Review Article

Perspectives on regulatory actions of liver X receptors (LXR) in obesity

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Abstract

Liver X receptors are cholesterol sensing receptors and are the members of nuclear receptor superfamily. LXRs are generally present in two isoforms LXR α and LXR β. Initially LXRs were isolated as Orphan receptors form a rat cDNA libraray from oligonucleotide probe. In this review we focus on regulatory actions of LXR in obesity. LXRs directly act on various target genes like ABCA1, ABCG1, ABCG8, GLUT4, and various other rate limiting enzymes like PEPCK, G6P, F6P and thus play a crucial role in the therapeutics of obesity. LXR potentially interferes with obesity by different signaling pathways. The first is through ABC genes by promoting elimination of excess body cholesterol through lipid removal pathway from cholesterol loaded macrophages and intestinal lumen. The second is through by the up-regulation of GLUT4 expression by increasing glucose uptake by peripheral tissues and the third approach is through the inhibitory action on rate limiting enzymes PCPCK, G6P, F6P that ultimately suppress hepatic glucose production. These physiological roles of LXR indicate that it is an interesting potential target for drug treatment of obesity.

Keywords: liver X receptors, obesity, ABC transporters, GLUT4, rate limiting enzymes (PEPCK, G6P, F6P)

Introduction

Liver X receptors (LXRs) belongs to the superfamily of nuclear receptors and are ligand activated transcription factor that generally activated by the oxidized products of cholesterol (Oxysterols) (Apfel et al., 1994; Janowski et al., 1996, 1999). LXRs are central regulators of cholesterol, free fatty acids, and glucose metabolism. LXRs act as cholesterol sensors: when the concentration of cholesterol increases, as a result of increasing oxidized product of cholesterol the LXRs activates transcription genes that protect cell from cholesterol overload (Zhao et al., 2009).

Initially LXRs were isolated as orphan receptors (i.e receptors with no known physiological effect) from a rat liver c DNA library with the help of oligonucleotide probes (Apfel et al., 1994; Laudet et al., 2002). Currently too LXRs are isolated in the same manner using oligonucleotide probes because of various advantages like high specificity, resistance to other RNAses, instant availability of deoxynucleotides and better economic availability (Kreil et al., 2006).

The LXR molecules have four main functional domains in its structure: (1) An amino-terminal ligand-independent activation function domain (AF-1), which may trigger transcription when the ligand is not available on site; (2) A DNA-binding domain (DBD) containing two zinc fingers; (3) A hydrophobic ligand-binding domain (LBD) required for the formation of receptor diamers and ligand binding; and (4) a carboxy-terminal ligand-dependent transactivation sequence (activation function-2 (AF-2) domain) that activate transcriptional response through ligand binding (Rechavi et al., 2003).

In mammals Liver X receptors generally exist in two isoforms LXR α and LXR β that form obligate heterodimer with retinoid X receptors (RXR) (Edward et al., 2002). LXR α generally exists in three forms LXRα1, LXRα 2, LXRα 3 and LXR β exist in only one form (Chen et al., 2005; Repa et al., 2002). LXRs are closely related to PPARs, FXR, RXR, VDR receptors (Bettowrki et al., 2008). Till now no other new LXR isoform have been reported.

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The chief function of LXRs is to maintain cellular cholesterol homeostasis and glucose metabolism, but in addition to that LXRs also modulate immune responses in mammals by regulating gene expression in macrophages that turn out as a therapeutic target for treatment of many chronic inflammatory disorders (Gonzalez et al., 2010). Recent studies have revealed that LXR is a potential therapeutic agents in the treatment of atherosclerosis by adjusting metabolic and inflammatory gene expression (Millatt et al., 2003; Geyeregger et al., 2006). Activation of liver X receptors inhibit hepatic gluconeogenesis and lowers blood glucose level thus beneficial in the treatment of diabetes mellitus (Geyeregger et al., 2006).

Currently it has been observed that LXR activation in animal models suggest to have crucial role in the prophylaxis of common metabolic disorders, including hyperlipidemia, atherosclerosis and diabetes and obesity (Quinet et al., 2009; Nordstrom et al., 2005; Kase et al., 2007). In rodents, treatment with different LXR agonists leads to reduction in serum and hepatic cholesterol levels (Alberti et al., 2001).

