REVIEW

Farnesoid X receptor and reproduction

Cuevas Estela [1], Martínez-Gómez Margarita [1, 2], Castelán Francisco [1]

[1]*Centro Tlaxcala de Biología de la Conducta, Universidad Autónoma de Tlaxcala, Tlaxcala, México*
[2]*Depto. de Biología Celular y Fisiología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México (UNAM), México DF, México*

Correspondence: Estela Cuevas
E-mail: ecuevas@uatx.mx
Received: December 02, 2014
Published online: January 19, 2015

Farnesoid X alpha receptors (FXRα or NR1H4) are expressed in male and female reproductive tissues. Though the relevance of the FXRα on reproduction is unknown, endogenous ligands like farnesol, chenodeoxycholic acid (CDCA), and cholate acid (CA) have been involved in cell proliferation, apoptosis, cell differentiation, and steroidogenesis in reproductive tissues. FXRα modulates estrogen and androgen actions in these tissues. Since FXRα is structurally and functionally related to other nuclear receptors that are also expressed in reproductive tissues, such as the liver X receptors (LXR), peroxisome proliferation-activated receptor (PPAR), liver receptors homolog-1 (LRH-1), small heterodimer partner (SHP), and dosage-sensitive sex reversal (DAX1), the actions of FXRα on reproduction might be directly or indirectly mediated by its interaction with these nuclear receptors. The aim of the present review is to describe those actions of the most relevant ligands of FXRα and the interaction of this receptor with other nuclear receptors for understanding the possible role of FXRα in reproductive events.

Keywords: bile acid; breast; farnesol; FXRα; ovary; testis

To cite this article: Cuevas E, *et al*. Farnesoid X receptor and reproduction. Receptor Clin Invest 2015; 2: e463. doi: 10.14800/rci.463.

Introduction

Reproductive events highly depend on lipid and carbohydrate metabolism. Diverse nuclear receptors such as the liver X receptor (LXR), liver receptor homolog-1 (LRH-1 or Nr5a2), oxysterol-activated nuclear receptor, and peroxisome proliferation-activated receptor (PPAR) have been involved in proliferation, differentiation, steroidogenesis, and apoptosis of reproductive tissues [1-5]. Although less studied, the farnesoid X receptor alpha (FXRα or NR1H4) is also expressed in these tissues [6-10] in where seems to have a relevant participation, even directly or indirectly, in both male and female reproduction. In the present review, we expose the possibility to understand the role of FXRα on reproductive tissues analyzing the actions of most representative ligands and their possible relationship with other nuclear receptors. For this purpose, an extensive literature revision considering data from crustaceans to mammals was evaluated.

FXR overview

The farnesoid X receptor is member of the nuclear receptor superfamily of ligand-dependent transcription factors. FXRα forms heterodimers with the 9-cis-retinoic acid receptor (RXRα), and binds to FXR-response elements (FXREs) [11]. It also can bind with steroidogenic factor 1 (SF-1; NR5A1) response element [8]. Human and mouse genes of FXRα encode four isoforms: FXRα1 (RIP14-2), FXRα2, FXRα3, and FXRα4 (RIP14-1) [12-13], which are expressed in a tissue-specific manner and activate different FXREs [14-15]. Some co-activators of FXRα are the vitamin

D-interacting protein 205 (DRIP205), the Leu-Xaa-Xaa-Leu-Leu (LXXLL) motif, the co-integrator-associated protein (CBP or p300), the co-activator transformation/transcription domain-associated protein (TRRAP), and the protein arginine methyl-transferase type I (PRMT1) [16-20]. Meanwhile the dosage-sensitive sex reversal (DSS; DAX1; NR0B1) acts as a co-repressor [21].

In general FXRα is expressed in stomach, intestine, tongue, esophagus, hepatocytes, gall bladder epithelium, bladder, pancreas, skeletal muscle, heart, lung, adrenocortical cells, blood vessels, and white fat tissue [9, 13, 22-25]. Leydig cells, corpora cavernosa, epididymis, vas deferens, prostate, urethra, and spermatogonia [6-9]; as well as breast, ovary, oviduct, vagina, neurons of the paravaginal ganglia, and cells of the inguinal glands also express FXRα [10, 26].

