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Review

Farnesoid X receptor: An important factor in blood glucose regulation

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ABSTRACT

Farnesoid X receptor (FXR) is a transcription factor that can be activated by bile acid as well as influenced bile acid metabolism. β-cell bile acid metabolism is mediated by FXR and closely related to the regulation of blood glucose (BG). FXR can regulate BG through multiple pathways. This review summarises recent studies on FXR regulation of BG balance via bile acid regulation, lowering glucagon-like peptide-1 (GLP-1), inhibiting gluconeogenesis, increasing insulin secretion and enhancing insulin sensitivity. In addition, the current review provides additional insight into the relationship between FXR and BG which may provide a new theoretical basis for further study on the role of FXR.

1. Introduction

FXR is a ligand-activated transcription factor classified as a nuclear bile acid (BA) receptor. Physiologically, BAs act as potent endogenous ligands for the activation of FXR [1,2]. FXR is encoded by the NR1H4 gene and widely expressed in various tissues and organs including liver, intestine, kidney, adrenal gland, heart, adipose tissue, vascular system, etc. [1]. Moreover, FXR was expressed in normal adult islet cells [3], chromosome 12q23.1 in human and 7q13 in rat. FXR is involved in the regulation of various biochemical reactions, such as BA metabolism, lipid metabolism, glucose metabolism, liver protection, etc. Transgenic mice with FXR-deficiency ($FXR^{-/-}$) exhibited severe metabolic dysfunction symptoms, such as elevated serum triglycerides, free fatty acids (FFAs) and high-density lipoprotein cholesterol (HDL-C) [4], insulin resistance symptoms, including hyperglycaemia, impaired glucose tolerance and severe blunted insulin signalling in the liver and muscles [5]. The activation of FXR by adenovirus-mediated genes reduces BG in obese fa/fa rats, diabetic db/db and wild-type mice [5,6], suggesting that the potential role of FXR can prevent liver cell damage caused by BA overload as a result of metabolic dysfunction [7]. However, the main physiological function of FXR is to regulate the conversion of cholesterol into BAs, which form the basis for its participation in other biochemical reactions.

2. BA and blood glucose

2.1. FXR and BAs

Studies have shown that activated FXR regulates the synthesis, secretion and transport of BAs[1] via 3 aspects: (1) synthesis of bile acids, (2) expression of fibroblast growth factor and (3) repression of sodium taurocholate cotransporting polypeptide (NTCP) transcription. FXR regulates bile synthesis via 2 main pathways: the classical pathway {catalysed by cholesterol 7-α hydroxy-lase (CYP7A1) as speed limiting enzyme, feedback regulated by bile acids}and the alternative pathway {catalysed by cholesterol 27-α hydroxy-lase (CYP27A1), accounts for

Abbreviations: FXR, farnesoid X receptor; GLP-1, glucagon-Like Peptide-1; BA, bile acid; FFAs, free fatty acids; HDL-C, high-density lipoprotein cholesterol; CYP7A1, cholesterol 7-α hydroxy-lase; CYP27A1, cholesterol 27-alphaα hydroxy-lase; SHP, small heterodimer partner; HNF-4α, hepatocyte nuclear factor 4α; FGF, fibroblast growth factor; NCTP, sodium taurocholate cotransporting polypeptide; ASBT, apical sodium-dependent bile acid transporter; PEPCK, phosphoenol-pyruvate carboxykinase; PC, pyruvate carboxylase; G-6-Pase, glucose-6-phosphatase; FDPase-1, fructose double phosphatase-1; AKR1B7, aldo-keto reductase 1B7; PGC-1α, proliferator-activated receptor γ coactivator 1α; Fex, fexaramine ; KLF11:Kruppel-like factor 11; OCA, obeticholic acid; GPBAR1, G protein-coupled bile acid receptor 1

