SENNOS

Journal of Drug Delivery and Biotherapeutics (JDDB)

Journal homepage: https://sennosbiotech.com/JDDB/1

Review Article

Liver X Receptor (LXR) Activation as a Potential Therapeutic Strategy for the Management of Hypertension: A Comprehensive Review

Dipti Patil

Department of Pharmacology, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Vile Parle

ARTICLEINFO

ABSTRACT

Hypertension remains one of the leading causes of mortality globally, with complex mechanisms involving hormonal regulation and vascular reactivity. Recent studies have identified the Liver X receptor (LXR) as a potential key modulator in the regulation of blood pressure and vascular function. LXRs play a critical role in the modulation of the renin-angiotensin-aldosterone system (RAAS), which is central to blood pressure homeostasis. This review explores the relationship between LXRs and hypertension, emphasizing the role of LXR agonists in modulating renin gene transcription and angiotensin II (Ang II)-mediated vascular responses. LXR activation has been shown to downregulate angiotensin II receptor expression (AT1 and AT2), thereby reducing vascular responsiveness to Ang II and lowering blood pressure. Additionally, LXR agonists such as T0901317 and GW3965 have been demonstrated to decrease NF-κB and TNF-α expression in hypertensive models, contributing to reduced inflammation and improved endothelial function. Moreover, LXR agonists enhance nitrite production and improve nitric oxide (NO) bioavailability, which are crucial for vascular health. These findings highlight the potential of LXRs as therapeutic targets for hypertension management. Targeting LXR pathways could provide a novel approach to controlling blood pressure through modulation of the RAAS and inflammatory pathways, offering new avenues for therapeutic intervention in hypertensive patients.

Keywords: Osteoarthritis: Global Burden of Disease; Pathophysiology; Novel Drug Delivery Systems; Treatment Strategies

Corresponding Author:

Dipti Patil

Department of Pharmacology, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Vile Parle

E-mail addresses: dipti.sennosbiotech@gmail.com

Received date: 07-Nov-2024 Revised date: 20-Nov-2024, Accepted date: 15-Dec-2024

Crossref DOI: https://doi.org/10.61920/jddb.v1i03.157

1. Introduction

Hypertension, characterized by elevated systolic, diastolic, or both blood pressures beyond normal levels, is a widespread condition in both industrialized and developing nations, with its prevalence increasing with age [1]. It occurs when the long-term force of blood against the walls of the arteries becomes high enough to cause health complications such as heart disease. Chronic high blood pressure significantly raises the risk of developing severe health problems, including heart disease, heart attack, and stroke [2].

Blood pressure is determined by two primary factors: the amount of blood the heart pumps and the resistance the arteries exert against blood flow. When the heart pumps more blood or the arteries become narrower, blood pressure increases, measured in millimeters of mercury (mm Hg). Hypertension is the leading preventable risk factor for cardiovascular diseases (CVDs), which include coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation, and peripheral artery disease. It is also a significant contributor to chronic kidney disease (CKD), which remains one of the leading causes of death and disability globally, and is associated with cognitive decline [1]. Hypertension continues to be the primary cause of mortality and disability worldwide [2] and is projected to remain a leading health issue in 2040 [3].

According to the 2003 guidelines, hypertension is defined as a blood pressure exceeding 140/90 mm Hg. However, the 2017 guidelines have lowered the threshold for hypertension, now defining it as blood pressure higher than 120/80 mm Hg.

1.1 Types of Hypertensions

Primary (Essential) Hypertension

Primary hypertension, which accounts for 90–95% of hypertension cases, refers to high blood pressure without a specific identifiable cause. It is primarily influenced by a combination of genetic predisposition and lifestyle factors. Key risk factors include obesity, smoking, excessive alcohol consumption, and a diet rich in sodium.

Secondary Hypertension

Secondary hypertension results from an identifiable cause, such as chronic kidney disease, narrowing of the renal arteries, hormonal imbalances, or the use of certain medications like contraceptive pills. This type accounts for the remaining 5–10% of hypertension cases.

