Liver X Receptor Agonists as Potential Therapeutic Agents for Dyslipidemia and Atherosclerosis

Erik G. Lund, John G. Menke, Carl P. Sparrow

Abstract—The recent identification of liver X receptors (LXR) as regulators of the cholesterol and phospholipid export pump ABCA1 has raised the possibility that LXR agonists could be developed as HDL-raising agents, possibly also acting on the artery wall to stimulate cholesterol efflux from lipid-laden macrophages. Presently several pharmaceutical companies are working to develop such compounds, which will require finding a path for separating these beneficial effects from the detrimental stimulation of triglyceride synthesis also inherent to LXR agonists. Other challenges to the drug development process include species differences, which makes prediction of in vivo effects of LXR agonists in humans difficult. This review summarizes the present state of knowledge on LXR as a drug target and discusses possible solutions for dissociating the favorable effects of LXR agonists from their unwanted effects. (Arterioscler Thromb Vasc Biol. 2003;23:1169-1177.)

Key Words: atherosclerosis ■ liver X receptor ■ HDL ■ triglycerides

Atherosclerosis and its clinical sequelae, myocardial infarction and ischemic stroke, are a major cause of premature death and disability in the industrialized world.1 Multiple studies have shown that statins, drugs that inhibit the enzyme HMG-CoA reductase, improve clinical outcomes for patients with atherosclerosis.2 There are also reports of favorable clinical outcomes using fibrates, drugs that bind to and activate the nuclear receptor PPARα.3 Neither statins nor fibrates reduce the risk of a heart attack in dyslipidemic patients by as much as 50%, however, so there is clearly a need for additional drugs to combat atherosclerosis.

What biological effects might be desired in a new antiatherosclerosis drug? One possibility is HDL raising, which is supported by the strong epidemiological evidence linking low HDL levels to increased risk of disease.4 Although it is true that HDL raising can be achieved using fibrates5 or certain statins such as simvastatin,5 these effects are fairly modest (usually <20%). Niacin raises HDL more dramatically and has shown clinical benefits in placebo-controlled trials; however, adverse effects associated with this drug make compliance poor.6 A second desired effect of a new drug would be to act on the cells of the artery wall to directly stimulate the exit of cholesterol from existing atherosclerotic lesions; available evidence suggests that lipid-rich lesions are more prone to rupture and thereby cause myocardial infarction.7 It may be possible to induce these two desirable effects, HDL raising and cholesterol efflux, through manipulation of a single drug target, the nuclear receptor liver X receptor (LXR).

Nuclear receptors are ligand-activated transcription factors; the first members of this superfamily to be described...
element-binding protein family of transcription factors. The liability is, at least in part, mediated by LXR-induced transcription of SREBP-1c, a member of the sterol regulatory element-binding protein family of transcription factors.

Clearly the successful development of LXR agonists into pharmaceuticals will require that a favorable balance be found between the potentially beneficial effects of induction of ABCA1 and the potentially detrimental effects of induction of SREBP-1c.

**Can LXR Agonists Help When and Where They Are Really Needed?**

The great hope for LXR agonists as novel therapeutic agents is that such molecules will be able to increase expression of ABCA1 in the artery wall, leading to enhanced cholesterol efflux and resolution of the lipid overload in atherosclerotic lesions. For this hope to be realized, synthetic LXR agonists must stimulate ABCA1 expression and cholesterol efflux in artery wall cells that are already cholesterol-loaded. On first principles, however, it is not clear that it would be feasible to additionally activate LXR in foam cells. Although not universally accepted, it is generally believed that the physiological ligands of LXR are cholesterol-derived oxysterols, although the relative importance of different oxysterols in this role is still a matter of debate. Oxysterols are present in atherosclerotic plaques in such large amounts that even if only 10% are present in an unesterified form, even if hydroxycholsterol in particular seems to be present at saturating concentrations with respect to LXR activation. It is therefore conceivable that the LXRs may already be fully activated in cholesterol-loaded cells such as those found in atherosclerotic lesions in the artery wall and that no additional activation with an exogenous LXR agonist would be feasible.

