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A Review on Advancements in Hypertension Research: Experimental Models, Mechanisms, and Therapeutic Targets

Reddy Prasad C[1], Bibi Umeza[1], Thirunavukkarasu Jayaraman[2*]

[1] PhD scholar, Department of Pharmacology, Saveetha Institute of Medical and Technical Sciences.
[2] Professor and Head, Department of Pharmacology, Saveetha Institute of medical and technical sciences, Saveetha Nagar, Thandalam, Chennai-602105.

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Abstract

Background: *Hypertension is one of the most prevalent cardiovascular disorders and a major global cause of morbidity and mortality, affecting approximately one billion individuals worldwide. Despite advances in screening and diagnosis, adequate blood pressure control remains suboptimal, particularly in countries such as India, where its prevalence among adults continues to increase. Limitations associated with conventional renin–angiotensin–aldosterone system (RAAS) inhibitors have prompted interest in novel therapeutic strategies for more effective blood pressure control and cardiovascular risk reduction.*

Methods: *This review examines the historical evolution of hypertension research and antihypertensive therapeutics, with particular emphasis on the limitations of conventional RAAS-targeting therapies and emerging pharmacological approaches. Contemporary evidence from clinical trials and relevant research on the ACE2/Ang-(1–7)/Mas receptor axis, neprilysin inhibition, technological advances, and innovative treatment strategies was critically evaluated. The review also considers relevant legislative and public health policy initiatives influencing hypertension management.*

Results: *The evidence indicates that modulation of alternative components of the RAAS may provide additional therapeutic benefits beyond conventional RAAS inhibition. Targeting the ACE2/Ang-(1–7)/Mas receptor axis may promote vasodilatory and cardioprotective effects, while neprilysin inhibition represents another promising approach for improving blood pressure regulation and cardiovascular outcomes. However, challenges related to therapeutic efficacy, patient heterogeneity, long-term cardiovascular benefits, and implementation remain. Advances in technology and emerging pharmacological strategies may further improve hypertension detection, monitoring, and treatment.*

Conclusions: *Hypertension management is evolving beyond conventional RAAS inhibition toward more targeted and innovative therapeutic approaches. Modulation of the ACE2/Ang-(1–7)/Mas receptor pathway and neprilysin inhibition represents promising areas for future drug development. Continued integration of clinical evidence, technological innovation, and effective health policies may contribute to more individualized and effective hypertension management and potentially transform cardiovascular outcomes in the future..*

Keywords: Hypertension, RAAS pathway, ACE2, Ang (1-7), Hypertension animal models, Mas R axis, Neprilysin inhibitors, Cardiovascular diseases.
***Corresponding to:** T Jayaraman, **Email:** thirunavukkarasu75@outlook.com

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Introduction

Hypertension persists as a predominant determinant of global morbidity and mortality. The condition, together with its associated comorbidities—such as coronary artery disease (CAD), myocardial infarction (MI), cardiac arrhythmias, and renovascular pathologies—exerts a profound impact on public health, with an estimated prevalence exceeding one billion individuals worldwide. Current estimates indicate that nearly half of adults in the United States and one-third of adults globally suffer from elevated blood pressure [1,2]. The escalating prevalence of hypertension has necessitated a growing reliance on antihypertensive pharmacotherapy to mitigate complications and reduce long-term risks. Despite advances in screening and diagnostic modalities, hypertension control in India remains suboptimal. Data from the National Family Health Survey (NFHS) reveal that the prevalence of hypertension among adults aged 15–49 years increased from 20.4% in NFHS-4 to 22.8% in NFHS-5 [3]. While enhanced screening initiatives improved detection, the proportion of newly diagnosed cases rose markedly from 41.6% to 52.1%. Notably, although the proportion of patients with a known history of hypertension receiving antihypertensive therapy increased from 32.6% to 40.7%, the rate of adequate blood pressure control declined from 80.8% to 73.7% [3]. Comparable trends have been observed in global surveys, aligning with the NFHS-5 findings. For instance, the Demographic and Health Surveys (DHS) report a prevalence of 19.99% in India, surpassing that of Nepal and Bangladesh, while remaining slightly lower than that of Peru (19.77%) [4,5]. These comparative data underscore India's disproportionately high burden of hypertension and highlight the need for more effective, targeted strategies to optimize blood pressure control and improve long-term cardiovascular outcomes [6,7]. Historically, therapeutic innovation has been central to hypertension management. A significant milestone was the development of RAAS inhibitors in the 1980s, a transformative advance that improved quality of life and survival among patients with hypertension [8]. Since then, an array of pharmacological classes—including angiotensin receptor blockers (ARBs), beta-adrenergic blockers, calcium channel blockers (CCBs), renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, diuretics, and mineralocorticoid receptor antagonists (MRAs)—has become standard in antihypertensive therapy [9]. These agents act primarily by modulating angiotensin II and aldosterone pathways through their respective receptor systems. Although such agents effectively lower blood pressure, they provide limited protection against end-organ damage and are often accompanied by mechanistic drawbacks. For instance, ARB