1.2 Pathophysiology of Hypertension

1.2.1 Blood Pressure Regulation

Blood pressure is regulated through several interrelated factors, including cardiac output (the volume of blood the heart pumps per minute), blood volume, and arterial tone. These factors are influenced by intravascular volume and various neurohumoral systems. Key regulators include the sympathetic nervous system (SNS), immune system, natriuretic peptides, endothelial function, and the renin-angiotensin-aldosterone system (RAAS). Disruptions or malfunctions in any of these systems can lead to sustained high blood pressure, blood pressure fluctuations, or both. Over time, these conditions can result in organ damage, such as left ventricular hypertrophy, chronic kidney disease, and cardiovascular complications [4].

1.2.2 Sodium Homeostasis

Excess sodium in the blood leads to water retention, which in turn increases blood volume and raises blood pressure. Individuals who experience a significant increase in systolic blood pressure (at least 10 mmHg) within hours of consuming salt are

considered salt-sensitive. Salt sensitivity is often associated with endothelial dysfunction, which may arise due to genetic predispositions or environmental factors. These individuals tend to have an overproduction of transforming growth factor (TGF) and lower levels of nitric oxide, making them more vulnerable to oxidative stress and tissue fibrosis. Even in those who are generally resistant to salt, prolonged high salt intake can impair endothelial function, alter gut microbiota, increase salt sensitivity, and eventually contribute to the development of hypertension [5]. Additionally, high salt intake activates T-helper cells, which can trigger autoimmune responses, further exacerbating hypertension [5].

1.2.3 Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS plays a pivotal role in the development of hypertension by regulating blood pressure and sodium balance. It is crucial in controlling sodium retention, pressure natriuresis (reduced sodium reabsorption and increased sodium excretion), salt sensitivity, vasoconstriction, endothelial dysfunction, and vascular damage [4]. The RAAS maintains the kidney's pressure-volume balance. Renin, produced and stored by the juxtaglomerular cells in the kidneys, is released in response to external stimuli. Renin cleaves angiotensinogen to form angiotensin I, which is further converted to angiotensin II. Angiotensin II is a potent vasoconstrictor and a key mediator of hypertension.

1.2.4 Natriuretic Peptides

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) play essential roles in regulating hypertension and salt sensitivity. These peptides are crucial for maintaining blood pressure and sodium homeostasis, particularly during periods of sodium loading [6]. Their natriuretic and vasodilatory properties help control blood volume and reduce blood pressure. ANP and BNP are released in response to sodium overload, which causes stretch in the atria and ventricles, leading to systemic vasodilation, a reduction in plasma volume (due to fluid movement from the intravascular to the interstitial space), and a decrease in blood pressure [7].

These peptides exert direct effects by reducing the activity of sodium-glucose co-transporters and Na+-K+-ATPase in the proximal tubule, as well as inhibiting the epithelial sodium channel in the distal nephron. Indirectly, they reduce the release of aldosterone and renin. A deficiency in natriuretic peptides has been associated with exacerbated hypertension. Corin, a serine protease primarily expressed in the heart, is responsible for activating ANP and BNP from their precursor forms (pro-ANP and pro-BNP). Corin deficiency has been linked to conditions such as volume overload, heart failure, and salt-sensitive hypertension [8]. Additionally, reduced levels of natriuretic peptides are associated with insulin resistance and type 2 diabetes, and obesity has been shown to exacerbate this shortage, possibly due to increased expression of the natriuretic peptide scavenger receptor NPR-C in adipose tissue [9].

1.2.5 Sympathetic Nervous System

The sympathetic nervous system (SNS) is more active in individuals with hypertension compared to normotensive individuals. It is also more pronounced in obese individuals, men, and those with advanced renal disease [10]. Elevated sympathetic activity has been identified in normotensive individuals with a family history of hypertension, as evidenced by increased catecholamine spillover and higher sural nerve activity, measured through microneurography [11]. Increased sympathetic activity is correlated with

more severe hypertension [12]. It is particularly evident in conditions such as obesity-related hypertension, metabolic syndrome, and hypertension exacerbated by heart failure or renal disease [13].

