Fibroblast growth factor 21 is a metabolic regulator that plays a role in the adaptation to ketosis[1–5]

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ABSTRACT

Fibroblast growth factor 21 (FGF21) was originally identified as a member of the FGF family in homology studies and is a member of the endocrine FGF subfamily that lacks heparin binding domains and is released into the circulation. A potential role as a metabolic regulator emerged when FGF21 was shown to increase glucose uptake in adipocytes. Subsequently, marked elevations in FGF21 expression were observed in mice that ate a ketogenic diet and when fasting, which suggests that FGF21 expression plays a role in the adaptation to metabolic states that require increased fatty acid oxidation. Consistent with this evidence, FGF21 knockout mice were not able to respond appropriately to consumption of a ketogenic diet. FGF21 expression is downstream of peroxisome proliferator-activated receptor (PPAR) α in the liver and PPARγ in adipose tissue. FGF21 concentrations are higher in both rodent and human obesity, and recent data suggest that obesity may be an FGF21-resistant state. Recent data increasingly suggest that FGF21 is an important metabolic regulator that may have potential clinical implications. *Am J Clin Nutr* 2011;93(suppl):901S–5S.

INTRODUCTION

The ketogenic diet, which is a high-fat and low-carbohydrate diet, has emerged as an important nonpharmacologic therapeutic option for children with intractable epilepsy (1). Closer analysis of carbohydrate-restricted diets in humans has shown that they are effective in causing weight loss and in reducing insulin resistance (2–5), lowering serum triglyceride concentrations, and raising HDL-cholesterol concentrations (2, 3, 6, 7).

Consumption of a ketogenic diet induces a metabolic state similar to fasting. During periods of fasting, the liver uses fatty acids, and through a series of oxidative reactions produces ketone bodies, which serve as fuel for the organism and are the predominant source of energy for the brain (8, 9). The pattern of improved metabolic variables observed in humans is also seen in normal and diet-induced obese mice fed a ketogenic diet and is also associated with a concomitant suppression of transcription factors and enzymes involved in lipid synthesis in the liver. Furthermore, a ketogenic diet leads to a reversal of high-fat, diet-induced obesity along with increased energy expenditure, improved glucose homeostasis, and increased expression of genes in the fatty acid oxidation pathway (10). Beneficial effects of ketogenic diet are also seen in mice that lack leptin (*ob/ob* mice) because the prolonged ketogenic diet feeding of these mice leads to the improvement of glycemic and insulinemic profiles in the absence of weight loss (11). Thus, the manipulation of the dietary macronutrient content can have significant effects on metabolic status, and consumption of fat is not necessarily associated with the development of obesity and impaired glucose homeostasis.

Potential mechanisms that explain the effects of a ketogenic diet might be mediated by the brain. Hypothalamic neuropeptides, such as neuropeptide Y (NPY), agouti-related peptide (AgRP), and proopiomelanocortin (POMC), play a role in the regulation of energy-expenditure changes under different dietary conditions. Increases in NPY and AgRP are associated with decreased energy expenditures, whereas increased POMC is associated with increased energy expenditures (10, 12–14). In animals that ate a ketogenic diet, the expression profile revealed an increase in NPY and AgRP and a decrease in POMC, which was consistent with the low peripheral leptin concentrations but inconsistent with the observed increase in energy expenditure (10). This observation led to the exploration of peripheral pathways that might play a principal role in the metabolic changes associated with a ketogenic diet (10) and to the identification of fibroblast growth factor 21 (FGF21) as a key mediator of lipid oxidation in animals that eat a ketogenic diet as well as potentially during fasting (9).

