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Review Article

Therapeutic Role of the Liver X Receptor in Modulation of Metabolic Diseases and Future Scenarios

Renu Kumari Rana, Souravh Bais*

ABSTRACT
Liver X receptors (LXRs) are part of the nuclear receptor superfamily and are cholesterol-detecting receptors. LXRs are commonly found in two isoforms: LXR and LXR. LXRs were initially identified as orphan receptors from a rat cDNA library using an oligonucleotide probe. The regulatory activities of LXR in obesity are the subject of this review. LXRs directly operate on numerous target genes such as ABCA1, ABCG1, ABCG8, GLUT4, and other rate-limiting enzymes such as PEPCK, G6P, and F6P, and so play an important role in the treatment of obesity. LXR may interfere with obesity via several signaling mechanisms. The first is through ABC genes, which promote the clearance of excess bodily cholesterol via the lipid removal route from cholesterol-loaded macrophages and intestinal lumen. The second strategy involves boosting GLUT4 expression by increasing glucose absorption by peripheral tissues, and the third involves inhibiting rate-limiting enzymes PCPCK, G6P, and F6P, which eventually decrease hepatic glucose synthesis. LXR's physiological activities suggest that it might be a promising target for obesity therapy.
Keywords: Liver X receptors, Obesity, ABC transporters, GLUT4, Rate limiting enzymes (PEPCK, G6P, and F6P).

Renu Kumari Rana, Souravh Bais*

Institute of Pharmaceutical Sciences, SAGE University, Indore, Madhya Pradesh, INDIA.

Correspondence

Dr. Souravh Bais,

Institute of Pharmaceutical Sciences, SAGE University, Indore-452012, Madhya Pradesh, INDIA.

E-mail: souravh2008.123@rediffmail.com

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INTRODUCTION

Liver X receptors (LXRs) are nuclear receptor superfamily ligand-activated transcription factors that are generally activated by oxidized cholesterol derivatives (Oxysterols).[1-2] LXRs are involved in the metabolism of cholesterol, free fatty acids, and glucose. LXRs have a role in cholesterol regulation. When the content of cholesterol rises, the LXRs activate transcription genes that protect the cell from cholesterol excess by increasing the oxidized product of cholesterol.[3]

Using oligonucleotide probes, LXRs were first identified as orphan receptors (receptors with no known physiological function) from a rat liver c DNA library.[4-5] Because of several benefits such as high specificity, tolerance to other RNAses, rapid availability of deoxynucleotides, and improved economic availability, LXRs are currently separated in the same way utilizing oligonucleotide probes.

The LXR receptors have four major functional domains: (1) an amino-terminal ligand-independent activation function domain (AF-1) that can activate transcription even when the ligand is absent; (2) a DNA-binding domain (DBD) with two zinc fingers; (3) a hydrophobic ligand-binding domain (LBD) required for receptor dimer formation and ligand binding; and (4) a carboxy-terminal.[6]

In mammals, there are two isoforms of liver X receptors: LXR and LXR, which form an obligatory heterodimer with retinoid X receptors (RXR).[7] LXR is found in three different forms: LXR1, LXR 2, LXR 3, and LXR.[8-9] PPARs, FXR, RXR, and VDR receptors are all closely linked to LXRs.[10] There hasn't been any other novel LXR isoform discovered yet.

LXRs are primarily responsible for maintaining cellular cholesterol homeostasis and glucose metabolism, but they also modulate immune responses in mammals by regulating gene expression in macrophages, making them a promising therapeutic target for the treatment of a variety of chronic inflammatory disorders.[11] LXR has been discovered to be a potential therapeutic agent in the treatment of atherosclerosis by regulating metabolic and inflammatory gene expression in recent research.[12] The activation of liver X receptors inhibits hepatic gluconeogenesis and reduces blood glucose levels, making it useful in the treatment of diabetes.[13]

Activation of LXR in animal models has been found to have a critical role in the prevention of major metabolic diseases such as hyperlipidemia, atherosclerosis, diabetes, and obesity.[14] Treatment with several LXR agonists causes a decrease in serum and hepatic cholesterol levels in rats.[15]