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18% of total BA synthesis. In a condition of ectopic bile secretion, FXR reduces BA synthesis by indirect inhibition of CYP7A1 transcription, which occurs through 2 FXR-dependent mechanisms. The mechanism first involves activation of a small heterodimer partner (SHP), a nuclear receptor family that lacks a DNA-binding domain that represses CYP7A1 expression. The termination of CYP7A1 occurs via the inhibition of hepatocyte nuclear factor 4α (HNF-4α) and liver receptor homologue 1 (LRH-1), an orphan nuclear receptor that positively regulates CYP7A1 expression activities [8]. Moreover, the activation of fibroblast growth factor 19 (FGF-19, human) and FGF-15 (mice) [9] downregulated CYP7A1 through the JNK pathway by adhering to liver receptor complex FGFR4/JNK pat, which promotes the expression of FXR [10]. It has been accepted that gut microbiota influences host health status by promoting biotransformation of BAs. For instance, Degirolamo et al. have shown that the changes of BA metabolism induced by intestinal probiotics requires an enterohepatic FXR-FGF15 axis [11] that suppresses HNF-4α, LRH-1, which enhances FXR expression to allow BA secretion, bile salt export pump (BSEP) causing BA conversion to bile and repressing sodium taurocholate cotransporting polypeptide (NTCP) transcription [12], thereby inhibiting BA uptake, avoiding liver toxicity and damage.

2.2. BAs and blood glucose

Vincent et al. found that patients with type 2 diabetes (T2D) had higher BA and postprandial peak changes in total glycine bound bile acids ($P < .05$) [13], indicating that obese patients with T2D respond more to postprandial bile acids. It has been demonstrated that T2D patients exhibited higher level of plasma BA and deoxycholic acid. However, administration of BA sequestrant led to reduced BG levels [14,15].

These results suggest that FXR is related to BA metabolism and BG regulation. Numerous studies have proven that BA can maintain BG balance by activating FXR while feeding back on inhibiting self-synthesis via the FXR signalling pathway (Fig. A1).

3. FXR and GLP-1

GLP-1, a polypeptide of 30 amino acids synthesised by post-translational processing in intestinal L-cells which is released in response to food ingestion, has been found to play a critical role in regulation of gut hormones involved in the regulation of BG homeostasis [16,17]. GLP-1 induces hypoglycaemic effects through enhancing insulin secretion by islet β cells and inhibits glucagon secretion in α cells, indicating a hypoglycaemic effect. The hypoglycaemic effects of GLP-1 alleviate BG levels to normal concentrations and maintain relatively stable BG without hypoglycaemia. In addition, GLP-1 can inhibit the apoptosis of β cells, promote the regeneration and proliferation of β cells and enhance the ability of insulin synthesis [18].

GLP-1 is one of the pathways linking FXR to BG regulation. Apical sodium-dependent bile acid transporter (ASBT) on the ileum wall plays an important role in the enterohepatic circulation of BA [19]. Chen et al. demonstrated that administration of 10 mg of 264W94, an ASBT inhibitors, significantly enhanced GlP-1 secretion which led reduced BG after 3 week of treatment in rats [20]. There is evidence that BA sequestrant (BAS) complex induces GLP-1 production in L-cells. However, an increase FXR activation in L-cells decreases GLP-1 secretion and inhibits glycolysis, while FXR-deficiency increases GLP-1 gene expression and secretion metabolism in mice [21], suggesting the role of GLP-1 and FXR in glucose metabolism. In addition, the correlation between BA concentration, GLP-1, thiobarbituric acid (TBA) and FXR has been reported. GLP-1 and TBA concentrations were found to have a significant positive correlation in rat plasma. The reason may be attributed to the inhibitory effect of FXR on BA and GLP-1 production [22].

