Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

LXRs: The Key Regulators of Intermediary Metabolism in Metabolic Syndrome

Hassan Mehrad-Majd (Ph.D)[1]*, Javad Akhtari (Ph.D)[2], Yalda Ravanshad (MD)[1]

[1]*Clinical Research Unit, Mashhad University of Medical Sciences, Mashhad, Iran.*
[2]*Molecular and Cell Biology Research Center, Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Mazandaran University of Medical Sciences, Sari, Iran.*

ARTICLE INFO

Article type
Review article

Article history
Received: 16 Jan 2017
Revised: 7 Feb 2017
Accepted: 28 Feb 2017

Keywords
Liver X Receptor
Metabolic Syndrome
Metabolic Disorder

ABSTRACT

Metabolic syndrome and its various manifestations are considered to be a significant health epidemic in the developed and developing countries across the world. Metabolic syndrome is characterized by a series of metabolic abnormalities, such as central adiposity, insulin resistance, hypertension, glucose intolerance, and dyslipidemia. Patients with metabolic syndrome are at a higher risk of major complications, including fatty liver, type II diabetes mellitus, and cardiovascular diseases. Nuclear receptors are the key regulators of gene transcription, as well as several metabolic pathways. Among these receptors, LXRα and β play a major role in the regulation of lipogenesis, cholesterol/glucose homoeostasis, and inflammatory pathways through the induction or repression of target genes. In addition to metabolic homeostasis and diseases, lipogenesis and hypertriglyceridemia are regarded as the most significant adverse effects of liver X receptor (LXR) activation. Given the importance of lipid and carbohydrate metabolism and inflammation in the development of metabolic disorders, the present study aimed to review the impact of LXR signaling on the risk of metabolic syndrome and its phenotypes, with an emphasis on their potential therapeutic applications in the treatment of metabolic syndrome. In general, growing evidence supports the notion that LXRs may represent the potential drug targets for the treatment of metabolic syndrome.

Please cite this paper as:
Mehrad-Majd H, Akhtari j, Ravanshad Y. LXRs: The Key Regulators of Intermediary Metabolism in Metabolic Syndrome. Rev Clin Med. 2017;4(4):180-184.

Introduction

Metabolic syndrome, also known as syndrome X or insulin resistance, refers to a series of metabolic abnormalities, such as central obesity, dyslipidemia, insulin resistance, hyperglycemia, and hypertension (1). Patients with metabolic syndrome are at a higher risk of diabetes and cardiovascular diseases compared to normal individuals (2). Statistics suggest that the prevalence of the metabolic syndrome is on the rise across the world, while the patterns vary depending on the geographical region and ethnicity. The prevalence of the metabolic syndrome has been reported to increase at an alarming rate in Asia (3).

Developing proper strategies to reduce the incidence of the metabolic syndrome requires a thorough examination of the genetic and environmental contributing factors, as well as a comprehensive knowledge of the development and pathophysiology of this syndrome. Etiology of metabolic syndrome remains unknown. Similar to many other multifactorial diseases, the full expression of the syndrome depends on a complex interaction between genetic susceptibility and environmental factors (e.g., sedentary lifestyle and

***Corresponding author:** Hassan Mehrad Majd.
Clinical Research Unit, Mashhad University of Medical Sciences, Mashhad, Iran.
***E-mail:** mehradmajd.h@gmail.com*
***Tel:** 09151734425*

high-energy diets) (4).

Several large population-based studies have demonstrated that the mutations and polymorphisms in the genes associated with insulin resistance, obesity-related dyslipidemia, hypertension, chronic inflammation, and autonomic imbalance may be polygenic contributing factors to predisposing the components of the metabolic syndrome (5-10).

Identification of the genes associated with the metabolic syndrome could elucidate the mechanisms of the pathways leading to the metabolic syndrome, thereby discovering new molecular-based strategies for the treatment of metabolic disorders. Some epidemiological and animal studies, which have investigated the liver X receptor (LXR) genes in terms of the risk of metabolic syndrome and the related parameters, have denoted the potentially significant regulatory role of the LXRs in several metabolic signaling pathways that are involved in the metabolic syndrome. Accordingly, they support the hypothesis that the drugs targeting the LXRs may be beneficial in the treatment of metabolic disorders (11-16).

Liver X receptors (LXRα and LXRβ)

LXRs, commonly known as LXRα and LXRβ (encoded by the NR1H3 (nuclear receptor subfamily 1 group H member 3) and NR1H2 (nuclear receptor subfamily 1 group H member 2) genes, respectively), are ligand-dependent transcription factors belonging to the family of the nuclear receptors activated by oxysterols (17). As cholesterol sensors, LXRs sense the elevated cellular cholesterol and function in order to decrease the cholesterol level through the increased expression of the target genes associated with reverse cholesterol transport, intestinal cholesterol absorption, and cholesterol conversion into bile acid.