We addressed this issue experimentally by studying the regulation of ABCA1 mRNA and the stimulation of cholesterol efflux in primary human monocyte-derived macrophages. We confirmed previous observations that cholesterol loading increased mRNA levels for ABCA1 (2-fold) and ABCG1 (5-fold; Table 1). The synthetic LXR agonist APD was more effective, increasing these mRNA levels by 4- and 17-fold, respectively. The combination of cholesterol loading plus APD produced changes similar to those seen with APD alone. A similar superiority of APD was seen in assays of cholesterol efflux. This work strongly implies that synthetic LXR agonists are more effective than cholesterol loading at inducing ABCA1 expression and cholesterol efflux in human macrophages. Sim-
ilar conclusions for mouse macrophages were published by Joseph et al. Joseph et al also showed that the synthetic LXR agonist GW3965 decreased atherosclerosis in mice. This promising data must be interpreted cautiously given the significant species differences in LXR-responsive genes between mice and humans (see discussion below). Nevertheless, taken together, these results suggest that LXR agonists may be effective in the treatment of human disease.

The observation that upregulation of ABCA1 expression by synthetic LXR agonists is more effective than cholesterol loading is consistent with our recent findings implicating 27-hydroxycholesterol as a major endogenous LXR ligand in human monocye-derived macrophages. We demonstrated that cholesterol loading such cells leads to the production of micromolar levels of 27-hydroxycholesterol and its metabolite cholestenic acid (another LXR agonist) with little or no concomitant formation of other suggested natural LXR ligands. Furthermore, human fibroblasts deficient in CYP27, the enzyme responsible for synthesis of 27-hydroxycholesterol, did not upregulate LXR-regulated genes on cholesterol loading. Although 27-hydroxycholesterol is a bona fide LXR ligand, the maximal activation of LXR achieved by this ligand is less than the maximal activation obtained by synthetic ligands even at saturating conditions (and data not shown), thus mirroring the effects elicited by cholesterol loading.

**Effects of LXR Agonists on Lipid Metabolism in Small Animals**

The data described above demonstrate that LXR action induces ABCA1 expression and increases cholesterol efflux in cultured cells. Several studies also showed that synthetic LXR agonists can raise plasma HDL in experimental animals. Schulz et al. found a dose-dependent increase of HDL cholesterol in C57Bl/6 mice using the LXRα/β dual agonist T0901317, a result later confirmed by Grefhorst et al. and Cao et al. We have also observed HDL elevation using structurally unrelated LXR agonists (data not shown). Interestingly, the increase in HDL cholesterol chiefly occurred in a population of large HDL particles of low abundance in untreated animals. In contrast to the effects in C57Bl/6 mice, in mice deficient for either the LDL receptor or apolipoprotein E, prolonged treatment with the synthetic LXR agonist GW3965 did not raise HDL levels. The difference could possibly be explained by the disturbances of lipid metabolism induced by the gene deletions.

Encouragingly, recent studies have implicated LXR not only in HDL formation but also in the protection of the artery wall against atherosclerosis. Bone marrow transplantation from LXR double-knockout mice into mice deficient in either the LDL receptor or apolipoprotein E, prolonged treatment with the synthetic LXR agonist GW3965 did not raise HDL levels. The difference could possibly be explained by the disturbances of lipid metabolism induced by the gene deletions.

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**Speculation on Possible Effects of LXR Agonists in Humans**

Potential effects of LXR agonists in humans are suggested by extrapolating from existing published evidence on the effects of LXR antagonists in humans. It has recently been demonstrated that n-3 fatty acids, the major constituents of fish oil, are LXR antagonists (Figure 1). Dietary n-3 fatty acids have long been known to decrease plasma triglyceride levels in humans, an effect consistent with the triglyceride-raising effects of synthetic LXR agonists described above. In general, changes in VLDL triglyceride and HDL cholesterol are inversely correlated and, accordingly, most triglyceride-lowering regimens (exercise, weight loss, niacin, and fibrates) raise HDL. Interestingly, dietary n-3 fatty acids do not change HDL significantly in humans; this failure of dietary n-3 fatty acids to increase HDL may be attributable to their antagonism of LXR, which could lead to decreased ABCA1 expression. This model is consistent with our unpublished data showing that feeding fish oil to mice decreases both serum triglyceride and HDL.