Researchers have shown that BA promotes GLP-1 secretion by activating Takeda G-protein receptor 5 (TGR5), a G protein-coupled BA receptor 1 [23]. Nonetheless, recent study has indicated that FXR can crosstalk with TGR5 to control GLP-1 secretion. The activation of fexaramine, an FXR agonist, induced gut microbiome remodelling, which led to expression of lithocholic acid (LCA) and taurolithocholic acid (TLCA), potent TGR5 agonists, which stimulated TGR5 to increase GLP-1 secretion [24,25]. These data indicate that upregulation of GLP-1 induced hypoglycaemic effect during FXR inactivation, but the co-stimulation of FXR and TGR5 may enhance GLP-1 via LCA and TLCA activities. Therefore, targeting GLP-1 activation and concomitant stimulation of FXR and TGR5 may serve as strategies for the regulation of BG.

4. FXR and gluconeogenesis

Under the condition of starvation, humans rely mainly on gluconeogenesis to maintain BG balance through the activities of four key enzymes: phosphoenol-pyruvate carboxykinase (PEPCK), pyruvate carboxylase (PC), glucose-6-phosphatase (G-6-Pase) and fructose double phosphatase-1 (FDPase-1). Studies have demonstrated that FXR can affect BG by regulating gluconeogenesis. Cai et al. reported that FXR inhibited the expression of PEPCK and G-6-Pase mRNA by increasing the expression of diacylglycerol kinase theta in diacylglycerol kinase theta knockout cells and primary hepatocyte lines [26]. Moreover, Ge et al. have shown that Aldo-keto reductase 1B7 (AKR1B7) stimulation by GW4064 (FXR agonist) in the liver and intestine significantly lowered BG levels in diabetic db/db mice [27].

In addition, GE et al. found out that overexpression of hepatic AKR1B7 significantly reduced hepatic peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) mRNA levels but significantly increased hepatic orphan nuclear receptor small heterodimer partner (SHP) mRNA levels [27]. Activated hepatic PGC-1α and SHP are known to induce and inhibit hepatic gluconeogenic genes, respectively [28,29]. Fang et al. indicated that treatment of mice with fexaramine reduced diet-induced liver glucose production. The study further revealed that this metabolic process was mediated by FGF-15 because FXR activation completely terminated FGF-15 expression, resulting in gluconeogenesis inhibition [30]. Another study demonstrates that FXR inhibits gluconeogenesis through the FXR-FGF15/19 pathway [9]. Interestingly, a recent study showed that HS218, an FXR antagonist, inhibited FXR, upregulated PGC-1α associated gluconeogenesis and effectively improved glucose homeostasis in T2D mice [31]. However, the study has demonstrated that gluconeogenesis may occur even in the presence of FXR. It was explained that FXR activation enhanced gluconeogenesis gene transcription and gluconeogenesis in primary hepatocytes of mice, which was controlled by the novel glucagon/cAMP/PKA/FXR pathway [32]. Altogether, these data indicate that FXR reduce glycogen production by inhibiting gluconeogenesis. Nonetheless, appropriate activation of cAMP/PKA may promote gluconeogenesis even in the presence of FXR, which may lead to stability of the BG balance.

5. The effect of FXR on insulin function

5.1. BAs and insulin

Studies have established that BA activates FXR, which affects insulin function. Kobayashi et al. identified that T2D animal models treated with colestimide (BA sequestrant) showed improved insulin resistance and increased insulin response [33], suggesting that BA may be closely related to insulin resistance. Various phenomena of insulin resistance in FXR deficiency mice suggest that the loss of the regulation of FXR and BA metabolic disorders may affect insulin function [5]. FXR activation by BA also play a feedback regulatory role for BA synthesis through the several pathways as mentioned before and may maintain the stability of insulin function via a biological regulation axis [34]. Collectively, these results indicate that FXR was related to BA metabolism and insulin

function. The regulation of FXR and BA may provide a therapeutic avenue for the treatment of insulin-related metabolic abnormalities.

