Liver X receptor in cholesterol metabolism

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Abstract

The liver X receptors (LXRs) are nuclear receptors that are activated by endogenous oxysterols, oxidized derivatives of cholesterol. There are two isoforms of LXR, LXR\(\alpha\) (NR1H3) and LXR\(\beta\) (NR1H2). Both LXR\(\alpha\) and LXR\(\beta\) regulate gene expression by binding to DNA sequences associated with target genes as heterodimers with isoforms of the retinoid X receptor (RXR), RXR\(\alpha\) (NR2B1), RXR\(\beta\) (NR2B2), and RXR\(\gamma\) (NR2B3). LXRs act as cholesterol sensors: when cellular oxysterols accumulate as a result of increasing concentrations of cholesterol, LXR induces the transcription of genes that protect cells from cholesterol overload. In this review, we summarize the roles of LXRs in controlling cholesterol homeostasis, including their roles in bile acid synthesis and metabolism/excretion, reverse cholesterol transport, cholesterol biosynthesis and uptake, and cholesterol absorption/excretion in the intestine. The overlapping and distinct roles of the LXR\(\alpha\) and LXR\(\beta\) isoforms, and the potential use of LXRs as attractive targets for treatment of cardiovascular disease are also discussed.

Journal of Endocrinology (2010) 204, 233–240

Liver X receptor

The liver X receptors (LXRs), LXR\(\alpha\) (NR1H3) and LXR\(\beta\) (NR1H2), belong to the nuclear receptor superfamily of ligand-activated transcription factors (Janowski et al. 1996). LXR\(\alpha\) was initially isolated from a rat liver cDNA library (Apfel et al. 1994) as a novel orphan nuclear receptor, i.e. receptors with no known physiological ligands, hence the name LXR. Several groups identified the LXR\(\beta\) isoform by screening of different cDNA libraries (Shinar et al. 1994, Song et al. 1994, Teboul et al. 1995). The human LXR\(\alpha\) gene is located on chromosome 11p11.2, while the human LXR\(\beta\) gene is located on chromosome 19q13.3. LXR\(\alpha\) expression predominates in metabolically active tissues such as the liver, small intestine, kidney, macrophages, and adipose tissue, whereas LXR\(\beta\) is more ubiquitously expressed with particularly high levels in the developing brain (Fan et al. 2008), suggesting regulation of different physiological functions for the two receptors. Human LXR\(\alpha\) and LXR\(\beta\) share almost 80% amino acid identity in their DNA-binding domain and ligand-binding domain. The LXR paralogs are highly conserved between rodents and humans. Human LXR\(\alpha\) and rat LXR\(\alpha\) show close to 100% homology in amino acid sequence in their DNA-binding domain and ligand-binding domain (Lee et al. 2008).

With the discovery of oxysterols (Janowski et al. 1996, 1999) as endogenous ligands for LXRs, these receptors were included in the group of ‘adopted’ nuclear receptors, i.e. receptors where a physiological ligand has been identified subsequent to the identification of the receptor. Oxysterols, oxidized derivatives of cholesterol including 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, 24(S),25-epoxycholesterol, 20(S)-hydroxycholesterol, and 27-hydroxycholesterol, are ligands for LXRs. Among them, 24(S),25-epoxycholesterol is the most potent agonist. It has been demonstrated that these oxysterols bind directly to the LXRs with \(K_{d}\) values ranging from 0.1 to 0.4 \(\mu\)M. LXR\(\alpha\) and LXR\(\beta\) show similar affinities for these compounds (Janowski et al. 1999). However, cholesterol itself is not a ligand for LXRs (Janowski et al. 1999). Recently, high concentrations of D-glucose and phytosterols, particularly \(\beta\)-sitosterol, were reported to be activators of LXRs (Plat et al. 2005, Mitro et al. 2007a). A subset of natural bile acids has been reported to selectively activate LXR\(\alpha\) (Song et al. 2000), whereas \(N\)-acylthiadiazolines have selectivity for LXR\(\beta\), however with modest potency (Molteni et al. 2007). Recently, a phenethylphenyl phthalimide derivative has been shown to be a potent LXR\(\alpha\)-selective antagonist (Motoshima et al. 2009). As regulators of metabolism, LXRs have been considered as potential drug targets by the pharmaceutical industry, and synthetic LXR ligands have been developed, which are widely used as tools in biomedical research. Synthetic LXR ligands include T0901317 (Schultz et al. 2000) and GW3965 (Collins et al. 2002). In general, these synthetic ligands show
poor LXR subtype selectivity. The use of T0901317 as an LXR ligand is limited by its agonistic effect on farnesoid X receptor (Houck et al. 2004) and pregnane X receptor (Mitro et al. 2007b).

