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REVIEW ARTICLE

FARNESOID X RECEPTOR: ACTING THROUGH BILE ACIDS TO TREAT METABOLIC DISORDERS

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SUMMARY

The farnesoid X receptor (FXR) is a member of the nuclear receptor superfamily and plays an important role in maintaining bile acid, lipid and glucose homeostasis. Bile acids are endogenous ligands for FXR. However, bile acids may also activate pathways independent of FXR. The development of specific FXR agonists has provided important insights into the role of FXR in metabolism. Recent data have demonstrated that FXR is a therapeutic target for the treatment of certain metabolic disorders. This review will focus on recent advances in the role of FXR in metabolic disease.

INTRODUCTION

Nuclear receptors are ligand-activated transcription factors that play an important role in reproduction, development and homeostasis. There are 48 nuclear receptors in humans. The farnesoid X receptor (FXR, NR1H4) is a member of the nuclear receptor superfamily. It has an *N*-terminal activation function domain 1 (AF1), a highly conserved DNA-binding domain (DBD), a hinge region that links the DBD to a ligand-binding domain (LBD) and a transcriptional activation function domain 2 (AF2). FXR functions by binding to a response element in a target gene as a heterodimer with the retinoic X receptor (RXR). Upon ligand binding, FXR releases corepressors and recruits coactivators, often leading to increased gene transcription.

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Bile acids are end products of cholesterol catabolism. In 1999, bile acids were identified as endogenous ligands for FXR (1-3). The order of potency of bile acids is: chenodeoxycholic acid (CDCA) > lithocholic acid (LCA) = deoxycholic acid (DCA) > cholic acid (CA). Subsequent studies demonstrated that bile acids also activate the pregnane X receptor (PXR, NR1I2) (4, 5), vitamin D receptor (VDR, NR1I1) (6), c-Jun *N*-terminal kinase (JNK) 1/2 (7), protein kinase C (8-10), epidermal growth factor receptor (EGFR, erbB-1) (11, 12), G protein-coupled receptor GPR131 (TGR5) (13, 14), extracellular signal-regulated kinase (ERK) 1/2 and AKT (15). Bile acid-activated GPR131 (TGR5) signaling is known to promote energy expenditure (16). Thus, bile acids regulate many diverse pathways in both FXR-dependent and -independent pathways. The development of specific FXR agonists, such as GW-4064 (17), fexaramine (18), AGN-34 (19), 6α-ethylchenodeoxycholic acid (6-ECDCA, INT-747) (20) and turofexorate isopropyl (WAY-362450, XL-335) (21), has provided important insights into the role of FXR in metabolism. Synthetic FXR agonists are much more specific and potent in FXR activation than bile acids. For instance, synthetic 6-ECDCA, which is modified from CDCA, is very specific for FXR and is about 87-fold more potent than CDCA (20). The frequently used FXR ligands, including endogenous bile acids and synthetic FXR agonists, are summarized in Figure 1.

FXR is highly expressed in the liver, intestine, kidney and adrenal gland (22-25), and to a much lesser extent in white adipose tissue and heart (23, 26, 27). FXR has four isoforms (23, 24), termed FXRα1, FXRα2, FXRα3 and FXRα4. These four FXR isoforms differ at the *N*-terminus and the hinge region, and are differentially expressed in different tissues (23, 24). These four FXR isoforms may differentially regulate the transcription of certain genes (28). Recent data show that hepatic expression of constitutively active FXRα1, FXRα2, FXRα3 or FXRα4 lowers plasma cholesterol levels to a similar extent (29). Whether these four FXR isoforms have similar or differential effects on other metabolic pathways remains to be determined.

