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FXR an emerging target to combat obesity

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Abstract

Obesity and its associated diseases, including type 2 diabetes, has reached epidemic levels worldwide. However, available treatment options are limited and ineffective in managing the disease. There is therefore an urgent need for the development of new pharmacological solutions. The bile acid receptor FXR, has recently emerged as an attractive candidate. Initially described for their role in lipid and vitamin absorption from diet, bile acids are hormones with powerful effects on whole body lipid and glucose metabolism. In this review, we focus on FXR and how two decades of work on this receptor, both in rodents and humans, have led to the development of drug agonists with potential use in humans for treatment of conditions ranging from obesity associated diseases to bile acid dysregulation.

Introduction

Obesity is one of the biggest challenges of the 21st century for human health across the globe. According to the World Health Organization[1], 1.9 billion adults were overweight in 2014, as defined by having a Body Mass Index (BMI= weight (in kg) × height (in m)$^{-2}$) higher than 25. This represents 39% of the world adult population, and among them 600 million were obese (BMI>30). This problem is true for both men and women although the prevalence of overweight and obese people is slightly higher in men. Importantly, overweight and obese people are not only found at high levels in the USA and other occidental countries, but their incidence is now high all over the world with few exceptions such as Africa and India, Pakistan and Indonesia. It is clear that the increase in food abundance/availability combined with the general decrease in physical activity have largely contributed to this phenomenon over the last decades. Actually, obesity has doubled compared to 1980, and nowadays, obesity associated health problems are killing more people than any other cause of death in the lean population in most countries[1].

Individuals become overweight after an extended imbalance between their energy intake (food) and their energy expenditure (basal metabolic functions and physical activity). The excess of fat from the diet is then stored in the adipose tissue which eventually becomes inflammatory. This phenomenon has been well characterized[2,3]. Moreover, the excess of circulating lipids also results in fat accumulation in other major organs including liver, heart, muscle, kidney and pancreas. Collectively, this results in the development of systemic inflammation, insulin resistance, and eventually diabetes as well as cardiovascular diseases.

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On top of the coronary risk, cancer prevalence increases with obesity including cancers of the gastrointestinal tract, as well as other digestive organ pathologies such as severe pancreatitis, gall bladder disease, and non-alcoholic fatty liver disease.

Hence, 600 million people are at risk of dying younger because of these obesity-associated diseases. On one hand obesity is theoretically preventable, and better educating people on what they should eat, how much they should eat, as well as helping them to exercise more, is one way to solve the problem. On the other hand, lifestyle changes are for many people very difficult to put in practice and in a minority of people, obesity is the direct result of inherited gene mutations. Therefore there is a strong and urgent need for pharmacological solutions aiming at preventing obesity.

Targeting nuclear hormone receptors to cure obesity

Targeting nuclear hormone receptors appears as one promising way to tackle the obesity problem. In humans, the nuclear hormone receptor (NHR) superfamily comprises 48 members expressed throughout the body. NHRs are transcription factors that are activated by small molecule ligands. They share a structure comprising a non-conserved N-terminal region (AF1) with transactivation sites, a characteristic central DNA binding domain (DBD), and a homologous C-terminal ligand binding domain (LBD). Upon ligand activation, NHRs exert their physiological effect by controlling transcriptional programs. In this review we will focus on the Farnesoid X receptor (FXR) which is a Bile Acid (BA) receptor, and discuss how this receptor, in the intestine, controls body physiology.

Bile acids and FXR

BAs are historically known to be required for dietary absorption through their chemical detergent properties. They are synthesized by the liver from cytochrome P450-mediated oxidation of cholesterol. This represents the main form of cholesterol catabolism and accounts for ~50% of the daily turnover of cholesterol. The main bile acids produced by the liver in humans are cholic acid (CA) and chenodeoxycholic acid (CDCA). They are conjugated to glycine or taurine to increase their water solubility[4] before being exported as bile salts through the hepatic bile duct and being stored in the gallbladder. Upon feeding, BAs are released into the intestine to help absorb dietary fat, cholesterol, and vitamins via the formation of micelles. Interestingly, the microbiome regulates the BA composition. The intestinal bacterial flora present in the gut transforms the primary BAs synthesized by the liver into a new class of BAs called secondary bile acids, producing respectively deoxycholic acid (DCA) and lithocholic acid (LCA) from CA and CDCA. While a small percentage of BAs is eliminated with feces, the majority travels back to the liver via ileum absorption and portal blood stream circulation. They are then redisposed into the gallbladder from where they are secreted again. This process is known as enterohepatic circulation. More recently, BAs have been shown to act as hormones thereby regulating body physiology[5]. An important mediator of this hormonal signaling is the BA receptor FXR. This receptor was cloned in 1995 and initially shown to respond to supraphysiological levels of farnesol metabolites[6]. FXR forms an obligate heterodimer with the retinoid X receptor (RXR) and this complex binds to DNA on an FXR response element motif consisting of an inverted