In our present review we are focusing on the role on liver X receptors in obesity. Obesity is a public health complication that has elevated concern worldwide. (Korach-Andre et al., 2011) showed that both liver X receptors isoforms i.e. LXR α and LXR β increase activity of brown adipose tissue thus increase LXR mediated energy expenditure and thus proved to be a potential target for the treatment of obesity. LXR activation by GW3965 improved glucose tolerance in a mouse model of diet-induced obesity by up regulation of GLUT4 receptors that are direct target genes for liver X receptors (Laffitte et al., 2003). In another study it was revealed that basal glucose uptake was also enhanced after activation of LXR by T0901317 (a potent LXR agonist) in 3T3-L1 cells and in vitro differentiated human adipocytes (Ross et al., 2002).

Types of liver X receptor

Liver X receptors generally exists in two isoforms:

Liver X receptors α: LXR α is a isoform of LXR receptor that is encoded by NR1H3 gene that is generally located on chromosome 11 (Miyata et al., 1996; Willy et al., 1995). 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 (Chen et al., 2005; Repa et al., 2002), LXRα 2 mainly expressed in human testies 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 (Laurencikiene et al., 2012). 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) (Ou et al., 2011), the upregulation of LXR α is regulated by the activation of LXRE (LXR response elements) (Chen et al., 2009).

Liver X receptors β: LXR β is another isoform of LXR receptors encoded by NR1H1 gene that is generally located on chromosome 19 (Repa et al., 2002). Isoform LXR β (NR1H2) not abundantly expressed by all tissues (Repa et al., 2002) but LXR β is dominantly expressed by skeletal muscles that regulate lipogenesis and cholesterol efflux (Hessvik et al., 2010). Courtaut et al. (2015) 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).

Liver X receptors agonists and antagonists

The LXR agonists binds to Liver X receptors and thus activate it to produce certain biological responses where as LXR antagonists deactivates the Liver X receptors and thus inhibit the biological response driven by LXRs.

LXR agonists: Various natural and synthetic agonist analogues are there for initiating the biological response of LXRs. These are given in table 2.

Table 1. Difference between both isoforms of liver X receptors

S. 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, testies and lungs.	Less expressed by all tissues but dominantly expressed by skeletal muscles and colon cancer cell lines.
3.	**Exression**	Expressed through LXRE, SREBP and other essential cholesterol elements	Only expressed through LXRE.

LXR antagonists: Various substances inhibit the response of liver X receptors, few of them are given in table 3.

Transcriptional regulation of genes by LXRs

Various biological substances such as oxysterols, bile acids etc act as signaling molecule for the activation of various types of nuclear receptors (Janowski et al., 1996). Nuclear receptors are generally ligand activated transcription factors that regulate transcription of various genes and thus involved in various biological processes (Li et al., 2013). In the transcriptional regulation of liver X receptors, target genes get activated when LXR binds to some specific DNA sequences associated with those particular target genes (Zhao et al., 2009). LXRs binds to the isoforms of retinoid X receptors (RXR) i.e RXRa, RXRb and RXRc and thus in combination form constrain heterodiamers with each other (Makishima, 2006). LXRs generally regulate gene experssion via the activation of LXR response elements (LXREs) in the promotor region of DNA of target gene (Verreault et al., 2006). The constrain heterodiamer of LXR-RXR then activated LXR response elements (LXREs) that consist of two direct repeats AGGTCA spearated by four nucleotides (Li et al., 2013; Chawla et al., 2001). Through this mechanism LXRs known to regulate the various target genes such as polypeptide A3 and UDP Glucuronosyltransferase (Verreault et al., 2006), phospholipid transfer protein (Mak et al., 2002) etc.

Liver X receptors also known to regulate the transcriptional activity of various glucocorticoid receptors (Nader et al., 2012). Glucorticoids generally increases the transcription rate of glucose-6-phosphatase and its various enzymes and thus mediate gluconeogenesis and glycogenolysis (Lin et al., 1998). LXRs generally regulates the cholesterol turnover and the hepatic glucose metabolism by binding with various cholesterol metabolites which further heterodiamerise with Retinoid X Receptors thus leads to decrease the expression of glucose-6-phosphatase (Nader et al., 2012). LXRs also known to inhibit dexamethasone-stimulated GR transcriptional activity in HCT116 cells (Cell line human colon carcinoma) (Kino et al., 2007). But in case of HepG2cells LXRs regulate dexamethasone stimulated mRNA expression of endogenous glucocorticoid-responsive genes (Nader et al., 2012). LXRs also carry out the transcriptional regulation of Farnesyl pyrophosphate synthase (FPPS) that is a LXR target gene in astrocytes and neurons and play a major role in regulating cholesterol synthesis in the brain (Fukuchi et al., 2003). In

