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REVIEW

Farnesoid X receptor alpha: a molecular link between bile acids and steroid signaling?

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Abstract Bile acids are cholesterol metabolites that have been extensively studied in recent decades. In addition to having ancestral roles in digestion and fat solubilization, bile acids have recently been described as signaling molecules involved in many physiological functions, such as glucose and energy metabolisms. These signaling pathways involve the activation of the nuclear receptor farnesoid X receptor (FXRα) or of the G protein-coupled receptor TGR5. In this review, we will focus on the emerging role of FXRα, suggesting important functions for the receptor in steroid metabolism. It has been described that FXRα is expressed in the adrenal glands and testes, where it seems to control steroid production. FXRα also participates in steroid catabolism in the liver and interferes with the steroid signaling pathways in target tissues via crosstalk with steroid receptors. In this review, we discuss the potential impacts of bile acid (BA), through its interactions with steroid metabolism, on glucose metabolism, sexual function, and prostate and breast cancers. Although several of the published reports rely on in vitro studies, they highlight the need to understand the interactions that may affect health. This effect is important because BA levels are increased in several pathophysiological conditions related to liver injuries. Additionally, BA receptors are targeted clinically using therapeutics to treat liver diseases, diabetes, and cancers.

Keywords FXRα · Bile acid · Steroids · Physiologic functions

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Bile acids

Biosynthesis and physico-chemical function

Bile acids (BAs) are the main constituent of bile. BAs are present in the digestive tract during a meal and ensure solubilization and emulsification of fat, thus helping digestion [1]. They are produced in the liver from cholesterol through a series of enzymatic modifications. There are two different synthesis pathways that share common enzymes. The first, named the classical pathway, involves the P450 CYP7A1 and CYP8B1 cytochromes, among others. The alternate pathway involves cytochromes CYP27A1 and CYP7B1. Both pathways result in the production of the so-called primary BAs cholic acid (CA) and chenodeoxycholic (CDCA) [2]. Before being excreted by the hepatocytes, BAs are, in part, combined with amine residues (glycine or taurine) leading to the production of bile salt-, tauro-, or glyco-conjugates. Primary BAs and their conjugates are stored in the

gallbladder and are discharged during a meal into the duodenum to facilitate the digestion of fats and their passage through the enterocyte barrier.

In the ileum, BAs are partially deconjugated and are modified by enzymes of the intestinal flora [3]. These transformations lead to the synthesis of secondary BAs. Thus, deoxycholic acid (DCA) and lithocholic acid (LCA) are derived from CA and CDCA, respectively.

In the ileum and colon, the majority of BAs (95 %) are reabsorbed for recycling in the liver. Thus, the newly synthesized BAs will again be excreted during several rounds of digestion. This recycling mechanism, named enterohepatic circulation, involves a system of finely regulated carriers to maintain the homeostasis of BAs and cholesterol from which the BAs originate [4].

In addition to this mechanical function, BAs have been described as molecules that signal through two receptors: the nuclear farnesoid X receptor alpha (FXRα; NR1H4) and the membrane receptor TGR5 (GPBAR1, G protein-coupled bile acid receptor).

Here, we will focus on the potential involvement of FXRα and bile acids on steroid metabolism.

The nuclear receptor of BAs: FXRα

FXRα is a member of the nuclear receptor family [5]. This receptor was isolated from mouse livers in a screen of proteins searching for proteins that interact with the receptor of 9-cis retinoic acid (RXR) and thus was previously named RXR-interacting protein 14 (RIP14) [6]. It was renamed FXRα because it was shown to be activated by farnesol, an intermediate of the mevalonate pathway. FXRα regulates transcription through heterodimerization with RXR, and binds specific sequences on the promoter of target genes, named the FXR-response elements (FXREs), to regulate transcription. These sequences are composed of two copies of a six-nucleotide sequence (AGGTCA) that are arranged as inverted repeat motifs separated by one base (IR-1) [7]. Other FXREs have been described, including IR0, IR8 (separated by zero or eight base pairs, respectively), ER8 (an everted repeat motif) and DR1 (a direct repeated motif), but these response elements have a lower affinity than IR-1. If the FXRα/RXR heterodimer enhances transcription, it seems as FXRα can also repress transcription through potentially negative FXREs [8–10].

FXRα has also been shown to bind to certain genes as a monomer or a homodimer on negative FXREs [11]. These mechanisms are not yet fully understood.

FXRα/RXR is a permissive heterodimer, as ligands of both partners can synergize to regulate the transcription of target genes. In 1999, BAs were identified as ligands of FXRα [12–14]. This led to the renaming of FXRα as a "bile acid receptor" (BAR). The preferred ligands of FXRα are CDCA and its conjugated derivatives [15, 16]. Different bile acids have different potencies in regard to the activation of FXRα. The potencies are as follows, in decreasing order: (1) CDCA, (2) DCA, (3) LCA, (4) CA [13].

Human and mouse genes encode four isoforms of FXRα: FXRα1 (RIP14-2), FXRα2, FXRα3 and FXRα4 (RIP14-1) [17, 18]. The mouse FXRα gene is located on chromosome 10 C2, and the human FXRα gene is located on chromosome 12q23.1. These genes are composed of 11 exons and ten introns. The isoforms result from two alternate promoters that initiate transcription at either exon 1 or exon 3 [17, 19]. The alternative promoters at exon 1 or exon 3 regulate the expression of FXRα1 and FXRα2 or FXRα3 and FXRα4 transcripts, respectively. The FXRα3 and FXRα4 isoforms possess longer N-terminal regions than do FXRα1 and FXRα2. The isoform differences could impact the efficiency of the "activation function 1 domain" (AF-1) for interacting with cofactors. In the FXRα 1 and 3 isoforms, exon 5 is differentially spliced compared to FXRα 2 and 4. This alternative splicing event results in the addition of four amino acids (MYTG) adjacent to the DNA-binding domain in the hinge domain. The four FXRα isoforms present a degree of specificity at the mRNA level, which affects protein structure. However, all isoforms contain the classical domains of nuclear receptors, including the dimerization interface, the ligand binding domain, the DNA-binding domain, and the ligand-dependent activation function (AF-2) domain at the C-terminus. Indeed, the isoforms indicate classical activation by RXR and FXRα agonists, but could differentially regulate the expression of target genes in vitro [19, 20, 21]. Moreover, the isoforms are expressed in a tissue-specific manner.