therapy elevates plasma renin activity, subsequently increasing angiotensin II levels, which compete with ARBs for receptor binding [10]. Similarly, ACE inhibitors may raise angiotensin I concentrations, promoting its non-ACE-dependent conversion to angiotensin II [11,12]. These limitations reinforce the urgent need for adjunctive or alternative therapeutic strategies beyond conventional RAAS antagonism. Consequently, current research is directed toward identifying novel pharmacological agents, optimizing drug combinations, and exploring systemic and molecular refinements within the RAAS pathway. Such advancements hold promise for safer, more efficacious therapies with reduced adverse effects [13]. This review examines the historical evolution of antihypertensive pharmacotherapy, the mechanistic complexities and challenges of current RAAS inhibitors, and the potential of emerging therapeutic strategies to transform hypertension management and improve cardiovascular health outcomes. Given that a significant portion of the global hypertension burden is concentrated in low- and middle-income countries, particularly in populous regions like India, its status regarding hypertension control warrants close examination.

Emergence of effective therapies

Pivotal scientific advances provided decisive resolution to longstanding controversies in hypertension and therapeutic research. In 1948, the British Medical Research Council (MRC) initiated the first randomized, placebo-controlled clinical trial to evaluate streptomycin in the management of tuberculosis, thereby introducing a transformative methodology for therapeutic assessment [14]. This innovation subsequently influenced the systematic evaluation of antihypertensive therapies. From sulphonamide derivatives, thiazide and thiazide-like diuretics with pronounced natriuretic effects were developed [15]. The earliest of these, chlorothiazide, was followed by hydrochlorothiazide and later chlorthalidone, each demonstrating significant efficacy in reducing blood pressure. These agents, representing a novel pharmacological class, initially exhibited considerable therapeutic potential in smaller-scale investigations [16]. In parallel, Arthur Guyton advanced the seminal hypothesis that dysregulated pressure-natriuresis could serve as a unifying mechanism underlying hypertension pathophysiology [17]. Building on this conceptual framework, the Veterans Affairs Cooperative Study Program pioneered multicenter, large-scale clinical investigations, profoundly shaping contemporary hypertension management. By systematically evaluating and integrating emerging therapeutic modalities, this program established the foundation of modern evidence-based strategies for blood pressure control [18,19].

Hypertension pathophysiology and therapeutics

Endothelin (ET)

Endothelin-1 (ET-1), a potent vasoconstrictor peptide, plays a pivotal role in modulating vascular tone and endothelial dysfunction, thereby contributing to the pathogenesis of hypertension. Acting predominantly through smooth muscle cell ETA receptors, ET-1 elicits concentration-dependent vasoconstriction, as demonstrated in isolated porcine coronary artery models. Pharmacological blockade of ET-1 signaling effectively attenuates vascular contraction, underscoring its significance as a potential therapeutic target [20]. Experimental *in vitro* investigations utilizing coronary artery models confirm the potent vasoconstrictive action of ET-1, reinforcing its targeting potential for hypertension therapy. Moreover, endothelial function is intricately linked to transcription factors Sp1 and Sp3. Evidence demonstrates that the antihypertensive efficacy of ACE inhibitors, such as captopril, is markedly reduced in Sp1/Sp3-deficient animals. This suggests a regulatory role of histone deacetylase 1 in mediating the endothelium-dependent effects of ACE inhibition. Consequently, Sp1 and Sp3 emerge as promising molecular targets for the development of novel cardiovascular therapies.

Monocrotaline-induced pulmonary hypertension in rats

Monocrotaline, a Crotalaria spectabilis pyrrolizidine alkaloid, is commonly used to produce pulmonary hypertension. A classic model of monocrotaline-induced pulmonary hypertension in rats induces pulmonary arterial hypertension, right ventricular hypertrophy, endothelial damage, and vascular remodeling following a single dose. Captopril, which normalizes pulmonary pressure, improves autonomic regulation, and reverses lung and heart structural abnormalities, has been tested in the model [21].

Renal hypertension rat models

Renal hypertension rat models represent fundamental experimental systems for investigating the pathophysiological mechanisms underlying hypertension arising from renal dysfunction. By artificially inducing alterations in renal perfusion, sodium handling, and fluid balance, these models provide a controlled framework to explore the interplay between the RAAS, sympathetic nervous activation, and vascular remodeling in the progression of hypertensive states. They serve as invaluable tools for delineating the molecular and hemodynamic pathways driving renin-dependent and volume-mediated hypertension while allowing for the systematic evaluation of novel pharmacological interventions. Furthermore, these models facilitate the study of long-term sequelae, including cardiac hypertrophy, renal fibrosis, and end-organ damage, thereby bridging experimental observations with clinical relevance. Their continued refinement enhances translational research by enabling the development and preclinical validation of emerging antihypertensive strategies and cardiorenal protective agents.