repeat sequence of the canonical AGGTCA separated most frequently by one nucleotide (IR-1). A few years after its initial discovery, three groups identified BAs as the endogenous ligands for FXR[7–9].

FXR as a regulator of BA circulation and synthesis

One aspect of FXR activity is its regulation of genes involved in BA homeostasis, including BA synthesis and transport. BA homeostasis is essential to prevent toxic effects of their accumulation. FXR-mediated BA regulation happens essentially in the intestine and liver. In the distal ileum, post-prandial BA reabsorption by ileocytes through the apical sodium dependent bile acid transporter (ASBT) activates FXR and induces the expression of the FGF19/15 hormone (human and mouse names respectively). After exiting the portal circulation, FGF19/15 binding to its liver FGFR4/β-Klotho co-receptor complex ultimately leads to the inhibition of the rate-limiting enzyme of the BA synthesis: the cholesterol 7 alpha-hydroxylase, also known as cytochrome P450 7A1 (CYP7A1)[10]. Synergistically, BA activation of FXR in the liver induces the orphan nuclear receptor/transcriptional corepressor small heterodimer partner (SHP), resulting in the transcriptional inhibition of CYP7A1 and CYP8B1. CYP8B1 controls the ratio of CA to CDCA during BA synthesis[11]. BA transport in the intestine requires three proteins: ASBT (described above), the intestinal BA binding protein (IBABP) that shuttles BAs from the apical to the basolateral membrane of the enterocyte, and finally the heterodimeric organic solute transporter OSTα/β that secretes BAs into the portal vein. Upon FXR activation, ASBT is inhibited (in mice but not in rats)[12] while IBABP[13] and OST[14] are activated, resulting in a net decrease of BAs from the enterocyte, facilitating the enterohepatic circulation. In the hepatocytes, the sinusoidal Na+ taurocholate cotransport peptide (NTCP) and the organic anion-transporting polypeptide (OATP) uptake BAs, and their expression is negatively regulated by FXR activation. Similar to the intestine, the BA export pump (BSEP), and the multidrug resistance proteins MDR3 and MRP2, are involved in the secretion of BA from liver to the bile duct, and are induced upon FXR activation. Altogether FXR regulation in the intestine and liver mediates efficient BA circulation and dysregulation of these pathways contribute to several pathological conditions including cholestatic diseases. In accordance with the abovementioned roles of FXR in BA regulation, FXR is found at high levels in the entire gastrointestinal tract with a peak in the ileum and in the liver; kidney and adrenal glands also strongly express FXR, while adipose tissue, heart and breast have low FXR expression. Finally, it should also be noted that BA sulfation, hydroxylation or glucuronidation are additional FXR regulated mechanisms that protect the liver from BA toxicity[15–17].

FXR activity in pathologies

FXR null mice have been used to explore links between FXR activity and several pathologies. FXR KO mice display increased serum BAs, liver and serum triglyceride (TG) levels, and serum cholesterol and phospholipid levels[18]. In agreement with the direct regulation of BA metabolism by FXR, gene expression of SHP is reduced, Cyp7A1 is increased, while the IBABP and BSEP transporters are decreased in mutant mice. The phenotype is exacerbated when mice are supplemented with CA in their diet: mice experience severe wasting, hypothermia, decreased adipose tissue, and 30% of them die by day 7. In $FXR^{-/-}$ mice, five days of CA diet results in significant body weight decrease and

