Review

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Liver X receptors as regulators of metabolism

Abstract: The liver X receptors (LXR) are crucial regulators of metabolism. After ligand binding, they regulate gene transcription and thereby mediate changes in metabolic pathways. Modulation of LXR and their downstream targets has appeared to be a promising treatment for metabolic diseases especially atherosclerosis and cholesterol metabolism. However, the complexity of LXR action in various metabolic tissues and the liver side effect of LXR activation have slowed down the interest for LXR drugs. In this review, we summarized the role of LXR in the main metabolically active tissues with a special focus on obesity and associated diseases in mammals. We will also discuss the dual interplay between the two LXR isoforms suggesting that they may collaborate to establish a fine and efficient system for the maintenance of metabolism homeostasis.

Keywords: cholesterol; nuclear receptor; oxysterol; transcription.

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Introduction

Liver X receptors (LXR)α (NR1H3) and β (NR1H2) are two members of the nuclear receptor (NR) family involved in multiple metabolic pathways including energy expenditure (1–3), insulin signaling (4–6), and metabolism of glucose, lipid (7–17), and cholesterol (18–27). They play key roles in atherosclerosis (28, 29), inflammation (7, 30), and CNS development (31, 32). Their main function is to translate physiological (hormonal, metabolic, exercise, or dietary) signals into modification of gene expression. Following ligand binding, they repress or activate transcription of target genes by binding to specific sites on DNA and interacting with co-repressors or co-activators, respectively. Several natural ligands for LXR have been identified. These include oxysterols, bile acids, and fatty acids. There are also synthetic agonists such as T0901317 and GW3965. None of these ligands show preference for the α or β isoforms of LXR.

In addition to sharing the same ligands, and the same binding sites on DNA, LXRα and LXRβ share a high degree of sequence homology. The difference in their biological activity appears to be due to the differences in their tissue distribution. LXRα is mainly expressed in organs involved in lipid metabolism such as liver, intestine, adipose tissue, and macrophages. LXRβ is more widely expressed in the immune system, in glial cells in the central nervous system, the gall bladder, islets of the pancreas, skeletal muscle, and prostate epithelium. This review will focus on the roles of the two LXR isoforms in the main organs involved in metabolism with special focus on two prevalent diseases of Western society, type-2 diabetes and obesity. Because these receptors were discovered in the middle of the 1990s, their functions are still being elucidated, and results from different labs are sometimes dissimilar.

LXR function in liver

LXR in cholesterol homeostasis

LXRα, first discovered in the liver, is essential for triglyceride (TG) and cholesterol homeostasis in the liver. There is consensus in studies performed during recent decades that LXRα acts as a cholesterol sensor, and under conditions of excess cholesterol, it stimulates cholesterol transport to the liver and bile (33). Reverse cholesterol transport (RCT) refers to cholesterol trafficking from peripheral tissues to the liver where it is excreted as bile acids. Most of the steps of RCT are regulated by LXRs (26,

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27, 33). Both LXRs control the expression of the ATP-binding cassette *Abca1* and *Abcg1* genes, which play a key role in the RCT from plasma membrane to extracellular acceptors (such as macrophages) and to the liver (9, 25, 34–36). In addition to the ABC transporters that mediate cholesterol efflux, several apolipoproteins (Apo) and lipid-modulating enzymes involved in RCT are also targets of LXR including *ApoE* in macrophages and adipose tissue (20), and lipoprotein lipase (Lpl) in liver and macrophages (37). Loss of LXRα makes mice very sensitive to a high fat diet (HFD) (38), which induces severe cholesterol accumulation in the liver. Cholesterol storage in tissues peripheral to the liver is not affected under these conditions, and this is probably due to the efficiency of the RCT pathway in returning cholesterol to the liver (29) and to peroxisome proliferator-activated receptor (PPAR)γ stimulation of HDL-dependent cholesterol transport (39).

In rodents, but not in humans, LXRα upregulates expression of cholesterol 7 α-hydroxylase Cyp7a1, the rate-limiting enzyme for bile acid synthesis (24). In mice lacking LXRα, but not in those lacking LXRβ, removal of cholesterol from the body is severely impaired (18, 36). Conversely, systemic activation of LXR with LXR agonists reduces whole-body cholesterol levels in LXR WT mice and raises HDL levels in the plasma (40–42) confirming that in mice, LXR is the key regulator of cholesterol homeostasis in liver.

