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Bile Acids as Hormones: The FXR-FGF15/19 Pathway

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Abstract
While it has long been recognized that bile acids are essential for solubilizing lipophilic nutrients in the small intestine, the discovery in 1999 that bile acids serve as ligands for the nuclear receptor farnesoid X receptor (FXR) opened the floodgates in terms of characterizing their actions as selective signaling molecules. Bile acids act on FXR in ileal enterocytes to induce the expression of fibroblast growth factor (FGF)15/19, an atypical FGF that functions as a hormone. FGF15/19 subsequently acts on a cell surface receptor complex in hepatocytes to repress bile acid synthesis and gluconeogenesis, and to stimulate glycogen and protein synthesis. FGF15/19 also stimulates gallbladder filling. Thus, the bile acid-FXR-FGF15/19 signaling pathway regulates diverse aspects of the postprandial enterohepatic response. Pharmacologically, this endocrine pathway provides exciting new opportunities for treating metabolic disease and bile acid-related disorders such as primary biliary cirrhosis and bile acid diarrhea. Both FXR agonists and FGF19 analogs are currently in clinical trials.

Introduction

The important role of bile acids as intestinal detergents for the absorption of dietary lipids has been established for many years. However, the discovery in 1999 of a nuclear receptor for bile acids opened a new chapter in the bile acid field, one in which bile acids function as hormones to regulate diverse physiologic processes [1–3]. Bile acids are now known to signal through two receptors: the farnesoid X receptor (FXR), which is a member of the nuclear receptor family of ligand-activated transcription factors [1–3], and Gpbar1/M-BAR/TGR5, a G protein-coupled receptor [4, 5]. In this review, we will focus on FXR and its downstream effector, fibroblast growth factor (FGF)15/19, and their effects on bile acid homeostasis and metabolism.

Nuclear Bile Acid Receptor, FXR

FXR was originally named based on its weak, non-physiological activation by the terpenoid farnesol [6]. Subsequent studies showed that FXR is activated by physiological concentrations of bile acids, including the primary bile acids cholic acid and chenodeoxycholic acid [1–3]. FXR regulates the expression of target genes by binding to DNA response elements, termed farnesoid X response elements (FXREs), as a heterodimer with the

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9-cis retinoic acid receptor (RXR). The consensus FXRE is composed of two copies of the nuclear receptor binding motif, AGGTCA, organized as an inverted repeat and separated by a single nucleotide [7]. Many FXR target genes have been identified in liver and intestine as well as other tissues [8, 9].

The physiologic role of FXR as a bile acid receptor was confirmed in FXR-knockout (KO) mice, which have increased bile acid synthesis and pool size [10]. When challenged with a diet containing cholic acid, FXR-KO mice had severe hepatotoxicity and wasting that did not occur in wild-type mice [11]. FXR-KO mice also had elevated serum cholesterol, triglycerides, phospholipids, and low-density and very-low-density lipoproteins [11]. Thus, FXR plays a broad role in regulating lipid homeostasis.

FXR-FGF15/19 Enterohepatic Pathway

FXR is expressed in enterocytes throughout the small intestine and colon [12], where it induces genes such as the ileal acid-binding protein and organic solute transporter α/β, which are involved in regulating bile acid homeostasis [13]. Among the genes induced by FXR activation in murine ileum is *Fgf15*, which encodes an atypical FGF that is secreted into the portal circulation to function as a hormone [14]. FXR binds to a response element located in the second intron of the *Fgf15* gene to directly regulate its transcription [14]. Following its induction by bile acids, FGF15 has two prominent effects. First, it circulates to liver, where it inhibits bile acid synthesis by repressing transcription of cholesterol 7α-hydroxylase *(Cyp7a1)*, which encodes the first and rate-limiting enzyme in the classic bile acid synthetic pathway. FGF15-KO mice have increased CYP7A1 expression and activity and a corresponding increase in bile acid synthesis [14]. Second, FGF15 causes the gallbladder to fill with bile [15]. FGF15-KO mice have a virtually empty gallbladder, even in the fasted state, when the gallbladder is normally full. Notably, injection of FGF15-KO mice with recombinant FGF15 causes a rapid filling of the gallbladder without stimulating bile flow. This effect is mediated in part via relaxation of the gallbladder smooth muscle [15]. Thus, FGF15 released from the small intestine plays a crucial role in coordinating bile acid homeostasis in other tissues including the liver and gallbladder. In liver, FGF15 acts through a cell surface receptor complex composed of the FGF receptor 4 (FGFR4), which has tyrosine kinase activity, and βKlotho, a single transmembrane protein. Both FGFR4-KO and βKlotho-KO mice phenocopy the FGF15-KO mice in having increased *Cyp7a1* expression and small gallbladders [16, 17].