The heart and adrenal glands express only FXRα1 and FXRα2. These isoforms are expressed at low levels in the lung and white adipose tissue. FXRα3 and FXRα4 are expressed in the kidney and stomach [22]. Volle et al. [23] showed the expression of FXRα in the testis, specifically in the interstitial compartment. This result was supported by a further study on testicular cell lines [24]. In humans, Bishop-Bailey et al. [25] showed expression of FXRα in biopsies of cardiac muscle, the small intestine and the adrenal glands. The liver and adrenal glands express FXRα1 and FXRα2 exclusively, while the kidney and the colon express FXRα3 and FXRα4. All four isoforms are found in the small intestine and duodenum. FXRα is detected in human immune cells, peripheral blood mononuclear cells and subsets of lymphocytes and monocytes [26, 27].

These expression patterns of FXRα suggest that it might have major physiological roles. The use of a mouse model lacking the gene encoding *FXRα* (*FXRα*$^{-/-}$) highlights the involvement of *FXRα* in many physiological functions (digestion, immunity) and diseases, such as diabetes and cancers [28]. The first described roles of FXRα were the

regulation of the enterohepatic cycle and the regulation of BA biosynthesis [29]. *Fxrα*$^{-/-}$ mice exhibit high plasma concentrations of BAs, highlighting the critical role of FXRα in the repression of *Cyp7a1,* which codes for a key enzyme in BA biosynthesis. At the molecular level, this pathway involves several members of the nuclear receptor superfamily, such as SHP (small heterodimer partner), LRH1 (Liver receptor homolog-1), and LXRα (Liver X receptor) [30, 31]. In parallel, FXRα protects the liver from the toxic effects of the accumulation of BAs, promoting the excretion of BAs into the bile by the transcriptional induction of specific transporter *Bsep* (bile salt export pump) [32]. *Fxr*$^{-/-}$ mice consistently show decreased excretion of BAs in the digestive tract [29]. In the intestine, FXRα induces the expression and secretion of fibroblast growth factor 15/19 (FGF15/19) into the portal circulation. After binding with the fibroblast growth factor receptor 4 (FGFR4) in the liver, FGF15/19 represses the enzymes of BA synthesis [33].

FXRα is also involved in the control of lipid and carbohydrate metabolism [11]. Its action in the liver limits triglyceride production through the repression of genes such as stearoyl coenzyme A desaturase [34]. Consistently, *Fxrα*$^{-/-}$ mice show high plasma triglyceride concentrations. In addition, FXRα also controls glucose metabolism through the regulation, in the liver, of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase genes encoding key enzymes of gluconeogenesis and glycogenolysis [35].

Crosstalk between bile acids and steroid metabolism

In addition to the primary roles of bile acids, many recent studies have reported potential connections between bile acids and steroid metabolism.

It has recently been demonstrated that steroids can control bile acid homeostasis. For example, long-term therapy with glucocorticoids (GC) presents several limitations due to side effects such as hyperglycemia or insulin resistance. Cholestasis remains a major side effect. BA serum levels are correlated positively with serum GC concentrations in humans. Increased GC levels in Cushing's patients were associated with elevated BA levels [36]. Furthermore, hepatic GC receptor deficiency in mice resulted in a reduction of the hepatic BA pool in obese mice [37].

Similarly, estrogens are thought to contribute to the etiology of intrahepatic cholestasis during pregnancy, which is associated with an increase in the total bile acid pool [38]. This disease usually develops in the third trimester of pregnancy when concentrations of estrogens are the highest. These patients can develop cholestasis outside pregnancy when they are taking oral contraceptives containing 17αethinyloestradiol. High doses of estradiol and its metabolites also cause cholestasis in rodents, and mice lacking estrogen receptors are resistant to these effects [39, 40].

In this review, we will discuss data indicating that bile acids can regulate steroid homeostasis and interfere with steroid signaling pathways through FXRα. This hypothesis relies on studies demonstrating that FXRα is expressed in many steroidogenic tissues. Moreover, bile acids, FXRα ligands, and steroids are derived from the same precursor molecule (cholesterol). Although several of the reported data rely on in vitro studies, they highlight the need to understand these interactions because they may affect health.

Impact of bile acids on glucocorticoid pathways

Glucocorticoids are produced by the adrenal glands and are essential for life. In humans, cortisol is the most important glucocorticoid (GC). The name of the GCs is based on their well-established roles in glucose metabolism during the stress response. GCs are involved in the stimulation of gluconeogenesis, particularly in the liver, the mobilization of amino acids from extrahepatic tissues, the inhibition of glucose uptake in muscle and adipose tissue, as well as the stimulation of fat breakdown in adipose tissue [41]. GCs regulate or support cardiovascular, metabolic, immunologic, and homeostatic functions. The adrenals also produce mineralocorticoids, mostly aldosterone. The main target of aldosterone is the distal tubule of the kidney, where it stimulates the exchange of sodium and potassium.

The potential role of FXRα in adrenals was expected as it was described to be highly expressed in the adrenocortical cells of the *zona fasciculata* [42, 43]. These potential interactions with GC metabolism could be either at the level of GC synthesis, catabolism, or either through the alteration of their physiological functions.

Glucocorticoid synthesis

As summarized in Fig. 1, the impact of FXRα on GC synthesis was recently demonstrated. *Fxrα*$^{-/-}$ mice show the same plasma glucocorticoid concentrations as wild-type mice, suggesting that FXRα might not be involved in the regulation of the adrenal steroidogenesis under normal conditions. However, FXRα might have an impact in adrenal physiology in mice [44], as its activation increases the expression of scavenger receptor class B, member 1 (SR-BI), which is involved in the transport of cholesterol esters, the specific cellular cholesterol pool used for steroidogenesis [45]. C57BL6 female mice treated with GW4064, a synthetic FXRα agonist, have an increased plasma corticosteroid concentrations [46].