Pithed rodent model

The neurogenically denervated pithed rat model represents a classical and widely utilized experimental approach in cardiovascular pharmacology, designed to dissociate peripheral hemodynamic responses from central neural regulation. This preparation provides an advantageous platform for evaluating the direct cardiac and vascular effects of pharmacological agents, particularly antihypertensive drugs, as well as adrenergic agonists and antagonists [22]. In this model, adult male Wistar rats (250–350 g) are initially anesthetized with halothane. For hemodynamic monitoring, the carotid artery is cannulated to facilitate continuous blood pressure recording and periodic blood sampling, while the trachea is cannulated to enable artificial ventilation at a fixed rate of 60 cycles per minute with oxygen supplementation delivered through a T-piece. Intravenous drug administration is achieved by cannulation of the jugular vein. Pithing is accomplished by carefully inserting a steel rod (2.2 mm × 11 cm) via the orbital

cavity and foramen magnum into the spinal canal, thereby abolishing central reflex activity. After a stabilization period of 30 minutes, arterial blood samples (0.3 mL) are analyzed for key physiological parameters, including pO_2, pCO_2, pH, and bicarbonate concentration. Dose–response relationships are subsequently constructed using selective α_1-adrenergic agonists, namely phenylephrine (0.1–30 µg/kg, i.v.) and BHT 920 (1–1000 µg/kg, i.v.). Following administration of the investigational drug, agonist-induced responses are reassessed after 15 minutes to evaluate potential modulatory effects. The resulting changes in blood pressure are expressed as dose–response curves plotted on logarithmic–probit scales, permitting the calculation of potency ratios and quantitative characterization of pharmacological activity.

Tail cuff method for BP measurement

The tail-cuff plethysmography method represents a widely employed technique for non-invasive yet highly reproducible measurement of systemic arterial blood pressure in conscious rodents. Functionally analogous to the human sphygmomanometer, this approach involves occlusion of the caudal artery using an inflatable cuff, followed by detection of blood flow via volume-pressure transducers or photoelectric sensors. It is extensively utilized in genetically predisposed and experimentally induced hypertension models—including renovascular, SS, and chemically generated paradigms—to enable longitudinal monitoring of blood pressure dynamics without the confounding effects of anaesthetic-induced cardiovascular suppression. [23] Although it provides robust trend analysis across treatment timelines, the method necessitates habituation of animals to minimize stress-induced variability and demands precise calibration to ensure data accuracy. Consequently, tail-cuff plethysmography remains an indispensable tool for preclinical evaluation of antihypertensive efficacy, disease progression, and therapeutic responsiveness in rodent models of hypertension.

DOCA-salt hypertension model

The deoxycorticosterone acetate (DOCA)-salt hypertension model is a well-established experimental paradigm that induces volume-dependent hypertension through mineralocorticoid administration combined with high-salt loading. Chronic DOCA exposure stimulates sodium retention and plasma volume expansion, leading to persistent elevation of cardiac preload and activation of sympathetic nervous outflow, thereby contributing to increased vascular resistance and sustained hypertension. The DOCA-salt hypertension model is typically induced by unilateral nephrectomy followed by subcutaneous administration of DOCA and concurrent exposure to a high-salt regimen. Animals receive DOCA (20–30 mg/kg) twice weekly, combined with 1% NaCl and 0.2% KCl solution provided as drinking water to promote sodium retention and volume expansion. This combination of mineralocorticoid treatment, salt loading, and reduced renal excretory capacity leads to a progressive and sustained increase in arterial blood pressure, effectively reproducing the hemodynamic and structural alterations characteristic of salt-sensitive (SS) hypertension.[24] This model closely replicates SS hypertension observed in humans and is characterized by progressive left ventricular (LV) hypertrophy, structural vascular remodeling, and marked elevation of arterial blood pressure. Due to its predictable pathophysiological features, the DOCA-salt model is extensively employed to investigate the mechanistic interplay between mineralocorticoid receptor activation, electrolyte homeostasis, and neurohormonal regulation. Moreover, it provides a robust platform for assessing the therapeutic efficacy of emerging antihypertensive agents, particularly those targeting fluid balance, vascular tone, and sympathetic modulation, making it an indispensable tool in preclinical hypertension research.

