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Review Article

Liver X Receptor: A Potential Target for Hypertension

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ABSTRACT

The Liver X receptor (LXR) emerges as a key player in the intricate relationship between hypertension and cardiovascular health. According to recent research, LXRs bind to a non-canonical response area in the renin promoter to regulate the transcription of the renin gene, which may have an impact on blood pressure regulation. LXR agonists have also demonstrated potential in lowering the rise in blood pressure brought on by Angiotensin II (Ang II), in part due to their suppression of AT1 and AT2 receptor gene expression. LXRs may potentially affect hypertension by influencing the amounts of TNF and NF-κB. Furthermore, nitrite levels are raised by LXR agonists in both normotensive and hypertensive states. These findings demonstrate how LXR can be targeted at different phases of the management of hypertension, which makes it a compelling therapeutic target for additional research in the area of cardiovascular health

Keywords: Hypertension; Liver X Receptor; Cardiovascular disease; Renin-angiotensin-aldosterone system

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1. Introduction

Hypertension, defined as an increase in systolic, diastolic, or both blood pressures above normal ranges is widespread in both industrialized and developing countries, & its prevalence rises with age [1]. When the blood's long-term force against the artery walls is high enough to cause health issues like heart disease, it is referred to as hypertension or high blood pressure. The likelihood of developing additional health issues including heart disease, a heart attack, or a stroke increase with blood pressure [2].

The amount of blood your heart pumps, and the amount of resistance given by the arteries to the blood flow, influence your blood pressure. Your arteries become narrower as your heart pumps more blood pressure is measured in millimeters of mercury (mm Hg). Hypertension is the most common preventable risk factor for cardiovascular disease (CVD; including coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation, and peripheral artery disease), chronic kidney disease (CKD) is the greatest cause of death and disability worldwide, and it is linked to cognitive impairment [1] High blood pressure is still the greatest cause of mortality and disability [2] and it is expected to remain so in 2040 [3].

According to the 2003 Guidelines hypertensive blood pressure should be more than 140/90 mm Hg and according to 2017 Guidelines: hypertensive blood pressure should be more than 120/80mm Hg.

1.1 Types of Hypertensions

Primary (Essential) Hypertension

In 90–95% of instances, primary hypertension is defined as high blood pressure brought on by a nonspecific lifestyle and hereditary factors. Risk factors include high body weight, smoking, drinking alcohol, and eating a diet high in sodium.

Secondary Hypertension

Secondary hypertension is considered as high BP caused because of an obvious cause like chronic renal disease, constriction of kidney arteries, a hormonal problem, or use of contraceptive pills. Secondary BP contributes to the remaining 5–10% of cases.

1.2 Pathophysiology of Hypertension

1.2.1 BP regulation

This includes cardiac output, or the amount of blood the heart pumps out each minute, blood volume, and arterial tone, which is controlled by intravascular volume and neurohumoral systems. The sympathetic nervous system (SNS), the immunological system, natriuretic peptides, the endothelium, and the renin-angiotensin-aldosterone system (RAAS) are all involved in regulating physiological blood pressure. The failure or disruption of one or more of these factors may lead to elevated mean blood pressure, fluctuating blood pressure, or both. These conditions may eventually cause organ damage (such as left ventricular hypertrophy), chronic kidney disease, and cardiovascular disease [4].

1.2.2 Sodium Homeostasis

High blood Sodium content promotes water retention which in turn increases the Blood volume and blood pressure. Change in Systolic Blood pressure of a minimum of 10 mmHg under a few hours of ingestion of salt can give salt sensitivity. Individuals who are salt-sensitive have underlying endothelial dysfunction as a result of genetic or environmental factors. Because of their high salt load-induced overproduction of transforming growth factor (TGF) and low levels of accessible nitric oxide, these patients are more susceptible to

oxidative stress and fibrosis. Even in those who are resistant to salt, a prolonged high-salt diet can cause endothelial dysfunction and alter gut flora, which can raise salt sensitivity and cause hypertension [5]. Consuming salt stimulates T helper cells, which in turn promotes autoimmunity [5].