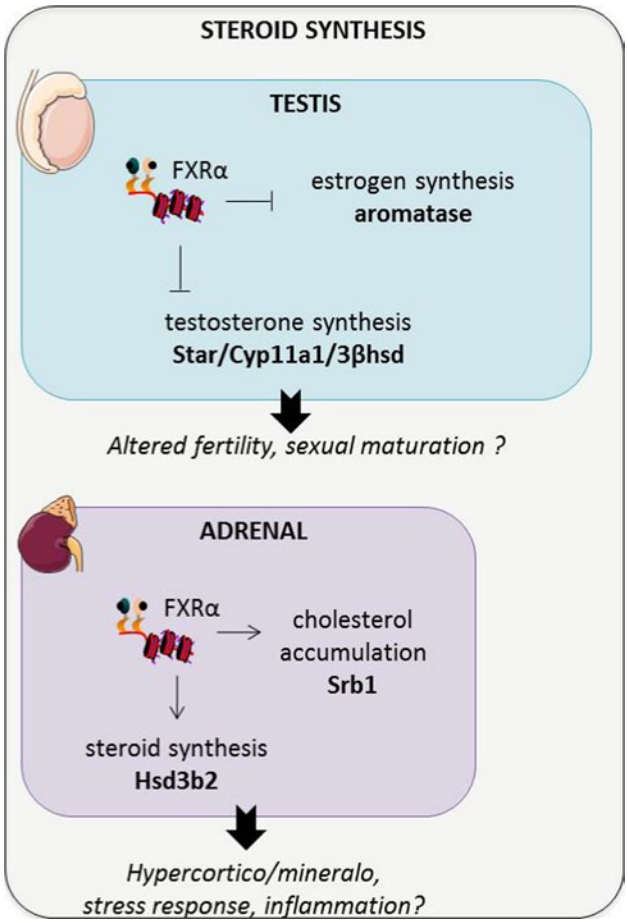

Fig. 1 Schematic representation of FXRα impact on steroid synthesis. In the testes, FXRα regulates the synthesis of both androgens and estrogens through the inhibition of the steroid acute regulatory proteins, cytochrome P450A1, 3β-hydroxydehydrogenase, and aromatase. This effect can lead to altered male fertility or sexual maturation at puberty. In the adrenal glands, the impact of FXRα on steroid synthesis is mediated through the regulation of the Srb-1 gene, leading to increased cholesterol mobilization for steroid synthesis and regulation of 3β-hydroxydehydrogenase type 2 in human adrenal cells. This effect can result in hypercorticosteroid or hypermineralocorticoid production and affects stress responses and inflammation

In the human adrenocortical cell line H295R, the use of GW4064 and CDCA shows that FXRα positively regulates the expression of 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2). This regulation does not exist in mice, which is consistent with the fact that no FXRE was identified in the mouse Hsd3β1 promoter region, the orthologue of human HSD3B2 gene [47].

Glucorticoid catabolism

In target tissues, the concentration of steroids results from the equilibrium between synthesis and catabolism processes. The efficiency of GCs relies on an inactivation or a degradation of the steroids.

Cellular availability The ability of cells to respond to glucocorticoids and aldosterone is dependent on 11β-hydroxysteroid dehydrogenases (11betaHSDs), which catalyze the reversible conversion of physiologically active glucocorticoids to the inactive 11-ketometabolites. There are two isoforms of the 11β-hydroxydeshydrogenease: 11β-HSD1 and 11β-HSD2, and 11β-HSD deficiency is responsible for the hypermineralocorticoid, which results in hypertension.

There is much evidence to suggest that bile acids are able to enhance the intracellular availability of cortisol by abrogating the 11β-HSD2 activity. BA-dependent inhibition of 11βHSD2 enzyme activity was demonstrated using total renal microsomes. Various BAs, such as CDCA and DCA, are able to inhibit the oxidative activity of 11βHSD2. However, in vitro studies suggest that CDCA might affect the activity of 11β-HSD2 in HEK-293 cells only at very high non-physiological concentrations. Consistently, the induction of cirrhosis by bile duct ligation decreased the transcriptional levels of the 11β-HSD enzyme (Fig. 2). Inhibition of 11βHSD2 may contribute to the sodium retention and potassium excretion observed in patients with liver cirrhosis or cholestasis [48, 49].

In agreement with reports showing that bile acids can inhibit both 11β-HSD isoforms in various tissues, it was demonstrated that CDCA inhibited 11β-HSD1 in Leydig cells [50]. It can be hypothesized that FXRα can regulate the impact of cortisol in Leydig cells through the regulation of 11β-hydroxysteroid dehydrogenase 1 (Fig. 2). It is well established that glucocorticoids play a critical role in the control of Leydig cell function. High levels of glucocorticoids are associated with a reduced circulating testosterone level and with reproductive dysfunction [51, 52]. It has been reported that excess corticosterone reduces the expression and activity of 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD) in adult rat Leydig cells in vivo and in vitro [53].

Glucocorticoid degradation Glucuronidation is catalyzed by enzymes belonging to the uridine 5, diphosphate glucuronosyl transferase family (UGT) [8, 54]. These enzymes have been divided into two major subfamilies, UGT1A and UGT2B, based on their amino acid sequence homology. The UGT2 family includes enzymes that are able to glucuronidate both bile acids and steroids.

Expressed in the liver, kidney, brain, and gastrointestinal tract, *UGT2B7* is considered the major human mineralocorticoid and glucocorticoid metabolizing UGT enzyme (Fig. 2). It has also been demonstrated that a single mutation in this gene greatly affects the level of aldosterone glucuronidation.

Ugt2b7 expression seems to be repressed by LCA treatment in vitro. LCA-FXRα activation dramatically