Dahl SS rat model

The Dahl SS rat strain represents a genetically predisposed model of hypertension in which inherited defects in renal sodium handling, vascular reactivity, and neurohormonal regulation contribute to exaggerated pressor responses to dietary salt. Genetic studies have identified multiple quantitative trait loci (QTLs) influencing blood pressure regulation, encompassing genes associated with ion transport, oxidative stress, and inflammatory signaling. Pathophysiologically, these rats exhibit impaired natriuresis, increased sympathetic nervous system activity, endothelial dysfunction, and progressive renal injury, all of which synergistically promote volume expansion and vascular remodeling. Collectively, the Dahl SS model provides a robust framework for dissecting the molecular mechanisms underlying genetically determined, SS hypertension. The kidneys exhibit an extraordinary capacity to regulate sodium homeostasis by excreting substantial daily sodium loads without markedly expanding extracellular fluid volume. Epidemiological investigations consistently demonstrate a direct correlation between population-wide sodium intake and the prevalence of hypertension. Experimental evidence further substantiates these observations, as sustained consumption of high-salt diets induces hypertensive states in rodents, closely mirroring the morphological and physiological alterations documented in humans. Notably, Dahl SS rats develop severe, and often lethal, hypertension upon exposure to sodium-rich diets, whereas salt-resistant strains remain largely unaffected. Importantly, even under standard sodium intake, SS rats manifest elevated blood pressure, thereby establishing this model as a classical paradigm of genetically determined hypertension with an intrinsic element of salt sensitivity.[25–27] The model utilized a salt-loading protocol to induce experimental hypertension and cardiac hypertrophy in animal models through chronic exposure to a sodium chloride regimen. This model enabled evaluation of the pathophysiological changes associated with sustained high blood pressure and assessment of the therapeutic potential of the investigational compound. Overall, the approach provided a controlled framework to study cardiovascular remodeling and antihypertensive efficacy under hyper-saline conditions. In contrast to this genetically predisposed Dahl strain, the High-Salt Diet Model investigates the environmental and dietary influences of sodium intake on blood pressure regulation in non-genetically sensitive strains, such as Sprague Dawley or Wistar rats. In this model, animals are subjected to a chronic high-sodium chloride regimen (typically 8% NaCl in drinking water or diet), leading to moderate but reproducible elevations in systolic blood pressure and compensatory cardiac hypertrophy. Unlike the Dahl model, hypertension in this paradigm arises primarily from environmental sodium overload rather than inherited susceptibility. Therefore, the High-Salt Diet Model serves as a complementary tool to delineate the

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contribution of excessive dietary sodium to vascular and cardiac remodeling, independent of genetic predisposition, and to assess the preventive or therapeutic efficacy of antihypertensive compounds targeting salt-induced hemodynamic stress [28-30].

Fructose-induced hypertension model

Rodent models have been extensively utilized to elucidate the metabolic and cardiovascular consequences of high-fructose dietary intake. In these models, chronic fructose consumption induces pathophysiological alterations such as insulin resistance, hyperinsulinemia, dyslipidemia, and hypertension. These disturbances are largely mediated through the activation of angiotensin II type 1 receptors (AT1R) within adipose tissue, thereby establishing a mechanistic link between excessive fructose intake, impaired insulin signaling, and abnormal blood pressure regulation. Consequently, this experimental paradigm is regarded as a robust platform for investigating the interplay between metabolic and cardiovascular dysfunction and for assessing potential therapeutic strategies in hypertension and insulin resistance [31]. Chronic fructose consumption promotes excessive hepatic de novo lipogenesis and elevates circulating triglycerides and free fatty acids, leading to systemic insulin resistance and compensatory hyperinsulinemia. These metabolic disturbances activate the renin–angiotensin system, particularly through upregulation of AT1R within adipose and vascular tissues. Enhanced AT1R signaling triggers vasoconstriction, oxidative stress, and sympathetic nervous system activation, collectively contributing to endothelial dysfunction and elevated arterial pressure. Thus, fructose-induced hypertension arises as a secondary manifestation of metabolic imbalance driven by AT1R-mediated mechanisms. This experimental model serves as a valuable platform for delineating the molecular interplay between disordered glucose–lipid metabolism, vascular remodeling, and hypertension, and for evaluating therapeutic strategies targeting metabolic and renin–angiotensin pathways [32].

Spontaneously hypertensive rats

The spontaneously hypertensive rat (SHR) model represents one of the most rigorously characterized and extensively applied genetic models of primary hypertension, offering a well-established framework for exploring the hereditary determinants and complex pathophysiological processes of essential hypertension. Originating from the selective inbreeding of Wistar rats predisposed to elevated blood pressure, SHRs consistently develop early-onset, progressive, and sustained hypertension, which is accompanied by cardiac hypertrophy, renal impairment, and a pronounced tendency toward vascular remodeling. This model has proven invaluable in delineating the interrelationships among genetic susceptibility, endothelial dysfunction, neurohormonal activation, and target-organ damage in the natural course of hypertensive disease. Of particular significance, the stroke-prone SHR (SHR-SP) sub-strain demonstrates heightened cerebrovascular vulnerability, rendering it an exceptional preclinical platform for investigating the mechanisms of hypertension-associated stroke and evaluating neuroprotective interventions. Given its close pathophysiological congruence with human essential hypertension, the SHR model continues to be indispensable in translational research and remains a cornerstone for the development and preclinical validation of novel antihypertensive therapies [33,34].

