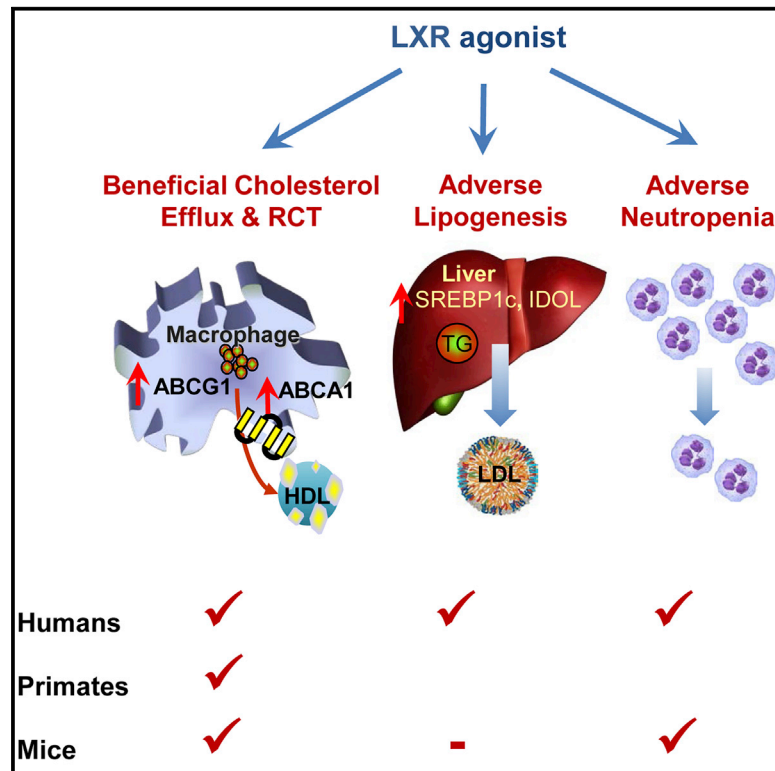


Cell Metabolism

Beneficial and Adverse Effects of an LXR Agonist on Human Lipid and Lipoprotein Metabolism and Circulating Neutrophils

Graphical Abstract



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In Brief

Kirchgessner et al. describe the effects of an LXR agonist in mice, cynomolgus monkeys, and humans. Although the LXR β -selective agonist increased reverse cholesterol transport pathways in clinical trials, adverse effects not predicted from the pre-clinical models, such as elevated LDL cholesterol and triglycerides and decreased neutrophils, occurred.

Highlights

- An LXR β -selective agonist caused positive and adverse effects in MAD clinical studies
- RCT pathways were stimulated clinically and in animal models
- Elevated plasma and liver lipids and neutropenia in healthy and statin-treated subjects
- Pre-clinical studies predicted therapeutic, but not adverse, effects



Beneficial and Adverse Effects of an LXR Agonist on Human Lipid and Lipoprotein Metabolism and Circulating Neutrophils

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SUMMARY

The development of LXR agonists for the treatment of coronary artery disease has been challenged by undesirable properties in animal models. Here we show the effects of an LXR agonist on lipid and lipoprotein metabolism and neutrophils in human subjects. BMS-852927, a novel LXR β -selective compound, had favorable profiles in animal models with a wide therapeutic index in cynomolgus monkeys and mice. In healthy subjects and hypercholesterolemic patients, reverse cholesterol transport pathways were induced similarly to that in animal models. However, increased plasma and hepatic TG, plasma LDL-C, apoB, apoE, and CETP and decreased circulating neutrophils were also evident. Furthermore, similar increases in LDL-C were observed in normocholesterolemic subjects and statin-treated patients. The primate model markedly underestimated human lipogenic responses and did not predict human neutrophil effects. These studies demonstrate both beneficial and adverse LXR agonist clinical responses and emphasize the importance of further translational research in this area.

INTRODUCTION

Free cholesterol levels are normally maintained within narrow limits in cells by a variety of homeostatic processes. However, some cells, most notably macrophages in atherosclerotic lesions, can accumulate excess cholesterol through uptake of modified lipoproteins. The resultant foam cells are key players in the pathophysiology of atherosclerosis. Reverse cholesterol transport (RCT) is a process whereby cholesterol is removed from peripheral tissues and returned to the liver for elimination (Rosenson et al., 2012). Stimulation of this process in foam cells is likely to be an effective therapy for atherosclerosis. The liver X

receptors, LXR α and LXR β , are oxysterol-activated nuclear hormone receptors (Janowski et al., 1999) that control the transcription of genes involved in all major phases of RCT, including efflux of excess cholesterol out of cells. They induce the expression of the key cholesterol transporters ABCA1 (Venkateswaran et al., 2000a) and ABCG1 (Venkateswaran et al., 2000b), which efflux cholesterol out of cells on to high-density lipoprotein (HDL) particles, as well as proteins such as cholesteryl ester transfer protein (CETP), ABCG5, and ABCG8, which facilitate cholesterol trafficking to the liver and ultimate excretion in feces (Luo and Tall, 2000; Tontonoz and Mangelsdorf, 2003). LXRs also modulate the immune system, regulating both innate and acquired immunity (Zelcer and Tontonoz, 2006). Due to their RCT and immunomodulatory effects, LXR agonists have robust anti-atherosclerotic activity in mouse (Joseph et al., 2002b; Terasaka et al., 2003) and rabbit models (Giannarelli et al., 2012; Vucic et al., 2012).

In animal models, LXR agonists also increase fatty acid and triglyceride (TG) synthesis through the induction of *SREBP1c*, *FAS*, *SCD1*, and other genes (Schultz et al., 2000), resulting in elevated, very low-density lipoprotein (VLDL) secretion from liver, hypertriglyceridemia, and hepatic steatosis. Other liver-derived proteins that result in inhibition of TG lipolysis in the circulation, including angiopoietin-like 3 protein (Inaba et al., 2003) and apolipoprotein AV (Jakel et al., 2004), are also modulated by LXR. The inducible degrader of LDL receptor (IDOL), an E3 ubiquitin ligase that targets the LDL receptor for degradation (Zelcer et al., 2009), is also upregulated by LXR and thus has the potential to elevate LDL through reducing hepatic LDL receptors. In addition, increased production of VLDL, induction of CETP, and stimulation of peripheral cholesterol trafficking to the liver, thereby inhibiting hepatic SREBP2-dependent LDL receptor expression, could all contribute to elevated LDL cholesterol (LDL-C). Thus, multiple LXR-regulated hepatic pathways have the potential to cause hepatic steatosis and dyslipidemia, and, indeed, LXR agonists including GW3965 and T0901317 have been shown to increase liver and plasma TG and LDL in mice and hamsters (Groot et al., 2005; Joseph et al., 2002a; Schultz et al., 2000). More limited experiments in primates have shown variable responses, depending on the agonist and study (Groot

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