Interestingly, species differences in response to LXR activation have been observed *in vivo* in studies performed on cynomolgus monkeys and C57Bl/6 mice (43). Hong et al. suggested that LXR agonist raises plasma LDL cholesterol levels in primates, but not in mice, through activation of the LXR-regulated E3 ubiquitin axis. Another study from Quinet et al. found that LXR ligand activation with the selective LXR agonist WAY-252623 lowers serum LDL cholesterol in cynomolgus monkeys, is neutral in Syrian hamsters, and reduces atherosclerosis in mouse (44). These results would question the relevance of ongoing efforts to target LXR in human diseases using rodent models. However, authors used different drugs, time of treatment, as well as different doses that have also been shown in rodent studies to modify metabolic response to LXR activation *in vivo*.

LXR in regulation of triglycerides

In addition to their roles in cholesterol metabolism, the LXRs have important functions in regulating hepatic TG homeostasis. This effect is mainly mediated via the transcriptional regulation by LXRs of the sterol regulatory binding transcription factor 1 (*Srebp1c*), the master regulator of TG synthesis (45, 46). It is well recognized that when fed an HFD, neither LXRαβ knockout (KO) mice nor LXRβ KO mice gain weight (38, 47–49). Although there is very little LXRβ expressed in hepatocytes, literature data diverge concerning the role of LXRs in liver TG accumulation. While some groups report that only LXRα is responsible for liver accumulation of TG (24), others have shown that both LXR isoforms may be responsible for liver lipogenesis (36, 38). In LXRα KO mice, lipogenesis in liver is less than in WT mice. However, in LXRα KO mice treated with GW3965, both *Srebp1c* expression and hepatic TG increased, implying that LXRβ contributes to this hepatic effect (36). Pharmacological activation of LXR with synthetic agonists markedly increases hepatic TG, stimulates very low-density lipoprotein secretion and transiently raises plasma TG levels (1, 13, 30, 48, 50). However, upon more prolonged exposure to GW3965 (5 weeks), there is a decrease in serum TG (1, 15, 51).

We and others have shown that LXR regulates lipogenesis in a tissue-specific manner (15, 38, 52, 53). While the absence of LXR stimulates lipogenesis in the adipose tissue, it suppresses lipogenesis in the liver (15). In line with this finding, Mohammadi et al. (53) demonstrated that garlic extract antagonized LXRα expression in the liver, while it enhanced LXRα expression in the intestine. This observation raises questions about the suitability of LXR agonist for lipid control. In conclusion, much more information is needed before the use of hepatic LXR as a target in the control of lipid metabolism can be of clinical relevance.

LXR in glucose homeostasis

Apart from their roles in lipid metabolism, LXRs have also a key role in glucose homeostasis in the liver. Treatment of mice with GW3965 for 1 week improves glucose tolerance by upregulation of the insulin-sensitive glucose transporter (GLUT4) in adipose tissue (5). In rodents with defective leptin signaling, *db/db* mice, fatty Zucker rats (a recessive trait (fa/fa) of the leptin receptor), and leptin deficient *ob/ob* mice, LXR activation lowers plasma glucose through a downregulation of *Pepck* expression and, thus gluconeogenesis, and improves insulin sensitivity (4). This beneficial effect on insulin signaling led to the suggestion that LXR could be a good target for pharmacological manipulation in metabolic diseases such as insulin resistance and type-2 diabetes. But LXR has not turned out to be a realistic pharmacological target. A study from Oosterveer et al. (54) identified LXRα as a

key mediator of the hepatic response to fasting: Hepatic glycogen depletion was slow in LXRα KO mice, and there was no increase in hepatic TG. We have also demonstrated that, through its regulation of fibroblast growth factor 21 (FGF21), a novel hormone that regulates glucose and lipid metabolism, LXR plays a key role in the hepatic response to fasting. We found that the fasting response to FGF21 was blunted by GW3965 treatment in both LXRα and LXRβ KO mice (55). The action of GW3965 in LXRα KO mice indicates that LXRβ is required for insulin sensitivity and glucose homeostasis (38, 48). Indeed, LXRβ KO mice are insulin resistant even though they stay lean on an HFD (38, 48). The resistance to diet-induced obesity may be a consequence of lipid malabsorption, which results from pancreatic insufficiency in these mice (56). Conversely, LXRαβ KO mice stay lean and insulin sensitive on the HFD (38, 48), and on high carbohydrate diet (HCD) (15), LXRαβ KO mice show lower TG accumulation in the liver compared to WT mice. The observation that metabolic control (TG, cholesterol, serum glucose, and insulin levels) is better in LXRαβ KO mice than in WT littermates on both high carbohydrate and high fat diet (6, 15, 38, 49) suggests that development of LXR antagonist could be considered as a novel pharmaceutical approach in the treatment of metabolic disorders including insulin resistance and type-2 diabetes.