Another clue to the possible effects of LXR agonists in humans comes from the study of patients taking certain CYP3A4-inducing anticonvulsants, including phenobarbital, carbamazepine, and phenytoin. It was recently shown that patients taking these drugs have highly elevated levels of plasma 4β-hydroxycholesterol. These authors propose that this is a result of 4β-hydroxylase activity of CYP3A4. In contrast, valproic acid, another anticonvulsant, does not induce CYP3A4 and did not raise 4β-hydroxycholesterol. Interestingly, 4β-hydroxycholesterol is a relatively potent...
LXR agonist in a cell-based transactivation assay. Numerous studies have been published describing effects on plasma lipids by anticonvulsants, and although some of these studies show an increase in HDL or triglyceride by the CYP3A4-inducing drugs but not valproic acid, others do not. Nevertheless, it was recently speculated that the effects of anticonvulsants on plasma lipids were attributable to LXR activation. Although caution must be exercised in interpreting these studies, taken together with the evidence on n-3 fatty acids, it is reasonable to expect that LXR agonists will increase both HDL and triglyceride in humans. Dissociating these findings might be; however, it can reasonably be expected that LXR agonists will increase both HDL and triglyceride in humans. Dissociating this expected dual effect is the great challenge for the development of LXR agonists as new therapeutics (see discussion below).

Other possible effects of LXR agonists should also be considered. Both isoforms of LXR are expressed in the brain, and disruption of the LXR genes alters brain lipid homeostasis. In addition, a recent study demonstrated increased secretion of Aβ from neuronal cells treated with LXR agonists. In diabetic rodents, the LXR agonist T0901317 was recently shown to suppress genes involved in gluconeogenesis. Also recently, it was recently speculated that the effects of anticonvulsants on plasma lipids were attributable to LXR activation. Although caution must be exercised in interpreting these studies, taken together with the evidence on n-3 fatty acids, it is reasonable to expect that LXR agonists will increase both HDL and triglyceride in humans. Dissociating this expected dual effect is the great challenge for the development of LXR agonists as new therapeutics (see discussion below).

LXR agonists induce SREBP-1c transcription but do not suppress activation, leading to an overshoot in fatty acid synthesis. The activation of LXR can be antagonized by polyunsaturated fatty acids, which also suppress SREBP-1c processing. SREBP-1c processing.

**Figure 1.** Regulatory pathways controlling intracellular cholesterol homeostasis. As a response to low intracellular cholesterol levels, SREBP-1c and SREBP-2 are activated by proteolytic processing. The mature form of SREBP-2 activates transcription of the LDL receptor and cholesterol biosynthetic genes, including HMG-CoA reductase. Also the transcription of SREBP-2 is increased in a feedforward loop. The net result is an increase in cholesterol synthesis and import. Under conditions of cholesterol sufficiency or excess, SREBP-2 processing and cholesterol synthesis are inhibited. Instead, cholesterol loading leads to generation of oxysterols, activation of LXR, and increased transcription of ABCA1, which catalyzes efflux of excess cholesterol. LXR also stimulates the transcription of SREBP-1c precursor, but this effect can be expected to be balanced by suppressed SREBP-1c activation, and, therefore, the resulting increase in fatty acid synthesis is modest. Synthetic LXR agonists induce SREBP-1c transcription but do not suppress activation, leading to an overshoot in fatty acid synthesis. The activation of LXR can be antagonized by polyunsaturated fatty acids, which also suppress SREBP-1c processing.

**Understanding the Multiple Effects of LXR Agonists**

If we accept that LXR can detect cholesterol overload, it is possible to rationalize why LXR would increase the expression of the cholesterol pump ABCA1. More difficult to understand is why LXR activation should increase fatty acid synthesis through induction of SREBP-1c. Whereas requirement of fatty acyl-CoAs for the synthesis of cholesterol esters may provide a partial explanation, another part of the answer may reside in the proposed mechanism of action of ABCA1. According to one model, LXR-stimulated cholesterol efflux through the ABCA1 pathway requires prior formation of acceptor vesicles containing phospholipids and apo A-I. Nevertheless, the increase in fatty acid synthesis seems to exceed the requirements for the formation of phospholipid acceptor vesicles and cholesterol esters, as shown in the resulting accumulation of triglycerides.