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

S. No.	LXR agonists	Type of agonists	Functions/ Mechanisms	References
1.	25-epoxycholestrol, 24 (s) hydroxyl cholesterol, 27-hydroxycolestrol and cholestenoic acid	Natural Ligands	Cholesterol metabolism, Glucose metabolism, Bile acid synthesis, Treatment of various metabolic disorders	Lehmann et al., 1997; Alberti et al., 2001; Huang et al., 2014
2.	GW3965	Selective agonists	Treatment of obesity, diabetes, atherosclerosis and inflammatory disorders.	Laffittee 2003; Joseph et al., 2003
3.	T0901317	Selective agonists	Treatment of atherosclerosis, obesity, prostate cancer, alzheimer and breast cancer.	Alberti et al., 2001; temml et al., 2014; Chuu et al., 2006; Im et al., 2011
4.	22 (R) hydroxyl cholesterol	Partial agonist	Treatment of prostate, breast cancer and various other metabolic disorders like obesity.	Chuu et al., 2006; Im et al., 2011
5.	Paxilline	Selective agonist	Potassium channel blocker	Bramlett et al., 2003
6.	Desmosterol	Selective agonist	Lipid metabolism	Vainio et al., 2005; Yang et al., 2006
7.	L-783483	Selective agonist	Cholesterol regulation	Menke et al., 2002
8.	TSPO	Selective agonist	Inducing the expression of LXRα, PPARα, ApoE, ABCA1 and ABCG4	Taylor et al., 2014
9.	Pravastatin	Selective agoists	Promoting CYP7A1 and ABCG5/ABCG8 expression through the PPARγ/LXRα pathway	Byun et al., 2014
10.	Metformin	Selective agonist	Promoting HO-1 and LXRβ expression through the AMPK-ATF1 pathway	Wan et al., 2013

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

S. No.	LXR Antagonists	Type of antagonist	Functions	References
1.	GSK2033	Selective LXR antagonist	Used in cell biology study as chemical probe. Treatment of inflammatory and autoimmune diseases	Solt et al., 2012; Zuercher et al., 2010; Griffett et al., 2016
2.	Cinnamamides	Selective LXR antagonist	Treatment of fatty liver (non-alcoholic). Decrease lipogenic gene expression.	Sim et al., 2015
3.	22 (S) hydroxyl cholesterol	Partial and dose dependent LXR antagonist	Treatment of skin fibroblasts.	Gondcaille et al., 2014
4.	Rhein	Selective LXR antagonist	Treatment of obesity and other metabolic disorders.	Sheng et al., 2012
5.	Geranylgeranyl pyrophosphate (GGPP)	Non selective LXR Antagonist	Down regulate mevalonate metabolism.	Beltowski, 2008
6.	Polyunsaturated fatty acids (PUFAs)	Competitive LXR antagonist	Downregulate SREBP-1c	Yoshikawa et al., 2002

addition to that Hepatocyte Nuclear Factor 4 α (HNF-4α) controls transcriptional regulation of LXR α (a isoform of LXR) that plays a major role in cholesterol homeostasis, overexpression of HNF-4α in HEK 293T cells increased the expression of all LXRα thus alter cholesterol homeostasis.

LXR mediated ATP transport in cholesterol efflux

ATP binding cassette (ABC) transporters plays pivotal role in enhancing acceptor's cholesterol efflux through liver X receptors, ABCA1, ABCG1, ABCG4, ABCG5, ABCG8 of ABC transporter family are target genes of LXRs (Zhu et al., 2012). ATP binding cassette transporters are also called cholesterol efflux regulatory protein (CERP) encoded by various target genes like ABCA1, ABCG4, ABCG5, ABCG8 (Luciani et al., 1999; Zhu et al., 2012) which are major regulator for cholesterol homeostasis (Luciani et al., 1999). ABCA1 protein is essential for the efflux of extra cellular cholesterol to Apo Receptors such Apo 1 (the first step in cholesterol transport) (Hozoji Inada et al., 2011). Transcriptional level of LXR receptor regulate ABCA1 mediated cholesterol efflux (Donkin et al., 2010). ABC transporter contain 4 domains (a) two membrane spaning transmembrane domains (b) two nucleotide binding domains, hydrolysis of ATP in nuclear binding domain provide energy for transport of substrate (Vaisman et al., 2001). Laun et al. (1999) established that ABCA1 play crucial role in cellular apolipoprotein mediated lipid removal pathway.