5.2. FXR affects insulin signalling

Popescu et al. showed that FXR deficiency in mice exhibited significantly lower levels of islet specific hormone, (insulin, islet amyloidal polypeptide) mRNA expression which led to abnormal BG signalling pathways in pancreatic β cells [3]. In addition, Renga et al. demonstrated that the FXR-KLF11 (Kruppel-like factor 11) regulatory pathway regulates glucose-induced insulin transcription and secretion [35] that facilitate the maintenance of pancreatic β cells function in human normal islet cells as well as in a variety of islet β cell lines, such as HIT-T15, INS832/13, β -TC3 and MIN6. The study indicates that KLF11 combines the specific sequence of the insulin gene promoter directly, has the transcriptional activation effect and increases the expression of insulin [36]. FXR activation failed to regulate the transcription of the insulin gene in the absence of KLF11 [35], which confirms that transcription factor is essential for FXR activity on glucose-induced insulin gene transcription. Another study showed that mice treated with fexaramine had improved insulin responsiveness and BG balance [30,37]. Maneschi et al. have reported that FXR is positively associated with the expression of genes implicated in insulin signalling in homogenates of visceral fat [38]. Therefore, FXR affects insulin signalling by affecting β cell-specific hormone expression and FXR-KLF11 regulatory pathways.

5.3. FXR increases insulin secretion

Popescu et al. indicated that insulin concentration in FXR deficient mice expressed significantly lower insulin levels, which led to hyperglycaemia [3]. In addition, Düfer et al. demonstrated that FXR agonist treatment increased insulin secretion in normal mice but had no significant effect on FXR deficient mice [34]. This occurred as a result of FXR's inhibitory effect on the membrane potassium channels, which increased calcium influx, causing glucose-induce insulin secretion [34,39]. Renga et al. have reported that FXR increased insulin transcription and secretion in cultured human pancreatic islets with 6E-CDCA in high glucose conditions via both genomic and non-genomic effects. The genomic effects occurred via the activation of KLF11, while non-genomic effects were associated with Akt-mediated stimulation of glucose-induced relocation of glucose transporter-2 (GLUT2) in β-cells, which upregulate the insulin secretion and glucose uptake in pancreatic β-cells [35]. Interestingly, FXR is not involved in the transposition of GLUT4 to the plasma membrane but induces GLUT4 expression through the FXR response element (FXRE) in the GLUT4 promoter [40]. Researchers have indicated that FXR deficiency in mice exhibited altered kinetic of insulin release in β-cells, suggesting that FXR directly regulates insulin release through some signal pathway [41,42]. Recent studies have shown that calcium channels play an important role in the secretion of insulin by β-cells in the manner of exocytosis [43,44]. FXR enhances the glucose-induced insulin secretion by regulating the expression of the calcium channel in the β-cells. A study has affirmed that FXR expressing mice showed 3-fold higher insulin secretion than FXR deficient mice, suggesting that reduced levels of FXR are correlated with reduced insulin secretion [45]. From the above studies, it is obvious that FXR affects insulin signalling via different mechanisms, which are closely related to the development of glucose metabolism.

5.4. FXR increases insulin sensitivity

It has been accepted that FXR not only affects insulin signalling and insulin secretion, but also increases insulin sensitivity. Mudallar et al. reported that obeticholic acid (OCA), an FXR agonist, increases insulin sensitivity in patients with non-alcoholic fatty liver disease and T2DM [46]. In addition, Maneschi et al. confirmed that OCA improved insulin resistance via specific activation of FXR in patients with T2DM [38]. Cipriani et al. have proven that individual or combined treatment with 6E-CDCA and rosiglitazone (FXR agonists) restored insulin sensitivity in rats with severe insulin resistance. A study has explained that the mechanism for the role of FXR in insulin regulation occurs via reduction of IRS phosphorylation on Ser(312) and increases AKT phosphorylation on Ser(437) in the liver and muscles [6], which triggers the transcription and release of insulin.