a 23-fold increase in serum BA, while the total pool of BA falls to half of that found in wild-type mice. These results emphasize the importance of FXR-mediated control of BA synthesis and transport, especially regarding feedback mechanisms in case of BA overload. When diet is supplemented with 1% cholesterol, KO mice show increases in liver cholesterol and TGs, increase in liver to body weight ratio as well as a pro-atherogenic profile with elevated serum cholesterol, phospholipids, and triglycerides. Along the same lines, in the ApoE$^{-/-}$ model of atherosclerosis, absence of FXR extends the severity of aortic plaques and lipid abnormalities[19]. These data indicate the importance of FXR in lipid metabolism regulation. In the absence of FXR, cholesterol concentration increases due to reduced catabolism into the BA synthesis. FXR appears also to be involved in the direct control of glucose homeostasis in the liver. Hepatic FXR expression is reduced in several rodent models of diabetes[20]. FXR$^{-/-}$ mice display alterations in peripheral insulin signaling and hepatic carbohydrate metabolism, elicited especially during fast-refeeding paradigms[21]. While FXR KO mice display glucose intolerance and insulin insensitivity, activation of FXR with the GW4064 agonist, or with a virus overexpressing a constitutively active form of FXR in the liver, lowered blood glucose levels in both diabetic db/db, ob/ob and wild-type mice by repressing gluconeogenic genes in the liver and activating hepatic glycogen synthesis[22,23]. However, in the context of genetic (ob/ob mice) or diet-induced (high-fat diet, HFD) obesity, Prawitt *et al* demonstrated that FXR deficiency was protective, with mice having reduced body weight gain, reduced adipose tissue, and importantly better glucose homeostasis with improved insulin sensitivity[24]. Interestingly, this effect is not mediated through FXR deficiency in the liver, since liver-specific FXR KO failed to demonstrate significant protection against obesity. Interestingly increased energy expenditure in brown adipose tissue has been proposed as a one mechanism through which overall improvements have been observed in obese FXR KO mice[25]. In a mouse model of FXR KO in which the DNA binding domain of FXR was deleted a slightly different phenotype was observed[26]. These mice display higher body weights without liver toxicity or hepatomegaly. They have increased BA serum pool concentration, but contrary to the other FXR KO model, the BA pool size is increased in these mutant mice. Their endogenous glucose production is decreased and they have reduced hepatic as well as peripheral insulin sensitivity[27]. Finally, in a third model of FXR KO mice, partial deletion of the ligand binding domain results in improved glucose tolerance and lower HOMA-IR index but spontaneous cholestasis and liver damage[28]. Despite the phenotypic differences, these studies establish FXR as a key regulator of bile acids synthesis and transport.

Interestingly, FXR agonists have consistently demonstrated beneficial results in treatments of cholestatic conditions, obesity and liver steatosis. The synthetic FXR agonist GW4064[29] is active both *in vitro* and *in vivo*, however its limited bioavailability precluded its use in clinical trials. Nevertheless in rodents, treatment of HFD and ob/ob mice with GW4064 prevents hepatic steatosis and insulin resistance[23,30]. A semi-synthetic derivative of CDCA, 6-ethyl-CDCA, also known as INT-747 or Obeticholic acid (OCA), displays 100 times higher affinity for FXR compared to CDCA, the most potent natural bile acid activator of FXR[31]. In rodents, OCA has been shown to confer protection in several models of liver cholestasis[32,33]. Treatment of Fa/Fa rats with OCA alleviates the fatty liver and insulin resistance in these animals[34]. In humans, OCA has recently been approved for the treatment

of primary bile cholangitis (PBC)[35]. By activating FXR directly in the liver but also by increasing FGF19 due to FXR activation in the intestine, OCA relieves BA stress in PBC patients: bile acid synthesis in the liver is decreased, hepatic import of bile acids reduced, and export of bile acids into viable bile ducts is increased. Interestingly, a phase 2 clinical trial has also revealed that administration of OCA to patients with type 2 diabetes and non-alcoholic fatty liver disease increased insulin sensitivity and reduced markers of liver inflammation and fibrosis[36,37]. However, another phase 2 clinical trial on patients with NASH showed that although OCA resulted in improvements in liver histology, a large number of patients developed pruritus, increased HOMA-IR as well as elevated HDL[38]. The increase of pruritus is also an adverse event commonly observed in patients treated with OCA for PBC[39]. Altogether, these results indicate that FXR agonism appears as an attractive route to treat conditions such as obesity, cholestasis, and fatty liver diseases, however, OCA can result in frequent and strong side effects, indicating that development of new FXR agonists with more tissue specificity and therefore less side effects would be desirable.