ABCA1 is an inherent membrane transporter that play a crucial role in generation of high density lipoproteins (HDL) (Bodzioch et al., 1999). ABCA1 mediate post transational regulation as well as transcriptional response to maintain cholesterol homeostasis (Zhu et al., 2012). Along with that ABCA1 also play remarkable role in removing lipid from cholesterol loaded macrophages (Vaisman et al., 2001), it tremendously occurs in inhabitant macropahges where it play important role in cholesterol transport (Schaefer et al., 1981; Meurs et al., 2008). Elevation of cholesterol loaded macrophages inside the body serves as a key for the activation of LXR/RXR heterodimer (Venkateswaran et al., 2000; Vaughan et al., 2005) which further bind to the promoter region of ABCA1 and activates ABCA1 transcription (Costet et al., 2000; Schwartz et al., 2000). Macrophages cholesterol then get oxidized and get converted to oxysterol that are prime activator of LXR (Vaughan et al., 2005). LXR-RXR heterodimer act as sensor for cellular cholesterol that further functions as a mediator for cholesterol efflux by initiating the expression of cholesterol shuffling vehicle i.e. ABCA1 and Apo A-1, abnormal increased expression of these vehicles leads to cholesterol dys-homeostasis (Akran et al., 2010).

At cellular level activation of LXRs initialize the response of ABCA1 and ABCG1 genes and thus transport cellular cholesterol to Apo A-1 (produced by liver), Apo A-1 accept free cholesterol and phospholipids from macrophages that further form HDL particles furthermore those nascent HDL get mature into spherical HDL with the help of cholesterol esterifying enzyme (lysolecithin cholesterol acyl transferase) and cholesterol esters. Mature HDL then move to liver by SR-B1 (Scavenger receptor class B type 1) to other lipoprotein by CETP (Cholesteryl ester transport protein) (Oram and Heinecke et al., 2005; Shah et al., 2001; Rye et al., 2004; Zhu et al., 2012). HDL then moves to liver and cause increase in LXR dependent 7-α-hydroxylase expression result in increase bile acid synthesis and elimination. With increase in the biliary excretion there is increase in intestinal uptake of cholesterol by LXR mediation that eliminate excess body sterol by ABC sterol transport (Repa et al., 2002; Berge et al., 2005). After endocytosis low density lipoproteins get moved to hepatocytes by LDLR (Low density lipoprotein receptors),

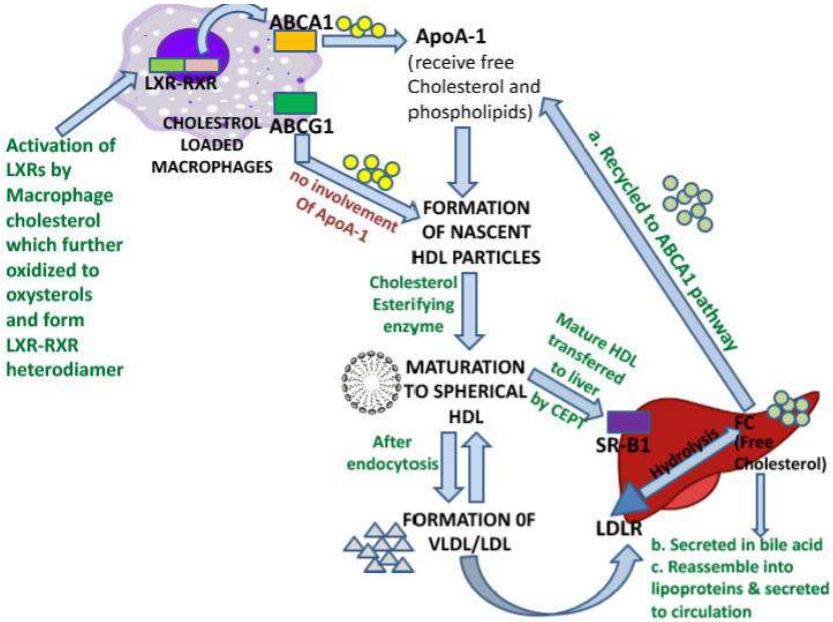

Figure 1. Cholesterol transport by ABCA1 and ABCG1 mediated by liver X receptors

then LDL get hydrolysed to free cholesterol, from where it either get recycled in ABCA1 pathway which further secreted in bile acid or get reorganized into lipoproteins and is secreted to circulation (Oram and Heinecke, 2002).