1.2.3 Renin Angiotensin Aldosterone System

An important part of the pathogenesis of hypertension is the role of the RAAS in regulating blood pressure. In addition to playing a significant role in controlling blood pressure, it is in charge of Na+ retention, pressure natriuresis (which is defined as decreased Na+ reabsorption and increased Na+ excretion), salt sensitivity, vasoconstriction, endothelial dysfunction, and vascular damage [4]. It controls the kidney's pressure-volume equilibrium. Renin and its precursor pro-renin are produced and stored by the kidney's juxtaglomerular cells, which release them in response to external stimuli. Renin cleaves angiotensinogen to produce angiotensin I. The RAAS produces angiotensin II, which is what causes hypertension.

1.2.4 Natriuretic peptides

ANP and BNP, the atrial and brain natriuretic peptides, regulate hypertension and salt sensitivity, respectively. Their significant natriuretic and vasodilator properties enable the maintenance of blood pressure and Na+ homeostasis during Na+ loading [6]. ANP and BNP are released in response to a Na+ load through atrial and ventricular stretch. This results in systemic vasodilation, a drop in plasma volume (from fluid transfers from the intravascular to the interstitial compartment), and a reduction in blood pressure [7]. Direct effects include decreased activity of the sodium-glucose co-transporter and Na+-K+-ATPase in the proximal tubule, as well as inhibition of the epithelial sodium channel in the distal nephron. Two indirect effects are inhibition of aldosterone release and renin. A shortage of natriuretic peptides exacerbates hypertension. Corin is a serine protease that is mainly expressed in the heart and is responsible for converting the ANP and BNP precursors pro-ANP and pro-BNP to their active forms. Corin deficiency has been linked to volume overload, cardiac failure, and salt-sensitive hypertension [8]. The lack of natriuretic peptide is indeed linked to insulin resistance and type 2 diabetes. Obesity has been associated with natriuretic peptide shortage, which is thought to be caused by adipose tissue overexpression of the natriuretic peptide scavenger receptor NPR-C [9].

1.2.5 Sympathetic Nervous System

The SNS is more active in people with hypertension than in people who are not hypertensive. It is also more active in people who are obese, in men than in women, and in people who have advanced renal disease [10]. Identified indicators of sympathetic overactivity in normotensive people with a familial history of hypertension, such as elevated catecholamine spillover and sural nerve activity measured by microneurography [11]. Microneurography measurements of greater sympathetic activity are associated with a higher degree of hypertension [12]. Higher sympathetic activity is seen in patients with obesity-related hypertension, metabolic syndrome, and hypertension made worse by heart failure or renal disease [13].

1.2.6 Endothelial dysfunction

Vascular endothelial cells are important in cardiovascular regulation because they produce a variety of powerful local vasoactive agents, including the vasodilator chemical nitric oxide and the vasoconstrictor peptide endothelin. In humans,

essential hypertension has been linked to endothelial dysfunction.

An appealing therapeutic strategy for trying to reduce some of the major consequences of hypertension is endothelial function modification. The generation of nitric oxide appears to be restored by clinically successful antihypertensive medication, although endothelium-dependent vascular relaxation and the vascular response to endothelial agonists do not appear to be restored. This suggests that once the hypertension process is begun, such endothelial damage is primary and irreversible.

2. Liver X Receptor

The liver X receptors (LXR) receptors belong to the nuclear receptor superfamily of ligand-activated transcription factors. Nuclear hormone receptors are a group of transcription regulators that play a role in a variety of physiological processes including cell proliferation, death, cancer, and angiogenesis. Because their natural ligands were unknown when they were discovered in the mid-1990s, they were dubbed "orphan receptors."[14][15][16]. Soon later, oxysterols and cholesterol metabolites were discovered to be endogenous LXR activators, and LXRs were "deorphanized."

Two isoforms of LXR, LXRbeta (NR1H2) and LXRalpha (NR1H3), combine to form heterodimers with retinoid X receptor (RXR). LXRs are intriguing therapeutic targets for the treatment of atherosclerotic and metabolic diseases since they have been shown to be critical regulators of inflammation, lipid and glucose metabolism, and cholesterol homeostasis [17].