FGF21 ACTION

The encoding complementary DNA of FGF21 was initially identified in mouse embryos and subsequently in humans; its product is a secreted protein of 210 amino acids in mice and 209 amino acids in humans with a 75% correspondence between the 2 species (15). The expression of FGF21 in mice is predominantly in the liver and adipose tissue, whereas a relatively lower expression has also been shown in other tissues, including the thymus, muscle, and pancreas (15–17). The potential role of FGF21 as a metabolic regulator was first considered when it was

discovered that it could act in 3T3-L1 cells to increase glucose uptake via expression of glucose transporter-1 (18). FGF21 is a member of the broad FGF family, which includes a total of 22 factors in humans that are involved in the regulation of cell survival, mitogenesis, cell growth, tissue repair, and tumor growth (19). FGF21 belongs to the endocrine subfamily of FGFs that includes FGF19 in humans (FGF15 in mice) and FGF23. These members lack a heparin binding domain, are released from the cell, and require a co-receptor to mediate binding to the various FGF receptor (FGFR) isotypes (20–22). The various subfamilies of high-affinity FGFRs have intrinsic tyrosine kinase activity. FGF21 has a specific affinity for FGFR1 but can also act through different isoforms such as FGFR2 and FGFR4 (18, 23, 24). Unlike the classic FGFs, FGF21 has no known mitogenic properties (18).

The target tissue action specificity of FGF21 derives from the interaction of FGF21 with its receptors; this requires the presence of βKlotho, which serves as a direct binding subunit of the FGF21 receptor and forms a complex with it (23, 24). βKlotho is a type 1 transmembrane protein member of the Klotho family, and it is known to be expressed in the pancreas, adipose tissue, and liver (25). βKlotho and FGFR1 form an inactive complex on the surface of the cells, which is activated upon the binding of FGF21. This activation leads to the phosphorylation of a signaling molecule, FGFR substrate 2 (FRS2), as well as the downstream phosphorylation of extracellular signal-regulated kinase 1 and 2. In adipose tissue, this interaction leads to the increased expression of glucose transporter-1, which leads to enhanced glucose uptake (18, 26). Additional studies of FGF21 action have shown a decrease of serum free fatty acids; we recently showed that this was downstream to the decreased expression of lipolytic genes in white adipose tissue in the short term (**Figure 1**). These effects were more accentuated in lean mice than in obese mice (27).

FGF21 actions in the liver enhance fatty acid oxidation and tricarboxylic acid cycle flux during prolonged fasting. These actions may be mediated by inducing the expression of peroxisome proliferator-activated receptor (PPAR) γ coactivator protein-1α (PGC-1α), which is a transcriptional regulator of energy homeostasis (Figure 1). One group reported that mice that lacked FGF21 were unable to increase PGC-1α expression in response to prolonged fasting and also showed an impaired ability in gluconeogenesis and ketogenesis (28). These data supported a preeminent role for FGF21 in the regulation of carbohydrate and fatty acid metabolism during the progression from fasting to starvation.

