Putative Metabolic Effects of the Liver X Receptor (LXR)

Knut R. Steffensen and Jan-Åke Gustafsson

The nuclear receptors liver X receptor (LXR)α and LXRβ are sensors of cholesterol metabolism and lipid biosynthesis. They have recently been found to be regulators of inflammatory cytokines, suppressors of hepatic glucose production, and involved in different cell-signaling pathways. LXRα is a target gene of the peroxisome proliferator-activated receptor-γ, a target of drugs used in treating elevated levels of glucose seen in diabetes. Furthermore, insulin induces LXRα in hepatocytes, resulting in increased expression of lipogenic enzymes and suppression of key enzymes in gluconeogenesis, including PEPCK. LXR seems to have an important role in the regulation of glucocorticoid action and a role in the overall energy homeostasis suggested by its putative regulatory effect on leptin and uncoupling protein 1. The physiological roles of LXR indicate that it is an interesting potential target for drug treatment of diabetes. *Diabetes* 53 (Suppl. 1):S36–S42, 2004

Type 2 diabetes accounts for >90% of the cases of diabetes and is caused by defective insulin secretion and insulin resistance. Type 2 diabetes is often of polygenic origin, but the molecular defects are still not fully known. However, the genetic background of maturity-onset type diabetes of the young is known.

A class of nuclear receptors has recently become the focus for its important role in cholesterol, lipid, and carbohydrate metabolism, namely the liver X receptor (LXR). A number of recent studies have shown that LXR is a key player in these biological functions. The main target tissues for LXR action are liver and adipose tissue, where its function has been carefully studied, but LXR has recently been suggested to be involved in lipid and carbohydrate metabolism in muscle as well. Important target tissues of insulin action are also liver, muscle, and adipose tissue, where insulin stimulates the uptake of excess glucose from blood and inhibits hepatic glucose production. A salient feature of type 2 diabetes is insulin resistance in these tissues, which leads to hyperglycemia and hyperlipidemia, both pathological conditions where, based on recent studies, LXR may be a key player. The LXR subfamily consists of two members, LXRα and LXRβ, which are activated by oxysterols. Whereas LXRβ is ubiquitously expressed, high expression of LXRα is restricted to liver, adipose tissue, small intestine, and macrophages. LXR target genes have been shown to be involved in lipid and cholesterol metabolism, glucose homeostasis, and inflammatory response (Table 1). This review will focus on physiological roles of LXR and highlight why LXR could be an important potential target for drug treatment of lipid and carbohydrate disorders.

LXR IN CHOLESTEROL AND LIPID METABOLISM

The phenotypes of LXR knockout mice generated in our laboratory and by Mangelsdorf and colleagues have shown that LXR is important for cholesterol and lipid metabolism (1,2). These were the first of many articles reporting LXR as a sensor for metabolites of lipid and cholesterol metabolism. Thus, Mangelsdorf and colleagues reported impaired expression of hepatic genes involved in cholesterol and fatty acid metabolism, such as cholesterol 7α-hydroxylase, hydroxymethyl glutaryl (HMG)-CoA synthase/reductase, farnesyl diphosphate synthase, squalene synthase, sterol response element-binding protein (SREBP), stearoyl CoA desaturase (SCD)-1, and fatty acid synthase in LXRα$^{-/-}$ knockout mice. Our study showed a similar phenotype in LXRα$^{-/-}$ knockout mice. In addition, we investigated the LXRβ$^{-/-}$ knockout mice as well, but these mice failed to show the phenotype observed in LXRα$^{-/-}$ knockout mice. This suggests a more prominent role of LXRα than LXRβ as a regulator of these enzymes. Several of these genes have been shown to be under direct transcriptional control of LXR by its cognate response element in their respective promoters (Table 1). Of particular interest is the regulation of SCD-1. Recent experiments in our group have shown that both SCD-1 and SCD-2 are highly induced in several tissues upon feeding of mice with an LXR agonist (36; K.R.S., S.Y. Neo, T.M. Stulnig, V.B. Vega, S.S. Rahman, G. Schuster, J.-Å.G., and E.T. Liu, unpublished data). SCD is the rate-limiting enzyme in the cellular synthesis of monounsaturated fatty acids from

From the Department of Medical Nutrition and Biosciences, Karolinska Institutet, Huddinge, Sweden.