The utilization of both loss-of-function and gain-of-function approaches has greatly increased our understanding of the role of FXR in both physiology and disease processes. FXR is one of the most important regulators of bile acid metabolism. It regulates bile acid synthesis, conjugation, secretion and uptake (28, 30, 31). Activation of FXR protects against cholestasis (32) and cholesterol gallstone formation (33), likely due to induction of the bile salt trans-

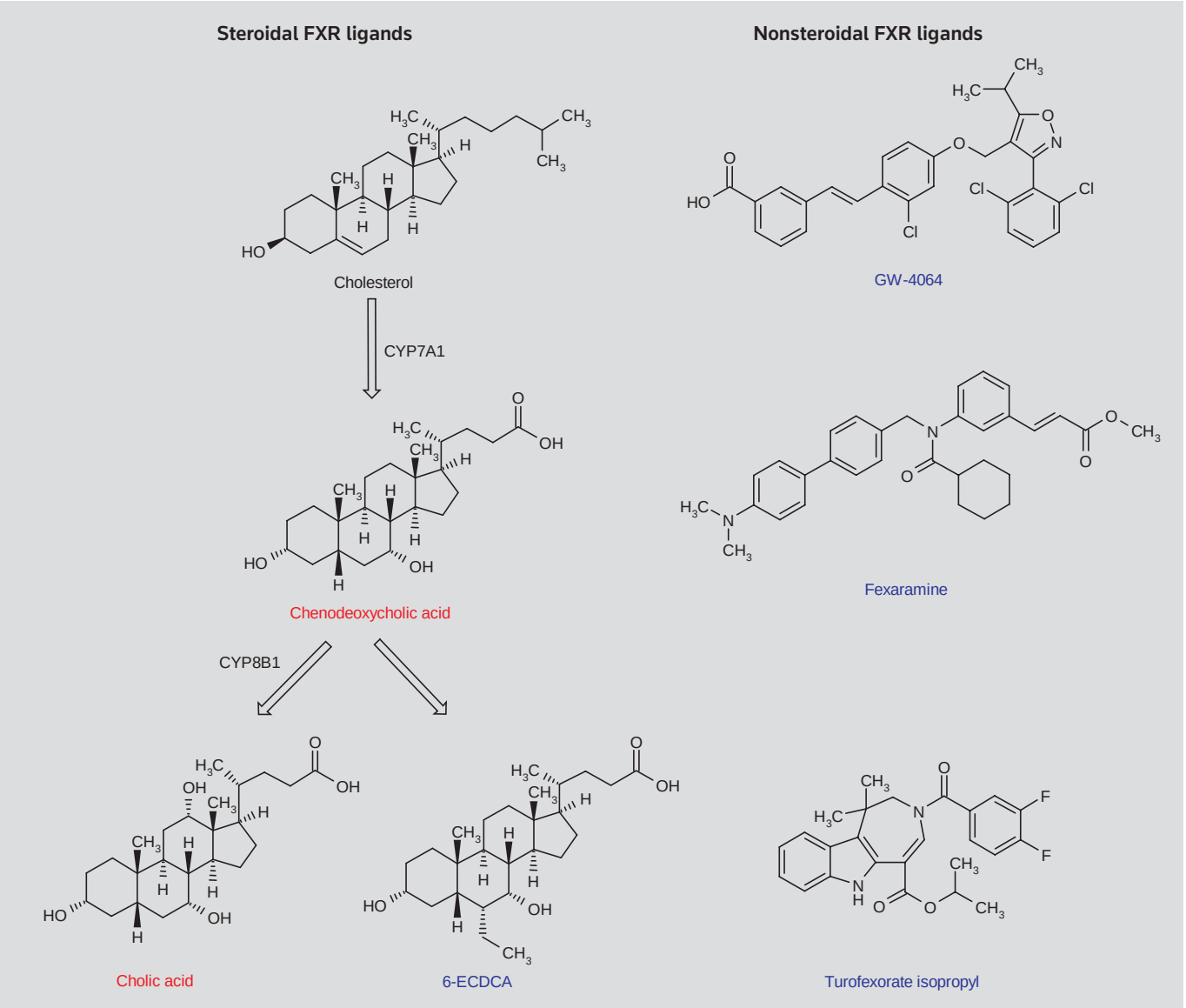

Figure 1. Natural and synthetic farnesoid X receptor (FXR) ligands. Bile acids, the endogenous ligands for FXR, are end products of cholesterol catabolism. Cholesterol 7α-hydroxylase (CYP7A1) is the rate-limiting enzyme of the neutral pathway of bile acid synthesis, which converts cholesterol to chenodeoxycholic acid (CDCA). Sterol 12α-hydroxylase (CYP8B1) converts CDCA to cholic acid (CA). 6α-Ethylchenodeoxycholic acid (6-ECDCA) is modified from CDCA and is a synthetic FXR agonist. CDCA, CA and 6-ECDCA are steroidal FXR ligands. Nonsteroidal FXR ligands include GW-4064, fexaramine and turofexorate isopropyl (WAY-362450, XL-335). Endogenous FXR ligands and synthetic FXR ligands are indicated in red and blue, respectively.

porter BSEP and the multidrug resistance protein MDR3 (Mdr2 in mice) (32, 33). FXR also has an antimicrobial effect in the ileum, which is associated with induction of angiopoietin-1 (ANG-1), inducible nitric oxide synthase (iNOS) and interleukin-18 (IL-18) (34). Huang et al. showed that FXR and bile acid signaling are