LXRs are connected to LXR response elements (LXREs) in target gene regulatory regions and form obligatory heterodimers with the retinoid X receptor (RXR) in the nucleus. Though it is expressed in every part of the body, metabolically active systems such the liver, adipose tissue, and macrophages, as well as the heart, skeletal muscle, kidney, and lung, are where LXR is most commonly found [18].

When LXR target genes are activated, LXR binds to the LXR response element in the promoter region to regulate the expression of those genes. These genes are involved in the metabolism of glucose, lipids, fatty acids, and cholesterol. These consist of fatty acid synthase (FAS), lipoprotein lipase, sterol regulatory element-binding protein-1c (SREBP-1c), apolipoprotein E (ApoE), cholesteryl ester transfer protein, ATP-binding cassette (ABC) transporter isoforms A1 (ABCA1) and G1 (ABCG1), and glucose.

LXR is an oxysterol sensor with LXRα which contains 447 amino acids and LXRβ which contains 461 [19] amino acids in its structure. The four functional domains that make up the LXR molecules are: the hydrophobic ligand-binding domain (LBD), which is necessary for ligand binding and receptor dimerization; the amino-terminal ligand-independent activation function domain (AF-1), which can stimulate transcription in the absence of a ligand; and the DNA-binding domain (DBD) with two zinc fingers.

LXRα and LXRβ have 75.6 percent and 74% sequence identity in their DBD and LBD regions, respectively [20]. The LBD of LXR has a three-layered -helical sandwich shape with ten α-helices, which is similar to all known nuclear receptors [21]. LXR/RXR is a "permissive heterodimer" that can be activated by either an LXR agonist or a particular RXR ligand called 9-cis retinoic acid. The LXR/RXR complex binds specifically to an LXR responsive element (LXRE), which is made up of two direct repeats of hexameric nucleotides, AGGTCA, separated by four or one nucleotide(s) in

the promoter region of target genes (DR4 or DR1) [22].

A large number of LXR target genes have been found, including fatty acid synthase (FAS), ATP binding cassette (ABC), transporter isoforms A1, G1, G5, and G8, apolipoprotein E (ApoE), cholesteryl ester transfer protein (CETP), cytochrome P450 isoform 7A1 (CYP7A1)—cholesterol 7α-hydroxylase, and carbohydrate regulatory element binding protein (ChREBP) [23]. LXRs are connected to LXR response elements (LXREs) in target gene regulatory regions and form obligatory heterodimers with the retinoid X receptor (RXR) in the nucleus. The LXR/RXR complex undergoes a conformational shift upon binding with either natural or synthetic ligands, such as T0901317 (T09) and GW3965, which subsequently activates target gene transcription.

2.1 Function

There are different functions of LXR in the body such as cholesterol metabolism regulation, boosting insulin secretion, and enhancing insulin sensitivity. Also, LXRs are anti-inflammatory and anti-autoimmune receptors. LXRs are anti-atherosclerotic [24] also cause renin secretion regulation [25], and inhibit the formation of amyloid plaque in the central nervous system [26], LXRs also have Gonadal function and steroidogenesis control in the gonads and adrenals [27]. Changes in endogenous LXR activity are seen in a variety of clinical situations, including atherosclerosis, cancer, neurological illnesses such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, arthritis, and skin diseases.

2.2 Liver X receptor Agonists

2.2.1 Endogenous agonist

Oxysterol has been discovered to be an endogenous ligand for LXRs in mammals, with two separate types of ligands that activate LXRs [28][29]. 20(S)-, 22(R)-, 24(S)-, 25-, and 27-hydroxy cholesterol, as well as 24(S), 25- epoxy cholesterols, are oxidized derivatives of oxysterol. The intermediates of cholesterol production are the second class of LXR-activating oxysterols. The oxysterol 24(S), 25-epoxycholesterol is formed in a shunt of the mevalonate pathway.