The involvement of liver X receptors in obesity is the subject of our current review. Obesity has become a global public health problem. Marion Korach-Andre *et al.*[15] demonstrated that both liver X receptor

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isoforms, i.e. LXR and LXR, improve brown adipose tissue function, boosting LXR-mediated energy expenditure and demonstrating to be a potential therapeutic target for obesity. By up regulating GLUT4 receptors, which are marker gene genes for liver X receptors, LXR stimulation by GW3965 improved glucose tolerance in a diet-induced obesity mouse model.[16] another study found that activating LXR with T0901317 (a strong LXR agonist) increased basal glucose absorption in 3T3-L1 cells and *in vitro* differentiated human adipocytes.[17]

TYPES OF LIVER X RECEPTOR

Liver X receptors generally exists in two isoforms:

- Liver X Receptors α (LXR α)
- Liver X receptors β (LXR β)
- **Liver X Receptors α:** LXR α is an isoform of LXR receptor that is encoded by NR1H3 gene that is generally located on chromosome 11.[18] LXR α generally exists in three forms LXRα1, LXRα 2, LXRα 3, in which LXRα1 is the most active and generously expressed by all almost tissues like spleen, liver, adipose tissue, intestine, kidney and lungs,[19] LXRα 2 mainly expressed in human testis and cancer cell lines, and LXRα 3 is produced via an alternative recognition of a 30-splice site in exon 6 and is expressed by human lung, thyroid gland, spleen and cancer cell lines.[20] The expression of human LXRα is down regulated by a microRNA *has-miR-613* that is known to transcriptionally activate LXRα by SREBP-1c (sterol regulatory element binding proteins),[21] the up regulation of LXR α is regulated by the activation of LXRE (LXR response elements) (Table 1).[22]
- **Liver X Receptors β:** LXR β is another isoform of LXR receptors encoded by NR1H1 gene that is generally located on chromosome 19.[23-24] Isoform LXR β (NR1H2) not abundantly expressed by all tissues[22] but LXR β is dominantly expressed by skeletal muscles that regulate lipogenesis and cholesterol efflux. Courtaut F[22] showed that LXR β receptors are predominantly expressed in colon cancer cells but not in normal colon epithelial cells. Down regulation of Liver X receptors in neuronal micro columns, and malformed cells also participate in the prophylaxis of FCD (Focal cortical dysplasia) (Table 1).[23]

LIVER X RECEPTORS AGONISTS AND ANTAGONISTS:

The LXR agonists binds to Liver X receptors and thus activate it to produce certain biological responses whereas LXR antagonists deactivates the Liver X receptors and thus inhibit the biological response driven by LXRs (Table 2).

Table 1: Difference between both isoforms of liver X receptors.

Sl. No	TYPE	LXR-α	LXR-β
1.	Encoded Gene	NR1H3 gene (lies on chromosome 11)	NR1H1 gene (lies on chromosome 19)
2.	Location	Ubiquitously in all tissues like spleen, liver, adipose tissue, intestine, kidney, testis and lungs.	Less expressed by all tissues but dominantly expressed by skeletal muscles and colon cancer cell lines.
3.	Expression	Expressed through LXRE, SREBP and other essential cholesterol elements	Only expressed through LXRE.

- **LXR Agonists:** Various natural and synthetic agonist analogues are there for initiating the biological response of LXRs. These are as follows:
- **LXR ANTAGONISTS:** Various substances inhibit the response of liver X receptors (Table 3), few of them are as follows:

Table 2: Various LXR agonists used as therapeutic drugs in various diseases.

