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# Farnesoid X Receptor is an Exciting New Perspective Target For Treatment Of Diverse Pathological Disorders: Review

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**Abstract**

The principal action of Farnesoid X Receptor (FXR) in numerous features of inflammation and metabolism makes it an exciting therapeutic target for treatment of several biological disorders.

Herein we review the up-to-date facts of systemic FXR pathophysiology in different organs. In addition, we outlined and analyzed the current possible signaling mechanisms underlying the implication of FXR in the pathological disorders such as cholestasis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), type 2 diabetes (T2DM), obesity, atherosclerosis, cardiac ischemia, male infertility and hepatocellular carcinoma. At this fact, it is required, however, to discuss most of the *in vivo* studies concerning the herein outlined biological disorders that were achieved in rodents, particularly in mice.

According to our analysis, the FXR seems to be a promising pharmacological target for treatment of many pathological disorders. However, due to the multiple phenotypic effects of FXR, it is essential to create FXR-selective, but also gene- and tissue-spesific targeted ligands in order to decrease related adverse reactions. Finally, clinical trials with selective FXR agonists/ antagonist should shed more light on the precise role of this receptor in diverse pathological disorders.

**Keywords:** Farnesoid X receptor, Cholestasis, NAFLD, Male infertility, nuclear receptor; pharmacological application.

## INTRODUCTION

Farnesoid X receptor is a nuclear receptor (NR) subfamily 1 group H member 4 (FXR, 2 NR1H4) [Reference]. It is a unique nuclear hormone receptor (NR) superfamily which has a crucial regulatory function in multiple biological processes [1]. FXR is an embraced member of the metabolic NR subfamily. Initially, FXR was named on the basis that farnesol metabolites are legends for this receptor [2]. Subsequently, in 1999, studies discovered that bile acids such as (Please, write full name when it is mentioned for first time) (CDCA) and cholic acid are endogenous legends for this receptor [3, 4]. In addition, bile acids can activate another signaling in an FXR-independent way [5]. With no ligand existing, FXR accordingly is bound to the response elements (REs) of goal genes as long as the co-repressors. After its binding to a ligand, a conformational modification in FXR leads to detachment of the co-repressors besides to their interchange with co-activators resulting in the beginning of expression of FXR targeted genes. FXR is type 2 nuclear receptor located in the nuclease and involved in metabolism [6,7]. Most of type 2 nuclear receptors bind to retinoid X receptors ( RXR ) to form heterodimers which in turn, binds to hormone RE located on DNA that up- or down-regulates the implicated protein sequence expression [7].

## THE EXPRESSION PATTERN OF FXR IN TISSUES

FXR is vastly hosted in liver, kidney, intestine, and adrenal gland [9-12], however, lesser extent of FXR is identified in adipose tissue, testis and heart [13, 14].

A particular FXR gene in humans and in rodents expresses two dissimilar isoforms of FXR, FXR α (NR1H4) and FXR β (NR1H5), that exhibit a durable homology to each other [Reference]. Both genes are evolutionally preserved crossways species, starting from fish towards humans, however, many studies revealed that FXR β is non-functional genomic sequences in humans and primates [7].

As a transcriptional element, FXR binds to the RE of targeted genes by means of a heterodimer that regulates the expression of DNA sequences implicated in the breakdown of bile acids (BAs), lipids, and carbohydrates [16,17]. In addition, the FXR has the ability to join with DNA in a monomeric way although it rarely happens [18] .