Address correspondence and reprint requests to Jan-Åke Gustafsson, Department of Medical Nutrition and Biosciences, Karolinska Institutet, S-14157 Huddinge, Sweden. E-mail: jan-ake.gustafsson@mednut.ki.se.

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11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; Angptl3, angiopoietin-like protein 3; IL, interleukin; LXR, liver X receptor; PPAR, peroxisome proliferator-activated receptor; SCD, stearoyl CoA desaturase; SREBP, sterol response element-binding protein; TNF, tumor necrosis factor; WAT, white adipose tissue.

TABLE 1
LXR target genes

	Function	Direction	Reference
Lipid cholesterol metabolism			
Cyp7α*	Rate-limiting enzyme in the conversion of cholesterol to bile acids	↑ LXRE	43
CETP	Mediates transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins	↑ LXRE	44
ABCA1	Mediates the active efflux of cholesterol from cells to apolipoproteins	↑ LXRE	6,7,45,46
ABCG1	Mediates the active efflux of cholesterol and phospholipids from cells to apolipoproteins	↑	8
ABCG4	Cellular transmembrane transport of endogenous lipid substrates	↑	9
ABCG5/8	Important role in entero-hepatic sterol transport	↑	47
SREBP1c	Transcription factor that regulates expression of lipogenic enzymes	↑ LXRE	13,14,48
SCD-1/2	Rate-limiting enzyme in the cellular synthesis of monounsaturated fatty acids from saturated fatty acids, an important step in producing triglycerides	↑	20§
FAS	Catalyzes the formation of long-chain fatty acids from acetyl-CoA	↑ LXRE	16,20
ACC	Carboxylation of acetyl-CoA to malonyl-CoA for the synthesis of long-chain fatty acids	↑ T3RE†	17,20
ApoE	Facilitates cholesterol efflux outside the enterohepatic axis	↑ LXRE	11,12
ApoC	Cofactor for LPL in hydrolysis of triglyceride	↑ LXRE	12
LXRα	Autoregulation	↑ LXRE	49,50
LPL	Hydrolyzes triglycerides in circulating large lipoproteins	↑ LXRE	51
PLTP	Transfer phospholipids from triglyceride-rich lipoproteins to HDL	↑	52
SR-B1	HDL receptor involved in reverse cholesterol transport	↑ LXRE	53
Angpt13	A family member of the secreted growth factor angiopoietins	↑ LXRE	21
Carbohydrate metabolism			
PEPCK	Rate-limiting enzyme in gluconeogenesis	↓	24–26
Fbp1	Gluconeogenic enzyme	↓	24
G6P	Glucose-6-phosphatase	↓	24,26
Pfkfb3	Glycolytic enzyme	↓	24
PDK4	Glycolysis inhibitor	↑	24
GLUT4	Glucose transporter	↑	24
Inflammatory response			
TNF-α	Proinflammatory cytokine	↑/↓ LXRE	36,54
iNOS	Inflammatory mediator	↓	37
Cox-2	Inflammatory mediator	↓	37
IL-6	Inflammatory mediator	↓	37
Energy homeostasis			
UCP-1	Proton carrier in the mitochondrial membrane	↓	24§
Others			
Renin	Generates angiotensin from angiotensinogen, initiating a cascade of reactions that produces an elevation of blood pressure and increased sodium retention by the kidney	↑ CNRE‡	39
c-myc	Transcription factor that seems to activate the transcription of growth-related genes	↑ CNRE‡	39
11β-HSD-1	Catalyzes the conversion of inactive cortisone to active cortisol	↓	25

Only genes with an LXR response element found in the promoter or regulated by exposure to an LXR agonist are included. ↑, Upregulated; ↓, downregulated. *Not directly LXR regulated in humans (42). †LXR is involved in a complex that binds a thyroid hormone (triiodothyronine, T3) response element. ‡Response to LXR mediated through a *cis*-acting DNA element (CNRE). §K.R.S., S.Y. Neo, T.M. Stulnig, V.B. Vega, S.S. Rahman, G. Schuster, J.-Å.G., and E.T. Liu, unpublished data.