Sl. No.	LXR Agonists	Type of Agonists	Functions/ Mechanisms	References
1.	25-epoxycholestrol, 24 (s) hydroxyl cholesterol, 27-hydroxycholestrol and cholestenoic acid	Natural Ligands	Cholesterol metabolism Glucose metabolism Bile acid synthesis Treatment of various metabolic disorders	46-48
2.	GW3965	Selective agonists	Treatment of obesity, diabetes, atherosclerosis and inflammatory disorders.	49
3.	T0901317	Selective agonists	Treatment of atherosclerosis, obesity, prostate cancer, Alzheimer and breast cancer.	50
4.	22 (R) hydroxyl cholesterol	Partial agonist	Treatment of prostate, breast cancer and various other metabolic disorders like obesity.	6,51
5.	Paxilline	Selective agonist	Potassium channel blocker	52
6.	Desmosterol	Selective agonist	Lipid metabolism	16,31
7.	L-783483	Selective agonist	Cholesterol regulation	68
8.	TSPO	Selective agonist	Inducing the expression of LXRα, PPARα, ApoE, ABCA1 and ABCG4	19
9.	Pravastatin	Selective agonists	Promoting CYP7A1 and ABCG5/ABCG8 expression through the PPARγ/LXRα pathway	4
10.	Metformin	Selective agonist	Promoting HO-1 and LXRβ expression through the AMPK-ATF1 pathway	24

Table 3: Various LXR antagonists used as therapeutic drugs in various diseases.

Sl. No.	LXR Antagonist	Type of Antagonist	Functions	References
1	GSK2033	Selective LXR antagonist	Used in cell biology study as chemical probe. Treatment of inflammatory and autoimmune diseases	17,33
2	Cinnamamides	Selective LXR antagonist	Treatment of fatty liver (non-alcoholic). Decrease lipogenic gene expression.	18
3	22 (S) hydroxyl cholesterol	Partial and dose dependent LXR antagonist	Treatment of skin fibroblasts.	77
4	Rhein	Selective LXR antagonist	Treatment of obesity and other metabolic disorders.	21
5	Geranylgeranyl pyrophosphate (GGPP)	Non selective LXR Antagonist	Down regulate mevalonate metabolism.	22
6	Polyunsaturated fatty acids (PUFAs)	Competitive LXR antagonist	Down regulate SREBP-1c	23

TRANSCRIPTIONAL REGULATION OF GENES BY LXRS

Various biological compounds, such as oxysterols and bile acids, function as signaling molecules for nuclear receptor activation.[12-13] Nuclear receptors are ligand-activated transcription factors that control gene transcription and consequently play a role in a variety of biological processes. Target genes are activated in the transcriptional control of liver X receptors when LXR binds to certain DNA sequences linked with those genes.[16] LXRs bind to the three isoforms of retinoid X receptors (RXR), RXRa, RXRb, and RXRc, and therefore limit heterodiamers in combination.[17] LXRs control gene expression by activating LXR response elements (LXREs) in the target gene's promoter region of DNA. LXR response elements (LXREs), which are made up by two direct repeats AGGTCA speared by four nucleotides, were triggered by the constrain heterodimer of LXR-RXR.[22] LXRs are known to control a variety of target genes by this method, including polypeptide A3 and UDP Glucuronosyl transferase, phospholipid transfer protein,[16] and others.

The transcriptional activity of different glucocorticoid receptors is also known to be regulated by liver X receptors.[17] Glucorticoids promote gluconeogenesis and glycogenolysis by increasing the rate of transcription of glucose-6-phosphatase and its different enzymes. LXRs control cholesterol turnover and hepatic glucose metabolism by binding to a variety of cholesterol metabolites, which then heterodiamerise with Retinoid X Receptors, resulting in a reduction in glucose-6-phosphatase production.[11] In HCT116 cells (human colon cancer cell line, LXRs have been shown to suppress dexamethasone-stimulated GR transcriptional activity.[12] LXRs, on the other hand, control dexamethasone-stimulated mRNA expression of endogenous glucocorticoid-responsive genes in HepG2 cells. In astrocytes and neurons, LXRs regulate the transcription of Farnesyl pyrophosphate synthase (FPPS, an LXR target gene that plays a key role in controlling cholesterol production in the brain.[13] Furthermore, because Hepatocyte Nuclear Factor 4 (HNF-4) regulates the transcription of LXR (a isoform of LXR) that plays a key role in cholesterol homeostasis, overexpression of HNF-4 in HEK 293T cells raised the production of all LXR, causing cholesterol homeostasis to be disrupted.[14]