LXR function in gastrointestinal tract

Intestinal cholesterol absorption is a complex process whose regulation is still being actively investigated. The intestine is dedicated to a tight control of whole-body cholesterol homeostasis not only as an absorptive organ but also by contributing to the removal of excess cholesterol from the periphery. Both reverse cholesterol transport (RCT) pathway and trans-intestinal cholesterol excretion (TICE) are involved in this process (57), and LXR has been identified as a key player in both pathways in the intestine (26, 28, 58–61). The non-biliary RCT pathway targets plasma cholesterol to the proximal part of the small intestine and, thereby, induces the cellular cholesterol secretion into the intestine lumen. In this pathway, LXR activation induces the expression of the reverse cholesterol transporters, *Abcg5*/*Abcg8* and *Abca1* and, thus, reduces the cholesterol content in the intestinal absorptive cells, the enterocytes (25, 62). Moreover, when ABCG5/8 is inactivated, LXR activation can no longer induce RCT (63), indicating that the intestinal expression of *Abcg5/8* is required for TICE. Interestingly, no differences of hepatobiliary and fecal cholesterol excretion upon LXR activation were observed between DBA/1 wild type and ABCA1 KO mice (64) suggesting a limited contribution of ABCA1 in the control by LXR of the intestinal cholesterol absorption.

Recently, Lo Sasso et al. (21), using mice in which there is intestinal specific LXR activation, showed that intestinal LXRα activation moderates cholesterol absorption and induces RCT as opposed to hepatic-selective LXR activation. They demonstrated that the intestinal expression of the constitutively activated form of LXRα controlled the regulation of LXR target genes involved in cholesterol metabolism in both luminal (Abcg5/8) and plasma (Abca1) compartments, resulting in an important reduction of cholesterol absorption together with an increase in pre-βHDL particles. GW6340, an intestine-specific LXR activator, has been shown to stimulate RCT from macrophages and to promote fecal excretion of sterols in mice (65). However, LXR agonist in macrophages alone was insufficient to substantially promote RCT in the absence of hepatic and intestinal LXR expression. This would suggest that macrophage LXR, itself, does not play a leading role in the promotion of RCT during LXR activation.

Hu et al. recently reported that in LXRα KO mice, LXRβ activation increased intestinal cholesterol absorption and apoB-containing lipoprotein secretion (66). This LXRβ effect was counteracted by LXRα. Thus, it appears that overall intestinal cholesterol absorption is a balance between the pro-absorptive effects of LXRβ and the reverse cholesterol excretion mediated by LXRα. The question raised by these observations is the relative distribution of the two LXRs and how they communicate to maintain optimal cholesterol absorption, and this underscores the relevance of developing an isoform-specific LXR modulator. LXRβ appears to be ubiquitously expressed in the intestinal mucosal epithelium, while LXRα is mostly expressed in the fully differentiated cells lining the intestinal epithelium of the colon and in the villi of the ileum (67). Importantly, overexpression of LXRα in the intestine has been shown to protect from diet-induced atherosclerosis without any side effects such as liver steatosis and increased fatty acid synthesis (21). These results would support LXRα as a key player in the intestine RCT pathway. In zebrafish, activation of LXR in the intestine regulates the delivery rate of absorbed lipids by a temporary induction of lipid intestinal droplet storage (59). These recent results might suggest that the beneficial reduction of lipid absorption observed after LXR activation could be transitory and would question the beneficial effect of LXR activation in the intestine in a long-term treatment of lipid disorders. However, in intestine-specific LXRα activation,

mice fed a high cholesterol diet, both serum and hepatic TG levels were reduced (21). All together, these results would support the beneficial effect of LXRα activation in the intestine.

Thus, a review of the recent literature supports the role of LXR as a master regulator of whole-body cholesterol and TG metabolism: LXR [1] reduces cholesterol and TG uptake from the intestine; [2] induces cholesterol efflux from the peripheral tissues; and [3] induces cholesterol breakdown in the liver leading to an overall reduction of whole-body cholesterol content. Mounting evidence supporting the physiological importance of the intestine in systemic lipid metabolism raises the possibility that the intestine-specific LXR pathway could be an attractive drug target. Recent data on intestine-specific LXR activation strongly suggest intestines as a key organ in the treatment of lipid disorders using LXR-targeting drugs.

LXR function in fat depots

LXR action in adipocytes has been explored, but its function has remained unclear. Indeed, for practical reasons, human studies have mainly focused on the effect of LXR activation/knockdown in isolated adipocytes from subcutaneous (SC) adipose depots as opposed to murine experiments carried out on visceral (VS) fat depots, the metabolically most active fat site. It is well recognized that SC and VS adipose depots have different metabolic functions (68). To our knowledge, there is almost no data, so far, on the regulation of lipid metabolism by LXR in human visceral fat, and the discrepancies observed between human studies and animal studies could be due to this difference in fat depot studied.