Fexaramine, a promising new class of FXR agonist

Fexaramine is a non-bile acid synthetic activator with marked selectivity for FXR over other BA receptors including pregnane X receptor (PXR), constitutive androstane receptor (CAR), and vitamin D receptor (VDR)[40]. Moreover, oral treatment of mice with Fexaramine results in strong activation of intestinal FXR with very minimal entry of this drug into the body via the portal vein[41] limiting systemic FXR activation. Thus, administering Fexaramine orally mimics the natural process of FXR activation in the intestine that occurs normally upon feeding, when the gallbladder releases BAs into the intestine. Interestingly, even though Fexaramine action is restricted to the gut, its strong anti-obesity effect has recently been reported[41]. In mice, only a few weeks of Fexaramine treatment prevents the gain of weight due to high fat diet feeding. Glucose tolerance was improved in the drug-treated animals, in part because of improved insulin sensitivity. The decrease in body weight was achieved without any change in food intake and was mainly due to a reduction in fat mass. Mechanistically, Fang *et al* showed that FGF15 induced by activation of intestinal FXR affected both brown and white adipose tissue as well as the liver. Similar results have been described in transgenic mice overexpressing FGF15/19[42–44]. Moreover, transgenic mice overexpressing FXR solely in the intestine display elevated levels of FGF15 and are protected from liver cholestasis. It would be interesting to know whether these mice are protected from obesity, and whether they exhibit increased thermogenesis[45]. Indeed, Fexaramine treatment increases thermogenesis and oxygen consumption, and accordingly the core body temperature of Fexaramine-treated mice was elevated by 1.5°C. Upon HFD feeding, excess dietary fat stored in adipose tissue results in elevated leptin and resistin, ultimately increasing blood cholesterol and fasting insulin levels. However, these parameters as well as circulating inflammatory cytokines such as TNFα, IL1α, IL1β, IL17, and MCP1 were all improved when HFD mice were supplemented with Fexaramine. Another positive metabolic aspect of Fexaramine treatment relates to improved suppression of hepatic glucose production by insulin. Future studies will prove helpful in understanding whether this observation is a consequence of the decreased liver steatosis occurring in Fexaramine-treated mice.

Another benefit of intestinal FXR activation relates to the improved gut health observed in these animals[46,47]. The mucosal defense that protects intestinal mucosa from physical attack by the acid present in the gastro-intestinal lumen is known to be compromised upon HFD treatment. As a consequence, obese mice and humans present with a “leaky gut” condition, where the barrier function normally ensured by the tight junctions of the enterocytes is compromised, allowing toxins and bacteria to enter the circulation and create infection and inflammation[48]. Importantly, Fexaramine treatment in HFD mice strengthens this mucosal defense as revealed by increased gene expression of occludin and muc2 in drug-treated mice and consequently, the intestinal barrier from HFD-Fexaramine-treated mice was improved.

Conclusion

Beyond its direct role in BA synthesis and transport, FXR has emerged as a regulator of whole body metabolism. FXR appears as a promising target to treat obesity-associated diseases. However, previously developed FXR agonists including GW4064 and OCA result in problems ranging from poor bioavailability to pruritus, increased HOMA-IR and lipid dysregulation. A new synthetic FXR agonist, Fexaramine, with a non-bile acid structure has recently been described for its anti-obesity effects in mice. Contrary to previously developed agonists, Fexaramine treatment restricts FXR activation to the intestine, resulting in increased gut peptides including FGF15, a healthier gut, and decreased systemic inflammation. This makes Fexaramine a strong candidate for therapeutically targeting obesity and associated diseases including type 2 diabetes and fatty liver diseases. Intriguingly, Fexaramine mimics some of the beneficial metabolic effects of bariatric surgery, an efficient procedure to decrease body weight and improve the health of obese people. In both cases, FGF19/15 levels increase, insulin sensitivity is improved, glucose levels decrease, bile acid profile is improved, intestinal inflammation is lowered, and ultimately body weight is reduced[49]. Future studies will help to reveal whether Fexaramine will lead to new treatments for obesity.

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