## LIGANDS FOR FXR

Besides bile acids (BAs), as the most specific endogenous agonists which bind to and stimulate FXR [19-21], androsterone was found to be another endogenous agonist for FXR, but with low efficacy [22]. Nevertheless, it is obvious that BAs are non-specific agonists of NR because they do not stimulate FXR only but also stimulate further nuclear receptors like Pregnane X receptor (PXR), vitamin D receptor (VDR) and the constitutive androstane receptor (CAR) [15]. Also, BAs can stimulate TGR5????, which is a G-protein coupled receptor (GPCR) [23], therefore, they are able to control different metabolic processes by diverse pathways. However, there is a number of known endogenous and synthetic agonists for FXR. The potent and selective synthetic FXR agonists are: Fexaramine, GW 064 [24], AGN 34 and 6-ECDCA [25]. INT-747, Tropifexor (LNJ-452), GS-9674 (Px-104) and EDP-305 are synthetic FXR ligands currently available in clinical trials [26]. In addition, Cafestol, which is present in coffee, is a natural agonist for FXR [27] whereas Obeticholic acid (OCA) is a semisynthetic bile acid analogue which was the first selective FXR agonist to be used in human drug studies [28].

## PARAMETERS THAT AFFECT FXR EXPRESSION AND ACTION

The mRNA for FXR, expressed in liver, is increased by a long-time starving. In addition, FXR mRNA levels are induced after increasing the expression of PGC-1a in primary hepatocytes [29]. New studies have revealed that mRNA levels of FXR gene are elevated in cultured cells in response to elevation of glucose level [30]. This response may have physiological significance because hepatic FXR expression is increased in diabetic mice model [30].

## BIOLOGICAL ROLES OF FXR IN TREATMENT OF DIFFERENT DISORDERS IN VARIOUS ORGANS

The FXR regulates the expression of DNA sequences that are implicated in BAs, glucose, and lipid homeostasis [Reference]. Upon activation by BAs, the principal action of FXR in the various aspects of metabolism and inflammation makes FXR an attractive drug target for several diseases.

The emphasis of this literature review will be on the latest advancement in FXR biological activities in several organs. Also, it will analyse current possible signaling mechanisms underlying the implications of FXR in the pathological disorders such as cholestasis, NAFLD, NASH, T2DM, obesity, atherosclerosis, cardiac ischemia, male infertility and hepatocellular carcinoma (Figure 1). Moreover, we will outline and discuss most of the *in vivo* studies concerning the herein mentioned biological disorders that were accomplished in rodents, particularly in mice, and the

potential therapeutic developments of FXR ligands/ modulators for developing drugs to treat various pathological disorders.

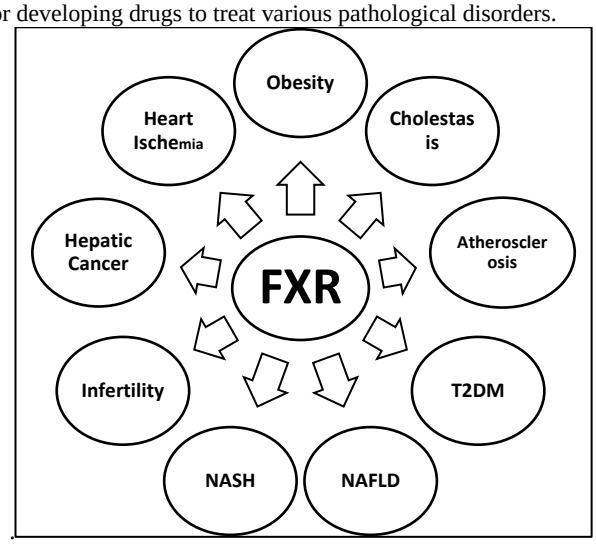


**Figure 1: The implications of FXR in different pathological disorders**

**1-Cholestasis by modulation of bile acid homeostasis**

Cholestasis is diminishing in BAs drainage due to decreased excretion either by hepatocytes or by impediment to bile outflow [31]. BAs act as a detergent that facilitates digestion and subsequent immersion of dietary fats and cholesterol in the intestinal tract. Furthermore, catabolism of cholesterol to form bile acids is the principal means for elimination of cholesterol from the body [32]. BAs are synthesized mainly by hepatocytes by oxidation of cholesterol via the CYP7A1 enzyme [33]. FXR regulates BAs homeostasis by modulating the expression of crucial genes implicated in BAs biosynthesis, conjugation, secretion and uptake [34].