1.2.6 Endothelial Dysfunction

Vascular endothelial cells are critical in cardiovascular regulation due to their role in producing potent vasoactive substances, such as nitric oxide (a vasodilator) and endothelin (a vasoconstrictor). Endothelial dysfunction has been closely associated with essential hypertension in humans.

One potential therapeutic approach for mitigating the adverse effects of hypertension is the restoration of endothelial function. Certain antihypertensive medications have been shown to improve the production of nitric oxide, which helps in vascular relaxation. However, despite this improvement, the endothelium's response to agonists remains impaired in many hypertensive individuals, suggesting that endothelial damage may be a primary and irreversible consequence of the hypertension process once it has begun. This irreversible endothelial damage highlights the difficulty in fully restoring vascular function after chronic hypertension has developed.

2. Liver X Receptor (LXR)

Liver X receptors (LXRs) are members of the nuclear receptor superfamily, functioning as ligand-activated transcription factors. These nuclear hormone receptors regulate various physiological processes such as cell growth, death, cancer progression, and angiogenesis. Initially identified in the mid-1990s, LXRs were considered "orphan receptors" because their natural ligands were unknown. However, the discovery of oxysterols and cholesterol metabolites as their endogenous activators led to the recognition of LXRs as functional receptors. There are two main isoforms of LXR: LXRα (NR1H3) and LXRβ (NR1H2), both of which partner with the retinoid X receptor (RXR) to form heterodimers. These complexes play a significant role in regulating inflammation, lipid and glucose metabolism, and cholesterol homeostasis, making LXRs potential therapeutic targets for conditions like atherosclerosis and metabolic diseases [14-16].

LXRs are expressed in several tissues involved in metabolism, including the liver, adipose tissue, macrophages, heart, skeletal muscle, kidneys, and lungs. They regulate gene expression by binding to LXR response elements (LXREs) in the promoter regions of target genes. These genes include those that control lipid, glucose, fatty acid, and cholesterol metabolism, such as fatty acid synthase (FAS), apolipoprotein E (ApoE), sterol regulatory element-binding protein-1c (SREBP-1c), and ATP-binding cassette (ABC) transporters like ABCA1 and ABCG1. The LXR receptor consists of functional domains: a hydrophobic ligand-binding domain (LBD), an activation function domain (AF-1), and a DNA-binding domain (DBD) with two zinc fingers. The LBD adopts a helical sandwich structure, characteristic of many nuclear receptors [17-21].

LXR forms a permissive heterodimer with RXR, which can be activated by either LXR-specific agonists or RXR ligands, such as 9-cis retinoic acid. Upon ligand binding, the LXR/RXR complex binds to the LXRE, a DNA sequence consisting of two direct repeats of hexameric nucleotides separated by either four or one nucleotide(s). This complex regulates the expression of various target genes, including those involved in lipid metabolism and cholesterol transport, such as FAS, ABC transporters, ApoE, and cholesteryl ester transfer protein (CETP) [22, 23].

2.1 Function

LXRs are involved in multiple physiological functions, including the regulation of cholesterol metabolism, insulin secretion, and sensitivity. They also play anti-inflammatory and anti-autoimmune roles, and have been shown to reduce the formation of amyloid plaques in the central nervous system. Furthermore, LXRs regulate steroidogenesis and gonadal function, contributing to various health conditions, including atherosclerosis, cancer, neurological disorders (such as multiple sclerosis, Alzheimer's, and Parkinson's diseases), arthritis, and skin diseases [24-26].