LXR in lipogenesis

LXRαβ and LXRβ KO mice are resistant to diet-induced obesity (38, 48, 49). Although LXR is a direct activator of *Srebp1c* gene (46), the rate-limiting enzyme of the lipogenesis pathway in the liver, in adipose tissue of LXRαβ KO mice, *Srebp1c* expression was upregulated compared to WT littermates (38, 49). These results clearly identify opposite regulation of lipogenesis pathway by LXR between liver and adipose tissue as already observed in other tissues. However, treatment with T0901317 *in vivo* upregulates the expression of both *Srebp1c* and *Fas* genes in mouse adipose tissue (69, 70). In obese *ob/ob* mice, chronic LXR agonist treatment induced expression of the main genes involved in lipogenesis pathway, including *Srebp1c*, in both VS and SC fat depots (7). The discrepancies between the findings reported above might depend on differences of experimental conditions and/or insulin or glucose levels that are known to affect lipogenesis.

Experiments on single KO mice fed a regular diet and treated with GW3965 for 5 weeks confirmed a key role of LXRα and LXRβ in the regulation of adipocyte metabolism (1). Interestingly, basal lipogenesis was blunted in LXRα KO mice only, highlighting the critical role of LXRα in the regulation of lipid homeostasis in murine white adipocytes (1). In contrast, another study found no differences in any of the selected markers of lipogenesis in adipose tissue (AT)-LXRα KO compared to WT mice on an HFD (69). LXRβ KO mice show five times higher level of basal lipogenesis compared to control mice (1). This result would suggest LXRβ as a probable repressor of basal lipogenesis in mouse white adipocytes. Most likely, a balance between the two isoforms defines the metabolic response to LXR activation in adipocytes, and the differences observed between studies may be explained by different experimental conditions.

LXR in lipolysis

In human fat cells isolated from SC fat, LXRα has been identified as the main isoform involved in lipolysis (71). In obese female *ob/ob* mice treated with GW3965 for 5 weeks, expression of the main lipolytic proteins, adipose triglyceride lipase (ATGL), and hormone-sensitive lipase (HSL) was increased in VS fat but decreased in SC fat (7). As a consequence, VS and SC fat contents were reduced and induced, respectively. All together, these data suggest LXR as a valuable target in the treatment of obesity. Recent work on LXRα/β KO mice on an *ob/ob* background (LOKO) has shown that LOKO mice are more insulin sensitive and show reduced liver TG content but induced adipose depots compared to the control *ob/ob* mice (8). In LOKO mice, PPARγ signaling pathway, a hallmark of improved insulin sensitivity, in adipose tissue was highly induced. These results would suggest that in the absence of LXR, PPARγ could be the main player in the regulation of fatty acid metabolism and insulin sensitivity.

Paradoxically, in lean mice, opposite regulation of lipolysis pathway by LXR was observed. Lean LXRαβ KO mice show higher lipolysis in adipocytes isolated from VS fat compared to WT littermates (15). Accordingly, in lean-WT mice, long-term activation of LXR has been shown to reduce lipolysis activity in VS fat (1). These data reinforce a key role of LXRs in the regulation of lipid pathway in adipocytes possibly through the regulation of the main

lipolytic enzymes. However, data diverge between animal studies (obese vs. lean animals) making the role of LXR unclear in the regulation of lipid metabolism in white adipocytes. Again, differences in experimental conditions (time of treatment, lean vs. obese) and insulin concentration may explain these differences between studies.

Experiments performed on single KO animals showed that LXR isoforms may have different influence on the regulation of lipolysis in adipocytes. LXRα KO mice showed lower and LXRβ KO mice higher lipolysis in response to norepinephrine than WT littermates, implying that LXRα and LXRβ could regulate lipolysis in different directions in adipocytes (1). LXR activation by GW3965 wipes out lipolysis in WT mice only and LXRα KO mice show blunted lipolysis. These results identify LXRβ as a possible repressor of lipolysis in adipocytes and indicate LXRα as a key player in lipolysis (1). Dib et al. recently generated LXRα adipose-specific (AT-LXRα) KO mice and found that these mice gain more fat on HFD than do control mice (69). In line with our study (1), they conclude that LXRα is required for lipolysis in both SC and VS adipocytes. Overall data demonstrated that LXRα has a key function in lipolysis in white adipocytes, while LXRβ would act as a repressor.

Recently, studies on animal models and cell lines clearly show a cross talk between PPARγ and LXR in the regulation of adipocyte metabolism (8, 72, 73). This new finding could explain some discrepancies observed in the literature between LXR knockout studies and LXR activation studies in mouse models. Indeed, in the absence of LXR, PPAR may be the main contributor of fatty acid regulation and overcome the absence of LXR. Taken together, these data confirm the complexity of LXR regulation of lipid metabolism in adipocytes. We and others showed that LXRα is required for lipolysis, while LXRβ may act as a repressor.