The name of FXR was given by its binding to farnesol (trans, trans-3, 7, 11-trimethyl-2, 6, 10-dodecatrien-1-ol), an intermediate product of the mevalonate pathway [26]. Bile acids such as chenodeoxycholic acid (CDCA), deoxycholate (DCA), cholate (CA), and ursodeoxycholate (UDCA) are also endogen ligands for FXRα [27]. Intermediate metabolites in the synthesis of bile acids and steroid hormones like the 5beta-A/B cis-bile alcohols (5beta-cyprinol and bufol) [28] and oxysterols [22(R)-hydroxycholesterol] [29] act as ligands for FXRα. Other steroids as the epiallopregnanolone sulfate (3β-sulfated progesterone) [30], 5alpha-androstan-3alpha-ol-17-one (androsterone), 5beta-androstan-3alpha-ol-17-one (etiocholanolone), and forskolin are considered FXR agonists [7, 31-32]. Moreover, metabolites like triterpenes (alisol M 23-acetate and alisol A 23-acetate), tetrahydroflavanones (cryptochinones A-D), and cafestol, all obtained from plants, show agonistic activity on FXRα [33-35]. Additionally, some FXRα agonists like the 6α-ethyl-chenodeoxycholic acid (6-ECDCA, INT-747), (E)-3-(2-chloro-4-((3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl)methoxy)styryl)benzoic acid (GW4064), and N-oxide pyridine analog have been synthesized [7,9, 36-37]. In contrast, thiazolidinediones (Troglitazone, an agonist of PPAR) [38]; the 15-deoxy-Δ (12,14)-PGJ2 (15d-PGJ2), a metabolite from prostaglandin D2 in arachidonic acid metabolic pathway [39]; guggulipids (guggulsterone) [40]; sesquiterpenoids (atractylenolide II and III) [41], theonellasterol, a 4-methylene-24-ethylsteroid isolated from the marine sponge *Theonella swinhoei* [42]; and stigmasterol, a phytosterol compound of soy-derived lipids [43], are antagonists of FXRα.

In metabolic organs, FXRα regulates the bile salt synthesis, the fat metabolism, and the glucose homeostasis [15, 24, 29, 44-45]. However, new target genes involved in proliferation, apoptosis, drug transporter, autophagy, differentiation, hypoxia, inflammation, glucocorticoid synthesis, DNA-repair, RNA processing, xenobiotic detoxification, innate immunity, and modulation of transcriptional regulators have been linked to metabolism and non-metabolic tissues [7-8, 26, 46-55]. The diversity of functions attributed to the FXRα is related to its capacity to regulate the transcription of other nuclear receptors or transcription factors such as the pregnane X receptor (PXR) [56], fibroblast growth factor 19 (FGF19) [57], PPARs α and γ, PPAR coactivator-1α (PGC-1α) [58-59], and small heterodimer partner (SHP) [18, 27, 32]. In turn, the expression of FXR is regulated by Toll like receptors (TLRs) [54] and vitamin D receptors (VDR) [60], as well as by transcription factors as the sterol regulatory element-binding protein-2 (SREBP-2) [61]. The regulation of gene expression exerted by FXRα can be accompanied by the activation of LRH-1 [62] and PPAR [63].

FXR and male reproduction

As mentioned before, FXRα is found in cells from male reproductive tissues such as Leydig cells, corpora cavernosa, epididymis, vas deferens, prostate, urethra, and spermatogonia in humans and other mammals [6-9]. A possible role of FXRα in reproductive events of males could be inferred through some actions triggered by their ligands.