FGF21 MEDIATES THE EFFECTS OF KETOGENIC DIET IN MICE

The induction of hepatic gene expression and the increase of circulating serum concentrations of FGF21 have been observed with ketogenic diet feeding and fasting. Refeeding after a fast was followed by rapid FGF21 suppression (9). In mice that consumed a ketogenic diet, the knockdown of FGF21 by using silencing RNA constructs delivered through an adenovirus vector led to a marked metabolic impairment that included hepatosteatosis secondary to the accumulation of triglycerides. These mice also showed hyperlipidemia, including increases in serum triglycerides, cholesterol, and nonesterified fatty acids (9). In addition, FGF21 knockout mice, when placed on a ketogenic diet, showed an atypical response to the diet and a mild weight gain instead of
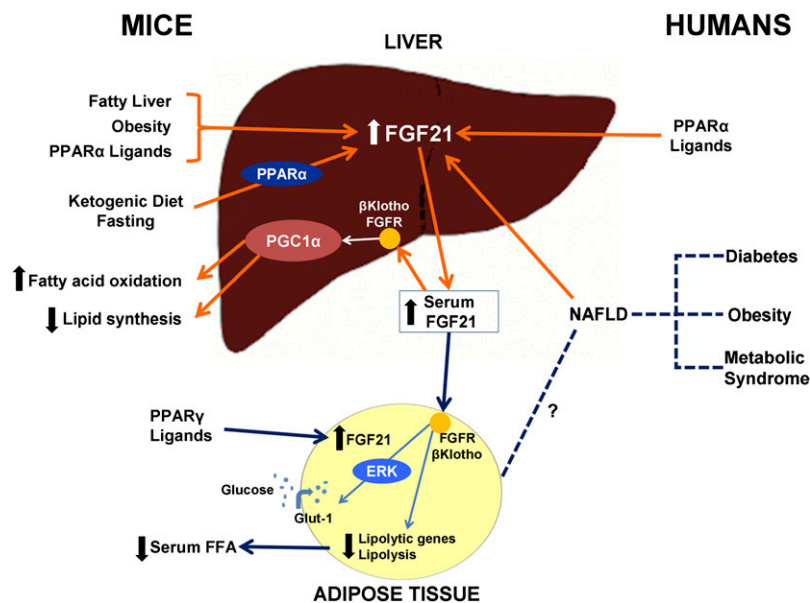

FIGURE 1. Summary of fibroblast growth factor 21 (FGF21) physiology in mice and humans. In mice, consumption of a ketogenic diet leads to a peroxisome proliferator-activated receptor (PPAR) α–dependent increase of FGF21 in the liver and an increase in serum FGF21 concentrations. FGF21 expression in the liver is also induced by fatty liver disease, obesity, and PPARα ligands in mice. PPARα ligands, such as fenofibrate, also increase FGF21 messenger RNA expression in human hepatocytes. FGF21 interacts with the FGF receptor (FGFR) in the presence of βKlotho in the mouse liver and adipose tissue. This interaction leads to a PPARγ coactivator protein-1α (PGC1α)–dependent up-regulation of fatty acid oxidation and down-regulation of lipid synthesis in the liver. In mouse adipose tissue, the presence of PPARγ ligands leads to the production of FGF21, and the short-term effect of FGF21 results in a decreased expression of lipolytic genes and leads to lower concentrations of circulating free fatty acids (FFA). FGF21-induced phosphorylation of extracellular signal-regulated kinase-1 (ERK) leads to the activation of glucose transporter-1 (Glut-1) and glucose uptake in mouse 3T3-L1 adipocytes and primary human adipocytes. In humans, serum concentrations of FGF21 are higher in diabetes, obesity, metabolic syndrome, and nonalcoholic fatty liver disease (NAFLD). This effect may be mediated by increased FGF21 liver expression.

a loss of weight, exaggerated hepatic steatosis, and impaired glucose tolerance with reduced ketone formation (29). Hepatic FGF21 is regulated by PPARα, which is critical to the physiologic regulation of lipid metabolism (9, 30). Mice deficient in PPARα also showed marked impairments when placed on a ketogenic diet. Thus, it appears that hepatic FGF21 production and action are necessary for the appropriate metabolism of lipids during states when fatty acids are the major fuel source.

REGULATION OF FGF21 IN MICE

In mice fed a ketogenic diet, the up-regulation of FGF21 gene expression was accompanied by an increased expression of PPARα-regulated transcripts, which suggests that the induction of FGF21 during ketotic states is PPARα dependent (9) (Figure 1). No induction of FGF21 gene expression was observed in PPARα-null mice during fasting, and a very attenuated induction was seen when these mice were fed a ketogenic diet, which suggests that, during ketosis, an alternative metabolic pathway may be involved that is PPARα independent (9, 30–33). Concentrations of FGF21 were noted to be low in animals with hypothyroidism; recently, we showed that T3 robustly increased FGF21 expression, and this action was dependent on PPARα (34). In addition, FGF21 induced glucose uptake in adipocytes in a PPARγ-dependent manner and led to an increase in glucose transporter-1 messenger RNA (mRNA) expression, whereas PPARγ agonists induced FGF21 expression in adipocytes (35–37) (Figure 1). Recent studies have shown that FGF21 may also be regulated by PGC-1α through the modulation of the heme and Rev-Erbα axis and also by retinoic acid receptor-related orphan receptor α (38, 39).