The human ortholog of FGF15 is FGF19. At the time they were cloned, the fact that FGF15 and FGF19 share only 53% amino acid identity left the nature of their relationship in question, hence their different names [18, 19]. However, there is now definitive evidence that FGF15 and FGF19 are orthologous proteins. For this reason, we refer to the hormone as FGF15/19 unless referring to a specific ortholog. The genes for human, mouse, and zebrafish FGF15/19 are on syntenic regions of the genomes [20], and the FXR binding site is conserved [14, 21]. Consistent with this latter finding, *FGF19* expression in humans is also regulated by bile acids. In humans, serum FGF19 levels have a diurnal rhythm with peaks occurring 90–120 min after the postprandial release of bile acids [22]. This peak precedes the repression of bile acid synthesis. Conversely, FGF19 levels decreased in subjects administered the bile acid sequestrant, cholestyramine [22]. Patients with bile acid diarrhea, who overproduce bile acids, also have lower circulating FGF19 levels [23]. Recently, an FGF19 analog was shown to efficiently repress bile acid synthesis in healthy volunteers taking part in a phase 1 clinical study [24]. Thus, FGF19 is induced by FXR and represses bile acid synthesis in humans.

Mechanism of *CYP7A1* Repression

Previous studies have shown that the feedback regulation of *CYP7A1* by bile acids is mediated by a nuclear receptor signaling cascade involving FXR and small heterodimer partner (SHP), an atypical orphan nuclear receptor lacking a DNA binding domain that functions as a potent transcriptional repressor [25, 26]. In liver, transcription of the *SHP* gene is induced by bile acids via FXR. SHP, in turn, binds to the *CYP7A1* promoter to repress gene transcription through mechanisms that involve recruitment of various proteins, including the mSin3A-Swi/Snf complex, G9a methyltransferase, and the corepressor subunit GPS2 [27–29]. Mice lacking SHP have increased basal *Cyp7a1* expression [30, 31]. SHP is recruited to the *Cyp7a1* gene via interactions with the nuclear receptors LRH-1 and HNF4α, which both bind to a promoter region that is important for bile acid-mediated repression [25, 26, 32, 33]. Studies with liver-specific KO mice have shown that either LRH-1 or HNF4α is capable of recruiting SHP to the *Cyp7a1* promoter [34].

Notably, SHP is required for FGF15/19 to efficiently repress bile acid synthesis. Mice lacking SHP are refrac-

tory to the inhibitory effects of either FXR agonists or FGF15/19 on *Cyp7a1* expression [14, 34]. HNF4α and LRH-1 induce active transcription histone marks on the *Cyp7a1* promoter that are reversed by FGF19 in a SHP-dependent manner [34]. FGF19 does not change SHP protein levels or its localization on the *Cyp7a1* gene promoter, suggesting that FGF19 stimulates the recruitment of other factors to the SHP complex [34]. Since basal *Fgf15* expression in intestine is low, its induction is required for repression of *Cyp7a1* [14]. In contrast, basal expression of *Shp* in liver is relatively high. Thus, further induction of *Shp* in liver by FXR contributes to – but is not essential for – repression of *Cyp7a1*. This model is borne out by studies with intestine- and liver-specific FXR-KO mice: elimination of FXR in intestine disrupts FXR-mediated suppression of *Cyp7a1*, whereas elimination of FXR in liver does not [35].