In contrast ABCG1 carry out the mediation of cholesterol efflux to HDL particles but not through Apos (Kennedy et al., 2005). Interestingly, the loss of ABCA1 and ABCG1 in mice model results in a synergistic increase in tissue lipid accumulation, induction of LXR agonist help to manage cellular cholesterol overload (Out et al., 2008; Yvan-Charvet et al., 2007; Aye et al., 2010).

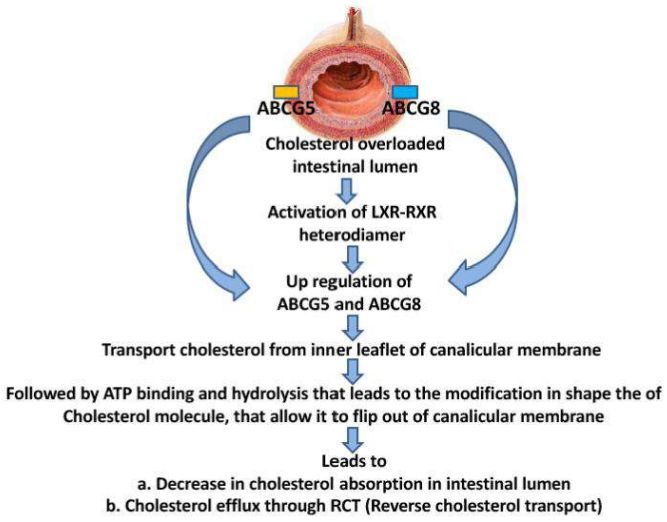

Figure 2. LXR mediated cholesterol transport in intestinal lumen

Obesity is corresponding to the accumulation of both cholesterol and TGs (triglycerides) in adipose tissues that generally occurs due to impairment in the expression of ABC transporters (Yu B-L et al., 2010; Dugail et al., 2003). Activation of LXR up regulate ABCA1, ABCG1 and ABCG8 expression and thus play potential role in the therapeutics of obesity and related syndrome by facilitating ABCA1 mediated efflux of cholesterol and phospholipids to lipid-poor lipoproteins (e.g., apoA-I), and its induction may contribute to the increase in plasma HDL levels seen with LXR ligand treatment (Repa et al., 2000).

Two other member of ABC transporters family are ABCG5 and ABCG8 genes encoded by proteins sterolin 1 and sterolin 2 respectively, which play a major role in regulation of sterol or cholestrol absorption and excretion (Lee et al., 2001). Both of them are predominately expressed in enterocytes and is a selective tool for sterol excretion by the liver into bile (Patel et al., 1998). Berge et al., showed that ABCA1, ABCG5, ABCG8 are direct genes for the activation of LXR/RXR heterodiamer in liver and intestine. In in situ hybridization LXR agonist elevate the level of ABCA1, G4 and G8 in hepatocytes and enterocytes that initiate transcriptional m RNA response of LXR-RXR heterodiamer in intracellular sterol sensor, that further transport cholesterol from the inner leaflet of canalicular membrane, followed by ATP binding and hydrolysis that leads to modification in the appearance of cholesterol molecule and thus flipping toward the outer leaflet of canalicular membrane (Wittenbury et al., 2002; Yu et al.,

2014). This whole process further leads to decrease in cholesterol absorption in intestinal lumen and leads to cholesterol efflux through RCT (Reverse cholesterol transport) (Graf et al., 2002; Yu et al., 2014). LXRα is considered as the one of the crucial regulator of ABCG5 and ABCG8 mRNA expression, in addition to that the LXR agonist T0901317 markedly increase the expression of ABCG5 and ABCG8 in the small intestine and liver of wild type but not LXRα knockout mice (Gonzalez-Granillo et al., 2012; Veen et al., 2007).