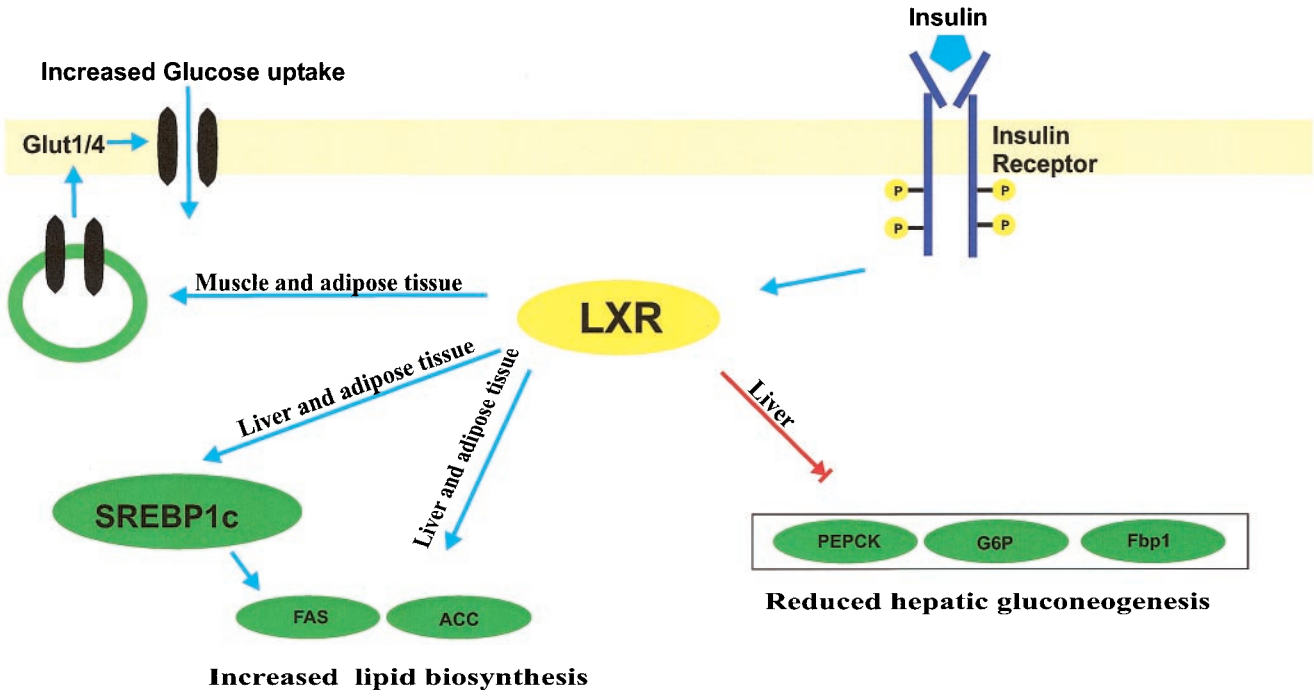

FIG. 1. Interplay of metabolic effects of insulin and LXR. The green areas indicate LXR target genes, blue arrows indicate activating effect, and the red arrow indicates inhibitory effects. Activation of LXR leads to increased glucose uptake in muscle and adipose tissue via the GLUT transporters. In liver and adipose tissue, LXR promotes lipid biosynthesis by inducing expression of lipogeneic enzymes. Furthermore, LXR suppresses gluconeogenesis in the liver by inhibiting vital gluconeogenetic enzymes. These are also known effects of insulin. Insulin induces expression of LXRα, indicating a pivotal role of LXR as a mediator of insulin signaling. Insulin exerts its effect via the insulin receptor that becomes autophosphorylated and further phosphorylates the insulin receptor substrates. This leads to activation of several downstream signaling pathways including phosphatidylinositol 3-kinase, pyruvate dehydrogenase kinase, protein kinase B, and variants of protein kinase C. The molecular mechanism behind the induction of LXRα by insulin is still unknown. Knowing what part of the insulin-signaling pathway induces LXRα expression would help to better understand the interplay between insulin and LXR on lipid and carbohydrate metabolism. ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; Fbp1, fructose biphosphatase 1; G6Pase, glucose-6-phosphatase.