Goldblatt hypertension model (2K1C and 1K1C)

The one-kidney, one-clip (1K1C) and two-kidney, one-clip (2K1C) experimental paradigms are extensively employed to induce renal artery stenosis, thereby serving as classical models for studying renovascular hypertension. These models underscore the pivotal role of renin release, impaired salt and water homeostasis, and subsequent activation of the renin-angiotensin system (RAS) in the pathogenesis of hypertension, making them invaluable for evaluating the pharmacodynamic properties of antihypertensive agents and RAS modulators [35]. Among these, the Goldblatt model represents a seminal approach in which renovascular hypertension is reproduced by partial occlusion of renal perfusion. In certain canine hypertension models, cellophane wrapping of a single or both kidneys induces the formation of fibro-collagenous capsules, leading to progressive renal compression, reduced perfusion, expansion of the extracellular fluid volume, and a consequent rise in systemic vascular resistance. Achieving hemodynamic stability typically necessitates the 1K1C configuration, after which blood pressure—commonly assessed via carotid cannulation or tail-cuff plethysmography—is monitored approximately six weeks post-procedure. Subsequently, candidate pharmacological agents are administered to delineate their antihypertensive efficacy. Despite being one of the earliest models, the Goldblatt technique remains a cornerstone in experimental pharmacology for investigating renin-dependent mechanisms of hypertension and evaluating the therapeutic potential of novel drug candidates. The major experimental models of hypertension, including 2K2C, DOCA-salt, SHR, and angiotensin II infusion models, are illustrated in Figure 1.

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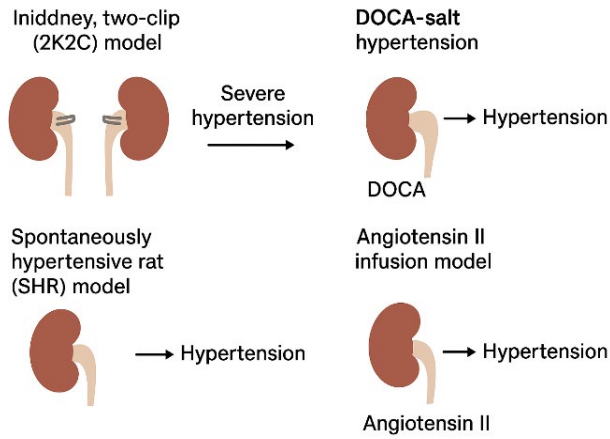

Figure 1. Experimental models of hypertension—2K2C, DOCA-salt, SHR, and angiotensin II infusion

Neurogenic hypertension models

Neurogenic hypertension models use baroreceptor dysfunction. Afferent stimulation to the nucleus tractus solitarius by carotid sinus and aortic arch baroreceptors controls blood pressure. Acute neurogenic hypertension results from carotid sinus nerve transection and vagotomy. Anesthetized dogs can be used to study blood pressure, heart rate, and ventricular function. After nerve ablation, test medicines are administered intravenously, and cardiovascular parameters are examined for changes, revealing central neurogenic pathway drugs [36,37].

Catheter in conscious rats

The methodology described facilitates accurate measurement of arterial blood pressure in conscious rats, thereby minimizing potential confounders introduced by anesthetic agents on cardiovascular regulation. Arterial catheterization in conscious rats is the gold standard for invasive BP measurement, providing accurate and continuous readings free from stress or anesthetic-induced error, and highly reliable and physiologically relevant technique for continuous measurement of cardiovascular parameters such as arterial pressure, heart rate, and pulse waveform dynamics. In this procedure, a sterile polyethylene or Teflon catheter (e.g., PE-50) is implanted into the femoral or carotid artery under anesthesia and exteriorized at the nape of the neck. After a suitable recovery period (24–48 hours), the animal is allowed to remain conscious and unrestrained while the catheter is connected to a calibrated pressure transducer and data acquisition system. This setup eliminates anesthetic interference, preserving normal autonomic regulation, vascular tone, and baroreflex sensitivity. The model's significance lies in its ability to provide high-fidelity, real-time hemodynamic data for both acute and chronic studies, enabling precise evaluation of blood pressure variability, circadian rhythms, and drug-induced cardiovascular responses. It is extensively used in hypertension research, pharmacological screening of vasoactive agents, and validation of noninvasive monitoring methods. Moreover, this approach allows direct correlation between physiological and biochemical parameters, making it an indispensable tool for understanding integrative cardiovascular control in translational and preclinical studies.[38]

Hypertension model in monkeys: renin inhibition

The marmoset model serves as a critical experimental platform in renin inhibitor research, primarily due to species-specific differences in the molecular structure and enzymatic activity of renin that limit the translational validity of rodent models. In this paradigm, renin release is pharmacologically stimulated through intravenous administration of furosemide, a loop diuretic that activates the RAAS by promoting sodium and volume depletion. Hemodynamic parameters are precisely monitored via femoral artery catheterization, enabling accurate and continuous measurement of arterial blood pressure. By closely mimicking human RAAS physiology, the marmoset model provides a translationally relevant platform for assessing the potency, selectivity, and therapeutic potential of novel RAAS-targeted agents, thereby bridging the gap between preclinical studies and human clinical trials.