LXR Mediated ATP Transport in Cholesterol Efflux

ABC transporters play a critical role in increasing acceptor cholesterol efflux via liver X receptors; ABCA1, ABCG1, ABCG4, ABCG5, and ABCG8 of the ABC transporter family are LXR target genes.[15] ATP binding cassette transporters, also known as cholesterol efflux regulatory protein (CERP), are key regulators of cholesterol homeostasis and are encoded by different target genes such as ABCA1, ABCG4, ABCG5, and ABCG8.[16] The ABCA1 protein is required for extracellular cholesterol efflux to Apo Receptors such as Apo 1 (the first stage in cholesterol transport).[17] LXR receptor transcript levels influence ABCA1-mediated cholesterol efflux.[18] The ABC transporter has four domains: a) two membrane-spanning trans membrane domains (b) two nucleotide binding domains, where ATP hydrolysis provides energy for substrate transport.[19] According to Nelson JK *et al*., ABCA1 plays a critical part in the cellular apolipoproteins-mediated lipid elimination process, according to Nelson JK.[20]

ABCA1 is a naturally occurring membrane transporter that is important in the production of high-density lipoproteins (HDL).[21] To maintain cholesterol homeostasis, ABCA1 mediates post-translational regulation as well as transcriptional responses.[22] ABCA1 also plays a significant function in removing fat from cholesterol-loaded macrophages,[23] and it is abundantly found in resident macrophages, where it is involved in cholesterol transport.[24-25] The activation of the LXR/RXR heterodimer [25] is triggered by an increase in cholesterol-loaded macrophages inside the body.[26-28] The cholesterol in macrophages is subsequently oxidized and transformed into oxysterol, which is a key LXR activator.[28] The LXR-RXR heterodimer acts as a cholesterol sensor and then as a mediator for cholesterol efflux by inducing the expression of cholesterol shuffling vehicles like ABCA1 and Apo A-1. Abnormally high expression of these vehicles causes cholesterol dyshomeostasis.[29] At the cellular level, LXR activation triggers the ABCA1 and ABCG1 genes to respond, delivering cellular cholesterol to Apo A-1 (produced by the liver). Apo A-1 recognizes free cholesterol and phospholipids from macrophages and forms HDL particles, which develop into spherical HDL with the help of the cholesterol esterifying enzyme (lysolecithin cholesterol acyl tranferase). The SR-B1 (Scavenger receptor class B type 1) transports mature HDL to the liver, where it is then transferred to other lipoproteins via the CETP (Cholesteryl ester transport protein).[30-31] HDL then travels to the liver, where it causes an increase in LXR-dependent 7-hydroxylase production, which leads to more bile acid synthesis and elimination. Increased biliary excretion leads to increased intestinal cholesterol absorption by LXR mediation, which eliminates excess body sterol via ABC sterol transport.[32] LDLR (Low Density Lipoprotein Receptors) transports low density lipoproteins to hepatocytes, where they are hydrolyzed into free cholesterol, which is subsequently recycled into the ABCA1 pathway and released into bile acid, or reformed into lipoproteins and secreted into circulation.[33] ABCG1, on the other hand, mediates cholesterol efflux to HDL particles but not through Apos.[34] In a mouse model, the deletion of ABCA1 and ABCG1 causes a synergistic rise in tissue lipid accumulation. However, activation of LXR agonists helps to control cellular cholesterol excess.[35-38]

Obesity is defined as the accumulation of cholesterol and TGs (triglycerides) in adipose tissues, which is caused by a decrease in the