When the levels of hepatic BAs are high, FXR stimulates the small heterodimer partner (SHP) which down-regulates the transcription of cholesterol 7-alpha-hydroxylase (CYP7A1) enzymae, which is the rate-limiting enzyme in BAs biosynthesis. Furthermore, FXR down-regulates the expression of bile acid salts importers such as NTCP (Na- taurocholate Co-transporting polypeptide) in a way that it blocks the entrance of intestinal bile acid into hepatocytes [35]. BAs, which are considered end step in hepatic cholesterol fate, play an important role in digestion and intestinal absorption of lipids and act as crucial factors for eliminating cholesterol from the body. previous studies have shown that SHP-independent pathway is implicated in the inhibition of Cyp7α1 through BAs [33].

Other studies have documented another signaling pathway that is dependent on FGF15 by which stimulation of intestinal FXR by agonist GW4064 induces release of fibroblast growth factor (subtype 15) protein from cells of intestinal tract. The latter, induces FGFR4 expression which contained on the plasma membrane of hepatic cells leading to stimulation of the c-Jun N-terminal kinase signaling cascade and reducing the Cyp7α1 enzyme level [36].

Moreover, the activation of FXR induces the expression of three hepatic pumps that have an importance in exporting BAs out of hepatocytes. These transporters are ATP-binding cassette (ABC) transporters including multidrug resistance-associated protein subtypes 3 and 4. They are provoked independently on FXR, bile salt export protein (BSEP) and the multidrug resistance transporters 3 including MDR3 and ABCB4 [Reference]. These proteins are expressed on the membrane of cholangiocytes of bile duct and efflux BAs and other molecules from the hepatocytes into the lumen of canaliculi [15,16]. A recent study [37] reported that an FXR-targeted gene, FGF15, controlled the typical filling of gall bladders. This study established that the replenishing of gall bladder subsequent to cholecystokinin-motivated draining is controlled by the production and excretion of FGF15 from the distal end of the small intestine. The induced FGF15 consequently activates FGF15 receptors on gall bladder then stimulates the reduction of smooth muscle contractility of the gall bladder to permit its refilling [37]. In addition to OCA, which is an FXR natural ligand, other FXR agonists, LJN- 452, GS- 9674 and EDP-305, emerged as potential therapies for cholestasis [31, 38].

**2- NAFLD and NASH by regulation of lipid metabolism**

NAFLD is the furthermost public reason of chronic liver disease worldwide as its incidence is as great as one billion [39]. NAFLD might result in advanced NASH, fibrosis, and, eventually, hepatocellular carcinoma (HCC) with subsequent liver failure [40]. Previous studies have revealed that stimulation of FXR decreases hepatic lipids and cholesterol levels. In detail, the stimulation of FXR raises the expression of genes implicated in lipoprotein breakdown and elimination, and inhibits the hepatic genes concerned with synthesis of triglycerides (TGs). Experimentally, stimulation of FXR in rodents inhibited the expression of Srebp-1c levels in hepatic cells of mice or the sequestered primary hepatocytes in mice. Also, hepatic triglyceride biosynthesis and excretion were decreased by hepatic down-regulation of Srebp-1c via FXR modulation [41].

However, in comparison with the improvement of FXR agonists, there might be furthermore action for FXR antagonists in the management of metabolic disorders [Reference]. A recent study showed anti-dyslipidaemic perspective effect of an FXR antagonist; Compound-T1. The latter, augmented the level of HDL-cholesterol and decreased the intensities of non-HDL-cholesterol and TG in the plasma of dyslipidaemic hamster model [42].