LXR function in brown adipose tissue (energy regulation)

In 2002, our team showed that LXR regulates key genes of the energy pathway in the brown adipose tissues (BAT) (74). After gene expression profiling of BAT, we found that UCP1, as well as cytochrome c, and mitochondrial ribosomal proteins, were highly upregulated after LXR activation. The resistance to diet-induced obesity observed in LXR KO mice was explained by an ectopic expression of UCP1 in white visceral adipose (beige cells) fat and an increased fat oxidation (38, 49). On a normal chow diet, we found a 10-fold induction of *Ucp1* expression in VS fat and BAT in LXRα KO, but not in LXRβ KO mice (2). On HFD, LXRα KO, but not LXRβ KO mice, gained as much weight as the WT mice, supporting a possible repressive role of LXRα on UCP1 expression (38, 69). To date, no study has demonstrated a potential implication of LXR in the beiging process of white adipocytes.

In lean mice, UCP1 expression in BAT was four times higher in LXRα KO compared to WT mice but similar in LXRβ KO mice, suggesting a repressing role of LXRα in the regulation of UCP1 in this tissue (2). In line with our study, Wang et al. showed that LXRα is a direct transcriptional inhibitor of *Ucp1* expression in brown adipose tissue (3). However, administration of GW3965 for 5 weeks markedly repressed UCP1 expression in both LXRα and LXRβ KO mice and elicited a fivefold increase in GLUT4 (2). These results imply that both LXRα and LXRβ regulate BAT activity (energy dissipation through UCP1 and lipid storage through GLUT4). Supporting a key role of LXR on BAT metabolism, a recent study from Sheng et al. showed that Rhein, a natural compound from *Rheun palmatum* L., acts as an antagonist of LXR in brown adipose tissue. Rhein directly binds to LXRα and LXRβ and activates *Ucp1* expression in brown fat of wild-type mice but not in LXRαβ KO mice (75).

In summary, these data reveal a role for both LXRα and LXRβ in regulation of brown adipose tissue metabolism (2, 3). LXRα could be the main player in the browning process of white adipocytes, but both isoforms control energy metabolism in brown adipose tissue. There is a growing interest in targeting beige and brown adipose tissue metabolism to combat obesity and in developing tissue-selective LXR agonists that could modulate beige/brown adipocyte activity without the lipogenic side effect observed in the liver. Such a selective tissue-specific agonist would be necessary to reach the appropriate cells using LXR as a target in the control of lipid homeostasis. But to date, more work is needed to unravel the role of LXR in the beiging process.

LXR function in skeletal muscle

Both LXR isoforms are present in SM (1, 22), but surprisingly, relatively little research effort has been devoted to elucidate the action of LXR in the regulation of metabolism in SM, and there is not a clear consensus on the role of LXR in SM. Because skeletal muscles (SM) utilize large amounts of substrates (glucose and fatty acids), when there is a SM insulin resistance, whole body glucose and lipid homeostasis is perturbed. However, no differences in *Lxrα* and *Lxrβ* gene expression have been observed

Table 1: Summary of studies on LXR function in rodents.

References	Genetic background	Drug and duration of treatment	Targeted tissue			
			Liver	Intestine	Adipose	Skeletal muscle
Males						
Grefhorst et al. [51]	C57Bl6J and ob/ob mice	GW3965 (10 days)	↑ Liver weight in lean only ↑ TG in lean and ob/ob mice ↓ Glycogen in ob/ob mice	–	↑ Srepb1c in both strains ↑ Glut4 in ob/ob mice only	↑ Srepb1c in both strains ↓ Hk1/2 in Ob/Ob mice only
Kalaany et al. [49]	C57Bl6J/129Sv/Ev versus LXRαβ KO mice	High cholesterol diet	↓ TG (lipogenesis) ↑ Cholesterol ↑ Energy production (DIO1/2)	= Lipid absorption	↓ Fat storage	↑ Lipid oxidation ↑ Ucp1 ↑ VO_2 consumption
Cha and Repa [93]	A129/C57Bl/6 mice	T0901317 (7 days)	↑ Chrebp, Fas, Scd1 and L-pk	–	–	–
Wang et al. [3]	C57Bl6J/129Sv/Ev WT versus LXRα KO mice	Brown adipose culture cells w/ T0901317	–	–	LXRα dependent: ↑ UCP1 in VS and brown fat ↑ Mitochondrial density	–
Oosterveer et al. [54]	Sv129/OlaHsd C57Bl76J WT versus LXRα KO mice	Fed /fasted (9 h) / starved (12 h)	↓ TG at 9 h and 24 h ↓ Hepatic glucose production = Insulin sensitivity at 9 h	–	= Insulin sensitivity at 9 h	–
Colin et al. [94]	C57Bl/6 mice	T0901317 or GW3965A (3 days)	↓ Pparα ↑ Srebp1c, Abca1, Abcg5/8 and Scd1	↑ Pparα, Abca1, Abcg5/8 ↑ Srebp1c and Scd1	–	–
Inoue et al. [95]	C57Bl6J mice	One dose of T0901317	= Pparα ↑ Srebp1c and Abca1	↑ Pparα, Abca1 and Srebp1c	–	–
Quinet et al. [44]	LDLR KO mice	8 weeks atherogenic diet w/GW3965 or WAY-252623	= Liver weight ↓ Cholesterol = TG w/GW3965 ↓ TG w/WAY-252623	–	–	–
Quinet et al. [44]	Golden Syrian hamsters	WAY-252623 (7 days)	= Liver weight = TG	–	–	–
Grefhorst and Parks [96]	C57Bl6J mice	T0901317 (6 days)	↑ Liver weight and TG = Chrebp ↑ Lpl and VLDL-Tg excretion ↑ Microsomal TG transfer proteins	–	–	–