LXR mediated GLUTs (GLUT4) in glucose transport, storage and utilization

Glucose transporters are immense category of membrane obligated proteins that are found in all mammalian tissues and promote transport of glucose across plasma membrane (Hruz et al., 2001). Among all categories of GLU transporters GLUT1 and GLUT4 impersonate crucial part in glucose transport and thus sustain glucose homeostasis (Laffitte et al., 2003). GLUT1 is ubiquitously found in erythrocytes and endothelial barrier cells of central nervous system, where as GLUT2 is widely exhibited by liver cells, pancreatic beta cells and kidneys (specifically renal tubular cells), GLUT4 is extensively expressed by adipose tissues and striated muscles (skeletal and cardiac muscles) (Thorens et al., 2010). But enormously defect in the signaling pathway of GLUT4 in adipose tissue plays extended role in obesity and related syndrome Favaretto et al., 2012). Glut 4 receptors have moderate Km values that means they have moderate infinity for glucose (Olson et al., 2012). GLUT4 generally carry out insulin dependent glucose uptake (Ebeling et al., 1998). Under the condition when insulin level is low, GLUT4 primarily reside in intracellular membrane. When there is rise in circulating insulin levels after ingestion of a carbohydrate containing meal, intracellular GLUT4 redistribute to the plasma membrane, thus initiate glucose uptake and metabolism in these tissues and preventing rapid elevations in blood glucose level (Kahn, 1996).

Glucose transporters such as GLUT4 are the immediate recipient (or direct target) by liver X receptors in adipose tissue and skeletal muscles (Laffitte et al., 2003). LXR able to transmit ligand activated transcription of GLUT4 genes and perform important role in essential or basal regulation of GLUT4 in adipose tissues and skeletal muscles (Laurencikiene et al.,2012; Kase et al 2005). LXRE (Liver X receptor elements) are located on GLUT 4 promoter region and are positive regulators of GLUT4 (Dalen et al, 2000). Certain levels of glucose or cholesterol in blood causes immediate activation of LXRs. LXR then leads to generation the of LXR-RXR heterodiamer, which further act on GLUT4 receptors and perform cascade of various events (Kase et al., 2005; Dalen et al., 2003). Liver X receptor elements directly act on GLUT4 promoter region in adipose tissues and skeletal muscles, thus cause insulin dependent glucose flux (Dalen et al., 2003). In skeletal muscles LXR stimulation cause increase in uptake of glucose and fatty acid, increase storage of fatty acids and increase glucose and fatty acid oxidation, where as in adipose tissue there is increase in uptake of glucose and aid in storage of fatty acids (Steffensen et al., 2006; Olson et al., 2012).