To understand the seemingly paradoxical hyperstimulation of fatty acid synthesis by LXR, it may help to recall that the underlying cause for nonpharmacologic LXR activation in a physiological setting is cholesterol excess and to consider what other effects on cellular lipid homeostasis are induced by that state. A cell exposed to excess cholesterol responds not only by activating LXR but also by suppressing SREBP processing. The SREBP family of lipogenic transcription factors, including the LXR-regulated gene SREBP-1c, is synthesized as inactive precursors whose activation by proteolytic processing is blocked by intracellular cholesterol excess. Thus, cholesterol loading seems to modulate the expression of SREBP-1c-regulated genes by the following 2 independent and counteracting mechanisms: (1) generation of LXR agonists, which would tend to raise SREBP-1c expression; (2) suppression of SREBP-1c activation through inhibition of proteolytic processing. Thus, activation of LXR induced by cholesterol excess would not be expected to increase lipogenesis dramatically. This effect of cholesterol stands in sharp contrast to synthetic LXR agonists, which induce the transcription of the SREBP-1c gene but do not
pressed in a small number of tissues (liver, small intestine, expressed. 10 LXR/H9252 direct target ABCA1 as well as SCD through SREBP-1c. Choles-
rophages. Treatment of macrophages with 1 μmol/L of the syn-
thetic agonist APD21 for 24 hours boosts the expression of its
direct target ABCA1 as well as SCD through SREBP-1c. Choles-
terol loading with Ac-LDL (72 hours, 300 μg/mL) also increases the
expression of ABCA1, although to a lesser degree, because
27-hydroxycholesterol, the major natural LXR ligand under these
conditions, is a partial agonist of LXR.26 Despite increased LXR
signaling, SCD expression is reduced. Combination of Ac-LDL and
APD leads to an intermediate response; however, the expression of
SCD is much suppressed compared with what is seen with APD
alone. This apparent attenuation of LXR-mediated SCD induction
by cholesterol loading can likely be explained by suppression of
SREBP processing.
suppress SREBP activation, thereby leading to an overshoot
in fatty acid synthesis. Confirmation of this model for the
excessive lipogenesis in animals treated with synthetic LXR
agonists will require immunoblot determination of the mature
and precursor forms of the hepatic SREBPs, as has been done
previously under other experimental conditions.17 A sum-
mary of these concepts is presented in Figures 1 and 2. Figure
1 is a representation of pathways pertinent to intracellular
cholesterol homeostasis, and Figure 2 is an example of
differential effects of an LXR agonist and cholesterol loading
on the expression of ABCA1 (a direct LXR target) and
stearoyl-CoA desaturase (SCD; an SREBP-1c target).

Potential Strategies for Dissociating
Antiatherosclerotic Effects From
Triglyceride Raising

Based on the evidence described above, it is reasonable to
believe that activation of LXR would decrease atherosclerosis
in humans. The challenge to drug discovery, however, is to
identify an LXR agonist that will not cause unacceptable
triglyceride accumulation. Below we shall discuss 3 potential
strategies for dissociating the HDL- versus triglyceride-raising
properties of LXR agonists.

1. LXRβ-Selective Agonists

Evidence from gene expression studies in LXR knockout
mice suggests that it may be possible to dissociate the
HDL-raising effects from the triglyceride-raising effects of
LXR agonists by identifying LXRβ-selective agonists, ie,
compounds that selectively bind and activate LXRβ but not
LXRα. The 2 LXR subtypes, LXRα and LXRβ, have very
similar sequences but probably do not play identical roles in
vivo, as judged by their pattern of expression and the
phenotypes of the knockout mice. LXRα is strongly
expressed in a small number of tissues (liver, small intestine,
adipose, and macrophages), whereas LXRβ is ubiquitously
expressed.10 LXRα knockout mice, but not LXRβ knockout
mice, massively accumulate hepatic cholesterol on cholester-
ol of feeding.52,53 No observable phenotype has yet been as-
cribed to LXRβ knockout mice.

LXRα knockout mice show reduced plasma triglyceride
levels as well as reduced hepatic mRNA levels for multiple
enzymes of fatty acid synthesis, including fatty acid syn-
thase.52 LXRβ knockout mice do not show these effects,
implying that LXRα is the subtype most responsible for
controlling SREBP-1c transcription in liver.53 Conversely,
peritoneal macrophages from LXRβ knockout mice, but not
LXRα knockout mice, show altered basal expression of
ABCA1 mRNA,54 suggesting that LXRβ is the subtype most
responsible for controlling ABCA1 transcription in macro-
phages. The possibility that the LXR subtypes control differ-
ent genes can be rationalized by their tissue distribution,
combined with the idea that both LXR subtypes are activated
by oxysterols that signal cholesterol excess or high rates of
cholesterol synthesis. LXRα is expressed in tissues that
synthesize triglyceride. In these tissues, such as liver, a slight
excess of cholesterol could activate LXRα, leading to en-
hanced triglyceride synthesis, which would drive lipoprotein
assembly and secretion of the excess cholesterol. Conversely,
in typical extrahepatic tissues, the appropriate response to
excess cholesterol would be activation of LXRβ leading to
increased expression of ABCA1, allowing export of the
excess cholesterol. It is possible that these apparent gene
selectivities of LXRα and LXRβ can be explained by
different ratios of LXRα versus LXRβ expression in different
tissues. At present, the only bona fide gene selectivity of the
LXR subtypes that has been described is that the LXR
response element controlling the lipoprotein lipase gene
responds only to LXRα and not to LXRβ.35