(**Table 1:** Continued)

References	Genetic background	Drug and duration of treatment	Targeted tissue			
			Liver	Intestine	Adipose	Skeletal muscle
Peng et al. [97]	C57Bl6J mice	T0901317 for 4 weeks	↑ Lipid synthesis and VLDL-TG output = Lipoprotein lipase activity ↑ Lipolysis of VLDL in plasma ↑ Lipase activity in plasma	–	–	–
Caton et al. [98]	Sv/129 mice	T0901317 (5 days)	–	–	–	↑ Srebp1c and Scd1, Pgc1α during fasting
Baranowski et al. [99]	Wistar rats	T0901317 (7 days)	↑ Lipogenesis pathway = Glycogen		↑ Atgl and Hsl (lipases)	↑ Lipid oxidation and lipolysis ↑ TG ↑ Srebp1c and Scd1
Hu et al. [66]	C57Bl6J WT versus LXRα and LXRβ KO mice	High cholesterol diet+GW3965 (2 days)	–	LXRα dependent: ↑ Cholesterol absorption ↓ Fecal neutral sterol excretion Both isoform: Npc1L1 and Abcg5 expression Bile acid composition	–	–
Zhang et al. [100]	C57Bl6J WT versus LivKO-LXRα mice	HFD+T0901317 (2 days)	LivKO-LXRα mice: ↓ TG ↓ ABCG5/8 ↑ Cholesterol	↓ Biliary cholesterol in LivKO-LXRα mice = ABCG5/8 ↑ Cholesterol absorption	–	–
Baranowski et al. [101]	Wistar rats	T0901317 (7 days)	–	–	–	↑ TG and PL ↓ CE, FC and NEFA
Ducheix et al. [102]	C57Bl6J/129 WT mice	T0901317 (4 days)	↑ TG ↑ Lipogenesis	–	–	–
Gao et al. [103]	C57Bl6J WT mice	T0901317 (5 days) and/or Fenofibrate	↑ TG ↓ Gluconeogenesis	–	↓ Adipocyte size ↑ Lipid breakdown ↑ Glut4 and Abca1/g1 ↓ Plin ↑ Hsl and Atgl	–
Beaven et al. [8]	WT and LXRαβ KO C57Bl6J mice	GW3965 (10 days)	= TG ↑ Cholesterol		↓ White fat storage	
Beaven et al. [8]	Ob/Ob and LOKO (Ob/Ob LXR KO) C57Bl6J mice	GW3965 (10 days)	↓ Liver weight and TG ↑ Cholesterol ↓ Glucose output		= White fat storage ↑ Glucose uptake	↑ Insulin sensitivty

(**Table 1:** Continued)