important for liver regeneration, which appears to result from regulation of both c-Myc and forkhead box protein M1 (FOXM1) (35). Chen et al. showed that *FOXM1* is a direct target gene of FXR and the binding of FXR to FOXM1 is diminished in aging regenerating livers (36). Finally, FXR deficiency results in an increased incidence of colon cancers (37, 38) and hepatocellular cancers (39, 40). Thus, FXR is a multipurpose nuclear receptor. The role of FXR in lipid and glucose metabolism will be discussed in detail below. The major FXR-regulated pathways are summarized in Table I. Since many excellent reviews on FXR have been published during the past several years (28, 30, 31, 41-45), this review will focus on recent advances in the role of FXR in metabolic disorders.

THE ROLE OF FXR IN CHOLESTEROL HOMEOSTASIS AND ATHEROSCLEROSIS

Atherosclerosis is characterized by lipid accumulation in macrophages and chronic inflammatory responses in the arterial

Table I. *FXR-regulated pathways.*

Major function	Major regulated pathway	Relevant disease(s)
Bile acid metabolism	Bile acid synthesis, conjugation, secretion and uptake	Cholestasis, cholesterol gallstone
Lipid metabolism	Triglyceride and cholesterol homeostasis	Atherosclerosis, nonalcoholic fatty liver disease
Glucose metabolism	Gluconeogenesis and insulin sensitivity	Type 2 diabetes
Antibacterial	ANG-1, iNOS and IL-18	Bacterial infection in the distal small intestine
Hepatocyte proliferation	c-Myc and forkhead box protein M1	Liver regeneration
Antitumor	Apoptosis	Colon, hepatocellular cancer