It has been proposed that the bile acids are important for the testicular function. The FXRα activation by CDCA affects the sex steroid production in Leydig cells [64]. Furthermore, the FXR activation by INT-747 avoids the reduction of smooth musculature in the corpora cavernous and the erectile dysfunction promoted by a high fat diet in animal models [9]. A similar effect has been observed in the bladder smooth musculature of rats fed with a high-fat diet, in which the damage of the muscle induced by the diet is partially blunted by testosterone, but almost completely reverted by INT-747 [25]. In testis, FXRα regulates the presence of organic anion-transporting polypeptides (oatp1, oatp2, oatp3, and octn1) [65]. These transporters participate in the transmembrane pass of endogenous molecules (bile acids, steroid hormone conjugates, prostaglandins, testosterone, and thyroid hormones) and xenobiotics [66], and have been associated with cancer [67]. Mice fed a diet supplemented with CA have a reduced fertility as consequence of testicular defects such as apoptosis of spermatids, a decreased protein accumulation of connexin-43 and N-cadherin, and a high intra-testicular bile acid concentration [68]. In addition, a possible role of FXRα in reproductive tissues of males might be assumed considering the actions that bile acids have in cancer tissues. The activation of FXR by CDCA or GW4064 negatively interferes with the formation of inactive metabolites of androgens in malign cells of prostate [7]. The FXR activation also reduces proliferation on tumoral Leydig

Table 1. FXRα in reproductive tissues and structures in agreement with actions attributed to bile acids (CA and CDCA), farnesol, and some agonists (INT-747 or GW4064) in vertebrates and invertebrates.

	Reproductive tissues in which FXRα ligands have actions	
Expression of FXRα	**Normal tissues**	**Malign tissues**
Male: Leydig cells, corpora cavernous, epididymis, vas deferens, prostate, urethra, and spermatogonia [6-9]	Testis [64, 68-70], corpora cavernous [9], and prostate [72-73]	Prostate [7] and tumor Leydig cells [8]
Female: Breast, ovary, oviduct, vagina, neurons of the paravaginal ganglia, and cells of inguinal glands [10, 26]. Less inmunolocalization in uterus [10]	Granulose cells, oocytes [74-76, 79-82], and uterus [76]	Breast [26, 46-48, 77-78, 83]

cells [8], increases the p53 expression in testis cancer cells inducing apoptosis [8], and reduces the aromatase expression in tumor Leydig cells [8]. In this way, FXR activation seems to control the tumor growth in testis (Table 1).

For its part, the possible activation of FXR by farnesol could be also important to control reproductive functions in males. The farnesyl pyrophosphate synthetase, which catalyzes the formation of farnesyl diphosphate, is found in testis [69], where its synthesis is decreased by hypophysectomy and is increased by the treatment with gonadotropins [70]. Additionally, the role of farnesol in tumors from male reproductive tissues has been reported. The administration of farnesol decreases significantly the volume of prostatic tumors by inducing apoptosis [71]. Farnesyl derivatives such as the farnesyl-O-acetylhydroquinone suppress the proliferation of human prostatic cancer cells [72]. Farnesol also protects against the prostatic oxidative damage induced by cigarette smoke extract, decreasing the xanthine oxidase activity and lipoperoxidation, as well as increasing activities of antioxidant enzymes [73]. Thus, farnesol may play a protective role in the development of cancer and oxidative stress in male reproductive tissues (Table1).

