Editorial

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Fibroblast Growth Factor 21: A Novel Metabolic Regulator

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Fibroblast growth factor (FGF) 21 belongs to a superfamily of FGF peptides predominantly produced by the liver but also by other tissues involved in carbohydrate and lipid metabolism. FGFs are classically considered to be paracrine factors, but the FGF19, FGF21, and FGF23 subfamily has recently become known as a group of endocrine factors [1].

FGF21 expression is induced in the murine liver by fasting as an adaptive response through a mechanism requiring peroxisome proliferator-activated receptor alpha (PPARα) [2]. In the liver, FGF21 induces gluconeogenesis, fatty acid oxidation, and ketogenesis but does not stimulate glycogenolysis [2,3]. It suggests that FGF21 does not play a conspicuous role during the early stage of fasting. However, FGF21 stimulates gluconeogenesis and ketogenesis in a state of prolonged fasting and starvation. In fact, an increase in plasma FGF21 during 72-hours fasting was absent, but the effect was present during 7-days of starvation in human studies [4,5].

There is evidence that FGF21 is a promising target for the treatment of type 2 diabetes and metabolic syndrome. When administrated systemically to rodents and monkeys with obesity and diabetes, recombinant FGF21 causes body weight loss, decrease of plasma glucose and triglycerides, and reduction of insulin resistance and hepatic steatosis [6-9] although little is known about the physiologic roles or regulation of FGF21 in humans. FGF21 treatment potently stimulates glucose uptake in adipocytes in an insulin-dependent manner [7]. In obese, insulin-resistant animals, FGF21 regulates mitochondrial activity and enhances oxidative capacity through an AMPK–SIRT1–PGC1α–dependent mechanism in adipocytes [10] and decreases hepatic triglyceride contents associated with a decrease in hepatic lipogenic gene expression (e.g., sterol regulatory element-binding protein-1 [SREBP-1]) [9].

The 24-hour circadian rhythm of FGF21 is displayed under fasting conditions in both humans and mice [4,11]. FGF21 levels began to rise at midnight, reaching a peak in the early morning and then decline to basal concentrations early in the afternoon [4,11]. A number of metabolic hormones including leptin, growth hormone, melatonin, and cortisol have been shown to exhibit a nocturnal increase. In addition, E4-binding protein 4 (E4BP4), which is a key circadian output protein transcriptional repressor, directly bound to the D-box cis-element in the distal promoter region of the FGF21 gene and downregulated its transcription and secretion in primary mouse hepatocytes [12]. Insulin significantly increases E4BP4 expression, which can subsequently repress hepatic FGF21 expression [12]. Other key factors of the circadian clock that regulate the hepatic expression of FGF21 in cultured cells are retinoic acid receptor-related orphan receptor α (RORα) and Rev-Erbα [13,14].

However, Lee et al. [15] were unable to observe a distinct diurnal variation of serum FGF21 concentrations over 24-hours in a small group of healthy Korean men (n=10) fed standardized meals. Although the basis for these differences is not clear, the methods of the FGF21 assay and the characteristics of study subjects could have caused the discrepancy. Because most studies on circadian variation of FGF21 were performed

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using a fasting state, feeding-dependent FGF21 expression may be different in liver and adipose tissues [16]. The molecular mechanism responsible for feeding-induced regulation of FGF21 is less well known than that for fasting-induced stimulation, and further studies in a non-fasting condition should be performed because they are more physiologically relevant.

There are many controversial issues regarding serum FGF21 levels in human studies. In fact, the effects of ketogenic diet on circulating FGF21 concentrations in humans are inconsistent [5,17,18] and circulating FGF21 concentrations in humans showed a broad 250-fold interindividual variation [5]. Although the magnitude of the peak circadian increase of circulating FGF21 is significantly blunted in obese Chinese [11], in a study by Lee et al. [15], the number of large oscillations of FGF21 concentrations was significantly greater in obese subjects. Several recent reports showed that circulating FGF21 concentrations were higher in subjects with obesity, type 2 diabetes, impaired glucose tolerance, dyslipidemia or nonalcoholic fatty liver disease than in controls [18-21]. It is unclear whether this reflects FGF21 resistance or a compensatory response. Although there are few studies to demonstrate the physiologic role of FGF21 in the human body, a recent study showing that diet-induced obese mice had increased expression of FGF21 in liver and white adipose tissue with a significantly attenuated signaling response to exogenous FGF21 suggests FGF21 resistance in obesity [22].

Taken together, FGF21 actions to regulate and coordinate metabolism have not yet been clarified, especially in humans. It is necessary to consider that the regulation of FGF21 is complex and can differ from tissue to tissue, according to nutritional conditions or circadian rhythm. Future investigations about the effects of exogenous FGF21 in humans will elucidate the possible usefulness of this protein as a novel treatment tool for metabolic diseases.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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