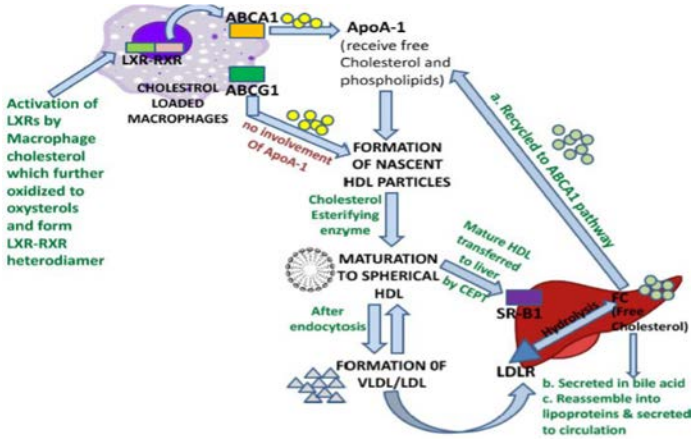

Figure 1: Cholesterol transport by ABCA1 and ABCG1 mediated by liver X receptors.

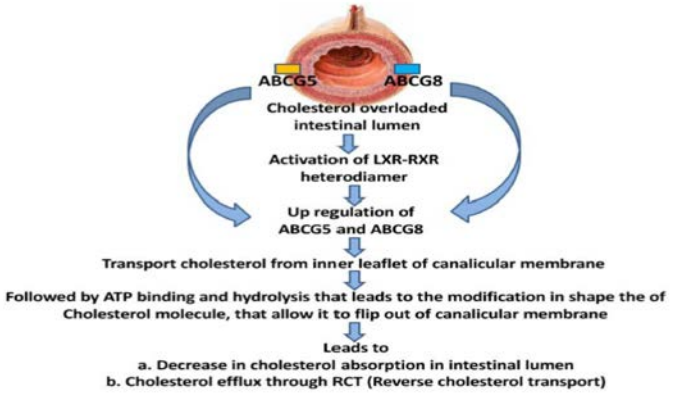

Figure 2: LXR mediated cholesterol transport in intestinal lumen.

expression of ABC transporters.[39] LXR stimulation up regulates the expression of ABCA1, ABCG1, and ABCG8, and thus plays a role in the development of obesity and its associated syndromes by facilitating ABCA1-mediated transport.[40]

The ABCG5 and ABCG8 genes, which are encoded by the proteins sterolin 1 and sterolin 2, respectively, play a key role in the control of sterol and cholesterol absorption and excretion.[41] Both are mostly expressed in enterocytes and serve as a selective tool for sterol excretion into bile by the liver.[42] ABCA1, ABCG5, and ABCG8 are direct genes for the activation of the LXR/RXR heterodimer in the liver and gut, according to Berge K.E *et al*. In *in situ* hybridization, LXR agonists raise the levels of ABCA1, G4, and G8 in hepatocytes and enterocytes, triggering a transcriptional mRNA response of the LXR-RXR heterodimer in the intracellular sterol sensor, which then transports cholesterol from the canalicular membrane's inner leaflet, followed by ATP binding and hydrolysis, which changes the appearance of the cholesterol molecule.[43-44] This results in a reduction in cholesterol absorption in the intestinal lumen, as well as cholesterol efflux via RCT (reverse cholesterol transport).[44-45] The LXR is regarded as a critical regulator of ABCG5 and ABCG8 mRNA expression, and the LXR agonist T0901317 significantly increased ABCG5 and ABCG8 expression in the small intestine and liver of wild type but not LXR knockout mice (Figure 1).[46-47]

LXR Mediated GLUTs (GLUT4) in Glucose Transport, Storage and Utilization

Glucose transporters are a large group of membrane-bound proteins found in all mammalian organs that aid glucose transport across the plasma membrane.[48] GLUT1 and GLUT4 are two types of GLU transporters that play a critical role in glucose transport and hence maintain glucose homeostasis.[49] GLUT1 is widely expressed in central nervous system erythrocytes and endothelial barrier cells, whereas GLUT2 is generally expressed in liver cells, pancreatic beta cells, and kidneys (particularly renal tubular cells), and GLUT4 is widely expressed in striated muscles (skeletal and cardiac muscles).[50] However, a malfunction in the GLUT4 signaling system in adipose tissue plays a significant role in obesity and associated syndromes.[51] Glut 4 receptors have a modest Km value, which indicates they have a moderate glucose infinity.[52] GLUT4 is responsible for insulin-dependent glucose absorption.[53] When insulin levels are low, GLUT4 is predominantly found in the intracellular membrane. Intracellular GLUT4 redistributes to the plasma membrane in response to a rise in circulating insulin levels following the intake of a carbohydrate-containing meal, therefore initiating glucose uptake and metabolism in these tissues and avoiding fast blood glucose rises (Figure 2).[54]