6. Conclusions and perspectives

Diabetes is among the most common chronic diseases. At present, the prevalence of diabetes is increasing each year, and effective ways to treat diabetes are urgently needed. From its discovery to the present, reducing BG levels has been recognised as a direct way to treat diabetes. From above studies, FXR is closely related to the regulation of blood sugar (Fig. A2).

There is a negative correlation between plasma BA and BG levels. BA activates FXR to regulate BG through the FXR signalling pathway. In addition, researchers have found that BA activates G protein-coupled bile acid receptor 1 (GPBAR1/TGR5) and reduces blood glucose through the BA-TGR5-cAMP pathway [47].

Experiments prove that FXR activation in L-cells decreases GLP-1 secretion by inhibiting glycolysis [21]. Conversely, FXR receptor deficiency or inactivation leads to GLP-1 secretion, which leads to glucogenesis regulation. BA sequestrants, including cholestyramine, colesevelam, colestilan, and sevelamer, have been found to improve BG in patients with T2D [48]. Colesevelam has been approved by the FDA for the adjuvant treatment of T2D in the United States [49]. The exact mechanism by which BA sequestrants regulate BG remains unexplained. However, it has been demonstrated that action on intestinal and intrahepatic FXR and intestinal TGR5 reduces the production of endogenous glucose [50]. Moreover, BA sequestrants promote the secretion of GLP-1 [49,50]. The current study reveals that GLP-1 secretion is related to the inhibition of BA-activated FXR, but the precise mechanism requires further study.

FXR can inhibit gluconeogenesis through various pathways and restrict some sources of BG in vivo to achieve a hypoglycaemic effect by inhibiting key enzymes associated with the process of gluconeogenesis. Researchers have confirmed that FXR can inhibit PEPCK and G-6-Pase in the process of hepatic gluconeogenesis. Recent studies have indicated that the role of FXR during the pathogenesis related to glucose metabolic disorders might differ between the liver and intestines [51,52]. In the liver, FXR deficiency substantially increased gluconeogenesis, while hepatic FXR activation by GW4064 improved hepatic gluconeogenesis-related gene expression [5]. However, in the intestine, GW4064 treatment at low doses can activate intestine FXR and promote hyperglycaemia. Researchers have reported that such mechanisms may occur through the intestinal FXR-ceramide pathway. When the intestinal FXR-ceramide pathway is suppressed, the activity of PC is decreased, reducing gluconeogenesis [53]. Nonetheless, the role of FXR in the liver and intestine due to distinct signalling pathways has not yet been confirmed. Moreover, there is no evidence that FXR activation has direct or indirect effects on FDPase-1.

Lately, numerous studies have shown that the role of insulin in blood glucose regulation cannot be ignored. This study has shown that FXR enhances insulin function by influencing insulin signalling, secretion and sensitivity. However, the mechanism of these effects is unclear. In addition, the mechanism that signals transmission from BA in β cells requires detailed explanation. Chen et al. have shown that 264 W94, the inhibitors of ASBT, increased insulin levels in diabetic obese male rats after 2 weeks [20]. Other studies have shown that CYP7A1 and CYP27A1 in rat livers can be inhibited by insulin [54]. These results indicate that there may be other pathways between BA and insulin. It remains to be determined whether FXR overexpression may also induce adverse or beneficial effects on insulin.

These studies confirm the results of previous research, which

indicated that FXR plays a crucial role in the regulation of BG. This suggests that targeting FXR may serve as a therapeutic strategy for the treatment of T2D [30,38,55,56]. Due to FXR agonist hypoglycaemic effects, a variety of drugs targeting FXR are under development [57]. However, the human and animal metabolic mechanisms cannot be ignored, indicating that the therapeutic effects of FXR regulation of BG in humans as a diabetes treatment require further investigation. OCA (INT747) is clinically approved for the treatment of primary biliary cirrhosis and non-alcoholic fatty liver disease, but in a clinical trial, it has been demonstrated to improve insulin sensitivity in patients with T2D [46]. However, recent reports indicate that patients on OCA showed increased insulin resistance, elevated serum cholesterol and itching [58], indicating that OCA administration for the treatment of diabetes requires further exploration for clinical application.