24(S)-hydroxycholesterol is a kind of 24(S)-hydroxycholesterol (cerebrosterol) is abundant in the brain. 24-hydroxylase is responsible for its production. It has been shown to be a good activator of the LXR-regulated gene ABCA1 [30]. The P450 enzyme sterol 27-hydroxylase produces 27-hydroxycholesterol from cholesterol. 27-hydroxylase then oxidises it to aldehyde and carboxylic acid (cholestenoic acid). The ligands for LXRs are 27-hydroxycholesterol and cholestenoic acid [31][32]. 25-hydroxycholesterol is a strong regulator of LXR-mediated pathways, is synthesised by 25-hydroxylase. It also has an effect on the expression of LXR-dependent genes such as LPL, ABCG5, and ABCG8 [32]. 24(S) 25-epoxycholesterol produced in the mevalonate pathway's shunt. The expression of LXR target genes ABCA1 is reduced when 24(S),25-epoxycholesterol is removed [33]. Desmosterol and zymosterol are two more intermediates that activate the LXR [34].

2.2.2 Natural agonists

Fucosterol, which is abundant in marine algae, exhibits hypocholesterolemic properties and raises plasma HDL activity. In HEK–293 cells, fucosterol greatly increased the transactivation of both LXRα and LXRβ [35]. Podocarpic acid is the LXR agonist produced from plant resins that is non-steroidal [36]. Experiments using LXR scintillation proximal binding demonstrated that compounds of podocarpic acid, including its dimer anhydride and imides, bind

to both LXRα and LXRβ. Cell-based transactivation experiments on HEK-293 cells showed that the anhydride dimer had an EC50 value of 1 nM against both receptors, with peak induction for the β and β LXR receptors being 50- and 8-fold, respectively. In hamsters, the more stable and powerful imide raises total plasma cholesterol by 28% while simultaneously raising HDL cholesterol by 22% and lowering LDL cholesterol by 11%. Similar findings were shown in mice with HDL cholesterol levels that were boosted by 19% [37]. Cyanidin, a flavonoid present in a variety of fruits and vegetables has been shown to affect cellular lipid metabolism. LXRα transactivation was increased by 32% (at 50 M), 59 percent (at 100 M), and 33% (at 100 M) in response to cyanidin. With an EC50 of 3.48 M of LXRα and 125.2 M of LXRβ, cyanidin activates the LXR. LXR-sensitive genes such as ABCA1, SREBP-1c, and ABCG5 were likewise activated by cyanidin. It also lowered cellular TG contents [38].

Cineole, a small fragrance component found in teas and plants, has been found to promote LXR transactivation. Cineole treatment of CHO-K1 cells increased LXR transactivation by more than 75% and LXR transactivation by more than 100%. Cineole reduced cellular cholesterol levels in RAW 264.7 macrophages. The mRNA expression of the LXR-responsive genes was similarly dramatically enhanced by cineole. Surprisingly, LXR-sensitive genes FAS, SREBP-1c, and SCD-1 were significantly downregulated in hepatocytes activated by cineole. Cineole acts as a partial agonist, activating LXRs selectively without promoting hepatic lipogenesis [39]

2.2.3 Synthetic Agonist

The synthetic ligands T0314407 and T0901317 both increased LXR transcriptional activity. T0901317 as a nonsteroidal LXRα ligand with exceptional potency and selectivity. While T0314407 and T0901317 bind to LXRα with EC50 values of 100 and 20 nM, respectively, they were substantially more powerful and had equivalent efficacy to 24,25-EC.

In a cell-free ligand-sensing test, GW3965 is a steroid receptor coactivator-1 to human LXRalpha with an EC(50) of 125 nM. In cell-based reporter gene assays, it profiles as a complete agonist on hLXRalpha and hLXRbeta with EC(50) values of 190 and 30 nM, respectively. increased plasma HDL cholesterol concentrations by 30% [40][41] and enhanced the expression of the reverse cholesterol transporter ABCA1 in the small intestine and peripheral macrophages following oral treatment of 10 mg/kg to C57BL/6 mice.

LXR-623, a Synthetic ligand for LXRs that has shown potential in atherosclerosis animal models. LXR activation increased ABCA1 and ABCG1 expression in a dose-dependent manner. A population pharmacokinetic-pharmacodynamic study was used to further evaluate the influence of LXR-623 concentration on ABCA1 and ABCG1 expression, producing EC50 estimations of 526 ng/mL and 729 ng/mL, respectively [42][43].