In adipose tissue and skeletal muscles, liver X receptors are the immediate receiver (or direct target) of glucose transporters like GLUT4.[55] LXR can transmit ligand-activated GLUT4 gene transcription and play a significant role in GLUT4 essential or basal regulation in adipose tissues and skeletal muscles.[56-57] LXRE (Liver X receptor elements) are positive regulators of GLUT4 and are found on the promoter region of the gene.[58] LXRs are activated as soon as blood glucose or cholesterol levels reach a certain threshold. LXR then causes the formation of an LXR-RXR heterodimer, which acts on GLUT4 receptors and triggers a series of actions.[58-59] In adipose tissues and skeletal muscles, liver X receptor elements operate directly on the GLUT4 promoter region, causing insulin-dependent glucose flow.[60] In skeletal muscles, LXR stimulation causes an increase in glucose and fatty acid absorption, fatty acid storage, and glucose and fatty acid oxidation, whereas in adipose tissue, LXR stimulation causes an increase in glucose uptake and aids in fatty acid storage.[61-62]

It is most often expressed by LXR receptors in brown and white adipose tissues, and very rarely by LXR receptors. LXR increases the expression of the GLUT4 gene in adipose tissue, resulting in increased glucose absorption and more fat being stored as neutral fat. By directly inducing lipogenic genes like SREBP-1c and FAs and increasing substrate availability for triglyceride synthesis, LXRs in adipose tissues promote a surge in triglyceride (neutral fat) formation. GLUT4 causes an increase in glucose uptake by tissues, a decrease in lipogenesis, a decrease in lipid oxidation, and an increase in lipolysis in brown adipose tissues, but a rapid increase in lipid oxidation, adipocyte differentiation, glucose uptake, reverse cholesterol transport, and lipogenesis in white adipose tissues.[63]

This method of GLUT4 mediation via liver x receptors has been shown to be effective in the treatment of obesity. Obesity is linked to a change in GLUT4 expression in the skeletal muscles, according to evidence.[64] Up regulating GLUT4 with the aid of liver X receptors increases glucose absorption in the peripheral bloodstream, which might be used to treat obesity.[65] In contrast, Ni M *et al*. discovered that Glut4 was up regulated by GW3965 (a selective LXR agonist) in 3T3-L1 cells *in vitro* and in murine adipose tissue, and that GLUT4 activation through LXR lowered blood glucose, improved glucose tolerance, and upregulated Glut4 expression in the adipose tissue of obese mice (ob/ob mice or diet-induced obese mice), but not.[66-67] Along with this, it was discovered that various plants used in high fat diet induced obesity, such as Bauhinia variegate and Bauhinia megalandra, increase glucose uptake via GLUT4 receptors, but the LXR mediated response to plant insulin is still unknown (Figure 3).[68-69]

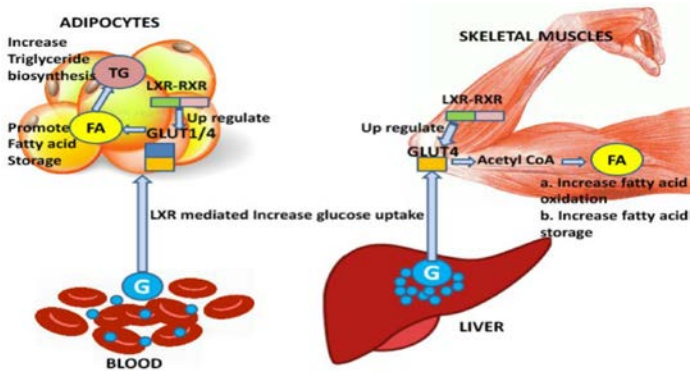

Figure 3: LXR mediated increase glucose uptake by GLUT4 receptors.