wall (46-48). Atherosclerosis is one of the major causes of coronary heart disease. Study of the role of FXR in atherosclerosis began with *Fxr*$^{-/-}$ mice. *Fxr*$^{-/-}$ mice display a proatherogenic lipid profile, demonstrated by increased plasma triglycerides, very-low-density lipoprotein (VLDL) cholesterol, low-density lipoprotein (LDL) cholesterol and pre-β high-density lipoprotein (HDL) cholesterol, on either a chow or a Western diet (49-51). Despite the proatherogenic lipid profile, *Fxr*$^{-/-}$ mice do not develop atherosclerotic lesions (50, 52). When *Fxr*$^{-/-}$ mice are crossed with *Apoe*$^{-/-}$ or *Ldlr*$^{-/-}$ mice, *Fxr* deficiency is reported to cause increased, unchanged or decreased atherosclerosis. Hanniman et al. reported that *Fxr*$^{-/-}$*Apoe*$^{-/-}$ double knockout (DKO) mice have increased atherosclerosis compared to *Apoe*$^{-/-}$ mice (52). In contrast, Guo et al. reported that *Fxr*$^{-/-}$*Apoe*$^{-/-}$ DKO mice have reduced atherosclerosis compared to *Apoe*$^{-/-}$ mice (53). We have generated *Fxr*$^{-/-}$*Ldlr*$^{-/-}$ DKO mice; the data show that male DKO mice have reduced atherosclerosis compared to male *Ldlr*$^{-/-}$ mice, whereas there is no change in lesion size between female *Fxr*$^{-/-}$*Ldlr*$^{-/-}$ DKO mice and female *Ldlr*$^{-/-}$ mice. The reduced atherosclerotic lesions in male *Fxr*$^{-/-}$*Ldlr*$^{-/-}$ DKO mice are associated with reduced plasma LDL-C levels and reduced expression of fatty acid translocase FAT/CD36 and adipose differentiation-related protein (ADRP) in macrophages (50). Guo et al. also reported that *Fxr*$^{-/-}$*Apoe*$^{-/-}$ macrophages have reduced CD36 expression and lipid accumulation (53).

The discrepancy in the role of FXR deficiency in atherosclerosis is unclear. One possibility is that different mouse genetic backgrounds, diets and length of study have been used in these studies. In contrast to the studies with *Fxr*$^{-/-}$ mice, studies that utilize synthetic FXR agonists have produced consistent and exciting data on atherosclerosis. Hartman et al. (54) and Flatt et al. (21) utilized turofexorate isopropyl (WAY-362450, XL-335), a highly potent and selective FXR agonist, to demonstrate that activation of FXR reduced atherosclerotic lesions in *Ldlr*$^{-/-}$ or *Apoe*$^{-/-}$ mice by 86-95%. Mencarelli et al. utilized a structurally distinct FXR agonist, INT-747 (6-ECDCA), to treat *Apoe*$^{-/-}$ mice; the data showed that INT-747 reduced atherosclerotic lesions by 95% (55). Thus, treatment with synthetic FXR agonists has beneficial effects on atherosclerosis. Although the findings that activation (21, 54, 55) or inactivation (50, 53) of FXR both result in reduced atherosclerosis appear to be contradictory, previous data have shown that activation or loss of a nuclear receptor may result in the same phenotype. For instance, activation (56, 57) or loss (58) of the nuclear receptor peroxisome proliferator-activated receptor PPARα is reported to reduce atherosclerosis in atherosclerosis-prone animal models. Nonetheless, since FXR deficiency results in many deleterious effects (26, 42, 49, 50, 59, 60), FXR agonists, but not antagonists, may be useful for treatment of cardiovascular diseases.

The mechanism by which activation of FXR prevents the development of atherosclerosis is not clear. Numerous studies have demonstrated that activation of FXR reduces plasma cholesterol levels (21, 59, 61, 62). A recent study showed that activation of FXR by either the synthetic FXR agonist GW-4064 or hepatic expression of constitutively active FXR primarily reduces plasma HDL-C levels. Although plasma HDL-C is reduced, activation of FXR increases reverse cholesterol transport (RCT), a process by which extrahepatic cholesterol is transported back to the liver for secretion into the bile and feces. RCT has been proposed to protect against atherosclerosis. The FXR-induced increase in RCT is associated with increased hepatic expression of scavenger receptor class B member 1 (SR-BI) and ATP-binding cassette transporters ABCG5 and ABCG8. SR-BI appears to be required for activated FXR to reduce plasma cholesterol levels (29). Recent data also show that a synthetic FXR agonist reduces plasma LDL-C in primates (63). The reduction in plasma LDL-C levels following FXR activation may be partly due to reduced expression of PC9 (proprotein convertase subtilisin/kexin type 9) (64). The beneficial effect of FXR on cholesterol homeostasis, together with other yet-to-be-determined mechanisms, may contribute to the inhibition of atherogenesis following FXR activation. The role of FXR in regulating cholesterol and triglyceride homeostasis is summarized in Figure 2.