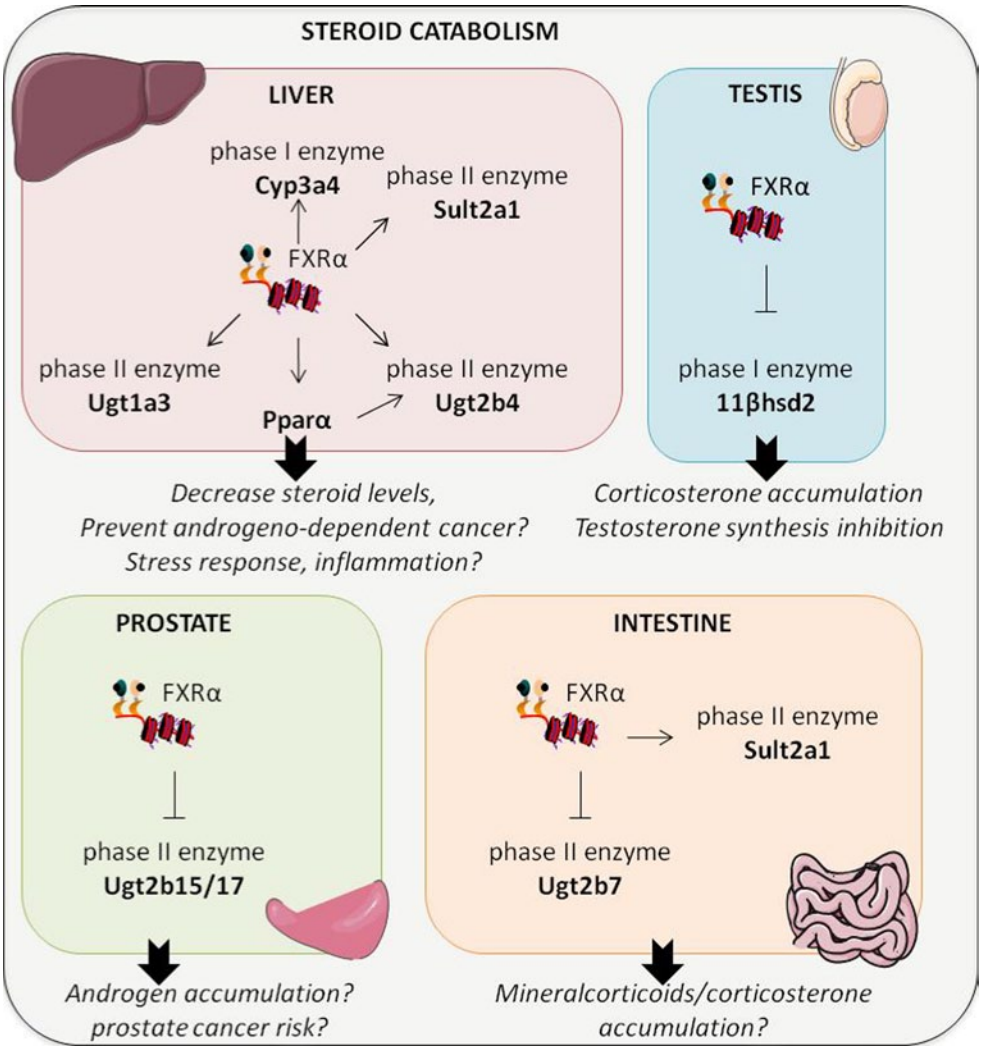

Fig. 2 Schematic representation of FXRα impact on steroid catabolism. In the liver, FXRα participates in the homeostasis of steroids by regulating the expression of many genes involved in steroid metabolism, such as Cyp3a4, Sult2a1, Ugt1a3, and Ugt2b4. Ugt2b4 regulation can be either direct or through PPARα. These types of regulation are also observed in the intestine (Sult2a1 and Ugt2b7). Modulating the local levels of mineralocorticoids and corticosteroids contributes to local inflammation processes. In the testis, the role of FXRα in BA repression of 11βhsd is unclear, but it may contribute to the repression of testosterone synthesis by FXRα. In the prostate, the repression of Ugt2b15/17 expression by FXRα leads to androgen accumulation and an increased risk of prostate cancer development

decreased accumulation of *UGT2B7* mRNA levels through the binding of FXRα to a negative FXRE [55]. Moreover, transfection of cells with hFXRα resulted in a significant suppression of *UGT2B7* expression in the absence of LCA and additional suppression was observed when the cells were treated with LCA.

FXRα interferes with glucose metabolism regulation by glucocorticoid signaling pathways

Regarding the impact of FXRα on GCs synthesis and catabolism, it is reasonable to speculate that bile acids could contribute to a pathologically increased serum level of mineralocorticoids and glucocorticoids [56].

The action of glucocorticoids is mediated through the glucocorticoid receptor (GR), which is a member of the nuclear receptor superfamily that regulates numerous transcription programs including immune suppression, anti-inflammatory responses, and glucose metabolism. Glucocorticoid binds to GR in the cytoplasm and promotes its translocation to the nucleus. Then, activated GR binds to a GR response element (GRE) in the promoter of downstream target genes and allows their transcription through the recruitment of various co-activators such as PGC-1.

GR is highly expressed in the liver, where it regulates the expression of rate-limiting enzymes in gluconeogenesis and plays an important role in the control of glucose metabolism. During conditions of high energy demand, systemic glucocorticoid concentrations increase and activate GR in the liver, leading to glucose mobilization via the expression of gluconeogenesis enzymes [57]. Among these enzymes, phospho(enol)pyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) are known to be positively regulated by glucocorticoids and also by glucagon, which both have strong gluconeogenic actions, while insulin suppresses hepatic gluconeogenesis [58]. Conditional mice harboring a disrupted GR in hepatocytes exhibit profound hypoglycemia after prolonged food withdrawal and

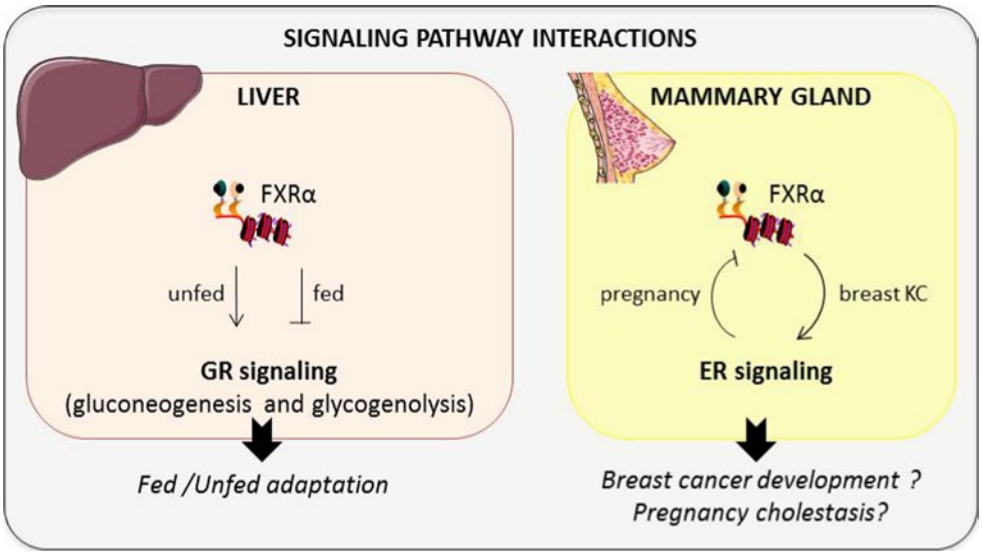

Fig. 3 Schematic representation of the crosstalk between steroids and FXRα signaling pathways. In the liver, the interaction of FXRα and glucocorticoid pathways is notably complex and can lead to either the induction or repression of this pathway. This process is correlated with fed/unfed adaptation processes. FXRα has a role in breast cancer. The expression of FXRα was significantly correlated with proliferation in post-menopausal women with lower estrogen concentrations who had ER-positive breast tumors. Additionally, estrogen levels are thought to contribute to the etiology of intrahepatic cholestasis in pregnancy

are unable to up-regulate the expression of gluconeogenic enzymes [59].

Bile acids exert regulatory effects to maintain glucose and insulin homeostasis. However, the precise role of FXRα in the regulation of hepatic glucose metabolism remains controversial, as it was described either as an inhibitor or an inducer of gluconeogenesis [22, 60, 61] (Fig. 3).