2.2 Liver X Receptor Agonists

2.2.1 Endogenous Agonists

Oxysterols, oxidized derivatives of cholesterol, are the endogenous ligands for LXRs. Key oxysterols, such as 24(S)-hydroxycholesterol, 27-hydroxycholesterol, and 25-hydroxycholesterol, have been shown to activate LXR pathways. These compounds regulate genes involved in cholesterol efflux, lipid metabolism, and other metabolic processes. For example, 24(S)-hydroxycholesterol is abundant in the brain and plays a significant role in activating LXR-regulated genes like ABCA1. Additionally, 27-hydroxycholesterol, produced from cholesterol by sterol 27-hydroxylase, acts as an LXR agonist. Desmosterol and zymosterol, other intermediates in cholesterol synthesis, are also potent activators of LXR [28].

2.2.2 Natural Agonists

Several natural compounds have been identified as LXR agonists. Fucosterol, found in marine algae, has hypocholesterolemic properties and enhances plasma HDL activity, thereby increasing LXR activation. Podocarpic acid, a non-steroidal compound from plant resins, has been shown to activate both LXRα and LXRβ, leading to changes in plasma cholesterol levels. Cyanidin, a flavonoid present in fruits and vegetables, also activates LXRα and LXRβ, affecting lipid metabolism and reducing triglyceride levels in cells. Additionally, cineole, a component found in teas and plants, has been shown to promote LXR transactivation and reduce cellular cholesterol levels in macrophages, although it selectively activates LXR without promoting lipogenesis in the liver.

2.2.3 Synthetic Agonists

Synthetic ligands, such as T0901317, T0314407, and GW3965, have been developed to activate LXRs. T0901317 is a potent non-steroidal LXRα ligand, while GW3965 is a synthetic ligand that enhances LXR transcriptional activity. These compounds have demonstrated efficacy in increasing HDL cholesterol concentrations and enhancing the expression of reverse cholesterol transporters like ABCA1. LXR-623, another synthetic ligand, has shown promise in animal models of atherosclerosis by upregulating ABCA1 and ABCG1 expression. AZ876, a novel high-affinity LXR agonist, has been found to modulate hypertrophic and fibrotic pathways, offering potential in heart failure prevention. Furthermore, partial agonists like BMS-779788 and BMS-852927 have been developed to selectively activate LXRβ or LXRα, showing therapeutic potential with reduced side effects compared to full agonists.

2.3 Role of LXR in Hypertension

Hypertension is a major risk factor for cardiovascular diseases, contributing to pathological hypertrophy of the heart, increasing arterial stiffness, and promoting atherosclerosis. One of the key hormonal signaling systems involved in the regulation of blood pressure, fluid balance, and systemic vascular resistance is the renin-

angiotensin-aldosterone system (RAAS). Recent research has highlighted the role of Liver X Receptors (LXR) in modulating RAAS activity, linking LXR signaling to blood pressure regulation.

LXR was first identified as a transcriptional regulator of renin, a key enzyme in the RAAS [50]. It has since been shown that LXR signaling interacts with the RAAS; for instance, acute treatment with LXR agonists increases renin mRNA levels in vivo, whereas LXR-null mice fail to upregulate renin in response to β-adrenergic stress. Furthermore, studies have demonstrated that the LXR agonist T0901317 (T09) effectively reduces the rise in blood pressure in mice subjected to chronic pressure-volume overload, suggesting a protective role for LXR in hypertension. However, this effect is lost in mice with a knockout of LXR in the heart, reinforcing the importance of LXR signaling in the cardiovascular system.

Additionally, LXR modulation has been shown to influence the expression of natriuretic peptides, which are involved in the regulation of blood volume and vascular tone. Specifically, cardiac overexpression of LXR increases natriuretic peptide expression, which may help mitigate RAAS activation and reduce hemodynamic stress on the heart. These findings suggest that LXRs could serve as a potential therapeutic target for controlling blood pressure and alleviating the cardiovascular strain caused by hypertension [29].