References	Genetic background	Drug and duration of treatment	Targeted tissue			
			Liver	Intestine	Adipose	Skeletal muscle
Dib et al. [69]	C57Bl/6J AT-LXRα KO mice	T0901317 (9 days)	–	–	↑ Fat mass ↓ Lipolysis and oxidation	–
Females						
Hessvik et al. [77]	C57Bl6J WT versus LXRα and LXRβ KO mice	Culture myotubes T0901317 (2 days)	–	–	–	LXRβ regulates: – Lipogenesis – Cholesterol efflux Glucose uptake
Korach-Andre et al. [38]	C57Bl6J WT versus LXRα, LXRβ and LXRαβ KO mice	HFD (8 weeks)	↑ Cholesterol and TG		LXRβ dependent: ↑ White fat storage (VS and SC)	↑ Lipid oxidation LXRβ dependent: ↑ TG storage
Korach-Andre et al. [15]	C57Bl6J WT versus LXRαβ KO mice	ND and HCD (3 weeks)	↓ Gluconeogenesis ↓ Glycogen storage ↓ Lipid storage	↓ PPARα expression = Glucose transporters	↓ VS fat ↑ Lipogenesis and lipolysis (ND) ↑ Lipogenesis and ↓ lipolysis (HCD)	↑ Energy expenditure ↓ LXR target gene (Srebp1c)
Korach-André et al. [2]	C57Bl6J WT versus LXRα, LXRβ and LXRαβ KO mice	ND and HCD+GW3965 (3 weeks)	–	–	LXRα and LXRβ control UCP1 and GLUT 4 expression in brown adipose ↓ UCP1 expression with GW3965 ↑ UCP1 expression in VS adipose of LXRα KO mice ↓ TG in LXRβ KO mice only	↑ Energy expenditure in LXRαβ KO mice ↑ Glucose and lipid oxidation in LXRαβ KO mice
Sheng et al. [75]	C57Bl6J WT mice	HFD+Rhein	↓ LXR target genes of lipid pathway	–	↓ LXR target genes of lipid pathway ↑ UCP1 expression in brown adipose	↓ LXR target genes of lipid pathway
Fan et al. [104]	C57Bl6J WT mice	HFD+Kunding Tea (LXRβ antagonist)	↑ Insulin sentivity ↓ TG storage = Cholesterol ↓ Lipogenic genes	–	–	–
Archer et al. [1]	C57Bl6J WT versus LXRα and LXRβ KO mice	GW3965 (5 weeks)	LXRα and LXRβ control of: TG storage TG lipase expression ↓ Gluconeogenesis with GW3965	–	LXRβ repressor of lipolysis lipogenesis LXRα regulation of lipolysis	↑ Energy expenditure with GW3965 ↑ Lipid oxidation with GW3965 ↓ TG and cholesterol storage

(**Table 1:** Continued)

References	Genetic background	Drug and duration of treatment	Targeted tissue			
			Liver	Intestine	Adipose	Skeletal muscle
Sex not defined						
Zheng et al. [73]	C57Bl6J WT mice	T0901317 (3 weeks)	↓ Insulin sensitivity	–	↓ Adiponectin signalling ↓ Fat mass ↓ Adipocyte size	–
Hong et al. 2014 [43]	SV129/C57Bl6J WT mice	GW3965 (3 days)	= LDLR level	↑ ABCA1 and ↓ LDLR in peritoneal macrophages	–	–

The role of LXR as an activator ↑ or a repressor ↓ of metabolic pathway involved in glucose and lipid metabolism. When no effect of LXR is reported it is marked as =. When experiments are reported on WT versus KO animals, the role of LXR is reported as changes compared to WT (control) animals.
TG, CE, FC for triglycerides, cholesterol ester and free cholesterol, respectively. NEFA and PL for none-esterified fatty acids and phospholipids, respectively. LDLR for low density lipoprotein receptors. ND, HFD and HCD for normal chow diet, high fat diet and high carbohydrate diet, respectively.

between type-2 diabetic patients and healthy controls (10, 76).

Muscat et al. first showed that well-known LXR target genes of cholesterol and lipogenic pathways were upregulated in rodent quadriceps SM and in cultured myotubes after treatment with T0901317 (22), and LXRβ appears to have a dominant role in the control of the lipogenic pathway (1). Hessvik et al. supported the idea of an LXRβ-specific effect in the regulation of TG in SM (77), and we showed that LXRβ is required for lipid accumulation in the SM on HFD (38). In line with this, lipogenesis was increased by 30% in cultured myotubes of LXRα KO and WT mice after exposure to T0901317, but not in LXRβ KO mice. Accordingly, chronic (5-week) GW3965-LXR activation largely induced *Srebp1c* expression in WT and LXRα KO mice only (1). As SREBP1C is the limiting step of the lipogenesis pathway in SM, these observations would propose LXRβ as one of the key actors in the control of TG synthesis in SM through *Srebp1c* regulation. In human myotubes, chronic treatment with T0901317 increases cellular uptake of palmitate as well as cellular uncoupling in both control and T2D patients (76). In line with Muscat et al., we and others demonstrated that chronic LXR activation *in vivo* for 5 weeks reduced cholesterol content in mouse SM (1, 77). We established that this reduction appeared in WT, LXRα KO, and LXRβ KO mice, indicating that both isoforms play a major role in RCT in SM.