In addition, the long-term benefits and safety of FXR require further consideration. As much as FXR agonists have exhibited beneficial effect, their adverse effects cannot be ignored and remain and important aspect of treatment. It should also be emphasised that FXR expressed in different tissues and plays different roles. Therefore, the function of FXR in various tissues requires further clarification to avoid drug complications. Studies have shown that non-steroidal agonists do not undergo enterohepatic circulation, indicating beneficial predictive pharmacokinetics for the treatment of diabetes. Non-steroidal agonist drugs, including GS-9674 and LJN452 are currently in clinical trials, with few adverse effect reported [57]. In addition, FXR intestinal-specific agonists, such as fexaramine have indicated lower adverse effects due to the reduced circulation as a result of its difficulty to be absorbed into the blood stream [59]. Fexaramine is currently used clinically to reduce weight gain and improve glucose tolerance and treatment of obesity-related diseases in mice. The mechanism may be related to increased insulin sensitivity [30,60]. Furthermore, whether FXR-involved signalling pathways are beneficial to the treatment of other glucose-related metabolic diseases is an area of intense concern.

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

All the authors agree.

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Appendix A

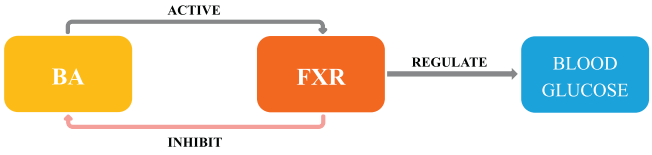

Fig. A1. The axis of bile acid regulating insulin function. Bile acids can maintain blood glucose balance by activating FXR while feeding back on inhibiting self-synthesis via the FXR signalling pathway.

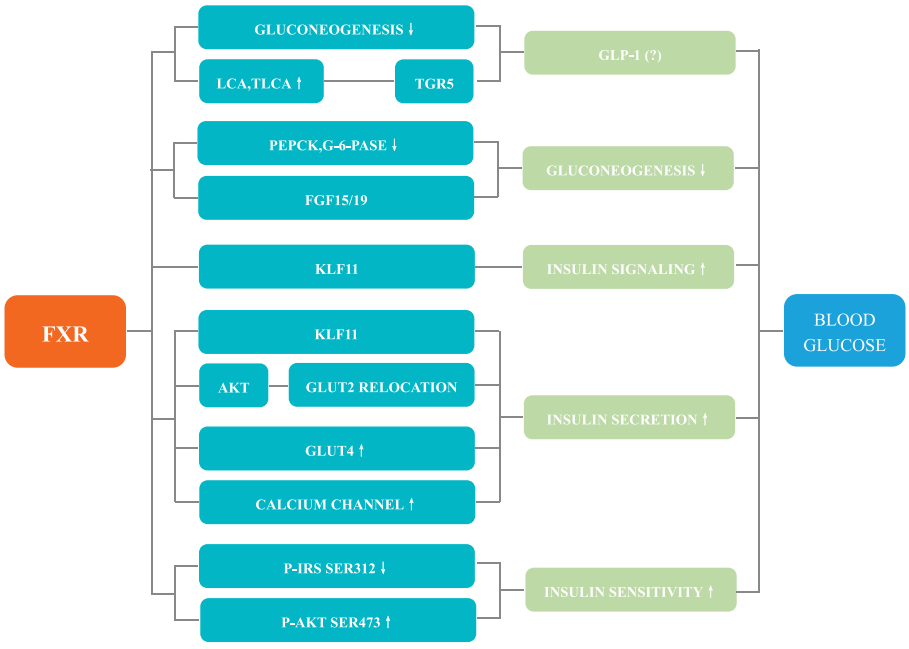

Fig. A2. Possible FXR regulates blood glucose signalling pathway.

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