Additional Metabolic Actions of FXR and FGF15/19

The biological actions of FXR extend well beyond the regulation of bile acid homeostasis [8, 9, 36]. As mentioned above, FXR exerts important effects on lipoproteins and lipid metabolism. Activation of FXR with either bile acids or synthetic FXR agonists decreases hepatic and circulating triglyceride concentrations [37, 38]. FXR also regulates glucose homeostasis. FXR-KO mice are insulin resistant and glucose intolerant [38–40]. Conversely, FXR activation improves insulin sensitivity and glycemia in rodent models of metabolic disease. These effects are due in part to FXR-mediated repression of hepatic gluconeogenesis and induction of hepatic glycogen synthesis [38–40].

Likewise, FGF15/19 has broad biological effects. Like insulin, FGF15/19 levels rise following a meal [22], and it stimulates hepatic protein and glycogen synthesis by acting on the FGFR4/βKlotho receptor complex in hepatocytes [41]. However, peak blood levels of FGF15/19 occur well after those of insulin, and its effects are mediated not by the AKT/PI3K signaling cascade but rather through an ERK1/2 pathway that activates components of the protein translation machinery and stimulates glycogen synthase activity [41]. FGF19 also represses gluconeogenesis through a mechanism involving the dephosphorylation and inactivation of the transcription factors CREB and FoxO1 [42, 43], which are both positive regulators of gluconeogenic genes. Thus, FGF15/19 acts subsequent to insulin to regulate diverse aspects of the postprandial response.

Pharmacologically, FGF15/19 also regulates energy expenditure and insulin sensitivity. Transgenic mice overexpressing FGF19 under the control of the muscle-specific myosin light chain promoter weighed less than their wild-type littermates [44]. Although FGF19-transgenic mice had increased food intake, they also had a higher metabolic rate. When challenged with a high-fat diet, FGF19-transgenic mice remained lean and had decreased muscle and liver triglyceride levels. These mice also had lower serum glucose and insulin levels, improved glucose tolerance, and improved insulin sensitivity compared to wild-type littermates [44]. Similar effects were seen after administration of recombinant human FGF19 to mice maintained on a high-fat diet. FGF19 improved glucose tolerance and decreased serum insulin and triglycerides [45]. These data suggest FGF19 acts as an insulin sensitizer.

A potential drawback of administering FGF19 as an antidiabetes drug is that it promotes liver growth at pharmacologic concentrations. FGF19 has been implicated in liver tumorigenesis [46], and chronic exposure to FGF19 causes hepatocellular carcinoma in mice [47]. Notably, however, variants of FGF19 have been developed that are nontumorigenic but still retain the ability to regulate bile acid metabolism [48]. One of these variants was shown to suppress bile acid synthesis in humans, providing direct evidence that FGF19 regulates bile acid homeostasis in humans [24].

Recent studies have shown that FGF15/19 can regulate metabolism by acting on the brain. Intracerebroventricular injection of FGF19 activated ERK1/2 in the hypothalamus of *ob/ob* mice and increased energy expenditure and improved glycemia in mouse and rat models of obesity [45, 49–51]. Interestingly, FGF19 administered centrally increased glucose disposal in *ob/ob* mice via an insulin-independent mechanism [51]. It remains to be determined precisely where and how FGF15/19 acts on the brain to regulate metabolism and whether FGF15/19 crosses the blood-brain barrier at physiologic concentrations to regulate these processes.

Closing Comments

The past 15 years have witnessed explosive growth in our understanding of bile acids as signaling molecules. Acting as hormones themselves and as inducers of FGF15/19, bile acids regulate diverse facets of hepatic metabolism ranging from their own synthesis to protein and carbohydrate homeostasis. Pharmacologically,

FXR agonists and FGF15/19 exert profound effects on metabolism, including effects on insulin sensitivity and energy expenditure. Remarkably, both FXR agonists and FGF19 analogs are already in clinical trials for treating various enterohepatic disorders including primary biliary cirrhosis, bile acid diarrhea, and nonalcoholic steatohepatitis. Thus, the future looks bright for harnessing the FXR-FGF15/19 pathway for treating human disease.

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Disclosure Statement

S.A.K. owns stock in Intercept Pharmaceuticals.

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