All together, these data support SM as an interesting organ to modulate lipid and glucose metabolism using LXR as a target. The two LXR isoforms may have different functions in SM, and further studies would be necessary to clarify the role of each isoform in this regulation. While the absence of LXRα promotes lipid oxidation in SM, LXRβ has been shown to be required for TG storage in the SM in mice, making both LXRs decisive elements of lipid homeostasis in SM. The development of a tissue-selective LXR agonist in SM would be of great interest in a cell type that accounts for about 40% of human total body weight.

LXR function: sex differences

Most of the experiments reported in literature utilize males, both for rodents and humans. In Table 1, we report the results from experiments performed in rodents regardless of genetic background, sex, and drug used to target LXR in metabolic diseases. It is obvious that 90% of the studies are done in males and that males and females show important differences in response to obesity, metabolic syndrome, and to environmental factors (diet, drugs…). Androgen deprivation has been shown to improve insulin

sensitivity in males (78), while 17β-estradiol (E2) treatment prevents fat storage in females (79). Conversely, androgen therapy has been shown to improve insulin sensitivity in men (80, 81). In both male and female rats, E2 reduced food intake and induced energy expenditure resulting in a reduction of body weight gain (82). Estrogen receptor α (ERα) seems to be a key factor for liver insulin sensitivity, and in male mice lacking ERα, there is insulin resistance in the liver. In addition, both male and female ERα KO mice show increased adiposity (83). Women generally have more body fat than males and a higher proportion of fat in the gluteal-femoral region (84), while males accumulate more fat in the abdominal/visceral region and, thereby, are more susceptible to obesity-associated metabolic diseases. After menopause, when estrogen level decreases, an increased visceral fat depot is observed, while hormone replacement therapy decreases adipose mass (85–88). These observations suggest a key role of estrogens in lipid distribution and metabolism homeostasis. In rodents, E2 treatment opposes obesity in both males and females (83) and reduces food intake, increases lipolysis and physical activity (89–91).

One interesting relationship that has not yet been fully addressed is the interaction between estrogen receptors and LXR in regulation of obesity and metabolic syndrome. LXRα is downregulated by estrogen (92): in ovariectomized mice, E2 treatment resulted in repression of LXRα expression and several of its target genes.

We conclude that gender differences in regulation of LXR and its control of metabolic pathways is one factor that has to be considered by pharmaceutical companies, which pursue the goal of developing drugs to treat obesity and associated metabolic diseases.

Conclusions

LXRs were initially characterized as nuclear regulators of cholesterol and TG homeostasis in liver. Basic research on LXR has increased the interest in pharmacological manipulation of LXR for human health. Efforts made to modulate LXR pathways using ligand and/or KO animals showed LXR as a promising target in the treatment of metabolic diseases. However, metabolic pathways are highly integrated, and therefore, perturbations of one pathway may cause compensatory or complementary responses of another pathway. It is, therefore, not surprising that LXRs are now well recognized to influence numerous aspects of physiology. In addition to controlling sterol metabolism, LXR modulates fatty acid and carbohydrate metabolism in several tissues, and LXR pathways have the potential to become pharmaceutical targets for the treatment of metabolic disorders including diabetes and obesity, as well as atherosclerosis and inflammation. However, further studies are required to better understand the tissue-specific effects of LXR pathways in order to eliminate potential side effects. In addition, a more detailed understanding of the mechanisms underlying the effects of LXR agonists in different cell types may allow the development of agonists with tissue-selective effects on beneficial metabolic pathways. Finally, in many studies, LXRα and LXRβ have been demonstrated to have opposite and/or different roles in regulating metabolic pathways, making the development of LXR-isoform-specific modulators an important aim in the perspective of using LXR as a future therapeutic target in metabolic diseases.

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List of abbreviations

LXR	liver X receptors
TG	triglyceride
RCT	reverse cholesterol transport
ABC	ATP-binding cassette
APO	apolipoproteins
LPL	lipoprotein lipase
KO	knockout
SREBP1c	sterol regulatory binding transcription factor 1
GLUT	glucose transporter
PPAR	peroxisome proliferator-activated receptor
Cyp7a	cholesterol 7-α-hydroxylase
PEPCK	phosphenolpyruvate carboxykinase
TICE	trans-intestinal cholesterol pathway
SC	subcutaneous
VS	visceral
WAT	white adipose tissue
ATGL	adipose triglyceride lipase
HSL	hormone sensitive lipase
PLIN	perilipin
BAT	brown adipose tissue
UCP	uncoupling protein
NPC1L1	Niemann-Pick C1-Like 1
DiO2	type II iodothyronine deiodinase
HK	hexokinase
L-PK	liver-pyruvate kinase
CHREBP	carbohydrate responsive element-binding protein
HFD	high fat diet
HCD	high carbohydrate diet
SM	skeletal muscle
E2	17β-estradiol

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