Transgenic hypertension models

Gene-mediated hypertension has been extensively investigated using transgenic animal models, which provide valuable insights into the molecular pathways of hypertension and its therapeutic targets. One well-characterized example is the TGR (mREN2)27 rat, which overexpresses the mouse renin gene. This model develops early-onset, severe hypertension (systolic BP 200–260 mmHg) accompanied by cardiac hypertrophy, endothelial dysfunction, and renal damage, thereby serving as a powerful tool for studying monogenic, RAAS-dependent hypertension and evaluating gene-targeted therapeutic approaches [39]. The advancement of genetic engineering has enabled the insertion of specific genetic constructs into animals, thereby broadening research avenues in hypertension [40]. For instance, transgenic rats generated by introducing the entire mouse Ren-2d gene develop lethal hypertension when the gene is overexpressed in homozygous strains [41]. This model is unique as it represents a genetically inherited form of hypertension triggered by a single genetic event, although the precise mechanism underlying the condition remains unclear. Elevated local angiotensin II production, highly sensitive to RAS inhibition, contributes

significantly to hypertension and organ injury in this paradigm. Moreover, the severity of hypertension is influenced by genetic background, as crossing TGR (mREN2)27 rats with Sprague-Dawley strains produces a more malignant and accelerated form of the disease [42]. Other transgenic approaches have also demonstrated the role of RAAS in hypertension. The co-introduction of renin and human angiotensinogen genes induces hypertension in both mice and rats [43]. Additionally, knockout models lacking nitric oxide (NO) synthase or atrial natriuretic factor (ANF) receptors highlight the roles of vasodilatory pathways, with ANF receptor deficiency producing distinct SS and salt-independent hypertension phenotypes. Such models are indispensable for elucidating disease mechanisms and testing potential antihypertensive therapies.

Hypertension induced by chronic nitric oxide inhibition

NO is a critical endothelium-derived mediator that regulates systemic vascular resistance by acting as a continuous vasodilator, thereby preserving arterial pressure homeostasis. Experimental inhibition of NO synthase using NG-nitro-L-arginine methyl ester (L-NAME) has been widely established as a reliable model for investigating the pathophysiology of hypertension. Sustained L-NAME administration promotes persistent vasoconstriction, increased vascular resistance, glomerulosclerosis, tubular ischemia, and interstitial inflammatory infiltration, culminating in chronic hypertensive states [44]. This model is hallmarked by augmented peripheral vascular resistance accompanied by maladaptive cardiovascular adaptations. Although systemic arterial pressure rises, chronic inhibition of NO synthase paradoxically diminishes cardiac output, indicating compromised myocardial efficiency. Enhanced sympatho-excitatory drive, triggered by dysregulated vasoconstrictor responses secondary to NO deficiency, contributes significantly to both the initiation and perpetuation of hypertension. Moreover, L-NAME–induced pressure overload precipitates unique patterns of LV remodeling. Such remodeling is typified by a reduced LV cavity dimension relative to wall thickness, occurring without a commensurate increase in LV mass, thereby distinguishing this model from other hypertensive paradigms that exhibit similar elevations in blood pressure [45]. The pathological impact of L-NAME is further exacerbated by high dietary salt intake. Excess salt amplifies hypertensive responses through maladaptive sympathetic nervous system activity, which fails to adequately counterbalance pressure elevation [46]. Thus, the L-NAME-induced hypertension model provides valuable insights into NO-deficiency-mediated vascular and cardiac pathology and serves as a platform to assess therapeutic strategies targeting NO signaling pathways. Additionally, phenylephrine-induced hypertension in rabbits complements this model by elucidating peripheral vasoconstrictive mechanisms [47]. Advanced experimental models and their associated mechanistic insights into hypertension pathophysiology and therapeutics are summarized in Figure 2.

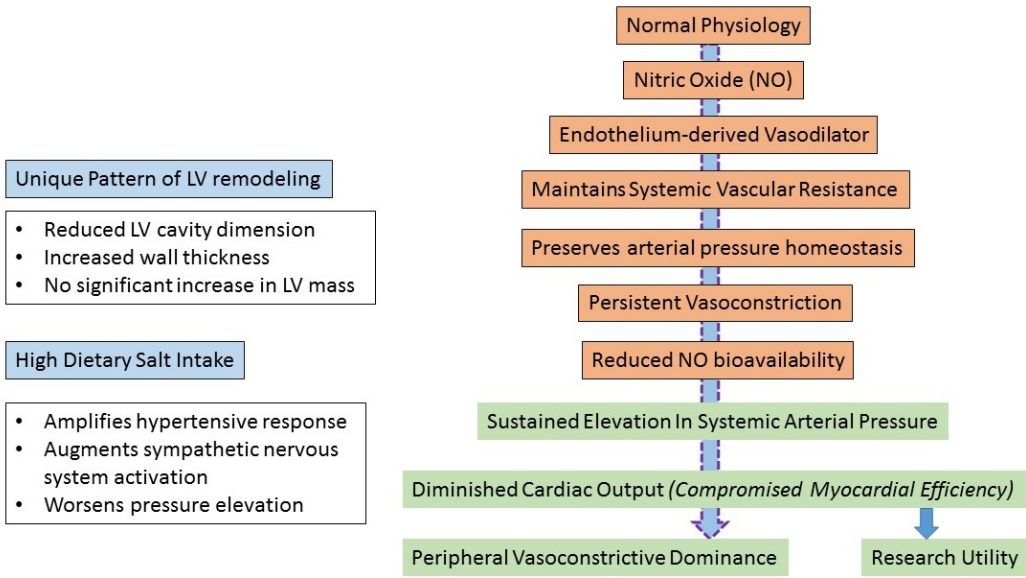

Figure 2. Advanced experimental models and mechanistic insights into hypertension pathophysiology and therapeutics