Transcriptional regulation by LXR

LXRs activate target genes by binding to DNA sequences associated with target genes. LXRs bind to consensus elements (LXR response elements, LXREs) as heterodimers with isoforms of the retinoid X receptor (RXR), RXRα (NR2B1), RXRβ (NR2B2), and RXRγ (NR2B3) (Makishima 2006). LXRE consists of two direct repeats (DR) of the consensus sequence AGGTCA separated by four nucleotides (DR–4) (Chawla et al. 2001). Inverted repeat of the same consensus sequence with no spacer region (IR–0) and inverted repeat of the same consensus sequence separated by 1 bp spacer (IR–1) have also been shown to mediate LXR transactivation (Mak et al. 2002, Uppal et al. 2007). LXRs have been shown to regulate gene expression via LXREs in the promoter regions of LXR target genes such as UDP glucuronosyltransferase 1 family, polypeptide A3 (UGT1A3; Verrecaut et al. 2006), fatty acid synthase (Joseph et al. 2002a), carbohydrate response element binding protein (Cha & Repa 2007), phospholipid transfer protein (PLTP; Mak et al. 2002), and sterol regulatory element binding protein 1c (Repa et al. 2000a, Yoshikawa et al. 2001). LXREs have also been reported to be present in introns of target genes such as the ATP-binding cassette transporter G1 (ABCG1; Kennedy et al. 2001, Sabol et al. 2005). LXRs have been shown to activate gene expression via the IR–1 sequence for genes such as the human ileal bile acid-binding protein and the organic solute transporter (Landrier et al. 2003, Okuwaki et al. 2007). LXRs induce expression of the mouse Sult2a9 gene through binding to an IR–0 sequence in the promoter (Uppal et al. 2007). Recently, Wang et al. (2008) have proposed a novel mode of regulation by LXR in which LXR represses gene expression via negative LXR DNA response elements present in the gene promoters.

Cholesterol metabolism

Cholesterol is the essential precursor of steroid hormones (progesterone, estrogen, testosterone, glucocorticoids, and mineralocorticoids), bile acids, and vitamin D. It is also a vital constituent of cell membranes, which modulates the fluidity and permeability of the membrane. Cholesterol can be derived from the diet as well as from endogenous biosynthesis, the latter being the major source in humans. Homeostasis of cholesterol involves the movement of cholesterol between peripheral tissues and the liver. The liver regulates de novo biosynthesis of cholesterol, the excretion of cholesterol into bile (directly or after conversion to bile acids), the secretion of cholesterol into blood as very low-density lipoproteins (VLDL), the modulation of receptor-mediated cellular cholesterol uptake, the formation of cholesteryl esters, which are more hydrophobic than cholesterol itself, and the storage of cholesterol. The intestine regulates cholesterol absorption and excretion into feces.

LXR as cholesterol sensors

LXRs act as cholesterol sensors: when cellular oxysterols accumulate as a result of increasing concentrations of cholesterol, LXR induces the transcription of genes that protect cells from cholesterol overload. LXR activation regulates bile acid synthesis and metabolism/excretion, reverse cholesterol transport (RCT), cholesterol biosynthesis, and cholesterol absorption/excretion in the intestine (see Fig. 1).