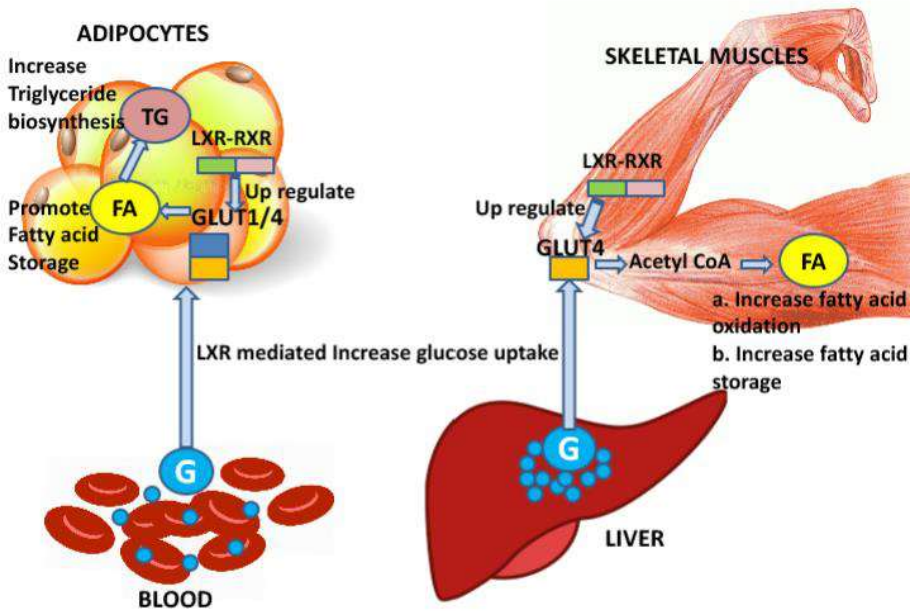

Figure 3. LXR mediated increase glucose uptake by GLUT4 receptors

More precisely in brown and white adipose tissues it is most commonly expressed by LXRα and very less by LXRβ receptors. LXR α causes up regulation of GLUT4 gene and thus increase its expression in adipose tissue that leads to increase in glucose uptake and more fat stored as neutral fat. LXRs in adipose tissues causes rise in triglyceride (neutral fat) accumulation by direct inducement of lipogenic genes like SREBP-1c and FAs and also increase substrate availability for triglyceride synthesis. In brown adipose tissues GLUT4 causes increase in glucose uptake by tissues, decrease in lipogenesis, decrease in lipid oxidation and increase in lipolysis, where as in white adipose tissues it causes rapid increase in lipid oxidation, increase in adipocyte differentiation, increase in glucose uptake, increase in reverse cholesterol transport and lipogenesis (Laurencikiene et al., 2012).

This approach of mediation of GLUT4 by liver x receptors is proved to be a important approach for the treatment of obesity. Evidences showed that altered expression of GLUT4 in the skeletal muscles leads to obesity (Pederson et al., 1990). Up regulation of GLUT4 with the help of liver X receptors increase peripheral uptake of glucose that serve as a potential approach for the treatment of obesity (Dalen et al., 2003). In contrast, Laffitte et al. (2001) found that Glut4, was upregulated by GW3965 (a selective LXR agonist) in 3T3-L1 cells *in vitro* and in murine adipose tissue, GLUT4 activation through LXR lowered blood glucose, improved glucose tolerance and upregulated the Glut4 expression in adipose tissue of obese mice (ob/ob mice or diet-induced obese mice), but not in that from lean mice and thus helpful in the treatment of obesity (Laffittee et al., 2003; Grefhorst et al., 2005).

Rate limiting enzymes mediated by liver X receptors

Phosphenol pyruvate carboxykinase (PEPCK), Glucose-6-phosphate (G6P), fructose 6 phosphate (F6P) these all are the rate limiting enzymes in Embden Meyerhof Parnas Pathway (Desantis et al., 1988; Holyoak et al., 2006). G6P and F6P are the direct enzymes involved in EMP (glycolysis) where as PEPCK act as juncture between kreb cycle and glycolysis, PEPCK generally involve in removal of carboxyl group (decarboxylation) and release carbon dioxide (Holyoak et al., 2006; Jia et al., 2010). Liver play plethoric role in body functioning, it is generally involve in multiple processes such as glycogen storage, production of bile acid, regulation of blood glucose, lipid metabolism, energy metabolism and detoxification (Postic et al., 2004). During fasting liver sustain continuous supply of glucose to body by hepatic gluconeogenesis along with that in post prandial state (i.e after meal time) it enhance uptake of hepatic glucose that further promote production of glycogen and increase the process of lipogenesis. Any malfunctioning in the regulation of lipid and hepatic carbohydrate metabolism leads to cause metabolic disorders (Fronzo et al., 1992; Rizza, 2010).