saturated fatty acids—an important step in the generation of triglycerides for transport and storage as well as maintaining cellular membrane fluidity. Altered SCD activity has been linked to several diseases including cardiovascular disease and obesity. Increased SCD activity in liver generates monounsaturated fatty acids, leading to synthesis of triglycerides and esterification of cholesterol for transport out of the liver. It is suggested that this increase in plasma lipids leads to cardiovascular disease. Obese hyperglycemic mice (*ob/ob* mice) were shown to have an elevated activity of SCD and, in addition, higher depositions of body fat than their lean counterparts. In type 2 diabetes, SCD activity is increased, probably in response to increased levels of insulin (3). SCD might therefore contribute to the hyperlipidemia seen in type 2 diabetes. A causal relationship between SCD activity and the various diseases is still unclear, but these results suggest that the LXRs could be involved in diseases caused by altered SCD activity.

Nebb and colleagues showed that LXRα expression, but not LXRβ expression, was induced by fatty acids in rat hepatoma cells and primary rat hepatocytes (4). A mechanistic explanation for this observation was given when peroxisome proliferator-activated receptor (PPAR) was shown to induce LXRα expression (5). In this study, Chawla et al. showed that cholesterol efflux from macrophages due to PPAR-γ activation was mediated by LXRα, and investigation of the LXRα promoter revealed a response element for PPAR. Furthermore, they showed that LXR induced expression of a transmembrane transporter, ABCA1—one of several ABC transporters later found to be regulated by LXR (6–10), which mediates cholesterol efflux from cells. This LXR-mediated cholesterol efflux from peripheral tissues, termed "reverse cholesterol transport," also involves apolipoproteins, another class of proteins regulated by LXR (11,12). These studies indicate that LXRα can mediate effects of PPAR-γ, a target for drug therapy in diabetes because of its hypoglycemic effects.

The pivotal role of LXR in lipid biosynthesis was established when Mangelsdorf and colleagues (13) and others (14) found that LXR induces SREBP1c expression via an LXR response element in its promoter. SREBP1c in turn induces lipogenic enzymes, thereby promoting lipid biosynthesis. Several LXR target genes such as SCD and SREBP1c are regulated by insulin signaling as well (Fig. 1), and in a collaborative effort with Nebb and colleagues, we showed that LXRα expression was induced by insulin in hepatocytes (15). This finding led us to believe that LXR is a mediator of insulin action and suggested novel biological functions for LXR. SREBP1c has a distinct function in mediating insulin signaling, where it stimulates expression of several enzymes involved in lipogenesis, such as fatty acid synthase and acetyl CoA carboxylase. Both fatty acid synthase (16) and acetyl CoA carboxylase (17) are direct as well as indirect targets of LXR (Fig. 1). A recent report also showed that overexpression of SREBP1c in β-cells of the islets of the pancreas leads to lipid accumulation and eventually apoptosis of these cells, a known feature of diabetes (18). This finding suggests an important role of LXR in the biosynthesis of lipids and lipid accumulation,

where LXR might mediate some of the effects of insulin on SREBP1c.