Figure 1 Role of LXR in cholesterol metabolism. In the liver, cholesterol biosynthesis/exflux and bile acid metabolism/excretion are all regulated by LXR. LXR increases efflux in the peripheral tissues, and in the intestine, LXR decreases absorption and increases fecal excretion. See text for details. Boxes represent LXR target genes, HDL-C, high-density lipoprotein cholesterol; ABC, ATP-binding cassette transporters; ApoE, apolipoprotein E; PLTP, phospholipid transfer protein; UGT1A3, UDP glucuronosyltransferase 1 family, polypeptide A3; CYP7A1, cholesterol 7α-hydroxylase; FDFT1, farnesyl-diphosphate farnesyltransferase 1; CYP51A1, cholesterol 14α-demethylase; ABCG5/G8, ABCG5/G8; NPC1L1, Niemann-Pick C1-like 1.
**LXR and bile acid synthesis, metabolism, and excretion**

Bile acid synthesis and secretion constitute the major route for elimination of cholesterol from the body. Oxysterols, natural ligands for LXRa, are generated when cholesterol levels are high. The classical pathway of bile acid synthesis is initiated by 7α-hydroxylation of cholesterol catalyzed by the cytochrome P450 cholesterol 7α-hydroxylase (CYP7A1), which encodes the rate-limiting enzyme of this pathway (Russell & Setchell 1992). In rodents, LXRα stimulates the expression of CYP7A1 via binding to an LXRE present in the CYP7A1 promoter. Thus, rats and mice have the capacity to convert dietary cholesterol into bile acids (Peet et al. 1998). As a consequence, these species quickly adapt to a diet rich in cholesterol by increasing its conversion to bile acids. The importance of LXRα activated CYP7A1 in regulating cholesterol balance in the rodent liver became evident from studies of LXRα knockout mice (Peet et al. 1998). LXRα, but not LXRβ (Alberti et al. 2001), knockout mice accumulate large amounts of cholesterol esters in the liver after being fed a high-fat cholesterol diet due to failure of inducing expression of the CYP7A1 gene.

In contrast to observations in rats and mice, LXRα agonist treatment suppresses the expression of CYP7A1 in primary human hepatocytes (Goodwin et al. 2003). This repression is, at least in part, due to the direct induction of small heterodimer partner, a gene that has a repressive effect on CYP7A1 via liver receptor homolog 1 (LRH1; also called FIF in rat and CPF in humans; Goodwin et al. 2000). These results suggest that different species may employ distinct molecular strategies to regulate cholesterol homeostasis, emphasizing the importance of valid experimental models for the development of pharmaceuticals for human use.

In addition to its role in controlling bile acid anabolism, LXR also plays a role in regulating bile acid catabolism. Recent reports indicate that ligand-activated LXRα upregulates human UGT1A3 gene expression through binding to an LXRE-like sequence in the promoter (Barbier et al. 2009). UGT1A3 is one of the most active enzymes for glucuronidation conjugation of bile acid. Bile acid glucuronidation allows their conversion into urinary excretable metabolites. Based on these observations, it was proposed that LXRα activation may facilitate definitive cholesterol elimination in the form of urinary bile acid glucuronides.

Most bile acids are N-acyl amidates with glycine or taurine to decrease toxicity and increase solubility for secretion into bile (Hofmann 1999). Taurine occurs naturally in many foods and is known to lower cholesterol profiles (Chen et al. 2004, Zhang et al. 2004). Additionally, taurine has been shown to induce CYP7A1 activity thereby increasing bile acid synthesis (Yokogoshi et al. 1999). Interestingly, it has been shown that taurohodeoxycholic acid can activates the LXRE in the CYP7A1 promoter via LXRα, suggesting that activation of LXR signaling is one mechanism by which taurine activates CYP7A1 activity (Song et al. 2000).

