, FGF21 suppressed glucagon secretion from isolated rat islets and reduced plasma glucagon concentrations in mice (12).

In summary, FGF21 has profound effects on carbohydrate and lipid metabolism in rodents and primates. Thus, FGF21 is a promising clinical candidate for the treatment of type 2 diabetes and perhaps other components of metabolic disease.

**FGF21 PHYSIOLOGY: ROLES IN THE ADAPTIVE STARVATION RESPONSE**

In 2007, 3 groups reported that FGF21 mRNA concentrations are markedly induced in murine liver by fasting through a mechanism requiring peroxisome proliferator-activated receptor α (PPARα), a nuclear receptor activated by fatty acids and the fibrate class of triglyceride-lowering drugs (17–19). Consistent with this finding, FGF21 is also induced by fibrates and other synthetic PPARα agonists as well as by a ketogenic diet (17–19). FGF21 in turn has diverse effects in mice that include altering metabolism, sensitizing the mice to the hibernation-like state of torpor, and blunting the growth hormone (GH)–signaling pathway. Because all of these effects can be elicited by prolonged fasting, we conclude that FGF21 plays an overarching role in coordinating the adaptive starvation response.

The effects of FGF21 on metabolism, torpor, and GH signaling are summarized below.

**Metabolism**

In liver, FGF21 induces gluconeogenesis, fatty acid oxidation, and ketogenesis, a metabolic profile characteristic of fasting (17, 18, 20). Notably, however, FGF21 does not stimulate glycolysis, and FGF21-transgenic mice accumulate significantly more hepatic glycogen than do their wild-type counterparts when fed ad libitum (20). These findings suggest that FGF21 does not play a prominent role during the early stages of fasting when glucagon is a dominant regulator of metabolism, but rather that FGF21 stimulates gluconeogenesis and ketogenesis in the context of prolonged fasting and starvation, when glycogen stores are already depleted. Consistent with this hypothesis, circulating FGF21 concentrations are induced in humans only after prolonged fasting (21).

How does FGF21 regulate hepatic metabolism? We recently showed (20) that, in liver, FGF21 administration induces expression of the peroxisome proliferator-activated receptor γ coactivator protein-1α (PGC-1α), a transcriptional coactivator protein that interacts with several different DNA-binding proteins to regulate metabolism in response to changes in nutritional status and other physiologic stimuli such as cold and exercise (20, 22). In liver, the induction of PGC-1α by fasting stimulates the transcription of genes involved in gluconeogenesis, fatty acid oxidation, and ketogenesis (23–25). Importantly, FGF21 is unable to induce gluconeogenic gene expression in mice lacking PGC-1α (20). Moreover, mice lacking FGF21 fail to fully induce PGC-1α expression in response to a prolonged fast and have impaired gluconeogenesis and ketogenesis (20). Thus, the metabolic actions of FGF21 are mediated in part through PGC-1α.

**Torpor**

In microarray analyses, we made the surprising observation that FGF21 induces a variety of pancreatic lipases, which include pancreatic lipase, pancreatic lipase–related protein 2, and carboxyl ester lipase, in liver (18). The induction of these lipases is likely to contribute to the increase in hepatic fatty acid oxidation effected by FGF21. Interestingly, the extra-pancreatic induction of pancreatic lipases was first described in hibernating ground squirrels (26). Because pancreatic lipases efficiently hydrolyze triglycerides over a broad range of temperatures, it was proposed that their induction provides a mechanism for the steady supply of fatty acids as an energy source under adverse environmental conditions. More recently, pancreatic lipases were shown to be induced in liver and other tissues in mice during torpor, the murine equivalent of hibernation (27). During torpor, both body temperature and physical activity plummet as a means to conserve energy. Our finding that FGF21 induces pancreatic lipases in liver suggested that FGF21 might regulate torpor. Indeed, FGF21-transgenic mice entered torpor during a 24-h fast whereas wild-type mice did not (18). Notably, ketone body concentrations are markedly elevated during torpor and hibernation. Thus, FGF21 sensitizes mice to torpor and elicits hallmarks of the broader torpor response, which include changes in lipase gene expression and metabolism.

