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Metabolic roles of endocrine fibroblast growth factors

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Considerable effort is currently being devoted to understanding the physiological and pharmacological action of the endocrine fibroblast growth factors (FGFs). These three proteins (FGF15/19, FGF21 and FGF23) act in a tissue-specific manner through a membrane-complex consisting of an FGF-receptor and α/βKlotho. FGF15/19 is produced in the intestine and regulates postprandial liver metabolism and gallbladder filling. FGF21 is largely liver-derived and co-ordinates adaptive changes in response to nutritional and physiological stresses. FGF23 signals from the bone to the kidney to maintain phosphate homeostasis. In pharmacological settings, FGF15/19, FGF21, and the prototypical FGF1, potentially represent novel treatments for obesity and diabetes. This review summarises the recent advances in our understanding of the biology of these important metabolic regulators.

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Introduction

The fibroblast growth factors (FGFs) are a group of proteins with diverse functions in development, wound-repair, angiogenesis, and metabolism [1,2]. They are named sequentially (*FGF1–23*). However, *FGF15* has not been identified in humans, and *FGF19* has not been identified in the mouse. There is clear evidence that mouse FGF15 and human FGF19 are orthologous proteins. As such, they will be referred to herein as FGF15/19, unless referring to a specific species. While some FGFs (FGF11–14) function as intracellular signalling molecules, most signal in an autocrine/paracrine manner by activating cell-surface FGF-receptors using heparan sulphate glycosaminoglycans as co-factors [3]. By contrast, the so-called 'endocrine FGFs' lack heparan-binding and can therefore enter the circulation and function as hormones [4]. These proteins (FGF15/19, FGF21, and FGF23) have attracted considerable interest due to their potent effects on metabolic homeostasis (Figure 1).

FGF15/19

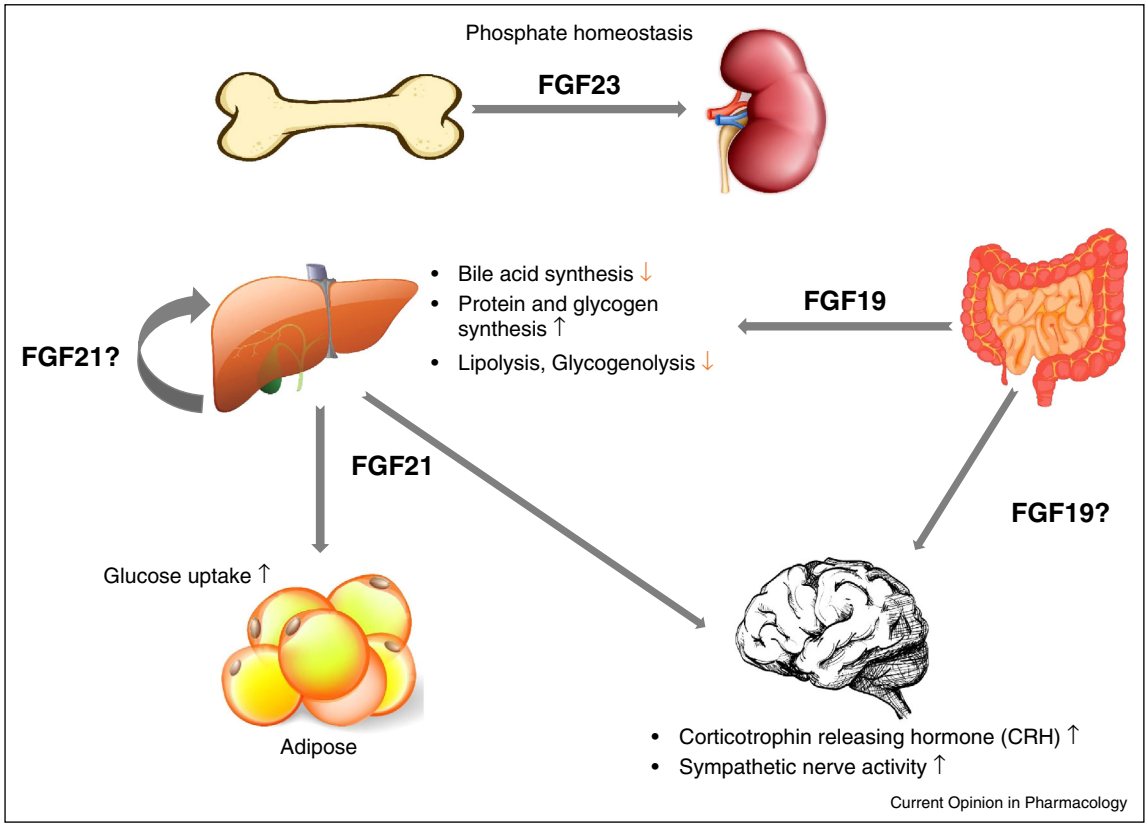
FGF15/19 is expressed in the small intestine and colon [5]. It is a direct target-gene of the farnesoid X receptor (FXR), which is activated by bile acids (BA) being reabsorbed from the intestinal lumen [6]. FXR-induced FGF15/19 enters the portal circulation and acts on the liver via the FGF-receptor 4 (FGFR4) in complex with the essential transmembrane protein βKlotho.