**3- T2DM by regulation of glucose homeostasis:**

Many recent studies verified that FXR has an important super action in regulating glucose homeostasis. The functional FXR is expressed in both human islets and β cell lines and protects the islets from lipotoxicity [Reference]. Activation of FXR by either GW4064 or by injection by an adenovirus, that expresses an active FXR-VP16 merging protein, leads to a noteworthy decrease in the murine plasma sugar concentration and enhanced insulin signaling [1, 13]. Moreover, stimulation of hepatic FXR declines plasma glucose levels and suppresses gluconeogenic genes [43].

In lean mice, however, GW4064 had no outcome on the insulin discharge of murine islets that feed a high fat diet, demonstrating that the FXR signaling in β cells is down-regulated in over-nutrition circumstances [44]. In addition, the hepatic glycogen storage might be changed because of the suppression of hepatic G6Pase following FXR stimulation. According to this suggestion, the triggering of FXR in both primary hepatocytes of the mice and livers of diabetic db/db mice results in elevation of transformation of D-glucose to glycogen or enhances glycogen storage in the liver [43].

These modifications were associated with enhancing phosphorylation of GSK3b, an important regulator of glycogen synthase [44]. Recent studies showed that there were improvements in metabolic control in mice fed a high-fat diet and treated with the BA sequestrate Colestimide. These improvements might happen through increasing energy expenditure and stimulating thermogenesis in brown adipose tissue [45]. In another study, Brufau et al. [46] had shown that treatment with colesevelam prompted the hydrophilicity of circulating bile acid pool, decreased insulin resistance, fasting glucose and hemoglobin A1C (HbA1c) levels.

**4- Obesity by inhibition of intestinal microbiota**

The gut microbiota is accompanying metabolic diseases including obesity, insulin resistance and NAFLD [47], In a new study, FXR plays a crucial role in inhibiting intestinal bacterial growth and, thereby, regulating host metabolism probably via autophagy signaling pathways [48]. Inagaki et al. [49] revealed that FXR-/- mice suffer from high bacterial growth in their ileum and epithelial barrier and this result is in agreement with the suggestion that FXR is important in regulating bacteria growth and preserving a proficient barrier in the intestine. Remarkably, in transplant experiments, after lean germ-free mice were treated with cecal microbiota obtained from obese mice, there was a rise in TG buildup in the liver [50]. When bacteria from slim humans were moved to germ-free mice, the mice developed resistance to obesity while mice getting bacteria from obese humans were likely to be obese [51].

**5- Hepatic tumorigenesis by induction of liver regeneration/repair**

Liver regeneration (LR) subsequent to partial hepatectomy (PH) is a multifaceted method of compensatory hyperplasia motivated by the replication of remained intact hepatocytes and is controlled by a network of signaling cascades such as growth factors, cytokines and transcription factors [52]. The activation of FXR function in the liver may be a potential therapeutic approach for patients with liver cancer. FXR may exert its tumor inhibitory function partially via direct inactivation of oncogenes and activation of tumor-suppressor genes [53]. Dropping BAs levels in the FXR-knockout mice by nurturing 2% cholestyramine had considerably repressed tumor injuries proposing the association between metabolic regulation and liver tumorigenesis [54]. The over expression of interferon gamma (IFN) in the liver of FXR-knockout mice reduced carcinogenesis by stimulating p53 transcriptions and reducing the activation of signal transducer and activator of transcription 3 (STAT3) [55]. These FXR-/-mice also showed over expression of genes important in inflammation and raised plasma BAs [55]. Consistent with these results, administration of a diet accompanied by 0.2% cholic acid food induced N-nitrosodiethylamine-promoted hepatic carcinogenesis while administration of a diet comprising the BAs sequestrate, cholestyramine, to reduce the BAs storage in the FXR-/-rodents had decreased the prevalence of hepatic tumor lesions [56]. According to these clarifications, there is a cross talk between FXR and hepatic tumorigenesis.