Regardless of the true mechanistic origins of the apparent
gene selectivities, the observations and rationales described
above suggest the tantalizing possibility that agonists selec-
tive for LXRβ, with a low expression in liver, may offer a
solution to the triglyceride-raising problems of the LXRα/β
dual agonists that have been disclosed to date. Final proof that
LXRβ-selective agonists will be superior must await the
identification and description of such molecules. The search
for LXRβ-selective agonists may be an arduous one, how-
ever, because of the high degree of sequence identity between
the ligand-binding domains of LXRα and LXRβ (Table 2).
As shown in Table 2, the ligand-binding domain of these two
receptors are more similar to each other than most other pairs
of related nuclear receptors.

2. Sterol-Mimicking LXR Agonists

Another approach for dissociating the triglyceride-raising
from HDL-raising effects of LXR agonists is to emulate
cholesterol loading by developing compounds, perhaps ste-
roid derivatives, that not only activate LXR but also
suppresses SREBP processing. As discussed above, this
suppression of SREBP activation would be expected to counteract
the upregulation of SREBP-1c synthesis by LXR and result in
an attenuated triglyceride response compared with other LXR
agonists. However, this is a problematic approach, taking into
the account the mechanism of action of statins. This class of
drugs acts by inhibiting HMG-CoA reductase, the rate-
limiting enzyme of cholesterol biosynthesis. When the hepa-
TABLE 2. Sequence Similarities for Various Pairs of Nuclear Receptors

<table>
<thead>
<tr>
<th>Nuclear Receptor A (Ligand Selective for A&gt;B)</th>
<th>Nuclear Receptor B (Ligand Selective for B&gt;A)</th>
<th>Ligand That Binds Both A and B</th>
<th>DNA-Binding Domain, %</th>
<th>Ligand-Binding Domain, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LXRα (hypocholamidide)</td>
<td>LXRβ (none described)</td>
<td>T0901317; APD</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>PPARα (fenofibrate)</td>
<td>PPARα (GW501516)</td>
<td>F3methylIA</td>
<td>86</td>
<td>74</td>
</tr>
<tr>
<td>PPARα (fenofibrate)</td>
<td>PPARγ (rosiglitazone)</td>
<td>LY-465608</td>
<td>83</td>
<td>69</td>
</tr>
<tr>
<td>Estrogen receptor-α (PPT)</td>
<td>Estrogen receptor-β (DPN)</td>
<td>17β-Estradiol</td>
<td>96</td>
<td>60</td>
</tr>
<tr>
<td>Glucocorticoid receptor (prednisone)</td>
<td>Mineralocorticoid receptor (aldosterone)</td>
<td>Cortisol</td>
<td>93</td>
<td>56</td>
</tr>
<tr>
<td>Glucocorticoid receptor (prednisone)</td>
<td>Progestosterone receptor (progestosterone)</td>
<td>Mifepristone (RU-486)</td>
<td>90</td>
<td>53</td>
</tr>
<tr>
<td>Retinoic acid receptor-α (all-trans-retinoic acid)</td>
<td>Retinoid-X-receptor (RXR)-α (Targetrin)</td>
<td>9-cis-retinoic acid</td>
<td>60</td>
<td>31</td>
</tr>
</tbody>
</table>


to cyte experiences lower cholesterol levels because of the inhibition of biosynthesis, it responds by an increase in SREBP processing and, as a result thereof, LDL receptor expression. This increase in LDL receptors leads to the desired result—an efficient removal of LDL particles from the circulation. Thus, an LXR ligand that also inhibits SREBP processing would also be expected to counteract statin action. This is clearly undesirable, especially because the intended patient population to a large extent overlaps with the patients who benefit from the statin class of drugs.