LXRα, which is encoded by the NR1H3 gene, is located on chromosome 11p11.2 and is expressed in the tissues involved in lipid metabolism, including the liver, spleen, kidney, small intestine, adipose tissue, and macrophages. LXRβ, which is encoded by the NR1H2 gene, is located on chromosome 19q13.33-q13.43 and is expressed throughout the body (18).

LXR-mediated gene regulation occurs through two mechanisms upon activation by glucose or the endogenous LXR ligands, including the cholesterol-derived oxysterols, particularly 22(R)-hydroxycholesterol, 24(S),25-epoxycholesterol, 24(S)-hydroxycholesterol, and 27-hydroxycholesterol (19, 20). One of the pathways is DNA-dependent, in which the LXR ligand is bound to the LXR response element of the target genes that are essentially involved in the lipid metabolism, lipogenesis, and cholesterol/glucose homeostasis after the formation of the heterodimer with the retinoid X receptor and recruitment of additional proteins, which are known as the co-factors in the nucleus (21, 22). The other pathway is an LXR response element-independent pathway, which interferes with the other transcription factor pathways (23).

Several co-regulators are involved in metabolic processes, including the peroxisome proliferator-activated receptor gamma coactivator 1-beta (PGC-1B), receptor-interacting protein 140 (RIP140), G protein pathway suppressor 2 (GPS2), and acetyl-coenzyme A synthetase 2 (ACS-2), which have been shown to interact with the LXRs and influence their transcriptional activity (24-26).

LXR Target Genes Involved in the Metabolic Syndrome

Depending on the nutritional state of the cell, LXR signaling induces the expression of various target genes that are involved in the lipid and glucose metabolism. Moreover, LXR has been shown to activate genes such as the sterol regulatory element binding protein 1c (SREBP-1c) (acting as a trigger for down-stream transcriptional events) (27), fatty acid synthase (FAS) (28), phosphoenolpyruvate carboxykinase (PEPCK) (29, 30), acetyl-CoA carboxylase (ACC) (involved in lipogenesis), and ATP-binding cassette transporters A (ABCA) (31) (involved in cholesterol transport).

According to the literature, LXRs could mediate the repression of inflammatory pathways through the mechanisms that are collectively known as trans-repression. Therefore, it could be inferred that the dysregulation of LXR signaling may increase the risk of metabolic syndrome.

Role of LXRs in the Regulation of Metabolic Functions

During the past decade, the physiological role of LXRs as the key regulators of several target genes involved in the cholesterol/glucose homoeostasis, inflammation, lipid uptake and efflux, and lipoprotein metabolism in different tissues has been investigated and confirmed.

In general, LXR activators promote the lipogenesis via the regulation of hepatic fatty acid biosynthesis in a SREBP1-c- and SREBP-1c-independent manner (32) and cellular transmembrane transport of the endogenous lipid substrates via the induction of ABCA1, ABCG1, ABCG5, ABCG4, and ABCG8 in human macrophages and intestine (35-33). Furthermore, they promote cholesterol homeostasis via inducing the transcription of the genes that protect the cells from cholesterol overload, as well

as cholesterol trafficking from the endosome/lysosome to the plasma membrane through the activation of Niemann-Pick type C (NPC1 and NPC2) expression in human macrophages (36).

Activation of LXRs results in bile acid synthesis and metabolism/excretion, reverse cholesterol transport (RCT), and cholesterol absorption/excretion in the intestine, while also inducing the expression of ABCA1 and ABCG1 cholesterol transporters and regulating the acceptors in the cholesterol efflux (e.g., apolipoprotein E [apoE], apoCI, apoCII, and apoCIV expression) in the adipocytes and macrophages (37). Another function of the LXR activators is the remodeling of lipoproteins through the control of modifying enzymes such as lipoprotein lipase (LPL) and phospholipid transfer protein (PLTP) in the liver and macrophages (38). Furthermore, they are involved in the hepatic conversion of excess carbohydrates into lipids via the regulation of the carbohydrate response element-binding protein (ChREBP) as a glucose-sensitive transcription factor.

LXR activation could increase the insulin-mediated glucose uptake into the adipose tissue and muscles via the up-regulation of the GLUT4 glucose transporter (39) and regulate inflammation and immunity through inducing classic inflammatory genes and various chemokines in response to bacterial lipopolysaccharide (LPS), tumor necrosis factor alpha (TNF-α) or interleukin1- β (IL1-β) stimuli, thereby inducing the expression of anti-inflammatory genes (39).