Detailed studies within our group have been performed to elucidate the physiological relevance of LXR in lipid metabolism and to characterize lipid profiles in LXR-deleted mice (19). We found an increase in LDL cholesterol content and a decrease in HDL cholesterol content in LXRα$^{-/-}$ and LXRα$^{-/-}$β$^{-/-}$, but not LXRβ$^{-/-}$, mice and a decrease in triglyceride levels in serum and VLDL in LXRα$^{-/-}$β$^{-/-}$, but not LXRα$^{-/-}$ or LXRβ$^{-/-}$, mice. We did not observe any changes in serum cholesterol levels. Similar findings have also been reported by others (20). Interestingly, LXR was found to upregulate angiopoietin-like protein 3 (Angptl3), a member of the family of vascular endothelial growth factors that is also a key regulator of lipid metabolism (21). The KK/San mouse strain has low levels of plasma triglycerides, total cholesterol, and nonesterified fatty acids because of a mutation in the Angptl3 gene. A study in this mice strain showed that overexpression of Angptl3 leads to increased circulating level of plasma cholesterol triglycerides and nonesterified fatty acids (22). This finding speaks in favor of a novel mechanism for LXR in regulation of lipid homeostasis. No studies have fully addressed the functional role of LXR in skeletal muscle, another main target organ of insulin signaling. However, expression of both LXRα and LXRβ has been detected in quadriceps from mice, and it was shown that treatment of a myoblast cell line (C2C12) with an LXR agonist induced genes involved in lipid and cholesterol metabolism (23).

In summary, LXR induces reverse cholesterol transport from peripheral tissue to liver via HDL by stimulating the production of apolipoproteins and ABC transporters, a positive effect of LXR in terms of counteracting atherosclerosis. LXR, however, also induces fatty acid production and serum triglycerides by stimulating expression of SREBP1c and Angptl3, leading to an increased risk of developing metabolic diseases such as type 2 diabetes.

LXR IN CARBOHYDRATE METABOLISM

Although the first reports about LXR placed the nuclear receptor as a sensor of cholesterol and lipid metabolism, new data indicate another physiological function of LXR. Published and ongoing studies in our laboratory indicate that LXR is a key regulator of carbohydrate metabolism. In two articles by Stulnig et al. (24,25), we report that feeding mice an LXR agonist significantly inhibits expression of gluconeogenic enzymes. In liver, treatment of an LXR agonist significantly inhibits expression of gluconeogenetic enzymes such as PEPCK, the rate-limiting enzyme in gluconeogenesis, fructose biphosphatase 1, and glucose-6-phosphatase (24,25). A study by Cao et al. (26) supports our findings; they treated diabetic rodents with an LXR agonist and showed a dramatic reduction of plasma glucose. Furthermore, they showed that an LXR agonist increased insulin sensitivity in insulin-resistant Zucker rats and that gluconeogenic genes were suppressed, leading to decreased hepatic glucose output.

MacDougald and colleagues showed that LXRα increased basal uptake of glucose in adipocytes (27). This is mediated mainly through the GLUT1 transporter, and an LXR agonist was shown to induce expression of GLUT1 mRNA as well as protein levels. We have also reported increased expression of GLUT4 mRNA in white adipose tissue (WAT) in response to an LXR agonist (24). GLUT4 expression is known to be highly upregulated in response to insulin in adipose tissue. Our findings suggest that this increase in GLUT4 expression might, at least partially, be mediated by LXR. Furthermore, MacDougald and colleagues showed that activation of ectopically expressed LXRα in adipocytes resulted in increased synthesis of glycogen and cholesterol in adipose tissue and elevated levels of glycerol and nonesterified fatty acids in serum. The authors suggest that LXR is involved in lipolysis in adipocytes as well as in several aspects of carbohydrate metabolism by stimulating glucose uptake and glycogen synthesis.

We have also found the LXR agonist to inhibit expression of enzymes involved in glycolysis. In WAT and brown adipose tissue, enzymes promoting glycolysis, including 6-phosphofructo-2-kinase 3, were suppressed. This enzyme is the most potent activator of 6-phosphofructo-1 kinase, the rate-limiting enzyme in glycolysis. Pyruvate dehydrogenase kinase 4, a negative regulator of glycolysis, was induced by an LXR agonist. Inhibition of glycolytic enzymes is also seen in other tissues (K.R.S., S.Y. Neo, T.M. Stulnig, V.G. Vega, S.S. Rahman, G. Schuster, J.-Å.G., and E.T. Liu, unpublished data). Additional studies are needed to elucidate this effect, and a careful study of LXR action on glycolytic enzymes in muscle would provide vital information about the physiological relevance of the observed regulatory effects on these enzymes.