RATE LIMITING ENZYMES MEDIATED BY LIVER X RECEPTORS

The rate-limiting enzymes in the Embden Meyerhof Parnas Pathway are phosphophenol pyruvate carboxykinase (PEPCK), glucose-6-phosphate (G6P), and fructose-6-phosphate (F6P).[70-71] PEPCK acts as a juncture between the kreb cycle and glycolysis, removing carboxyl groups (decarboxylation) and releasing carbon dioxide. G6P and F6P are direct enzymes engaged in EMP (glycolysis), whereas PEPCK acts as a juncture between the kreb cycle and glycolysis.[72] The liver is involved in a variety of activities in the body, including glycogen storage, bile acid synthesis, blood glucose control, lipid metabolism, energy metabolism, and detoxification.[73] During fasting, the liver maintains a constant supply of glucose to the body through hepatic gluconeogenesis, whereas in the postprandial state (i.e. after a meal), it increases hepatic glucose absorption, which promotes glycogen synthesis and accelerates the lipogenesis process. Metabolic diseases are caused by any error in the control of lipid and hepatic carbohydrate metabolism.[74-75]

Stulnig *et al.*[76] were the first to show that LXR activation causes downregulation of critical regulatory genes in the gluconeogenesis process in the liver of wild type mice, and that LXR agonists ameliorate diabetes and obese conditions by boosting hepatic glyconeogenesis. Overexpression of PEPCK in adipose tissue owing to increased fatty acid re-esterification leads to obesity, according to Franckhauser S *et al.*,[76] although therapy with LXRs reduces this process. A synthetic LXR agonist, GW3965, improves glucose tolerance in a mouse model of diet-induced obesity by down regulating PEPCK and G6P, which stimulates hepatic utilization, bound hepatic glucose output, and peripheral glucose uptake.[77] Synthetic LXR agonists like T0901317 and GW3965 significantly decreased hepatic glucose production in both ZDF and high-fat fed rats in several tests, indicating that they might be useful in the treatment of obesity.[78-79]

T0901317 was discovered to lower the expression of the glucocorticoid receptor and 11beta-hydroxysteroid dehydrogenase type 1 (the enzyme that aids the synthesis of active corticosterone in the livers of wild type and db/db mice).[80] Reduced glucocorticoid productivity might potentially help to lower hepatic gluconeogenesis, since LXR has been found to inhibit 11-HSD1 expression, which is a key enzyme in the transition of inactive corticosteroids to active corticosteroids.[81] In the LXR-mediated lipogenic effects, LXR-mediated effects on glucose metabolism were more pronounced than LXR-mediated effects on glucose metabolism (Figure 4).[82]

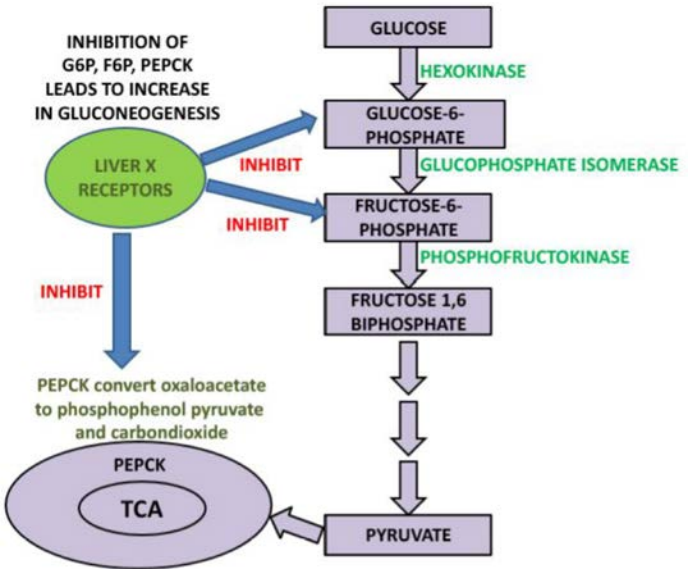

Figure 4: Rate Limiting Enzymes mediated by Liver X Receptors.