FXRα represses gluconeogenesis Several studies report a repressive effect of FXRα on the expression of gluconeogenic genes, suggesting that FXRα signaling could interfere with/counteract the role of glucocorticoids and GR signaling on hepatic glucose metabolism. C57BL6 mice treated with a 1 % CA-supplemented diet for 7–8 days showed decreased hepatic *Pepck* and *G6Pase* mRNA levels [62, 63]. The involvement of FXRα in *Pepck* and *G6Pase* downregulation was suggested in vivo by Zhang et al. [64], showing that oral GW4064 treatment, as well as adenoviral-mediated hepatic overexpression of FXRα, improved hyperglycemia in db/db diabetic mice. Feeding a CA-enriched diet has been shown to decrease fasting blood glucose levels associated with reduced expression of *Pepck* and *G6Pase* mRNA in wild-type but not *Fxrα*$^{-/-}$ mice. This effect was shown to be mediated through the classical FXRα target gene *Shp*, a known regulator of gluconeogenesis [65].

FXRα induces gluconeogenesis Some in vivo studies showed that treatment with the FXRα agonist GW4064 induces *Pepck* mRNA levels in an FXRα-dependent manner [35, 64]. Renga et al. [66] demonstrated that FXRα activates gluconeogenic pathways in the liver through the direct regulation of GR expression and activity. In *Fxr*-null mice, the decreased accumulation of rate-limiting gluconeogenic enzymes after a period of 15 h of withdrawal is associated with blunted liver expression of GR. Treating wild-type mice with a semisynthetic FXR ligand (6E-CDCA) increases the liver expression of GR, *Pepck*, and *G6pase* mRNA accumulation. *Fxrα*$^{-/-}$ mice failed to regulate *Pepck* and *G6Pase* in response to dexamethasone, suggesting that FXRα is essential for mediating GR gluconeogenic signaling. GR silencing by siRNA in vitro or its pharmacological antagonism in vivo with mifepristone reverses the effect of FXRα activation on the expression of gluconeogenic genes, suggesting that an FXRα-GR pathway regulates the activation of hepatic gluconeogenesis in the transition from the unfed to the fed state.

A diet issue? Such complex regulation of glucose metabolism in vivo has been recently addressed by Ma et al. [65] who showed that the activation of FXRα exerts opposite effects during unfed or fed conditions. In fed animals, the activation of FXRα downregulates the expression of *Pepck* and *G6Pase*, and the opposite effect was observed in the unfed state.

Fxrα$^{-/-}$ mice were defective in the induction of gluconeogenic genes, including *Pgc-1α* and *Pepck*, after 6 h of fasting and displayed lower basal hepatic glucose production, leading to an early hypoglycemia response. This defect in the starvation response was associated with a

significantly reduced hepatic glycogen content in the *Fxrα*$^{-/-}$ mice [67].

At the molecular level, such a model may be partially explained by the relative affinity of FXRα to different types of response element. It is well known that FXRα binds with high affinity to IR-1, while ER-8 sequences have low-affinity binding sites for FXRα [68, 69]. In the fed state, when *Fxrα* mRNA levels are low, the activated receptor regulates the transcription of target genes mainly by binding to IR-1 sequences such as the *Shp* target gene, a known repressor of gluconeogenesis. When *Fxrα* mRNA levels are high, as in the unfed state, the receptor might occupy low-affinity binding sites, such as the ER-8 sequences, which then allow induction of *Gr* transcription by FXRα. This induction of GR leads to increased *Pepck* and *G6pase* mRNA levels.

Integrative conclusions

Together, these data suggest that BA might have an impact on glucocorticoid metabolism at multiple levels. The results obtained in vivo using mice treated with a FXRα agonist correlated with the use of Fxrα$^{-/-}$ mice and demonstrate the induction of glucocorticoid levels (Fig. 1).

The increase of GC concentrations following BA exposure is also a result of the increased bioavailability of glucocorticoids and is associated with decreased liver catabolism and reduced inactivation by 11βHSD2 (Fig. 2).

The activation of FXRα by BA interferes with GC action on glucose metabolism in liver. When these data are combined with the well-established role of GR signaling on glucose metabolism, especially during adaptation between fed/unfed conditions, the data suggest that FXRα modulates the kinetics of glucose homeostasis during fasting. This result highlights a potential positive interaction between the two receptors for metabolic adaptations (Fig. 3).

The links between FXRα and GC on liver glucose metabolism were analyzed by Ma et al. for crosstalk between receptors. Thus, it is important to consider the ligand bioavailability. According to the hypothesis by Ma et al., the impact of BA/FXRα on glucose metabolism depends on the transition between the fed and unfed states, which corresponds to unstressed/stress situations. The impact of BAs on metabolism will be difficult to assess in normal physiology because during fasting, the GC levels are increased, and BA levels are decreased. The relevance of BAs on GR signaling pathways is difficult to integrate. However, it is important to examine these parameters in diseases with high BA levels.

Impact of bile acids on sex hormone pathways

There are limited data available on the interactions between bile acid/FXRα signaling pathways and sex steroid metabolism. As for GCs, these interactions will be at the levels of synthesis, catabolism, or by modification of the physiological functions of sex steroids.

Sex hormone synthesis

The only link between FXRα and sex hormone synthesis thus far has been obtained from studies on the testes. The testes are composed of seminiferous tubules outlined by a basal membrane that separates them from the interstitial compartment. In the adult, these two compartments ensure the exocrine (spermatozoa production) and the endocrine (hormone synthesis) functions [70]. The testes are involved in the synthesis of estrogens and testosterone. In males, androgens are responsible for the maintenance of fertility and the development of secondary sexual characters [71]. In addition, testosterone is essential for reproductive function, muscle and bone mass maintenance, cognitive function and other physiological parameters. Altered testicular functions may increase the risk of metabolic syndrome [72]. The testes also produce estrogen, which acts through the estrogen receptors ER*α* and ER*β*. Estrogen down-regulates the luteinizing hormone receptor (Lhcgr) and inhibits the Steroidogenic acute regulatory protein (StAR) gene and others genes implicated in steroidogenesis in Leydig cells [73].

In 2007, Volle et al. [23] detected transcripts of *Fxrα* in the interstitial cells. FXRα was also described as a regulator of the aromatase gene in tumor Leydig cells [24]. A decrease in aromatase expression was observed after induction with GW4064 or CDCA in Leydig cell lines in vitro (Fig. 1). FXRα interferes negatively with SF1 activity on sequences of the PII promoter of aromatase, where FXRα enters in competition with SF-1 for binding a common site. This results in an inhibition of estrogen synthesis.

The in vivo role of FXRα on androgen synthesis was demonstrated using a FXRα synthetic agonist (GW4064). If testosterone concentrations were similar between wild-type and *Fxrα*$^{-/-}$ mice, the administration of GW4064 repressed steroidogenesis after 12 h of treatment and was associated with a decrease in *Star*, *Cyp11a1*, and *3β-hsd* gene expression (Fig. 1). At the molecular level, it was demonstrated that this repressive effect is consistent with the up-regulation of *Shp*, which then inhibits LRH-1 and SF1 activity, two know inducers of steroidogenesis. It has also been shown that FXRα regulates the synthesis of androsterone [74].