AZ876 which is one of the novel high-affinity LXR agonists. LXR could thus be a potential target for antihypertrophic and antifibrotic treatments in the prevention of heart failure. The hypertrophic and profibrotic transforming growth factor β (TGFβ)-Smad2/3 signalling was further reduced by AZ876, which also repressed the up-regulation of genes linked to fibrosis and hypertrophy.AZ876 decreased insmooth muscle actin, inhibition of TGF and angiotensin II-induced fibroblast collagen synthesis, and modulation of the Myo fibroblastic marker. After receiving AZ876 therapy, liver weight and plasma triglycerides were unchanged. Comparing AZ876 to GW3965 (HY-10627), it is 25-fold and

2.5-fold more effective on human hLXRα and hLXRβ, respectively [44][45].

The partial LXR agonist BMS-779788 has IC50 values of 14 nM for LXRβ and 68 nM for LXRα, respectively. The selective partial agonist LXR was found in human whole blood. When it comes to stimulating the ATP-binding transporters ABCA1 and ABCG1, BMS-779788 is quite effective [46]. BMS-779788 has an EC50=610 nM, which is comparable to its in vitro blood gene induction potency, when it comes to inducing LXR target genes in blood in vivo. BMS-779788 is 29- and 12-fold less efficacious than the full agonist T0901317 in raising plasma triglycerides and LDL cholesterol, respectively. Similar outcomes are shown for plasma cholesteryl ester transfer protein and apolipoprotein B. BMS-779788 induces ABCA1 peripherally in mice, with no significant increase in plasma or hepatic triglycerides, indicating a better profile than a complete pan-agonist [47].

BMS-852927, LXRβ-selective agonist with 20% LXRα and 88% LXRβ activity compared to a full pan agonist in transactivation assays. BMS-852927 has a binding affinity to both LXRα and LXRβ in a similar way. In cynomolgus monkeys and mice, XL041 (BMS-852927) has a very good efficacy profile. Pre-treatment of C57BL/6J mice with XL041 for 7 days causes a significant, dose-dependent increase of cholesterol efflux in this system, with a maximum of 70% above vehicle in the initial efflux rate in the [48] 3 mg/kg/day dosing group. LDLR knockout (KO) mice produced similar results. A 12-week research on LDLR KO mice found that XL041 inhibited the progression of atherosclerosis. The dose response for inhibition of atherosclerosis is (0.1-3 mg/kg/day) [49].

2.3 Role of LXR in Hypertension

Hypertension damages the heart muscle by increasing hemodynamic afterload, which starts the growth of pathological hypertrophy. It also increases the risk of atherosclerosis and damages the arteries. An essential hormonal signalling mechanism in the control of blood pressure, fluid equilibrium, and systemic vascular resistance is the RAAS. Blood pressure modulation has been linked to LXR-mediated RAAS regulation. LXR was originally discovered to be a transcription regulator of renin [50][51]. LXR signalling and the RAAS are connected, as evidenced by the fact that acute LXR agonist treatment raised renin mRNA levels in vivo and LXR-null animals were unable to upregulate renin in response to -adrenergic stress [50]. The LXR agonist T09 was found to reduce blood pressure increase in mice with chronic pressure-volume overload, but this effect was lost in mice lacking LXR cardiac LXR overexpression increases natriuretic peptide expression. LXR modulation of natriuretic peptides might therefore be an indirect technique for RAAS suppression; hence, LXRs limit RAAS activation and could be a viable target for lowering the heart's hemodynamic stress [52].

2.4 LXR effect on hypertension

2.4.1 AT1R expression

Angiotensin II (Ang II) is mediated by Ang II receptors, of which there are now two isoforms known to exist: type 1 receptor (AT1R) and type 2 receptor. Most of Ang II's typical effects, such as cell proliferation and vasoconstriction, are mediated through AT1R. The promotion of atherogenesis by Ang II and the elevation of atherogenesis by an AT1R are well established [53]. AT1R expression was likewise decreased by 22-(R)-hydroxycholesterol, a well-known LXR ligand. T0901317 needed de novo protein synthesis to downregulate AT1R. LXR Agonist Reduced AT1R mRNA and Protein Expression At 6 hours after

incubation with T0901317, AT1R mRNA was reduced in a dose-dependent manner. T0901317 decreased AT1R protein levels, with a peak at 6 hours of incubation.