Evaluation of the gene expression in the LXRα- and LXRβ-deficient mice and LXR agonists has confirmed the numerous physiological roles of the LXRs (40-42). Accordingly, LXRs are essentially involved in many pathways associated with the onset of the metabolic syndrome, particularly in the HDL-cholesterol metabolism and fatty acid and carbohydrate metabolism in the liver, macrophages, and intestine.

LXRs as Potential Drug Targets for the Metabolic Syndrome

Considering that LXRs play a pivotal role in cholesterol metabolism and are the key regulators of lipogenesis affecting the systemic glucose homeostasis, recognition of the mechanisms through which the LXR signaling regulates various aspects of homeostasis has provided new insight into the pharmacological manipulation of the LXR pathways for therapeutic interventions on human metabolism (43). Ability of the LXRs to integrate metabolic and inflammatory signaling renders them appropriate for drug development purposes. In addition to the known endogenous oxysterols (i.e., oxidized derivatives of cholesterol) and ligands for LXR activation with similar affinities for both LXR isoforms, considerable effort has been made to develop the ligands of synthetic agonists in order to modulate the activity of LXR-signaling pathways.

Some synthetic LXR ligands have been generated to promote the cholesterol efflux, as well as to inhibit inflammation in-vivo, atherosclerosis, metabolic disorders, and inflammatory conditions in animal models, which suggests a broad spectrum of potential clinical applications (44). T0901317 and GW3965 are nonsteroidal compounds signifying such LXR activation, and their beneficial outcomes regarding cholesterol homeostasis have been confirmed in cell-base or in-vivo conditions in mice (45, 46). However, the data obtained the other in-vivo studies denote that the deleterious lipogenic effects of these first-generation synthetic ligands of LXR should be taken into account (27, 45, 46).

The lipogenic effects of LXRs are considered a major problem in the adoption of the strategies to develop LXR agonists. Recent efforts in this regard have benefited from the isoform-specific LXR ligands, which are among the most important options for the development of LXR ligands with partial agonistic properties and exhibiting a LXR subtype-specificity to activate or block the receptors in a tissue-specific manner (47). In other words, selective pharmacological activation of LXRβ might give rise to the cholesterol-related effects of LXR, while circumventing the lipogenic effects attributed to LXRα (48, 49). Recently, two synthetic LXR agonists of ATI-829([3a,6a,24-trihydroxy-24, 24- di(trifluromethyl)-5b-cholane]) and DMHCA ([N,N-dimethyl3-b-hydroxy-cholenamide]) have been developed, which selectively activate the LXR target gene expression in certain tissues with no impact on the genes involved in lipogenesis in the liver (50). These data suggest that developing LXR modulators with no effect on hepatic lipogenic genes may result in better therapeutic strategies.

Although several studies have investigated LXR agonists, the adverse lipogenic effects of the LXRs have prompted the development of LXR antagonists as an alternative approach for the pharmacological inhibition of LXR-driven lipogenesis and reduction of hepatic complications. According to the evidence from the studies focusing on the global loss of LXR activity, LXR antagonists might be of therapeutic application in the treatment of the metabolic syndrome through improving insulin sensitivity in a tissue-specific manner (51). In this regard, further investigation is required in

order to discover the proper balance between the positive and adverse effects of LXR agonists and antagonists on various aspects of the metabolic syndrome and other metabolic diseases before consideration for therapeutic purposes.

Conclusion

Considering the rising prevalence rate of the metabolic syndrome and its manifestations across the world, as well the associated consequences (e.g., type II diabetes and cardiovascular diseases), researchers have been concerned with the role of LXRs as the key regulators of intermediary metabolism in these receptors as targets for the development of new ligands for the treatment of the metabolic syndrome.

Some of the designed synthetic LXR ligands have been shown to have beneficial outcomes regarding cholesterol homeostasis, while also exerting certain adverse lipogenic effects. Therefore, further investigation is required to determine possible approaches to avoid these effects, especially in the case of high plasma levels of triglyceride. An alternative approach in this regard involves the selective pharmacological activation of the LXR subtypes through the development of LXR ligands with partial agonist properties or applying the LXR antagonists to repress the lipogenic gene expression in a tissue-specific manner.

In conclusion, it is notable that most investigations have demonstrated the beneficial outcomes of LXR activation in animal models, while no experiments have been conducted on humans. As such, considering the interspecies differences in metabolism and genetic evolution, these findings could not be applied to humans, and further human-based studies are needed to verify the animal-based findings.

Conflict of Interest

The authors declare no conflict of interest.

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