FXR AND NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide. It refers to a spectrum of liver disorders ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis (65-67). NAFLD is often associated with obesity, dyslipidemia, insulin resistance and type 2 diabetes (68-70). Recent data have suggested that FXR may be a therapeutic target for the treatment of NAFLD.

The central role of FXR in maintaining triglyceride homeostasis has been known for about 10 years. *Fxr*$^{-/-}$ mice have increased hepatic and plasma triglyceride levels (49). Consistent with this finding, activation of FXR reduces hepatic triglyceride or neutral lipid accumulation in wild-type (71), diabetic KKA^{y} (71) or *db/db* (59) mice and Zucker (*fa/fa*) rats (72). Activation of FXR also prevents hepatic inflammation and fibrosis in a mouse model of NASH (73) and promotes fibrosis resolution in a rat model of liver fibrosis (74). In contrast, FXR deficiency causes increased hepatic lipid accumulation (49) and induces NASH in *Ldlr*$^{-/-}$ mice (75). Together, these data indicate that FXR is a promising therapeutic target for the treatment of NAFLD (44, 76).

The mechanism by which FXR reduces hepatic triglyceride levels is controversial. Small heterodimer partner (SHP) is also a nuclear receptor and a known FXR target gene (77, 78). Watanabe et al. sug-

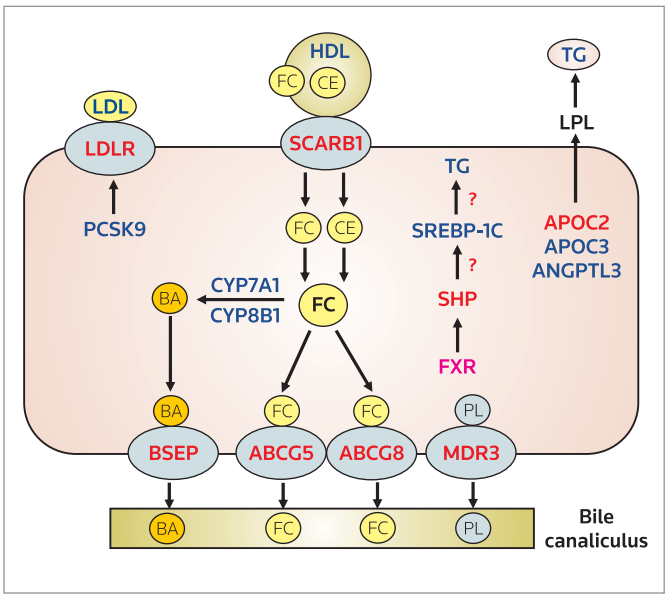

Figure 2. Regulation of cholesterol and triglyceride homeostasis by the hepatic farnesoid X receptor (FXR). Activation of FXR increases hepatic expression of *SCARB1, ABCG5/ABCG8, BSEP* and *MDR3*, and inhibits hepatic expression of *CYP7A1* and *CYP8B1*. Thus, activation of FXR increases hepatic uptake of HDL-derived cholesteryl esters (CEs) and free cholesterol (FC). CEs are further hydrolyzed to form FC. FC is subsequently secreted to the bile by ABCG5/G8 or converted to bile acids (BA) by CYP7A1/CYP8B1 for secretion to the bile via BSEP. FXR is also reported to inhibit *PCSK9* expression, thus increasing *LDLR* expression. Multidrug resistance protein MDR3 is a phospholipid (PL) transporter. The net result of FXR activation is reduced plasma HDL-C and LDL-C levels, and increased reverse cholesterol transport. Activation of FXR lowers plasma triglyceride (TG) levels likely by increasing hepatic expression of *APOC2* and repressing hepatic expression of *APOC3* and *ANGPTL3*. The mechanism by which activation of FXR lowers hepatic TG levels remains controversial; the reported FXR/SHP/SREBP-1C pathway is not supported by other studies. FXR-induced or -repressed genes are indicated in red and blue, respectively.