FXR and female reproduction

Breast, ovary, oviduct, vagina, neurons of the paravaginal ganglia, and cells of the inguinal glands have FXRα [10, 26]. A scarce immunolabeling for FXR is found in uterus of virgin female rabbits [10]. Similarly to males, a possible role of FXRα might be considered to analyze the actions of their ligands. The synthesis of bile acids is also carried out in female reproductive tissues. Granulose cells and oocytes express crucial enzymes involved in the acid bile synthesis such as cholesterol 7-α hydroxylase (CYP7A1), sterol 27 hydroxylase (CYP27A1), oxysterol 7-α hydroxylase (CYP7B1), and sterol 12-α hydroxylase (CYP8B1) [74]. The concentration of bile acids in the follicular fluid and the presence of the bile acid transporter (SLC10A2) in the dominant follicle is higher in lactating cows than in heifers [75], suggesting a possible role of bile acids in the follicle maturation and ovulation. Bile acids seem to be relevant to uterus contractions. Women with cholestasis require less oxytocin to elicit uterine contractions, and CA increases oxytocin sensitivity promoting the oxytocin-receptor expression in the uterus [76]. The presence of FXRα in cancer of reproductive tissues in women has been also reported. FXRα is highly expressed in breast tumors [26, 46], particularly in postmenopausal patients [47], and their expression is significantly correlated with the expression of estrogen receptors (ERs) [47]. Postmenopausal women newly diagnosed with breast cancer show high plasma levels of DCA [77]. The administration CDCA or GW4064 inhibits the growth of breast carcinoma cells [46, 78]; even in those tumors with estrogen resistance, blocking HER2/MAPK signaling [48]. These data suggest that the action of bile acid on cancer of reproductive tissues could be mediated by FXRα.

For its part, the farnesyl pyrophosphate synthase is found in ovary, where is up-regulated by the human chorionic gonadotropin (LH/hCG) [79]. Farnesol homologs have been involved in the oocytes maturation. The administration of methyl farnesoate stimulates and enhances ovarian maturation in crayfishes [80-81]. This effect can be suppressed by 17 alpha-hydroxyprogesterone [82]. The action of farnesol on malign cells from female reproductive tissues has been also described. Farnesol increases the expression of progesterone receptors and reduces the expression of ERs in breast cancer cells [26]. The administration of tamoxifen avoids the effect of farnesol [26], suggesting an action mediated by ER. Furthermore, farnesol induces the expression of thyroid hormone receptor (TRs) beta1 in human breast cancer cells but diminishes its signaling, possibly this could be related to the anti-mitotic action of farnesol [83] (Table1).

FXRα interaction with other nuclear receptors

FXRα ligands (bile acids, farnesol, and oxysterols) are also able to bind to other receptors such as PPARs [84-85], LXR [29], and LRH-1 [5] located in reproductive tissues [1-5].

Indeed, a closely relationship between actions of these nuclear receptors with FXRα [58-59, 63] has been previously described. In this way, actions of the ligands before mentioned on reproductive tissues could be mediated by FXRα in collaboration with these nuclear receptors.

The interaction of FXRα and gonadal hormones has been scarcely studied, in spite of the few information suggests that actions of these hormones might be modulated by FXRα and vice versa. Thus, FXRα reduces the androgen glucuronidation in prostatic cells [7], and regulates the aromatase expression in Leydig cells competing with the orphan receptor SF-1 [8]. For its part, the FXRα expression in breast cancer cells is correlated with ER expression [26]. Although, the regulation of the activation of the orphan receptor SF-1 and the androgen glucuronidation have not yet analyzed in female reproductive tissues, both processes are important to the ovarian follicles development and the ovarian function [86-87].

In addition, FXRα also regulates the transcription of SHP in reproductive and non-reproductive tissues [18, 27, 32]. The expression of SHP is modulated by estrogens or testosterone [88-89], and SHP can interact with ERs and androgen receptors [90-91]. Another orphan nuclear receptor, DAX1, which acts as a co-repressor of FXRα [21], is involved in proliferation, apoptosis and steroidogenesis of reproductive tissues [92]. In this way, the participation of FXRα in reproductive events could be direct or indirect involving these other nuclear receptors.

Conclusions

FXRαs have an extensive presence in both male and female reproductive tissues suggesting a possible role of this receptor in reproductive events. Understanding the participation of FXRα in reproduction requires considering the interaction between FXRα, their ligands, and other nuclear receptors.

Acknowledgments

This study was supported by the Universidad Autónoma de Tlaxcala (Proyecto CACyPI-UATx-2014) and the Consejo Nacional de Ciencia y Tecnología (CONACyT; 106226 to CE).

Conflicts of interest

Authors disclose any financial or personal relationships with other people or organizations that could inappropriately bias or influence in the work.

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