While the effect of LXR on glycolysis needs further investigation, these results show that treatment of LXR agonists in mice leads to decreased plasma glucose levels and decreased hepatic glucose production by inhibiting key enzymes that promote gluconeogenesis.

OTHER METABOLIC EFFECTS OF LXR

Many health problems in the Western world have been linked to obesity. Leptin is part of a biological mechanism that controls the nutritional status of the body. Although the effect of leptin is mostly studied in rodents, it is suggested that impaired function of this hormone, or lack of response to the hormone, results in obesity in humans as well (28). Obesity also occurs when energy intake exceeds energy expenditure or when energy balance is impaired in other ways. The uncoupling proteins (UCPs) represent a class of proteins that is involved in energy expenditure (29). They use the proton gradient generated by the electron transport chain to transport protons across the mitochondrial membrane to generate heat. Energy is thereby used to produce heat instead of generation of ATP. Recent reports connect LXR to both control of nutritional status and energy metabolism, where studies within our group have identified both leptin and UCP-1 as target genes of LXR (Fig. 2). Leptin expression was downregulated in WAT in mice fed an LXR agonist (24). The same study, as well as unpublished data (K.R.S., S.Y. Neo, T.M. Stulnig, V.B. Vega, S.S. Rahman, G. Schuster, J.-Å.G., and E.T. Liu), also showed a drastic downregulation of UCP-1 expression after administration of an LXR agonist. Decreased leptin levels would eventually lead to increased energy intake, and decreased UCP-1 leads to