Excretion of free cholesterol into the bile is another major route for eliminating excess cholesterol from the liver. In the liver, ABCG5 and ABCG8 have been proposed to transport cholesterol from hepatocytes to the bile canalculus. ABCG5 and ABCG8 are half transporters that form obligate heterodimers, and are both regulated by LXR activation (Berge et al. 2000, Repa et al. 2002). ABCG5 and ABCG8 are expressed in the apical membrane of enterocytes and at the canalicular membrane of hepatocytes. These transport proteins promote secretion of hepatic cholesterol into bile. Mice lacking ABCG5 or ABCG8 exhibit profound reduction in biliary cholesterol levels and an accumulation of cholesterol in the liver after cholesterol feeding (Yu et al. 2002). Mutations in the genes encoding either ABCG5 or ABCG8 result in β-sitosterolemia, an autosomal recessive disorder characterized by an increased risk of atherosclerosis and elevated plasma levels of phytosterols (Lee et al. 2001, Lu et al. 2001). The human ABCG5 and ABCG8 genes are oriented in a head-to-head configuration separated by a 374-bp intergenic region. No LXREs have been identified in the promoters of ABCG5 or ABCG8, but the intergenic region was found to act as a bidirectional promoter and be partially responsive to treatment with LXR agonists (Remaley et al. 2002).

**LXR and RCT**

RCT is a pathway by which accumulated cholesterol is transported from peripheral tissues to the liver followed by biliary secretion and subsequent disposal via the feces. High-density lipoprotein (HDL) cholesterol is believed to play a key role in the process of RCT, as it promotes the efflux of excess cholesterol from peripheral tissues and returns it to the liver for biliary excretion. Accumulation of cholesterol in macrophages in the vessel wall is considered a primary event in the development of atherosclerosis and, therefore, removal of excess cholesterol from these cells is important for prevention and/or treatment of atherosclerotic cardiovascular diseases.

LXR, by regulating expression of several genes including ABCA1, ABCG1, apolipoprotein E (APOE), and PLTP, plays a critical role in RCT. LXR activation increases cholesterol efflux important for RCT from peripheral tissues and has antiatherogenic potential by inhibiting the progression of and even promoting the regression of atherosclerosis in mice (Joseph et al. 2002b, Levin et al. 2005, Naik et al. 2006). Consequently, the development of pathway-selective LXR agonists represents an attractive therapeutic approach for atherosclerosis.

ABCA1 was initially found to be induced by pharmacological activation of LXR with T0901317 (Repa et al. 2000b), and later an LXRE was identified in this gene (Costet et al. 2000). ABCA1 is expressed at the basolateral membrane of the enterocyte, in hepatocytes and in macrophages. ABCA1 mediates transport of phospholipids and cholesterol to lipid-poor apolipoproteins such as apo-A1, apo-AII, apo-CIII, and apo-E, which are then transferred to HDL for delivery to the liver (Chiang et al. 2003). ABCA1 is also responsible for the efflux of cholesterol from the liver to HDL, known as the reverse cholesterol transport (RCT) pathway, which represents a major route for eliminating excess cholesterol from these cells.
which stabilizes the HDL particle and is thus responsible for the initial step of RCT. Accordingly, overexpression of hepatic ABCA1 raises HDL cholesterol levels (Basso et al. 2003, Wellington et al. 2003). Studies in mice with tissue-specific knockout of ABCA1 revealed that hepatic and intestinal ABCA1 contributes 80 and 20% respectively to HDL biogenesis in mice (Timmins et al. 2005, Brunham et al. 2006). ABCA1 is important for macrophages to regulate sterol homeostasis. In support of this, ABCA1 knockout mice show evidence of cholesterol accumulation in a variety of macrophage-rich tissues including lung, spleen, lymph nodes, thymus, and skin (Christiansen-Weber et al. 2000, McNeill et al. 2000). Recently, macrophage-specific knockout of ABCA1 in mice was shown to lead to an increase in free and esterified cholesterol in macrophages, and enhanced inflammatory responses (Zhu et al. 2008). Overexpression of ABCA1 in macrophages in VLDL receptor knockout (LDLR<sup>−/−</sup>) mice inhibits atherosclerotic lesion progression and exerts a protective role against atherosclerosis with minimal effects on plasma HDL (Van Eck et al. 2006).