Understanding the signaling pathways of LR, such as the relations of BA-FXR signaling in this complex path, is helpful for the improvement of novel pharmacological approaches for treatment of hepatic tumorigenesis.

**6- Myocardial ischemia by stimulation of cardiomyocytes apoptosis**

A recent study [Reference] showed that FXR is an innovative promising receptor in cardiomyocytes. Systematic studies demonstrated that stimulation of FXR had activated apoptosis through MPTP stimulation, mitochondrial potential degeneracy, cytochrome c release and activation of both caspase-9 and -3 [Reference]. Pharmacological suppression of FXR significantly decreased myocardial apoptosis by 29.0–53.4%, decreased infarct size by 23.4–49.7% and enhanced cardiac function in the ischemic/perfused cardiomyocytes [57].

**7- Male infertility by regulation testosterone synthesis**

In a recent *in vivo* study [14] it was demonstrated that testicular testosterone synthesis was repressed by a synthetic agonist of the FXR which in turn prompts an androgen-dependent apoptosis of germ cells. The latter is related to a reduced sexual maturation of males and subsequent infertility [14]. All of these effects were suppressed by means of anti-FXR antibody in addition to the FXR specific synthetic inhibitor (Z)-Guggulsterone. These data are determining a novel and unpredicted field of action for this nuclear receptor [58].

**8- Atherosclerosis by promoting cholesterol efflux/anti-inflammatory effect**

The FXR appears to be a hopeful therapeutic target in atherosclerosis. FXR agonist could exert defensive properties in the progression and evolution of atherosclerosis, however, concomitant adverse effects such as a decrease of plasma HDL had been stated [59]. High-density lipoprotein (HDL) and APO lipoprotein AI (ApoA-I) protect against the development of atherosclerotic cardiovascular disease, because of their role in promoting cholesterol efflux and reverse cholesterol transport [60].

Previous work showed that TMEM141 is a target gene for FXR in mice hepatocytes. Knockdown of Tmem141 in liver results in down-regulation of ABCA1, which is a crucial factor in HD biogenesis, down the reduction of ABCA1 level in mice resulted in reduction of plasma total cholesterol (approximately 8 folds) compared with that in controls. In the same study, the plasma lipoprotein cholesterol profiles shown that the amount of cholesterol was much lower in HDL-C fraction (< 80 %) and low LDL-C fraction (< 40-50 %) compared to control group where there was a reduction up to 80% in HDL level and cholesterol efflux [61]. In contrast, over expression of human ABCA1 had been reported to induce plasma HDL level and protect against atherosclerosis [62]. Activation of FXR in the liver induces the expression of miR-144 resulting in ABCA1 suppression and reduced HDL plasma levels [63]. However, the recent study proposed that simultaneous dual stimulation of FXR and TGR5 by INT-767 completely blocked the anti-atherogenic and anti-inflammatory effects of INT-767 in LDLR KO mouse.

## CONCLUSIONS AND FORTHCOMING STANDPOINTS

Studies in FXR cascades throughout the last 2 decades had attempted to investigate its significant roles in regulation of many genes implicated in metabolism and inflammation. Herein in this literature, we had briefly explored the activity of FXR in the up-to-date pathophysiological signaling in different disorders such as cholestasis, NAFLD, NASH, T2DM, obesity, atherosclerosis, cardiac ischemia, male infertility and hepatocellular carcinoma. Pharmacological targeting of FXR, therefore, offers an exciting novel perspective for the management of these diseases. Nevertheless, the potential benefits or risks of synthetic FXR ligands necessitate additional considerations in light of variances among species. Another encounter in manipulating FXR agonists is to discrete the preferred therapeutic effects from the undesirable adverse effects. The intention of organ- or gene-specific FXR modulators may increase their selectivity and diminish adverse effects. A well considerate of the cellular and physiological signaling of FXR and its cofactors will promote development of more discriminatory modulators and the improvement of more effective therapeutics for these disorders.

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