T0901317-Induced Downregulation of AT1R Expression Requires De Novo Protein Synthesis. T0901317-induced downregulation of AT1R expression was tested using CHX (10 g/mL, 1 hour), a protein synthesis inhibitor, to see if it was dependent on de novo protein synthesis. The expression of AT1R mRNA was unaffected by CHX alone. T0901317- induced AT1R mRNA downregulation was, however, blocked by CHX. De novo protein synthesis is required for AT1R mRNA downregulation by LXR. p16 suppressed Sp1-mediated gene transcription by suppressing cyclin A expression and phosphorylating Sp1 at the serine position. T0901317 (10 mol/L) enhanced p16 expression and decreased Sp1 phosphorylation at the serine residue, indicating that it boosted p16 expression and lowered Sp1 phosphorylation.

AT1R Downregulation Caused by T0901317 Reduced Angiotensin II Cellular Response Through AT1R, Ang II causes phosphorylation of ERK in VSMCs. When AT1R expression is maximally inhibited, ERK phosphorylation is dramatically reduced after 6 to 12 hours of preincubation with T0901317. However, after incubation with T0901317 for 6 to 12 hours, phorbol ester (100 nM) boosted ERK phosphorylation, indicating that T0901317 may not influence the ERK activation pathway (data not shown). As a result, AT1R downregulation resulted in a reduction in the cellular response to Ang II.

LXR-deficient (LXR-/) and wild-type (WT) C57Bl/6J mice were given T0901317 (T09, a selective synthetic LXR agonist) along with isoproterenol, a RAAS inducer, and then either ISO, T09, or both for seven days. Low-dose ISO treatment in WT mice increased renal renin mRNA, renin protein, and ACE protein; however, this increase was uncorrelated with elevated blood pressure. WT mice treated with both ISO and T09 exhibited decreased renal renin, ACE, and AT1R mRNA expression in comparison to mice treated with ISO alone. In addition, WT mice treated with ISO plus T09 showed lower cardiac ACE mRNA expression in their hearts than did those treated with ISO alone. Animals lacking LXR largely lacked transcriptional changes for renin, ACE, and AT1R.

A synthetic liver X receptor (LXR) agonist called GW3965 in Sprague-Dawley rats reduces angiotensin II-mediated pressor responses [54]. Synthetic LXR agonist GW3965 decreased vascular Ang II receptor gene expression and Ang II-mediated blood pressure increases. These novel results identify LXRs as key players in blood pressure regulation, RAAS, and lipid metabolism.

2.4.2 Renin modulation

Both LXRs controlled renin transcription in vitro by binding to a noncanonical responsive region in the renin promoter. While LXR was a cAMP-activated factor, cAMP had the opposite effect on LXR. In vivo, LXRs colocalized with the renin promoter in juxtaglomerular cells, where LXR was especially concentrated. Renin is an aspartyl protease that catalyzes the first and rate-limiting stage in the renin-angiotensin cascade, the cleavage of angiotensinogen to angiotensin I. Specialized juxtaglomerular (JG) cells strategically placed in the afferent arterioles of kidney glomeruli express and release circulating renin. Renin regulates the rate at which angiotensin is produced, which is important for salt-volume balance and blood pressure management.

LXRs bind to the renin promoter and hence control the expression of the renin gene. The intracellular

cAMP increase was followed by overexpression of renin mRNA in As4.1/LXR cells 6 hours after stimulation. Overexpression of LXR, on the other hand, was linked to greater basal levels of renin mRNA, whereas cAMP treatment was linked to a decrease in renin mRNA levels [51].

In JG cells in vivo, LXRs are expressed with a particular enrichment in LXR. LXR was expressed at equal quantities in both sorted and unsorted cells, whereas JG cells showed a substantial enrichment in LXR. As a result, independent methods revealed that both LXRs are expressed in JG cells' kidneys, with a particular enrichment in LXR.