ABCG1 expression is also induced by LXR activation, and LXREs have been identified in the promoter region of this gene (Kennedy et al. 2001, Sabol et al. 2005). Studies in ABCG1 knockout mice revealed that ABCG1 is primarily expressed in macrophages, endothelial cells, and lymphocytes. However, it is also found in Kupffer cells and hepatocytes (Kennedy et al. 2005). Based on the observation that ABCG1 knockout mice fed a high-fat and high-cholesterol diet accumulate considerable amounts of cholesterol and neutral lipids in macrophages and liver, it was proposed that ABCG1 plays an important role in cholesterol efflux (Kennedy et al. 2005). In contrast to ABCA1 that transports cholesterol to lipid-poor apolipoproteins, ABCG1 transports cholesterol to phospholipid-containing acceptors such as HDL. A synergistic relationship between ABCA1 and ABCG1 has been proposed. ABCA1 promotes lipidation of lipid-poor particles and generates acceptors for ABCG1-mediated cholesterol efflux (Gelissen et al. 2006).

APOE has been shown to be up-regulated by LXR activation through its direct interaction with LXREs present in the enhancers of this gene (Laffitte et al. 2001). Secretion of APOE promotes incorporation of cholesterol into the lipid-poor HDL particles. In agreement with this, a massive accumulation of lipoproteins and lipoprotein remnants has been observed in the plasma of both humans and mice lacking functional APOE (Plump et al. 1992, Zhang et al. 1992). APOE is also an important modulator of atherogenesis. This is supported by findings that Apoe<sup>−/−</sup> mice develop atherosclerosis on a normal chow diet (Reddick et al. 1994) and that selective re-expression of Apoe in macrophages of Apoe<sup>−/−</sup> mice through bone marrow transplantation or transgenic expression decreases atherosclerosis (Zhu et al. 1998).

PLTP is a target for LXR activation in the liver and in macrophages (Laffitte et al. 2003). It has been proposed that plasma PLTP facilitates the transfer of phospholipids and cholesterol from triglyceride (TG)-rich lipoproteins (TRL) into HDL. PLTP is capable of generating pre β-HDL through HDL conversion. The generation of pre β-HDL particles, a very efficient acceptor of peripheral cell cholesterol, enhances cholesterol efflux from peripheral cells (Lee et al. 2003). These results suggest that PLTP is important for the prevention of atherosclerosis. Consistent with the proposed role for PLTP in lipoprotein metabolism, the plasma of PLTP knockout mice showed a complete inability to transfer phospholipids from TRL into HDL both in vitro and in vivo (Jiang et al. 1999). In a transgenic mouse model engineered to overexpress human PLTP, there is a 30–40% decrease in plasma levels of HDL cholesterol compared to wild-type mice. In addition, these mice showed an increased capacity to produce pre β-HDL (van Haperen et al. 2000). Moreover, plasma from these animals prevents accumulation of intracellular cholesterol in macrophages more efficiently than plasma from wild-type mice. These results suggest that PLTP is mediating an increase in cholesterol efflux.

**LXR and cholesterol biosynthesis**

Recently, Wang et al. (2008) demonstrated that LXR<sub>α</sub> negatively regulated two genes, squalene synthase (FDFT1) and lanosterol 14α-demethylase (CYP51A1), which encode key enzymes in the cholesterol biosynthesis pathway. LXREs that confer LXR-mediated repression were identified in these two genes. Based on these observations, it was proposed that LXR<sub>α</sub> plays an important role in suppression of cholesterol biosynthesis.