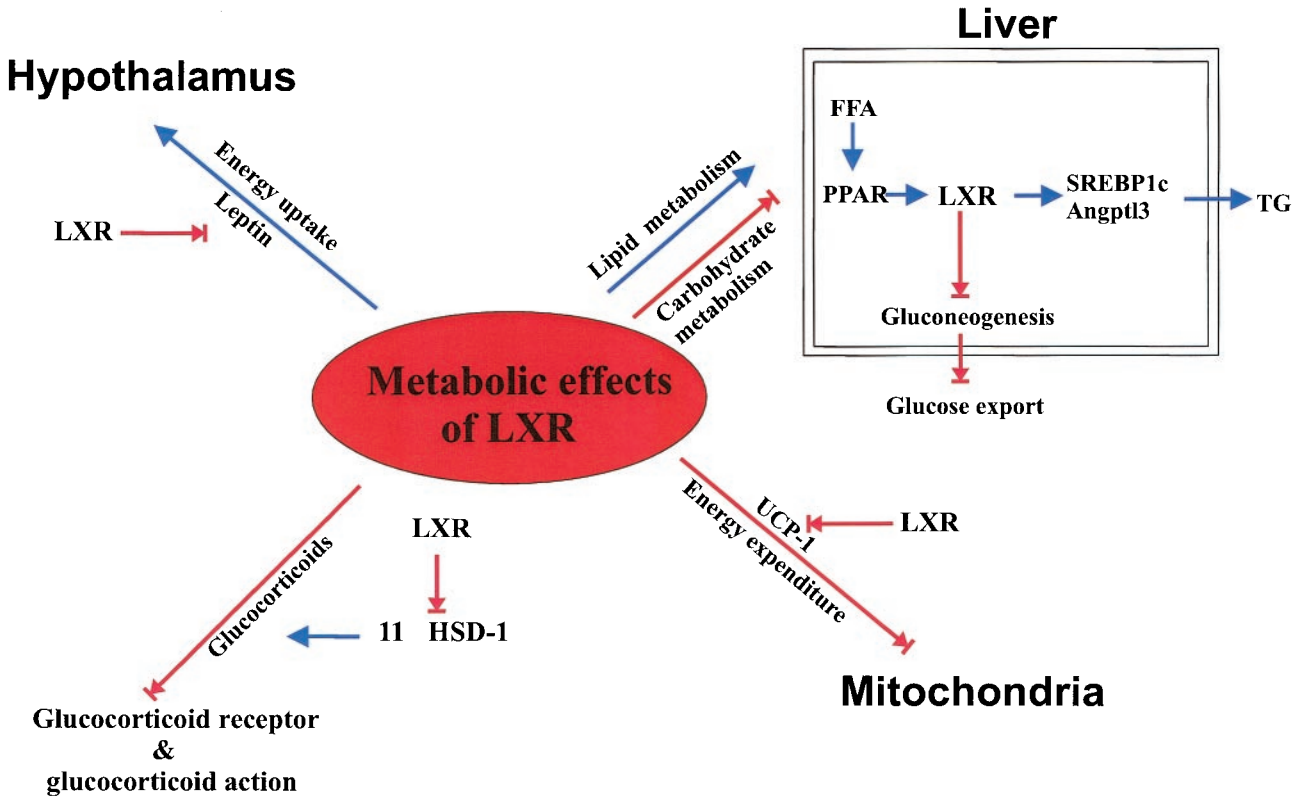

FIG. 2. Metabolic effects of LXR. The figure shows a simplified model of potential regulatory mechanisms of LXR. See text for details. Blue arrows indicate stimulatory effects, whereas red arrows indicate inhibitory effects. LXR induces lipogenesis and inhibits hepatic gluconeogenesis. LXR reduces leptin expression in adipocytes, promoting increased energy uptake, and suppresses glucocorticoid action by inhibiting 11β-HSD1 expression. The downregulation of UCP-1 expression seen by LXR probably leads to lower production of heat in the mitochondria. FFA, free fatty acid; TG, triglycerides.

decreased energy expenditure—both unwanted effects in terms of developing obesity. Although careful investigations are needed to elucidate these findings, this suggests a putative role of LXR in several aspects of metabolism.

Increased visceral adipose deposit increases the release of free fatty acids, and lipolysis is further enhanced by norepinephrine and glucocorticoids. Chronically high levels of free fatty acids eventually lead to increased hepatic gluconeogenesis and insulin resistance in liver, adipose tissue, and skeletal muscle. In particular, a visceral deposit of adipose tissue is associated with developing type 2 diabetes (30). Although the role of glucocorticoids in obesity is poorly understood, several findings suggest that they are important in this context. In Cushing's syndrome, elevated production of glucocorticoids and activation of the glucocorticoid receptor results in insulin resistance and obesity. In addition, glucocorticoid receptor antagonists have been shown to prevent obesity in rodents (31). 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an enzyme that reactivates inactive glucocorticoids (cortisone) to active glucocorticoids (cortisol) in humans. Enhanced 11β-HSD1 activity has been reported to promote obesity (32), and inhibition of this activity in liver improved the lipid profile in Zucker obese rats (33). The activity of the enzyme in adipose tissue has also been suggested to affect glucose uptake in adipocytes.

Studies within our group have shown that both a synthetic and a natural LXR agonist decreased 11β-HSD1 mRNA expression and activity by 50% in adipocytes generated from the 3T3-L1 cell line as well as in primary adipocytes in culture (25). The inhibitory effect depended on ongoing protein synthesis. That suggests an indirect effect of LXR on 11β-HSD1 expression, probably by stimulating expression of an inhibitor or by inhibiting expression of an activator of 11β-HSD1. Moreover, long-term treatment of mice with a synthetic LXR agonist downregulated 11β-HSD1 mRNA expression in both brown adipose tissue and liver of wild-type mice but not in LXR$\alpha^{-/-}\beta^{-/-}$ mice. The inhibition of 11β-HSD1 indicates that LXR might be involved in suppressing glucocorticoid effects, which might lead to reduced development of obesity and improved insulin sensitivity linked with glucocorticoid activity. Furthermore, LXR could decrease gluconeogenesis in liver by a direct inhibitory effect on PEPCK expression, as previously described, and indirectly by inhibiting glucocorticoid stimulatory effects on PEPCK expression. Taken together, these findings indicate a possible role of LXR in the hormonal regulation of overall energy metabolism (Fig. 2).