Bile acids and sex hormone catabolism

The potential interaction of FXRα with sex hormone metabolism was also demonstrated through the regulation of the catabolism of these steroids. Such cross-talks occur

via the regulation of several key genes as highlighted in Fig. 2 and detailed below.

CYP3A4 Expressed predominantly in the adult liver and intestine, the cytochrome P450 enzyme CYP3A4 has been shown both in vitro and in vivo to hydroxylate BAs at the 1β, 6α, and 6β positions, thus participating in the elimination of BAs [75, 76]. Several studies have shown that bile acids positively regulate *Cyp3a11* expression, the mouse orthologue of *Cyp3A4*, to initiate their catabolism when they are in excess [75, 77–79]. CYP3A11 plays an important role in the metabolism of both exogenous drugs and endogenous compounds such as cortisol [80], testosterone [81] or estradiol-17β [82]. This result suggests a potential association with steroid metabolism.

Studies using the HepG2 cell line exposed to either the natural ligand CDCA or to the specific synthetic ligand GW4064 have demonstrated that FXRα controls *Cyp3A4* expression in the liver [79]. This result was also observed in the mouse, as wild-type mice fed GW4064 have increased hepatic levels of *Cyp3a11*, which is the rodent homologue of human CYP3A4 [79]. However, this effect was not observed in *Fxrα*$^{-/-}$ mice.

Epidemiological and clinical evidence links a *CYP3A4* promoter variant (*CYP3A4*1B* (rs2740574)) with the incidence of prostate cancer and the clinical grade of the tumor and disease progression [83–85]. There is no significant association between the *CYP3A41B** genotype and the levels of serum testosterone. This result suggests that CYP3A4 might have a minimal impact on hepatic catabolism [86]. The decreased *CYP3A4* expression within prostate tissue is associated with a higher Gleason score and poorer cancer-specific survival [87, 88]. This result suggests that CYP3A4 may play a critical role in maintaining androgen homeostasis within the prostate and loss of CYP3A4 leads to the development of cancer.

SULT2A1 In addition to hydroxylation, sulphate or glucuronidate conjugation are important mechanisms for the detoxification of steroids. Upon conjugation, the substrates become more polar, less toxic and more water soluble, facilitating their clearance.

Dehydroepiandrosterone-sulphotransferase (SULT2A1/Sult2a1) are phase II metabolizing enzymes that catalyze the sulphating of various exogenous chemicals and endogenous compounds including testosterone, estrogen, and BAs [89–91].

Increased serum and urine levels of sulphated BAs were described in patients with cholestatic liver diseases [92, 93]. These clinical observations suggest a potential involvement of BAs in controlling their own sulphating though the regulation of enzymes such as *Sult2a1*. This is consistent with the fact that Sult2A1 is expressed abundantly in the liver and intestine, the two first-pass metabolic tissues where FXRα is also expressed. Song et al. have demonstrated that primary bile acid CDCA treatment was shown to induce rat/mouse Sult2a1 promoter activity in transfected Caco-2 and HepG2 cells in vitro. This rat/mouse Sult2a1 induction involved an activated FXRα/RXR heterodimer binding to an atypical FXRα response element (IR0) located in the 5′ flanking region [90].

However, sequence alignments have shown that this IR0 element does not exist in the human SULT2A1 5′-flanking region, demonstrating that the regulation by FXRα might not be conserved between species [94, 95]. Human *SULT2A1* mRNA levels failed to be modulated in cultured human primary hepatocytes treated with CDCA [95]. Further studies are needed to understand how FXR regulates human *SULT2A1* expression.

Consistently, in vivo investigations showed that FXRα may be involved in the repression of basal *Sult2a1* expression. Moreover, CDCA-fed mice present markedly decreased *Sult2a1* expression in wild-type mice. This is correlated with an increased level of *Shp,* suggesting a FXRα-dependant mechanism, which was confirmed by the lack of *Sult2a1* modulation in *Fxrα*$^{-/-}$ mice following a diet [96].

Interestingly, *Fxrα*$^{-/-}$ mice present an increased level of *Sut2a1* in basal physiology and are resistant to LCA induced liver toxicity compared to wild-type (WT) mice [97].

SULT2A1 was originally involved in the inactivation of androgen hormones. In the rodent liver, the high expression of *Sult2a1* during the androgen-insensitive state of the hepatic tissue in senescent males is thought to be a result of the efficient inactivation of androgens into androgen sulphates [98, 99]. Thomae et al. [100] reported 3 *SULT2A1* gene alterations that result in decreased *Sult2a1* expression and activity. Interestingly, these alterations were present only in African American patients and were suggested to be partially responsible for the androgen-associated risk of disease. A significant increase in the DHEA-to-DHEA-sulphate ratio was observed in African American participants with a heterozygous *SULT2A1* A63P/A261T genotype. However, the presence of the different *SULT2A1* alleles was not associated with prostate cancer.

Moreover, as FXRα and AR are both able to control *Sult2a1* gene expression, it is reasonable to think that bile acid and androgen metabolisms could crosstalk through *Sult2a1* regulation [101, 102].

UGTs Sex steroid catabolism also involves UDP-glucuronosyltransferases (UGT). Among the 18 functional UGT enzymes identified in humans, UGT2B7, UGT2B15, and UGT2B17 have a remarkable capacity to conjugate androgens [103].

UGT2b7 A tumor-suppressor function was suggested for *UGT2B7* by preventing the accumulation of mutagenesis compounds like 4-hydroxyestrone [104]. Indeed, reduced levels of the UGT2B7 protein and glucuronidation of 4-hydroxyestrone were shown in invasive cancers. However, the role of the bile acid challenge in vivo on UGT2B7 expression still remains to be determined.

UGT2B4 (liver) Barbier et al. [8] identified human UGT2B4 as a target gene of FXRα. Activation of FXRα by CDCA or GW4064 in primary human hepatocytes or in the HepG2 cell line resulted in increased *UGT2B4* expression through an atypical binding of FXRα as a monomer to a single hexameric DNA motif.

Interestingly, the PPARα agonist fenofibrate was shown to activate the *UGT2B4* gene promoter through a specific peroxisome proliferator activated receptor (PPAR) response element [105]. DCA also induces the transcription of PPARα gene via an FXRα-mediated mechanism. Thus, bile acids may induce *UGT2B4* expression directly through activation of FXRα and/or indirectly through FXRα-dependent induction of PPARα, which then activates *UGT2B4* transcription. Through these mechanisms, BAs may be part of a negative feedback mechanism by which BAs control their elimination to prevent pathophysiological toxicity.