2.4 LXR effect on hypertension

2.4.1 AT1R expression

Angiotensin II (Ang II) exerts its effects through two primary receptors: the type 1 receptor (AT1R) and type 2 receptor (AT2R). The majority of Ang II's physiological effects, including cell proliferation, vasoconstriction, and atherogenesis, are mediated via the AT1R. It has been shown that LXR activation, specifically through ligands such as 22-(R)-hydroxycholesterol, can downregulate AT1R expression. The synthetic LXR agonist T0901317 (T09) reduces both AT1R mRNA and protein expression in a dose- and time-dependent manner, with peak effects observed 6 hours after incubation.

T0901317-induced downregulation of AT1R expression requires de novo protein synthesis. Inhibition of protein synthesis with cycloheximide (CHX) blocked the T0901317-induced decrease in AT1R mRNA expression, indicating that new protein synthesis is required for this effect. In addition, T0901317 treatment enhanced p16 expression and reduced Sp1 phosphorylation, which is believed to play a role in the downregulation of AT1R. The modulation of Sp1 by p16 suggests a potential mechanistic pathway through which LXR agonists influence gene transcription and receptor expression.

Furthermore, T0901317-induced downregulation of AT1R expression has functional consequences on Ang II signaling. Ang II, through the AT1R, activates extracellular signal-regulated kinase (ERK) in vascular smooth muscle cells (VSMCs). In cells treated with T0901317, ERK phosphorylation was significantly reduced, correlating with the suppression of AT1R expression. However, when ERK activation was triggered by phorbol ester (a potent activator of protein kinase C), T0901317 did not seem to influence this pathway, suggesting that LXR agonists specifically affect AT1R-mediated signaling rather than global ERK activation.

In vivo studies in LXR-deficient (LXR-/) and wild-type (WT) C57Bl/6J mice further confirm the role of LXR in regulating RAAS components. WT mice treated with T0901317 and isoproterenol (ISO), a RAAS inducer, showed significantly decreased expression of renal renin, ACE, and AT1R mRNA, as well as lower cardiac ACE mRNA compared to

those treated with ISO alone. In contrast, LXR-deficient mice did not exhibit these transcriptional changes, underscoring the imp

In another study, the synthetic LXR agonist GW3965 administered to Sprague-Dawley rats was shown to attenuate Ang II-mediated pressor responses. This effect was associated with a reduction in vascular Ang II receptor gene expression, further establishing LXRs as key regulators in blood pressure control, RAAS activity, and lipid metabolism [30].

2.4.2 Renin Modulation

Both LXR isoforms (LXRα and LXRβ) regulate renin transcription through binding to a noncanonical responsive region in the renin promoter. In vitro studies have shown that while LXR is a cAMP-activated transcription factor, cAMP itself has an opposing effect on LXR activity. In vivo, LXRs are localized to the juxtaglomerular (JG) cells in the kidney, where they are particularly concentrated. These JG cells, located in the afferent arterioles of kidney glomeruli, are responsible for synthesizing and releasing renin, an aspartyl protease that catalyzes the first and rate-limiting step in the renin-angiotensin-aldosterone system (RAAS)—the cleavage of angiotensinogen to angiotensin I. Renin plays a crucial role in regulating blood pressure, fluid balance, and salt-volume homeostasis.

LXRs regulate the expression of the renin gene by binding to its promoter. In cultured As4.1/LXR cells, an increase in intracellular cAMP levels led to an overexpression of renin mRNA after 6 hours of stimulation. However, overexpression of LXR was associated with higher basal levels of renin mRNA, while cAMP treatment decreased renin mRNA levels. Furthermore, in vivo studies have shown that LXRs are highly enriched in JG cells, where they co-localize with the renin promoter. This suggests that LXRs are directly involved in modulating renin gene expression in the kidney.