gested that activation of FXR increases SHP, which in turn represses sterol regulatory element-binding protein SREBP-1C, and thus lipogenesis (71). SREBP-1C is a master regulator of fatty acid synthesis (79). Although activation of FXR inhibits SREBP-1C expression in hepatocytes (71, 80), subsequent studies suggest that FXR/SHP/SREBP-1C is unlikely to be the underlying mechanism by which activation of FXR reduces hepatic triglyceride levels. First, transgenic expression of human *SHP* in mouse livers increases *Srebp-1c* expression and triglyceride levels in the liver (81). Second, *Shp*$^{-/-}$ mice have reduced hepatic triglyceride levels when fed a high-fat diet (82). Third, the knockout of *Shp* in *ob/ob* mice prevents hepatic triglyceride accumulation (83). Thus, the mechanism by which FXR reduces hepatic triglyceride levels remains unknown.

FXR AND GLUCOSE HOMEOSTASIS

In 2006, three laboratories independently reported a role for FXR in glucose metabolism (26, 59, 60). Activation of FXR has been shown to lower plasma glucose levels in wild-type mice (60) and to improve insulin sensitivity in diabetic *db/db*, *ob/ob* or KKA^{y} mice, or *fa/fa* obese rats (26, 59, 72, 84). In contrast, *Fxr*$^{-/-}$ mice display insulin resistance (26, 59, 60).

Activation of FXR has been shown to repress the hepatic gluconeogenic genes phosphoenolpyruvate carboxykinase (*PEPCK*) (60) and glucose-6-phosphatase (*G6PC*) (59, 60, 85). The repression of both *PEPCK* and *G6PC* by FXR appears to be via the FXR/SHP pathway (60). However, *PEPCK* is also reported to be induced by FXR in the livers of wild-type mice (59, 85). Consequently, plasma glucose levels in wild-type mice have been reported to be reduced (59, 60) or unchanged (85). In diabetic animals, activation of FXR has been shown to reduce plasma glucose levels (59, 72, 84). In contrast, Cariou et al. reported that GW-4064 treatment tended to lower plasma glucose levels in *ob/ob* mice. Of note, GW-4064 was administered in corn oil via i.p. injection in the latter study (26), whereas GW-4064 is usually administered orally in different vehicles. The different approaches for GW-4064 administration may partly account for the discrepancy in plasma glucose levels between the study by Cariou et al. (26) and others (59, 72, 84).

Recent data show that FXR is also expressed in pancreatic islets and β-cells (86-88). Glucose-stimulated insulin secretion (GSIS) is impaired in islets isolated from *Fxr*$^{-/-}$ mice (86), whereas activation of FXR increases insulin secretion and GSIS in β-cells (87). Thus, pancreatic FXR may also play a role in FXR-controlled glucose homeostasis. The utilization of tissue-specific *Fxr*$^{-/-}$ mice will help elucidate the relative role of FXR in the liver, intestine and pancreas in glucose homeostasis. Therefore, FXR regulates glucose homeostasis likely through modulation of hepatic gluconeogensis and pancreatic insulin secretion. The beneficial effect of FXR on triglyceride homeostasis may also contribute to the increased insulin sensitivity.

CONCLUSIONS

Multiple lines of evidence have demonstrated that FXR is a promising therapeutic target for the treatment of atherosclerosis, NAFLD and type 2 diabetes. The generation and utilization of potent and specific FXR agonists with excellent bioavailability and little or no toxicity/side effects will be important for successfully targeting FXR in the future. FXR agonists are being used in clinical trials for various purposes. The data collected from the clinical trials will undoubtedly provide valuable information regarding the potential usefulness of FXR agonists for the treatment of metabolic disorders and associated syndromes, such as type 2 diabetes, NAFLD and atherosclerosis.

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DISCLOSURES

The author states no conflicts of interest.

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