There is strong evidence that FGF19 regulates postprandial BA homeostasis in humans. First, serum FGF19 levels peak approximately two-hours after feeding, and coincide with repression of bile acid synthesis [7]. Second, individuals administered the bile acid binding resin, cholestyramine, have decreased plasma FGF19 levels due to reduced intestinal FXR activation [8]. Third, an FGF19 analog represses BA synthesis in healthy individuals [9•]. Finally, bile acid diarrhoea, a disease caused by the over-production of bile, is associated with decreased FGF19 production [10].

Mechanistic studies in mice have revealed the details of how FGF15/19 regulates bile acid homeostasis. Measuring physiological levels of FGF15 had initially proved challenging. However, quantitative detection of FGF15 in plasma has recently been achieved by targeted mass spectrometry [11•]. Similar to human-FGF19, plasma FGF15 shows a diurnal rhythm with peak levels coinciding with repression of bile acid synthesis [11•]. As expected, FGF15-KO mice are largely phenocopied by mice lacking its receptors (FGFR4-KO mice and βKlotho-KO mice) [12]. They all over-express the rate limiting enzyme in BA synthesis, *Cyp7a1*. This finding demonstrates a role for FGF15 in repressing *Cyp7a1* transcription in the liver. At a molecular level, FGF15/19 reverses the active-transcriptional histone marks on the Cyp7a1 promoter that are induced by the nuclear receptors HNF4α and LRH-1 [13]. These effects on the Cyp7a1 chromatin landscape require expression of the transcriptionally repressive nuclear receptor SHP [14]. FGF15-KO mice also have small gallbladders [15]. This unexpected observation was the basis for further studies that showed that, in addition to its role in regulating BA synthesis, FGF15 also contributes to the control of bile flow, relaxing the smooth muscle in the gallbladder to allow it to re-fill with bile in anticipation of the next meal [15].

In addition to its effects on bile acid homeostasis, FGF15/19 has wider postprandial metabolic effects on the liver.

Figure 1



Summary of the major functions of endocrine FGF's.

Similar to insulin, it stimulates protein and glycogen synthesis and inhibits gluconeogenesis [16,17]. However, there are two important differences between the effects of insulin, and FGF15/19 on liver metabolism. First, peak postprandial levels of FGF15/19 occur in the blood substantially later, and last longer, than those of insulin [17]. Second, FGF15/19 activates the ERK1/2 intracellular signalling cascade, whereas insulin activates the AKT/PI3 K pathway [16]. As such, FGF19 represents a potential anti-diabetic therapeutic that could bypass insulin-signalling pathways and restore euglycemia in insulin-resistant individuals. Hope for such a therapeutic was initially curtailed by the mitogenic properties of FGF19 [18,19]. However, non-tumorigenic FGF19-varients have recently been developed that retain their ability to regulate liver metabolism [9•].

In a pharmacological setting, FGF19 regulates energy expenditure and insulin sensitivity. Peripheral FGF19 injections, or transgenic overexpression of hepatic FGF19, protect mice from diet-induced obesity, and its complications [20,21]. This is due, at least in part, to enhanced energy expenditure resulting from FGF19 signalling in the brain [22,23]. Intracerebroventricular injection of FGF19 increased energy expenditure in obese rats and mice. It also caused ERK1/2 phosphorylation in the hypothalamus of genetically obese mice. Whether FGF15/19 plays a physiological role in modulating energy expenditure remains to be determined. Indeed, FGF15/19 may not cross the blood-brain barrier as readily as some other protein-hormones, such as FGF21 [24•].

FGF21

FGF21 is expressed in several organs including the white adipose tissue (WAT), brown adipose tissue (BAT), muscle, heart, testes, and pancreas [5]. However, the elevated circulating levels of FGF21 observed after nutritional stress appear to be mostly, if not entirely, liver derived [25•]. While genetically altered animals, such as heart-specific FGF21-Tg mice [26] and cold-exposed UCP1-knockout mice [27], demonstrate that organs other than liver are capable of secreting FGF21 in to the circulation, the significance of extra-hepatic FGF21-secretion under physiological conditions remains to be determined.

FGF21 acts through the FGF-receptor 1c (FGFR1c) in complex with βKlotho. FGFR1c is broadly expressed