3. Tissue- or Gene-Selective Agonists

At least two more avenues toward suitable compounds can be envisioned. First, LXR agonists with suitable pharmacokinetic properties, allowing a substantial distribution in the extrahepatic tissues, may be identified. Such a compound may be able to exert favorable effects on the artery wall at doses sufficiently small to allow any increase in fatty acid synthesis to be manageable. A second possibility is that selective LXR modulators, analogous to the selective estrogen receptor modulators, can be found. The latter compounds are characterized by mixed agonist profile; for example, the estrogen receptor ligand tamoxifen functions as an estrogen agonist in bone, but it is an antagonist in breast tissue.56 At this point, however, it is unknown whether a similar behavior can be obtained with LXR agonists. Presently, LXRβ-selective agonists seem to offer the most promising path toward LXR agonists having the desired properties with respect to gene and tissue specificity.

Species Differences in the Genes Controlled by LXR: A Challenge to Drug Discovery

The development of new drugs requires the use of appropriate animal models. A suitable animal model should mimic the biochemistry and physiology of humans. One common obstacle to using small animals to develop novel therapeutics is the dramatic difference in binding affinities for receptors from different species; well-studied examples include β-adrenergic receptors and PPARα.57 Significant species differences for LXR ligands have not been reported to date; however, it has become clear that there exist important species differences with respect to which genes are controlled by LXR. Some of these differences are summarized in Table 1, which compares the effects of LXR activation on gene expression in mice and humans. These two species were chosen because humans are of greatest interest for drug discovery, whereas mice have been studied most extensively with respect to LXR function. The two most dramatic differences between the species are CETP and CYP7A1 (see Table 1). Luo and Tall59 have shown that the human CETP gene contains a functional LXR response element; we have extended these results by demonstrating that synthetic LXR agonists increase CETP expression in primary human hepatocytes (unpublished data, 2001). The finding that CETP is an LXR-responsive gene thus explains the original observation in rabbits that CETP expression is increased by cholesterol feeding.60 This potentially important effect of LXR agonists in humans is not recapitulated in mice because the mouse genome does not contain CETP.

Another important difference in LXR-mediated gene regulation between humans and mice concerns CYP7A1. The mouse CYP7A1 gene figure prominently in the early seminal work on LXR. Lehmann et al.61 showed that the mouse CYP7A1 promoter contained an LXR response element, which suggested that LXR might mediate the induction of CYP7A1 expression by cholesterol feeding in mice. Proof that LXR mediates this induction came from the work of Peet et al.,62 who showed that LXRα knockout mice fail to induce CYP7A1 expression on cholesterol feeding. In contrast, Chiang et al.62 demonstrated that the human CYP7A1 promoter does not contain a functional LXR response element. We have recently extended these findings by demonstrating that a synthetic LXR agonist induced CYP7A1 expression in rats in vivo and also in primary rat hepatocytes whereas the same molecule had no effect on CYP7A1 expression in primary human hepatocytes.29 The species difference was not caused by a difference in affinity for rat versus human LXR receptors, as judged by transactivation assays and the fact that
the synthetic agonist induced ABCA1 in the primary human hepatocytes. In a similar vein, Chen et al. demonstrated that mice transgenic for human CYP7A1 on a mouse Cyp7A1 knockout background did not increase expression of the transgene in response to cholesterol feeding.

Mice and humans show differences in LXR-mediated gene regulation other than CETP and CYP7A1 (see Table 1). For example, ABCG1 is very strongly induced in human cells by LXR agonists. In our experience, ABCG1 is often induced 2- to 3-fold by LXR agonists (also data not shown). The differences between mice and humans may complicate predictions of outcomes in humans based on the effects of LXR agonists in mice.

**Summary**

The last few years have seen an explosion of new information on the orphan nuclear receptors, including LXR, and in our understanding of the critical roles played by LXR-responsive genes such as ABCA1 and SREBP-1c. It has very recently become clear that LXR activation and ABCA1 expression can mitigate atherosclerosis in animal models. Taken together, the evidence makes a compelling case for attempting to develop LXR agonists as novel therapeutics for the treatment of atherosclerosis and its clinical consequences. The great challenges ahead include identifying means to circumvent the LXR-mediated overproduction of triglyceride and identifying appropriate animal models for the testing of novel LXR agonists.

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**References**


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