2.4.3 Vasoreactivity

LXR agonists, such as GW3965, have been shown to reduce Ang II receptor gene expression, which likely contributes to a decreased vasopressor response to Ang II. In hypertensive rats, GW3965 treatment was associated with a significant reduction in vasoreactivity, particularly in response to Ang II infusion. It was noted that this decrease in vasoreactivity correlated with a reduction in AT1 receptor gene expression. Notably, the reduced Ang II-mediated pressor response was observed primarily at the 6–8 hour post-treatment interval, coinciding with lower Ang II receptor gene expression during this period.

In addition to these findings, treatment with GW3965 for one week resulted in a marked reduction in systolic blood pressure in hypertensive rats ($p < 0.05$). In normotensive mice, GW3965 treatment also led to an increase in plasma nitrite levels ($p < 0.05$), further supporting the potential vasodilatory effects of LXR activation.

2.4.4 Nitrite Levels

The effects of GW3965 on plasma nitrite levels have been investigated in both hypertensive and normotensive rat models. In hypertensive rats, plasma nitrite levels remained stable, while GW3965 treatment resulted in a significant elevation of plasma nitrite levels in both hypertensive and normotensive rats. This increase in nitrite levels is likely linked to improved nitric oxide (NO) production. The LXR agonist GW3965 has been shown to reverse TNF-α-induced suppression of endothelial nitric oxide synthase (eNOS) expression and to improve NO bioavailability in endothelial cells. These findings suggest that the

beneficial vascular effects of GW3965 may, in part, be attributed to its impact on NO production.

2.4.5 NF-κB and TNF-α

In hypertensive rats, an upregulation of NF-κB and TNF-α expression has been observed in the mesenteric arteries and aorta. TNF-α is a pro-inflammatory cytokine that plays a critical role in the pathogenesis of hypertension by promoting vascular inflammation. Treatment with GW3965 resulted in a significant reduction in both TNF-α and NF-κB expression in hypertensive rats, bringing their levels down to those observed in control animals. Specifically, NF-κB protein expression in the aorta was markedly elevated in hypertensive rats but decreased significantly after treatment with GW3965 ($p < 0.05$). Similarly, TNF-α expression was significantly reduced following GW3965 administration, further suggesting the anti-inflammatory potential of LXR activation in the context of hypertension.

Conclusion

Hypertension remains a leading cause of mortality worldwide, underscoring the importance of identifying novel therapeutic targets. The Liver X receptor (LXR) emerges as a key player in the regulation of blood pressure, as evidenced by its involvement in modulating the renin-angiotensin-aldosterone system (RAAS). This review highlights the role of LXRs in regulating renin gene transcription through binding to a noncanonical response region in the renin promoter, suggesting a potential mechanism through which LXRs influence blood pressure regulation.

The administration of LXR agonists has been shown to attenuate Ang II-induced blood pressure increases, providing direct evidence of LXRs' involvement in blood pressure control. Specifically, LXR activation results in the downregulation of AT1 and AT2 receptor gene expression, leading to reduced vascular responsiveness to Ang II. Since AT1 receptor stimulation is primarily responsible for vascular dysfunction in the context of RAAS activation, the modulation of LXR activity offers a promising avenue for controlling hypertension.

Furthermore, LXR agonists have been found to regulate NF-κB and TNF-α levels, both of which are elevated in hypertensive conditions. By reducing these pro-inflammatory markers, LXRs may help mitigate the vascular inflammation associated with hypertension. Additionally, LXR agonists increase nitrite levels in both normotensive and hypertensive rats, potentially contributing to improved endothelial function and nitric oxide availability.

The synthetic LXR agonist T0901317 has also demonstrated inhibitory effects on AT1R mRNA and protein expression, further supporting the potential of LXRs as therapeutic targets. Given these findings, targeting the LXR pathway at various stages of hypertension could prove to be a promising strategy in the development of new antihypertensive therapies. Therefore, the Liver X receptor represents a viable and novel target for hypertension treatment, warranting further investigation and clinical exploration.

Acknowledgment

I would like to thank the Department of Pharmacology, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Vile Parle for the guidance and support.

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.