**LXR and cholesterol uptake**

The major part of cholesterol in human blood is transported within LDL-C. The LDLR mediates the removal of LDL and remnant lipoproteins from circulation by binding to apolipoprotein B-100 (APOB-100) and APOE. It also plays a major role in regulation of plasma cholesterol levels in humans (Brown & Goldstein 1986). Recently, Zelcer et al. demonstrated that LXR decreases LDLR-dependent cholesterol uptake through a LXR-Idol (inducible degrader of the LDLR) pathway. LXR induces the expression of Idol, which in turn catalyzes the ubiquitination of the LDLR, thereby targeting it for degradation (Zelcer et al. 2009). On the contrary, induction of LDLR expression via an LXRE by LXR agonist has been reported by Ishimoto et al. (2006). The use of different cell lines and different LXR agonists in the two studies may account for the contradictory results. Clearly, the exact role of LXR in regulation of LDLR expression and subsequent cholesterol uptake needs to be further explored.

**LXR and intestinal cholesterol absorption**

Intestinal cholesterol absorption has been shown to be a major determinant of plasma cholesterol levels. LXR activation results in a reduced absorption of intestinal cholesterol by regulating expression of several genes such as heterodimeric
ABCG5/ABCG8 and Niemann-Pick C1-like 1 (NPC1L1) involved in this process. LXR activation increases the expression of both ABCG5 and ABCG8, which transport absorbed cholesterol back to the lumen of the intestine. Consistent with this finding, administration of LXR agonists substantially decreases intestinal net cholesterol absorption in mice.

NPC1L1 is expressed in the small intestine, most likely in the brush border membrane of enterocytes, and it is required for intestinal cholesterol absorption (Altmann et al. 2004). It was recently reported that LXR activation downregulates NPC1L1 expression in both mice and in a human enterocyte cell line (Duval et al. 2006).

**LXR and fecal neutral sterol excretion via intestine**

Activation of LXR in mice leads to enhanced fecal neutral sterol loss (Ploshch et al. 2002). Recent studies have revealed a major contribution of the intestine in excretion of cholesterol. In a study by Kruit et al. (2005), increased fecal neutral sterol excretion by LXR activation was observed in both wild-type mice and in Mdr2−/− mice, which are unable to secrete cholesterol into bile. These results suggest that an important part of excess cholesterol is excreted directly via the intestine. In addition, recent studies by van der Veen et al. (2009) have revealed that transintestinal cholesterol excretion is a major route for removal of blood-derived free cholesterol in mice, and this process is stimulated by activation of LXR upon treatment with T0901317. Moreover, ABCG5 knockout mouse show evidence of impaired transintestinal cholesterol excretion, suggesting that ABCG5/ABCG8 heterodimers are involved in this pathway.

**LXRs as therapeutic targets**

As described above, LXRs function as cholesterol sensors with important roles in regulating cholesterol homeostasis, and thus there is a widespread interest in the development of synthetic LXR ligands as therapeutic agents. Indeed, the abundant expression of the LXRα protein in macrophages present in human atherosclerotic lesions supports the hypothesis that LXRα agonists could have a beneficial effect against development of atherosclerosis (Watanabe et al. 2005).