2.4.3 Vasoreactivity

Reduced Ang II receptor gene expression in response to LXR medication, possibly explaining the reduced Ang II-induced vasopressor response. Rats given GW3965 are anticipated to exhibit reduced vasoreactivity in response to Ang II infusions due to AT1 receptor downregulation. It's important to note that Ang II-mediated blood pressure was shown to be lower at the 6–8-hour time intervals, which were characterized by a tendency towards decreased Ang II receptor gene expression [51]

GW3965 therapy over the previous week resulted in a significant reduction in the hypertensive rats' systolic blood pressure ($p<0.05$). In normotensive mice, GW3965 therapy raised plasma nitrite levels ($p<0.05$)

2.4.4 Nitrite levels

The impact of GW3965 on the levels of plasma nitrite. The plasma nitrite levels in the hypertensive group were constant. Nitrite levels were elevated by GW3965 treatment in rats with normal and hypertension. It was discovered that the LXR agonist improved TNF-impaired NO production in endothelial cells and reversed the TNF-induced downregulation of eNOS expression [55]. Plasma NO levels were raised in rats with normotension by GW3965 treatment. The beneficial effect on vessels may be attributed in part to the LXR agonist GW3965's effects on NO levels.

2.4.5 NF-κB and TNF-α

It has been demonstrated that the mesenteric artery of hypertensive rats expresses more NF-κB protein. TNF is a cytokine that promotes inflammation and is regulated by transcription It has been observed that hypertensive rats exhibit increased levels of NF-κB TNF- and NF-κB protein expression in the aorta [55]. GW3965 treatment brought the increased TNF-TNF-expression level in hypertensive rats down to the control level. The administration of GW3965 has an impact on TNF expression and NF-κB levels. In hypertensive rats, the expressions of TNF- (A, C) and NF-κB (A, B) were markedly elevated, and GW3965 treatment greatly reduced them. NF-κB expression in the aorta was increased in hypertensive rats ($p<0.05$). In hypertensive individuals, GW3965 treatment decreased NF-κB protein expression ($p<0.05$).

5. Conclusion

Hypertension is the leading cause of death around the world. The Liver X receptor is the key receptor that can be a relationship between hypertension and the LXR receptor, as we saw in the report. The discovery that LXRs regulate renin gene transcription by binding to a noncanonical response region in the renin promoter has led to speculation that LXRs may play a role in facilitating this cross-talk. Blood pressure rises caused by Ang II were decreased by using an LXR agonist. The downregulation of vascular AT1 and AT2 receptor gene expression was linked to decreased vascular responsiveness to Ang II treatment. AT1 receptor stimulation is principally responsible for changes in

vascular function associated with RAAS activation. NF-κB expression increases in hypertensive rats, so LXR agonist acts on NF-κB and also TNF and decreases its level in hypertensive rats. Also, the LXR agonists increase nitrite levels in normotensive and also in hypertensive rats T0901317, a synthetic LXR agonist, inhibited AT1R mRNA and protein expression. So, targeting the liver X receptor at various stages can prove to be very useful with respect to hypertension. Thus, making a Liver X receptor a potential target for hypertension.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authorship contribution statement

Dipti Patil: Conceptualization, Writing – original draft.

Abbreviations

CVD: Cardiovascular diseases
CKD: Chronic obstructive disease
RAAS: Renin-angiotensin-aldosterone system
SNS: Sympathetic nervous system
TGF: Transforming growth factor
ANP: Atrial natriuretic peptide
BNP: brain natriuretic peptide
NPR-C: natriuretic peptide scavenger receptor
APA: Aminopeptidase
ACE2: Angiotensin-converting enzyme 2
NP: Natriuretic peptide
CNP: C-type natriuretic peptide
pGC: particulate guanylyl cyclase
PK-G: protein kinase G
MAPK: mitogen-activated protein kinase
PDE: phosphodiesterase
DOCA : Deoxycorticosterone acetate
LXR : Liver X receptor
ABC: ATP-binding cassette
FAS: Fatty acid synthase
ApoE: Apolipoprotein E
SREBP-1c: sterol regulatory element-binding protein-1c
DBD: DNA-binding domain
LBD: ligand-binding domain
ISO: Isoproterenol

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