Future Perspective

Liver X receptors have been linked to atherosclerosis, diabetes, inflammatory diseases, neurological problems, and obesity, according to recent research. LXRs have a key role in cholesterol, glucose, and bile acid production metabolism.[83] ABC genes, GLUTs, PPARs, ApoE, CETP, FAS, SREPB, and LPL are some of the target genes for LXRs. These data imply that LXR is involved in the metabolic regulation network. Energy consumption, thermogenesis, adipokine production regulation, insulin sensitivity, and glucose tolerance are all thought to be influenced by LXRs. LXR has a diet-dependent involvement in obesity, but it is important in its therapy. Importantly, the beneficial effects of LXRs on blood glucose levels and RCT (reverse cholesterol transfer) must be balanced against the undesirable consequences of enhanced lipogenesis, particularly in mammals, for effective pharmacological intervention.[84] These concerns, as well as the production of tissue LXR-specific medicines, will most likely be the focus of research during the next decade. Academic institutions and pharmaceutical companies may well collaborate to develop analogues that specifically target liver X receptors and thus treat LXR signaling to combat the new wave in diseases caused by improper lipid, cholesterol, and glucose metabolism, including obesity, which is a leading cause of other metabolic diseases.

CONCLUSION

LXRs are typical lipogenic receptors found in a variety of tissues, such as adipose tissue, skeletal muscles, the liver, and the gut, where they promote the conversion of cholesterol to bile acid, boost reverse cholesterol transport, and promote cholesterol excretion from the body. Furthermore, LXRs serve as a key mediator for insulin-dependent glucose transport via GLUT receptors. Thus, stimulation of liver X receptors has been demonstrated to be anti-obesity, increase glucose absorption by peripheral tissues, eliminate accumulated lipids from the body, and decrease hepatic glucose production rate. As a result, LXRs are an intriguing strategy in obesity animal models. Despite the fact that LXR and LXR play distinct functions, both appear to be important targets in the treatment of obesity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

LXR: Liver X Receptors; **cDNA:** Complementary DNA; **ABCA 1:** ATP-binding cassette- 1 family; **ABCG1:** ATP Binding Cassette Subfamily G Member 1; **ABCG8:** ATP Binding Cassette Subfamily G Member 8; **GLUT4:** insulin-regulated glucose transporter 4; **GLUT1:** insulin-regulated glucose transporter 1; **G6P:** Glucose 6 phosphate; **F6P:** Fructose 6-phosphate; **GW3965:** selective liver X receptor (LXR) agonist; **NR1H3:** nuclear receptor subfamily 1; **LXRα1:** Liver X Receptor α1; **LXRα2:** Liver X Receptor α2; **LXRα3:** Liver X Receptor α3; **HCT116:** human colorectal carcinoma cell line.

SUMMARY

- Obesity is linked to the development of a number of metabolic diseases.
- Liver X receptors are key regulators of lipid metabolism and glucose transport, making them attractive therapeutic targets for obesity therapy
- Liver X receptors are key regulators of lipid metabolism and glucose transport, making them attractive therapeutic targets for obesity therapy.
- LXRs boost cholesterol transport in the reverse direction.
- LXRs increase cholesterol excretion via feces by promoting cholesterol efflux to the gall bladder and inhibit cholesterol absorption in the gut.
- LXRs improve cholesterol to bile acid conversion in the liver; LXRs promote insulin-mediated basal glucose transport via GLUT4 receptors; LXRs decrease hepatic glucogenesis by inhibiting PEPCK, G6P, and F6P enzymes.
- Liver X receptors (LXRs) are key regulators of lipid, cholesterol, and glucose metabolism, making them a promising therapeutic target for obesity therapy.

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