Recently, synthetic LXR ligands have been characterized in several animal models for the treatment of atherosclerosis. In a study by Joseph et al. (2002b), the influence of a nonsteroidal LXR agonist GW3965 on the development of atherosclerosis was investigated in both Ldlr−/− and Apoe−/− mice. The results showed that GW3965 inhibits the development of atherosclerotic lesions in both murine models, providing direct evidence for an atheroprotective effect of LXR agonists. In the study by Terasaki et al. (2003), T0901317, a synthetic LXR ligand, was administered to LDLR−/− mice. T0901317 significantly reduced the atherosclerotic lesions in LDLR−/− mice without affecting total plasma cholesterol levels. Moreover, an agonist for RXR, the obligate heterodimeric partner of LXRs, has been shown to be effective in reducing atherosclerosis (Claudel et al. 2001). These results suggest that LXR ligands may be useful therapeutic agents for the treatment of atherosclerosis. However, this therapeutic strategy needs to address that LXR activation is associated with stimulation of lipogenesis resulting in increased plasma TG levels and hepatic steatosis. Several in vivo studies have shown that rodents treated with T0901317 have massive TG accumulation in the liver and increased plasma TG levels (Repa et al. 2000a, Schultz et al. 2000, Greffhorst et al. 2002). The LXR agonist, GW3965, also increases hepatic TG levels in mice (Greffhorst et al. 2005). Interestingly, a potent synthetic steroidal LXR activator, N,N-dimethyl-3b-hydroxy-chole-namide (DMHCA), has recently been demonstrated to reduce atherosclerosis in ApoE-deficient mice, without inducing hepatic and plasma TG levels. Based on these observations, DMHCA could be a candidate for further development as a therapeutic agent for treatment of atherosclerosis (Kratzer et al. 2009).

**Specific roles of LXR isoforms in cholesterol metabolism**

Isoform-specific knockouts have yielded valuable information on individual physiological roles of the LXRα and LXRβ isoforms. LXRα−/− mice challenged with high-cholesterol diets fail to induce CYP7A1 expression, and as a result, accumulate large amounts of cholesterol esters in the liver (Peet et al. 1998, Alberti et al. 2001). Moreover, a recent report demonstrates that on a high-fat diet, more cholesterol was accumulated in the liver of LXRα−/− and LXRβ−/− mice than in wild-type and LXRβ−/− mice (Korach-Andre et al. 2009). These studies suggest that in the liver, conversion of cholesterol to bile acids is controlled by LXRα. Although LXRβ is also expressed in the liver, its presence does not rescue the loss of LXRα in these mice. This is in line with literature showing that hepatic CYP7A1 and several genes involved in cholesterol metabolism were not induced in the liver of LXRα−/− mice treated with LXR ligands (Quinet et al. 2006).

Several studies have addressed specific roles of the LXRα and LXRβ isoforms in atherosclerosis. The work from Schuster et al. (2002) demonstrates that either receptor can play an atheroprotective role in macrophages and that the combined deficiency of both LXRα and LXRβ is required for foam cell-lipid accumulation in aortic lesions. Lund et al. (2006) found that a synthetic compound, which activates both LXRα and LXRβ, induced ABCA1 expression and stimulated cholesterol efflux in macrophages from both LXRα−/− and LXRβ−/− mice. Moreover, treatment with an LXR agonist reduced atherosclerosis in Apoe−/−/LXRα−/− mice, suggesting that LXRβ alone is sufficient to mediate the antiatherogenic functions of LXR activation.
(Bradley et al. 2007). One potential problem with LXRα/β agonists for treatment of atherosclerosis is their detrimental lipogenic effects dominated by LXRα. The overlapping and differential roles of LXRα and LXRβ imply that LXRβ-selective targeting may separate the antiatherogenic and hypertriglyceridemic effects of the current dual agonists.

Conclusions

Studies in recent years have significantly enhanced our understanding of the molecular mechanisms of LXR signaling as an important global regulator of cholesterol homeostasis. The recent progress in the development of novel LXR ligands that reduce atherosclerosis, without displaying induction of nondesired effects observed by previous generations of LXR agonists, such as liver lipogenesis, show therapeutic promise for treatment of cardiovascular diseases. The future development of LXR subtype-specific ligands would provide critical tools for defining the mechanisms of distinct roles of LXRα and LXRβ, and might provide drug candidates with improved therapeutic profiles. Additionally, the development of novel ligands that possess tissue-specific agonist/antagonist properties provides another promising avenue for drug discovery.

Declarations of interest

We have no specific funding for writing this review and no conflict of interest.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received in final form 14 October 2009
Accepted 16 October 2009
Made available online as an Accepted Preprint 16 October 2009

C ZHAO and K DHALMEN-WRIGHT • LXR in cholesterol metabolism


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