**GH axis**

Starvation inhibits growth by blocking the GH/insulin-like growth factor I (IGF-I) signaling pathway through mechanisms that are not well understood (28). We observed that FGF21-transgenic mice are 40–50% smaller than wild-type mice (29). We subsequently showed that FGF21 reduces circulating concentrations of IGF-I by ~50% without causing a corresponding decrease in GH concentrations. Thus, FGF21 causes GH resistance.

What is the mechanism underlying this phenomenon? In liver, FGF21 reduced concentrations of the active form of signal transducer and activator of transcription 5 (STAT5), a transcription factor that regulates IGF-I and other genes in response to GH (29). These data suggest that FGF21 inhibits growth as part of its broader role in promoting energy conservation during starvation.

**FGF21 IN WAT**

Both β-Klotho and FGFR1c, which constitute the preferred FGF21 receptor complex, are highly expressed in WAT (10). Consistent with this finding, FGF21 stimulates glucose uptake in mouse 3T3-L1 adipocytes and in primary cultures of human adipocytes (12). FGF21 also induces the expression of hormone-sensitive lipase and adipocyte triacylglycerol lipase in WAT in mice (13, 18), which suggests that FGF21 plays a role in the mobilization of fatty acids from WAT to liver during fasting. However, although we observed that treatment of 3T3-L1 adipocytes with FGF21 stimulated glycerol release—a surrogate measure of lipolysis—another group observed that FGF21 suppressed lipolysis in 3T3-L1 adipocytes and human adipocytes (18, 30). The basis for these differences is not clear. Interestingly, FGF21 is induced by the thiazolidinedione antidiabetic drugs in WAT of db/db mice (6) and in 3T3-L1 adipocytes.
FGF21 IN HUMANS

Several recent studies have examined FGF21 in humans. Galman et al (21) showed that in a population of healthy subjects, serum FGF21 concentrations varied over a 250-fold range and did not relate to age, sex, body mass index, serum lipids or plasma glucose. In addition, they showed that circulating concentrations of FGF21 increase in humans only after a 7-d fast and that hypertriglyceridemic patients had 2-fold elevated FGF21 concentrations, which were further increased by treatment with the PPARγ agonist fenofibrate. These data support the hypothesis that FGF21 is induced by prolonged fasting in humans as it is in mice, perhaps via a PPARγ-dependent mechanism.

Several recent reports showed that circulating FGF21 concentrations were increased in subjects who were either overweight or had type 2 diabetes or impaired glucose tolerance (32–35). Conversely, circulating FGF21 concentrations were significantly reduced in subjects with anorexia nervosa (36). FGF21 concentrations correlated with body weight and/or adiposity (33, 35, 36). Similarly, circulating FGF21 concentrations were increased in db/db mice as were FGF21 mRNA concentrations in both liver and WAT (35).

These findings raise a series of interesting questions: Why is a hormone that is induced during fasting also increased under conditions of obesity and insulin resistance? Does this perhaps reflect FGF21 resistance or a compensatory response? How does a hormone that enhances gluconeogenesis during fasting in lean mice cause insulin sensitization and decreased hepatic glucose output in insulin-resistant animals? And what is the role of FGF21 expression in WAT? Does WAT release FGF21 into the circulation as does the liver? Regarding this last question, plasma FGF21 concentrations are increased in db/db mice treated with thiazolidinediones (6).

In summary, FGF21 has emerged as a powerful hormonal regulator of metabolism. From a physiologic perspective, FGF21 has provided important insights into how diverse aspects of the adaptive starvation response, ranging from hepatic metabolism to adaptive starvation response, are elicited and coordinated. Pharmacologically, FGF21 is a promising new clinical candidate for the treatment of insulin resistance and other aspects of the metabolic syndrome. Despite the rapid progress that has been made in understanding FGF21’s myriad actions, there is still much to be learned about the physiology and pharmacology of this fascinating hormone. (Other articles in this supplement to the Journal include references 37–40.)

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