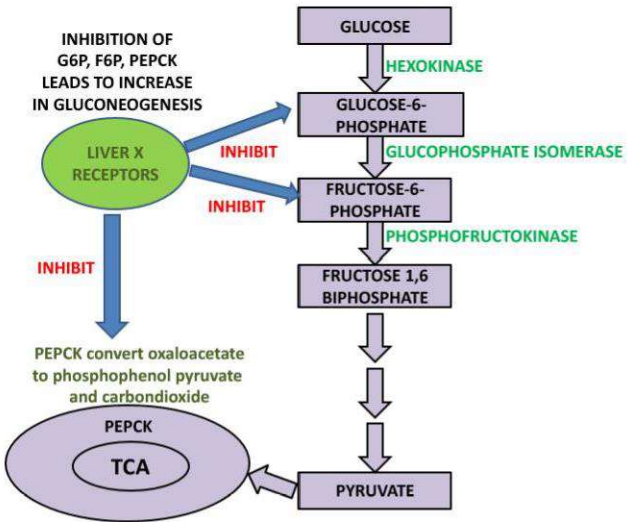

Figure 4. Rate limiting enzymes mediated by liver X receptors

Stulnig et al. (2002) was first to demonstrate that LXR activation resulted in manifestation of downregulation of the key regulating genes in the process of gluconeogenesis in the liver of wild type mice, further more LXR agonist improve the diabetic and obese condition by increasing hepatic glyconeogenesis. Franckhauser et al. (2002) showed that over expression of PEPCK in adipose tissue due to increased fatty acid re-estrification leads to obesity but treatment with LXRs show decrease in this process. In murine model of diet induced obesity, a synthetic LXR agonist i.e GW3965 improve glucose tolerance leads to down regulation of PEPCK, G6P that further stimulate hepatic utilization, bound hepatic glucose output and ameliorate pheripheral glucose uptake (Laffitte et al., 2003). Various experiments showed that synthetic LXR agonists like T0901317 and GW3965 noticeably reduced hepatic glucose output in both ZDF and high-fat fed rats respectively that proved to be a noticeable approach in the treatment of obesity (Cao et al., 2003; Commerford et al., 2007).

Another possible mechanism include the suppression of glucocorticoid signaling, T0901317 was manifested to reduce the expression of glucocorticoid receptor and 11beta-hydroxysteroid dehydrogenase type 1 (the enzyme mediating synthesis of active corticosterone in liver in wild type and db/db mice (Liu et al., 2006; Stulning et al., 2002; Gremper et al., 2005). Since LXR has been found to supress 11β-HSD1 expression that is a key enzyme in conversion of inactive corticosteroids to active corticosteroids (Stulnig et al., 2002). The effects of suppressed glucocorticoid productivity may also help to decrease in hepatic gluconeogenesis. In the LXR-mediated

lipogenic effects, LXRα more predominantly showed LXR-mediated effects on glucose metabolism rather than LXR β (Commerford et al., 2007).

Conclusion

LXRs are the traditional lipogenic factors in various tissues including adipose tissue, skeletal muscles, liver, intestine where they assist the conversion of cholesterol to bile acid, increase reverse cholesterol transport and promote excretion of cholesterol from body. In addition to that LXRs also are the important mediator for the insulin dependent glucose transport with the help of GLUT receptors. Thus, activation of liver X receptors has been shown to be anti-obesity, improve glucose uptake by peripheral tissues, remove accumulated lipids from body and inhibit the rate of hepatic glucose production. This makes LXRs an interesting approach in obesity animal models. However both LXRα and LXRβ have separate roles but both seems to be a major target in the treatment of obesity.

Future perspective

The field of LXRs signaling is developing rapidly. New and rousing biological functions of LXRs are observed consistently. Recent studies suggest the role of Liver X receptors in atherosclerosis, diabetes, inflammatory disorders, neurological disorders and obesity. LXRs are the important regulators of the cholesterol metabolism, glucose metabolism, and bile acid synthesis (Zhao et al., 2009; Laffitte et al., 2003). LXRs act through various target genes like ABC genes, GLUTs, PPARs, ApoE, CETP, FAS, SREPB, LPL (Edwards et al., 2002). These findings suggest that LXR participate in regulatory network of all metabolic disorders. LXRs seem to be involved in energy consumption, thermogenesis, control of adipokine production, insulin sensitivity and tolerance to glucose. The role of LXR in obesity is diet dependent but play a crucial role in its treatment. Importantly, the advantageous effects of LXRs on blood glucose levels and RCT (reverse cholesterol transport) towards the unwanted effects on increased lipogenesis must be addressed properly, more especially in mammals for successful pharmaceutical intervention. The next decade of research will most probably focus on these issues and the development of tissue LXR-specific drugs that are challenges for the pharmaceutical industry. The combined work of academic institutions and pharmaceutical industries might well produce the analogues that more specifically work through mediation of liver X receptors and thus will treat intervention of LXR signaling to combat the worldwide increase in diseases caused by improper regulation of lipid, cholesterol and glucose metabolism, including obesity that is a lead cause of other metabolic disorder.

Authors Contribution

Yash Prashar: Conceived idea of the study, participated in its design, coordinated and helped to draft the manuscript. Also, performed statistical analysis

Manisha Singha: Performed laboratory work and participated in the sequence alignment and drafted the manuscript.

Imroze Singh: Performed laboratory work and participated in the sequence alignment and drafted the manuscript.

Conflicts of interest: Not declared.

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