Targeting raas system[48]

By improving receptor dynamics and opening up new avenues for intervention, RAAS treatments hold great promise for the treatment of metabolic and cardiovascular disorders. The RAAS is regulated by the powerful vasoconstrictor angiotensin II (Ang II), which also causes inflammation, organ damage, and hypertension through the angiotensin receptor type 1. On the other hand, the AT2R and MAS receptors are engaged by the counter-regulatory vasodilator peptide Ang (1–7) produced by ACE2, and it demonstrates anti-inflammatory, antifibrotic, and protective properties. ACE2 activators, Ang

(1–7) mimetics, biased AT1R as well as AT2R agonists, along with MAS receptor modulators all use signaling pathways and receptor-ligand interactions to bring RAAS activity back into balance. The major components and counter-regulatory pathways of the RAAS system are illustrated in Figure 3.

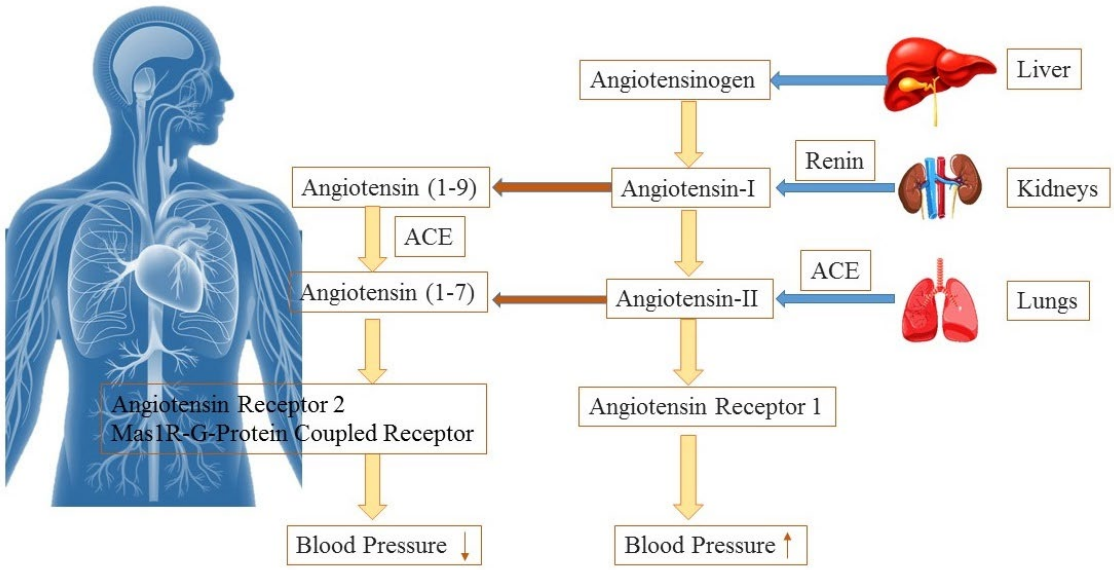

Figure 3. RAAS System. ACE – angiotensin-converting enzyme

Using structural research on receptors like AT1R and ACE2, specialized treatments like recombinant ACE2 (rhACE2) and β -arrestin-biased ligands have been developed to deal with pathogenic RAAS activity and enhance its protective axis. These new treatments pave the way for mechanism-driven, individualized therapy for heart failure, hypertension, and associated disorders; nevertheless, clinical translation is difficult owing to the intricate nature of systems as well as compensatory mechanisms. The major RAAS ligands, associated pathways, therapeutic targets, and their therapeutic implications are summarized in Table 1.

Table 1. Ligands, Pathways and therapeutic targets in the RAAS (Renin-Angiotensin-Aldosterone System)[49]