FGF21 concentrations are elevated in obese mice. This was initially observed in leptin deficient *ob/ob* mice (40). We recently showed that FGF21 mRNA expression was increased in the liver and white adipose tissue of mice with diet-induced obesity and showed evidence for FGF21 resistance in obesity (27). Furthermore, the systemic administration of FGF21 in diet-induced obese and *ob/ob* mice was shown to lower the mean body weight predominantly via a reduction in adiposity and to reduce fasting blood glucose and insulin concentrations (41, 42).

FGF21 IN HUMANS

Currently, the role of FGF21 in humans is unclear. A number of studies indicated that FGF21 serum concentrations correlated with the body mass index (43–45). With regard to changes in nutritional status, one small study reported that 7 d of fasting increased FGF21 serum concentrations (46), whereas another study showed a decline in FGF21 serum concentrations with 3 d of fasting (47). In addition, FGF21 serum concentrations were decreased in subjects with anorexia nervosa, which were more consistent with the fall seen with 3 d of fasting (48, 49). Blood samples of children after the ingestion of a ketogenic diet showed no increase in FGF21 concentrations (46). Furthermore, FGF21 serum concentrations were significantly increased in patients under fenofibrate treatment of primary hypertriglyceridemia than in a control group (46), which was consistent with the fact that PPARα ligands, such as fenofibrate, were shown to increase FGF21 mRNA concentrations in human hepatocytes (40).

Studies in humans with type 2 diabetes have shown that FGF21 expression was increased in baseline conditions and during fasting compared with the expression in control subjects (45, 50–52). It was also reported that obese patients had increased FGF21 blood concentrations, whereas FGF21 mRNA expression in visceral fat increased 2-fold in obese patients compared with in control subjects, and a very low–calorie diet induced a significant increase of FGF21 mRNA expression in the subcutaneous fat of obese patients (45). However, one group did not find detectable FGF21 in fat (47). FGF21 serum concentrations in humans have also been positively correlated with adiposity, fasting insulin, and triglycerides but negatively with HDL cholesterol after adjustment for age and body mass index (53). An independent association was also shown between serum FGF21 concentrations and metabolic syndrome (53). A recent study showed that FGF21 serum concentrations were increased in patients with nonalcoholic fatty liver disease (NAFLD) or steatohepatitis and reported, for the first time to our knowledge, that the mRNA expression of FGF21 was up-regulated in the liver of patients with NAFLD (47) (Figure 1). Another 2 groups reported an association between serum FGF21 concentrations and the degree of fatty liver accumulation (54, 55). These findings suggest that the regulation of FGF21 serum concentrations is different between humans and mice, and further investigations need to be performed. For example, measured circulating concentrations may be affected by as yet unidentified binding proteins, or the duration of fasting may lead to variable results.

CONCLUSIONS

Ketogenic diets increasingly gained attention as alternative and effective means for weight loss and which were also associated with marked improvements in insulin sensitivity and glucose tolerance. In mice, FGF21 expression and action were required to mediate an appropriate metabolic response to consumption of a ketogenic diet. FGF21 has also been shown to be an important regulator of energy expenditure and metabolism; in obese rodents, treatment with FGF21 led to improvement in many metabolic variables and was associated with weight loss. Studies in mice have provided useful information on the pathobiological pathways involved in FGF21 actions and regulation. However, data on FGF21 in humans are limited, and future clinical studies are necessary to provide insight into the role of FGF21 in humans, its potential use as a biomarker for NAFLD, and its potential as a therapeutic agent in states of insulin-resistance obesity and metabolic syndrome.

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