Refrences

1. Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Cífková R, Dominiczak AF, et al. Hypertension. Nat Rev Dis Prim.

2018 Jun 7;4(1):18014. Available from: http://www.nature.com/articles/nrdp201814

2. Forouzanfar MH, Afshin A, Alexander LT, Anderson HR, Bhutta ZA, Biryukov S, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016 Oct;388(10053):1659–724. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673616316798
3. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet. 2018 Nov;392(10159):2052–90. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673618316945
4. Hall ME, Hall JE. Pathogenesis of Hypertension. In: Hypertension: A Companion to Braunwald's Heart Disease. Elsevier; 2018. p. 33–51. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780323429733000056
5. Wilck N, Matus MG, Kearney SM, Olesen SW, Forslund K, Bartolomaeus H, et al. Salt-responsive gut commensal modulates TH17 axis and disease. Nature. 2017 Nov 15;551(7682):585–9. Available from: http://www.nature.com/articles/nature24628
6. Kerkelä R, Ulvila J, Magga J. Natriuretic Peptides in the Regulation of Cardiovascular Physiology and Metabolic Events. J Am Heart Assoc. 2015 Oct 27;4(10). Available from: https://www.ahajournals.org/doi/10.1161/JAHA.115.002423
7. Curry F-RE. Atrial natriuretic peptide: an essential physiological regulator of transvascular fluid, protein transport, and plasma volume. J Clin Invest. 2005 Jun 1;115(6):1458–61. Available from: http://www.jci.org/cgi/doi/10.1172/JCI25417
8. Armaly Z, Assady S, Abassi Z. Corin. Curr Opin Nephrol Hypertens. 2013 Nov;22(6):713–22. Available from: https://journals.lww.com/00041552-201311000-00019
9. Schlueter N, de Sterke A, Willmes DM, Spranger J, Jordan J, Birkenfeld AL. Metabolic actions of natriuretic peptides and therapeutic potential in the metabolic syndrome. Pharmacol Ther. 2014 Oct;144(1):12–27. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0163725814000953
10. Augustyniak RA, Picken MM, Leonard D, Zhou XJ, Zhang W, Victor RG. Sympathetic nerves and the progression of chronic kidney disease during 5/6 nephrectomy: Studies in sympathectomized rats. Clin Exp Pharmacol Physiol. 2010 Jan;37(1):12–8. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1440-1681.2009.05253.x
11. Grassi G, Mark A, Esler M. The Sympathetic Nervous System Alterations in Human Hypertension. Circ Res. 2015

Mar 13;116(6):976–90. Available from: https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.116.303604