The potential impact of BAs on steroid metabolism should be taken into consideration as UGT2B4 is known to be active on 5α-reduced androgens and polyhydroxylated estrogens, including estriol, 4-hydroxyestrone and 2-hydroxyestriol.

UGT1A3 (liver) Hepg2 cells treated with LCA, CDCA, and GW4064 present increased *UGT1A3* mRNA levels. The resulting CDCA-24-glucuronide was shown to exhibit an antagonistic effect on FXRα as feedback inhibition. *UGT1A3* is expressed in the liver, intestine, and large bowel [106–108]. Apart from BA, UGT1A3 metabolizes xenobiotics such as polyaromatic hydrocarbons as well as estrogens, and vitamin D derivatives [109–111]. Because *UGT1A3* is significantly induced by FXRα in response to bile acids, this regulation could link bile acid metabolism and steroid hormone metabolism alteration.

UGT2B15/17 (prostate) While glucuronidation was generally considered to be a hepatic/intestinal detoxification mechanism, extrahepatic glucuronidation is now established as an efficient way to locally inactivate endogenous bioactive molecules [103, 112]. This is particularly true for androgens, which are efficiently glucuronidated within their target tissues, such as the human prostate [113].

A regulatory function of the nuclear receptor FXRα in androgen metabolism has been shown in prostate cancer LNCaP cells [114]. CDCA or GW4064 repress gene expression and androgen-conjugating activity of the UGT2B15 and UGT2B17 enzymes in prostate cancer LnCaP cells. The regulation of UGT2B15 expression by FXRα seemed to be tissue-specific, as previous data have shown that CDCA does not modulate *UGT2B15* mRNA in human hepatocytes [8]. Moreover, *Fxrα*$^{-/-}$ mice present an increased level of *UGT* mRNA accumulation in the prostate compared to wild-type mice. The exact mechanism by which FXRα negatively regulates *UGT2B15* and *UGT2B17* genes, and the physiological implications of this regulation, remain to be determined because androgen glucuronidation is almost absent in the rodent prostate [114–116].

In contrast, the importance of glucuronidation for androgen metabolism in the human prostate was highlighted by the observation that polymorphisms within androgen-glucuronidating genes are associated with an increased risk for prostate cancer [117, 118]. A *UGT2B17* inactivation polymorphism was associated with an increased prostate cancer risk [119]. The D85 polymorphism of UGT2B15, which leads to a less efficient protein for conjugation of 3-diol and DHT, results in higher androgen exposure in prostate tissue. In accordance with these findings, the D85 allele has been reported to increase prostate cancer risk and aggressiveness [120, 121].

During cholestasis, plasma levels of bile acids are drastically increased [122], and it can be hypothesized that in such patients, glucuronidation of androgens may be reduced, resulting in the accumulation of androgens in the prostate, which may correspond to a pro-carcinogenic mechanism. Interestingly, the development of cholestasis has been reported in various patients with prostate cancer [123–125].

This conclusion is particularly important because FXRα agonists are currently considered as a promising treatment of several diseases such as hepatitis C or metabolic syndrome, as highlighted by several ongoing clinical trials (www.clinicaltrials.org).

FXRα interferes with sex hormone signaling pathways

Potential impact of FXRα on AR pathways (Fig. 3) The role of FXRα on androgen signaling pathways has not been clearly demonstrated and is still speculative. However, it can be hypothesized that by controlling *Shp* expression, FXRα could interfere with the actions of androgen. SHP is able to interact with numerous nuclear receptors. It has been demonstrated in vitro using GST-pull-down experiments that SHP interacts and inhibits the androgen receptor activity [126]. SHP acts by competing with AR co-activators. These data opened a new field of research concerning how BAs might interfere with androgen signaling pathways. This is

even more interesting in line with the described inhibitory effect of FXRα synthetic ligand on testosterone production.

Potential impact of FXRα on ER Any impact on breast cancer? (Fig. 3). Although no data describe links between FXRα and female hormone synthesis, reports suggest a potential role for FXRα in breast pathophysiology. Estrogen exposure has long been known to contribute to the etiology of breast cancers [127], and approximately two-thirds of these cases are characterized by dysregulation of the estrogen receptor α (ERα) signaling [128]. Therapy consists of blocking estrogen synthesis (aromatase inhibitors) or ER transactivation (estrogen receptor modulators, such as tamoxifen) [129, 130]. Evidence suggests a potential role for bile acids in breast cancer etiology (Fig. 3). The accumulation of bile acids has been reported in breast cyst fluid and has been proposed as a potential risk factor for breast cancer [131–133]. Women with breast cancer may have differences in the fecal excretion of BAs compared to controls [134–136]. In addition, long-term follow-up of women undergoing cholecystectomy has revealed a higher risk of breast cancer [137].

The potential involvement of FXRα was highlighted in several clinical studies. Interestingly, FXRα was shown to be expressed in normal breast tissue, and several studies established significant correlations between FXRα and ER expression in breast cancer samples [138, 139]. Fifty percent of ER-negative breast cancer samples had weak FXRα expression, and 70 % of ER-positive samples had FXRα expression suggestive of crosstalk between ER and FXRα signaling [139]. These clinical data are supported by semi-quantitative analyses revealing that the ER-positive breast cancer cell line MCF-7 has higher FXRα protein accumulation than the ER-negative MDA-MD 231 cell line [37]. A significant correlation between FXRα and the Ki67 proliferative marker has also been observed. FXRα expression was significantly correlated with proliferation in patients with ER-positive breast tumors in postmenopausal women, with lower estrogen concentrations [37]. In the context of low estrogen, FXRα expression may play a key role in proliferation. This hypothesis is further supported by the presence of high plasma levels of DCA in postmenopausal breast cancer patients [140], suggesting that bile acids might be involved in the onset and development of mammary gland cancers in an estrogen-independent context through the activation of FXRα.

If these correlations are established in patients, the molecular mechanisms remain unclear with contradictory results.

In vitro data show that activated FXRα induces a mitogenic response in a breast cancer cell line through positive crosstalk with the ER. Indeed, the ER-positive cell line MCF-7 shows increased proliferation in response to FXRα activation. This was associated with a pro-estrogenic response, as measured by the downregulation of ERα accumulation [37, 139]. These results suggest that in absence of estrogens, these pro-estrogenic patterns should a result of FXRα-mediated activation of ERα dependent transcription. At a relatively low concentration, CDCA glucuronidate increased MCF-7 growth combined with this same pro-estrogenic effect (decreased Erα accumulation and up-regulated ER target genes). However, while low doses of CDCA lead to this same estrogenic response, a contradictory decrease in proliferation was observed. These discrepancies might be explained by dose effects of bile acids on proliferative pathways through ER activation [141].