INFLAMMATORY RESPONSE AND LXR

Type 1 diabetes is an autoimmune disease where proinflammatory cytokines including γ-interferon, tumor necrosis factor (TNF)-α, and interleukin (IL)-4 play important roles. Inflammatory responses, particularly by TNF-α, have been linked to increased insulin resistance, and several studies in rodent models have revealed that manipulation of the cytokine network can delay or prevent diabetes. There are also indications that chronic inflam-

mation leads to a condition of insulin insensitivity where TNF-α has a central role of mediating insulin resistance (34,35). Mechanistically, it has been suggested that TNF-α may downregulate genes required for insulin action. Recently, two articles were published linking LXR to inflammatory responses. Fowler et al. (54) showed that LXR had anti-inflammatory effects in contact dermatitis models in rodents. Using immunohistochemistry on the LXR-treated foci of the skin, they showed that LXR inhibits production of TNF-α and IL-1α. Landis et al. (36) have shown that an LXR agonist induced TNF-α in macrophages and primary monocytes so the effect of LXR on TNF-α is not fully understood yet. In a transcriptional profiling study of lipopolysaccharide-induced macrophages carried out by Joseph et al. (37), an LXR-dependent downregulation of the expression of inflammatory mediators such as cyclooxygenase-2, inducible nitric oxide synthase, and IL-6 was demonstrated, suggesting a link between lipid metabolism and inflammation mediated by LXR. Furthermore, obesity may induce a cycle of inflammation leading to increased insulin insensitivity via adipocyte-derived TNF-α. Thus, LXR may work as a key player in responses to inflammation, and because it has been shown to be important in lipid metabolism, LXR might be involved in obesity-induced inflammatory responses as well.

SIGNAL TRANSDUCTION AND LXR

The involvement in various signaling pathways seems to be yet another novel function of LXR. Dexras1, the murine homolog of human activator of G-protein signaling, is involved in nitric oxide signaling and has been linked to the pathogenesis of insulin resistance (38). Gene expression profiling studies have shown Dexras1 to be downregulated by LXR in WAT, a finding that was confirmed by quantitative PCR. Furthermore, LXRα seems to be a cAMP-responsive modulator for a widespread number of genes including renin and c-myc via a CNRE (an overlapping cAMP response element and a negative response element). This response element has previously been shown to bind both a cAMP-induced transcription factor and a repressor of transcription (39). This is a unique LXR response element where LXR binds as a monomer (40). LXRβ has also been shown to interact with the transforming growth factor-β, called ALK-1, modulating signaling from the growth factor receptor (41). Thus, LXR appears to be a target and mediator of both cAMP and growth factor signaling pathways in addition to its previously demonstrated role in the insulin-signaling pathways. Further effort is indeed needed to unravel the role of LXR and its physiological relevance in different signaling pathways.

CONCLUSIONS AND PERSPECTIVES

Over the recent few years, much insight has been gained regarding the physiological functions of LXR. Although the first reports showed the involvement of LXR as a regulator of cholesterol metabolism, new findings suggest a role of LXR in lipogenesis, carbohydrate metabolism, inflammation, and various cellular signaling pathways. Interestingly, these biological mechanisms where LXR seems to play an important role are often linked to an increased risk of developing diabetes when they are dysfunctional. This makes LXR a highly interesting target for drug development for treating diabetes.

Whereas suppression of proinflammatory cytokines, limiting effects of glucocorticoids, inhibition of hepatic gluconeogenesis, and lowering serum glucose levels might be favorable features of a potential drug against diabetes, the increase in circulating lipids and triglycerides is not. Hence, the former effects need to be promoted by such a drug and the latter effect antagonized. The search for agonists and antagonists to LXR is prioritized in several pharmaceutical companies today. Generation of agonists and antagonists specific for LXRα and LXRβ, respectively, will help to elucidate isoform-specific functions of LXR. Clearly, we are yet only at the beginning of what promises to be an extremely interesting period of continuous revelations of new functions of the two LXR isoforms, and it is likely that novel approaches to treat diabetes will become apparent as a result of this new knowledge.

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