12. Grassi G, Cattaneo BM, Seravalle G, Lanfranchi A, Mancia G. Baroreflex Control of Sympathetic Nerve Activity in Essential and Secondary Hypertension. Hypertension. 1998 Jan;31(1):68–72. Available from: https://www.ahajournals.org/doi/10.1161/01.HYP.31.1.68
13. Smith P. Relationship between central sympathetic activity and stages of human hypertension. Am J Hypertens. 2004 Mar;17(3):217–22. Available from: https://academic.oup.com/ajh/article-lookup/doi/10.1016/j.amjhyper.2003.10.010
14. Song C, Kokontis JM, Hiipakka RA, Liao S. Ubiquitous receptor: a receptor that modulates gene activation by retinoic acid and thyroid hormone receptors. Proc Natl Acad Sci. 1994 Nov 8;91(23):10809–13. Available from: https://pnas.org/doi/full/10.1073/pnas.91.23.10809
15. Apfel R, Benbrook D, Lernhardt E, Ortiz MA, Salbert G, Pfahl M. A novel orphan receptor specific for a subset of thyroid hormone-responsive elements and its interaction with the retinoid/thyroid hormone receptor subfamily. Mol Cell Biol. 1994 Oct;14(10):7025–35. Available from: http://mcb.asm.org/lookup/doi/10.1128/MCB.14.10.7025
16. Willy PJ, Umesono K, Ong ES, Evans RM, Heyman RA, Mangelsdorf DJ. LXR, a nuclear receptor that defines a distinct retinoid response pathway. Genes Dev. 1995 May 1;9(9):1033–45. Available from: http://genesdev.cshlp.org/lookup/doi/10.1101/gad.9.9.1033
17. Tontonoz P, Mangelsdorf DJ. Liver X Receptor Signaling Pathways in Cardiovascular Disease. Mol Endocrinol. 2003 Jun 1;17(6):985–93. Available from: https://academic.oup.com/mend/article/17/6/985/2747382
18. Peet DJ, Janowski BA, Mangelsdorf DJ. The LXRs: a new class of oxysterol receptors. Curr Opin Genet Dev. 1998 Oct;8(5):571–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0959437X98800130
19. Shinar DM, Endo N, Rutledge SJ, Vogel R, Rodan GA, Schmidt A. NER, a new member of the gene family encoding the human steroid hormone nuclear receptor. Gene. 1994 Sep;147(2):273–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/037811199490080
20. Tice CM, Noto PB, Fan KY, Zhuang L, Lala DS, Singh SB. The Medicinal Chemistry of Liver X Receptor (LXR) Modulators. J Med Chem. 2014 Sep 11;57(17):7182–205. Available from: https://pubs.acs.org/doi/10.1021/jm500442z
21. Svensson S. Crystal structure of the heterodimeric complex of LXR and RXR ligand-binding domains in a fully agonistic conformation. EMBO J. 2003 Sep 15;22(18):4625–33. Available from: http://emboj.embopress.org/cgi/doi/10.1093/emboj/cdg456
22. Hu X, Li S, Wu J, Xia C, Lala DS. Liver X Receptors Interact with Corepressors to Regulate Gene Expression. Mol

Endocrinol. 2003 Jun 1;17(6):1019–26. Available from: https://academic.oup.com/mend/article/17/6/1019/2747398

23. Edwards PA, Kennedy MA, Mak PA. LXRs; Vascul Pharmacol. 2002 Apr;38(4):249–56. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1537189102001751
24. Lee SD, Tontonoz P. Liver X receptors at the intersection of lipid metabolism and atherogenesis. Atherosclerosis. 2015 Sep;242(1):29–36. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0021915015300010
25. Pan L, Gross KW. Transcriptional Regulation of Renin. Hypertension. 2005 Jan;45(1):3–8. Available from: https://www.ahajournals.org/doi/10.1161/01.HYP.0000149717.55920.45
26. Sandoval-Hernández AG, Buitrago L, Jiménez A, et al. Renin gene expression in rats and human beings. J Renin Angiotensin Aldosterone Syst. 2014 Dec 18;15(3):329–36. Available from: https://journals.sagepub.com/doi/abs/10.1177/1470320314531628
27. Fleming I, Busse R. Molecular mechanisms involved in the regulation of the endothelial nitric oxide synthase. Am J Physiol Cell Physiol. 2003 Mar;284(3):C599–C611. Available from: https://journals.physiology.org/doi/full/10.1152/ajpcell.00221.2002
28. Ziegler E, Terbach N, Eichelmann E, et al. Regulation of the expression of endothelial nitric oxide synthase (eNOS) gene: Role of nitric oxide. Pharmacol Res. 2007 Apr;55(4):287–92. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1043661807000469
29. Heffernan K, Marques-Pita L, El-Arman F. Vascular endothelium and endothelial nitric oxide synthase gene expression. Cardiovasc Drugs Ther. 2005 Apr;19(2):99–106. Available from: https://link.springer.com/article/10.1007/s10557-005-2997-0
30. Yoshida H, Sato M, Yamamoto T. The renin-angiotensin system and cardiovascular diseases. Biol Pharm Bull. 2005 Aug;28(8):1423–30. Available from: https://www.jstage.jst.go.jp/article/bpb/28/8/1423/_article