In contrast to previous reports [37, 139], Giordano et al. show that CDCA or GW4064 inhibited proliferation in the breast cancer cell line MCF-7 and in the Tam-resistant breast cancer cell line MCF-7/TR1. This anti-proliferative effect of FXRα suggests repression of the HER2 receptor, perhaps by enhancing formation of a FXRα and NF-κB complex inhibiting the binding of NF-κB to its responsive element located in the human HER2 promoter region.

High concentrations of FXRα ligands exert an anti-proliferative effect on breast carcinoma cell lines, regardless of their ER status. In breast cancer cell lines, FXRα agonists down-regulated the breast cancer target gene aromatase. These data could also be relevant, as aromatase inhibition is classically used in breast cancer treatment.

Integrative conclusion

Taken together, these data demonstrate complex interactions between BAs and sex hormone homeostasis. Several findings suggest that BAs decrease sex hormone synthesis (testosterone and estrogen) in male mice (Fig. 1), but this result has not been demonstrated in female mice and or in humans. The impact of the BAs/FXRα pathways in lowering the levels of sex hormones is also dependent on their effects on liver catabolism through the regulation of genes such as *Sult2a1* and *Cyp3a* (Fig. 2). These data are consistent with the known decrease in plasma testosterone levels in a male experimental model of liver injuries [142].

A decrease in sex hormone levels in males may have major effects on sexual maturation and/or the maintenance of secondary sexual characters.

Hormone concentrations are finely controlled in target organs such as the prostate. In cell lines, there is evidence for a link between FXR-mediated maintenance of BA homeostasis and hormone steroid inactivation. It has been hypothesized that FXRα transactivation in liver or prostate tissues may prevent androgen accumulation and the development of androgen-dependent cancers such prostate

cancer through the regulation of Ugt2b15/17. However, there are no data describing FXRα dependent regulation of Cyp3A4 within the prostate.

The interaction of FXRα with the estrogen receptor in breast cancer (Fig. 3) supports crosstalk between FXRα and ER in inducing tumor progression. However, no clear in vitro evidence has been provided. This issue highlights the need for a better understanding of these pathways to determine if FXRα agonists/antagonists could be useful drugs in some cases of breast cancers.

Conclusions and perspectives

BAs represent the main cholesterol catabolites. Because they share the same origin as steroids, there may be some crosstalk between BA metabolism and steroids. Recent studies have focused on bile acids and their nuclear receptor, FXRα (NR1H4).

Glucocorticoids and estrogen can inhibit BA-FXRα signaling pathways in the liver and mammary glands. Alternatively, as reported in this review, FXRα/BA pathways can affect steroid metabolism at the levels of synthesis, catabolism and downstream signaling pathways. This is highlighted by the fact that FXRα is expressed in steroidogenic tissues, such as the adrenal glands and the testis, where FXRα controls steroid production. FXRα also interferes with steroid signaling pathways in target tissues such as the liver through crosstalk with the glucocorticoid receptor (GR). The evidence for crosstalk between the FXRα/BA pathways and steroids has been reinforced by the recent identification of the impact of glucocorticoids and estrogen on the activity of FXRα.

Several FXRα polymorphisms have been detected in humans, and they are associated with pathologies including obesity and gallstone diseases, such as cholelithiasis or intrahepatic cholestasis of pregnancy (ICP) [143, 144], [145, 146]. The role of FXRα in the metabolism of either glucocorticoids or sex hormones could be used to determine if altered FXRα signaling pathways are involved in idiopathic diseases. Screening patients for FXRα polymorphisms could offer new insight into the origins of these pathologies and determine if FXRα is a diagnostic/prognostic marker.

The crosstalk between BAs and steroid metabolism has important roles in health. Further studies are needed to clearly identify all of the pathways activated by BAs through FXRα. The complexity of the system is important to understand because the activation of this receptor could lead to both beneficial [147] and deleterious effects. This phenomenon is of particular interest when these endogenous molecules abnormally accumulate in pathophysiological conditions, such as liver injury.

The incidence of liver disease is difficult to establish because the concept encompasses many different types of pathologies. The onset of many types of liver disease is insidious and is not detected until hepatic decompensation occurs. The real significance of steroid metabolism in the physiology of liver diseases must be underestimated.

Clinical data have suggested a link between liver dysfunction and male fertility disorders [148, 149]. Experimental models of cholestasis induced by bile duct ligation to increase plasma bile acid levels [150] have been associated with testicular alterations [151, 142]. In this pathological context, reduced plasma testosterone levels have been associated with loss of the germ line in the seminiferous tubules. This effect can result in reduced fertility or infertility and altered male sexual maturation.

The role BA in steroid metabolism should be considered with the fact that FXRα is targeted for pharmacological drugs in the treatment of such diseases as diabetes [152]. It will not be simple to target one BA receptor to manage a specific pathology. Therefore, we will have to consider that interfering with steroid metabolism might lead to deleterious side effects from this therapy.

In addition to their involvement in the control of gluconeogenesis in the liver [41], GCs also regulate or support a variety of important cardiovascular, metabolic, immunological, and homeostatic functions. Therefore, before using FXRα agonists as a long-term treatment for diseases, it will be necessary to ensure there are no deleterious effects on cardiac function, hypertension or immunity.

Studies will be required to determine whether long-term treatment with FXRα modulators affects testosterone synthesis in men and to verify the interactions with AR signaling pathways. The inhibition of androgens could affect secondary sexual characteristics. Additionally, there could be a long-term impact on pathologies, including the development of prostate cancer.

Pregnancy cholestasis leads to an increased risk of preterm delivery and perinatal mortality [153]. This condition is associated with increased bile acid levels and are treated with either cholestyramine or ursodeoxycholic acid. Previous reports have described a role for FXRα during pregnancy, and it is associated with increased hepatic bile acid concentrations in mice and reduced FXRα function [154]. Thus, we must analyze mouse models to determine the impact of FXRα agonists on fetal health before treating patients with preclinical diabetes.

Perspectives

As FXRα agonists are explored as potential therapeutic drugs for the treatment of several diseases, the development of strategy to avoid systemic effects will be needed. It will be necessary to target this receptor in a cell-specific

manner. It will be important to take into consideration the patient history (hormonal status) for developing personalized therapy. This highlights the fact that drug development must rely on a strong fundamental research in integrative physiology and that drugs cannot be developed based on molecular mechanisms characterized in vitro or in vivo in a single organ. This is a challenging, open field for future research that will require interdisciplinary approaches.

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