Ligand	Pathway	Therapeutic target	Therapeutic implication
Angiotensinogen	Cleaved by renin into Angiotensin I	Targets renin	Inhibits the initiation of the RAAS cascade, reducing blood pressure and cardiovascular risk.
Angiotensin I (Ang I)	Converted by ACE into Angiotensin II	ACE inhibitors (e.g., captopril, enalapril)	Reduces Ang II formation, resulting in decreased vasoconstriction and lowered BP.
Angiotensin II (Ang II)	Binds to AT1R and AT2R	AT1R blockers (e.g., losartan, valsartan); AT2R agonists	AT1R blockers reduce vasoconstriction, aldosterone secretion, and BP. AT2R agonists promote vasodilation and protective cardiovascular effects.
Angiotensin 1-7 (Ang 1-7)	Binds to MAS receptor	Mas receptor agonists	Promotes vasodilation, anti-inflammatory, and antifibrotic effects; counter-regulates Ang II/AT1R pathway.
Angiotensin-converting enzyme 1 (ACE 1)	Converts Ang I to Ang II and degrades Ang 1-7	ACE inhibitors (e.g., ramipril, benazepril)	Prevents Ang II synthesis and preserves Ang 1-7 levels, reducing hypertension and cardiovascular complications.
Angiotensin-converting enzyme 2 (ACE 2)	Converts Ang II to Ang 1-7 and Ang I to Ang 1-9	Recombinant ACE2 (e.g., rhACE2) and ACE2 activators	Reduces Ang II levels, enhances Ang 1-7 formation, and provides cardioprotective and antihypertensive effects.
Angiotensin II Type 1 receptor (AT1R)	Mediates vasoconstriction, aldosterone secretion, and inflammation.	At1R blockers (e.g., irbesartan, candesartan); β–arrestin–biased agonists	Blocks harmful effects of Ang II and improves receptor trafficking for selective pharmacological effects.
Angiotensin II Type 2 receptor (AT2R)	Promotes vasodilation, anti-inflammatory, and antifibrotic effects	AT2R agonists (e.g., compound 21)	Provides cardiovascular protection and anti-inflammatory effects, serving as a therapeutic target in hypertension and metabolic diseases.

MAS receptor	Activated by Ang 1-7	MAS receptor agonists	Enhance vascular relaxation, prevent oxidative stress, and support cardiovascular health.

Effect of different sources of salt on hypertension

The impact of dietary salt on blood pressure regulation extends beyond sodium chloride concentration alone, as the mineral composition and origin of salt sources—such as refined table salt, sea salt, rock salt, and mineral-enriched salts—can differentially influence cardiovascular outcomes. Conventional refined salt is composed almost exclusively of sodium chloride, which promotes extracellular fluid expansion, increased cardiac output, and vascular resistance, thereby elevating arterial pressure. In contrast, natural sea salt and rock salt contain trace minerals such as potassium, calcium, and magnesium, which exert mild vasodilatory and natriuretic effects that may partially counteract sodium-induced hypertension.[50] Experimental studies in hypertensive rat models have demonstrated that equivalent sodium loads derived from sea salt or mineral salts induce a comparatively attenuated rise in systolic blood pressure than purified sodium chloride, potentially due to modulation of endothelial function, renin–angiotensin–aldosterone system (RAAS) activity, and oxidative stress pathways. Furthermore, the presence of micronutrients in unrefined salts may enhance NO bioavailability and improve arterial compliance. However, despite these minor protective effects, excessive intake of any salt source ultimately leads to sodium overload and hypertensive pathology through renal sodium retention and neurohormonal activation. Therefore, while mineral-rich salts may confer modest benefits over refined salt, total sodium intake remains the primary determinant of blood pressure elevation. Understanding the comparative effects of various salt sources offers valuable insights into dietary modulation of hypertension and supports the development of nutritionally balanced, lower-sodium formulations for cardiovascular risk reduction.

Conclusion

Hypertension remains a leading determinant of cardiovascular morbidity and mortality worldwide. Over the past three decades, substantial progress has been achieved in delineating its complex pathophysiological mechanisms, with particular emphasis on the RAAS, endothelial dysfunction, and vascular remodeling. These insights have laid a robust scientific foundation for the formulation of targeted therapeutic strategies. Contemporary pharmacological management predominantly employs ACEIs, ARBs, and diuretics, which continue to serve as the cornerstone of antihypertensive therapy. Nonetheless, supplementary treatment approaches are often indispensable to address residual hypertension, minimize drug-related adverse effects, and accommodate interindividual heterogeneity in therapeutic responsiveness. Recent evidence highlights the therapeutic promise of adaptive interventions targeting RAAS modulation and other regulatory pathways. Of particular interest is the ACE2/Ang-(1-7)/Mas receptor axis, which counterbalances angiotensin II–mediated pathophysiology. Emerging pharmacological agents, including ACE2 activators, neprilysin inhibitors, and Mas receptor agonists, have shown potential to attenuate vascular inflammation, fibrosis, and oxidative stress while enhancing vasodilation and cardioprotection. In parallel, precision medicine approaches that incorporate baseline RAAS activity and genetic profiling may further refine patient stratification, thereby optimizing therapeutic efficacy. The pathogenic mechanisms and therapeutic strategies for hypertension have been extensively investigated through experimental models. Rodent models—such as monocrotaline-induced pulmonary hypertension, neurogenic hypertension, and transgenic rat strains—have been instrumental in delineating the molecular and physiological alterations associated with the disease, as well as in evaluating preclinical pharmacological agents with translational relevance. Furthermore, non-human primate models have provided critical insights into species-independent pharmacodynamics, particularly in the context of renin inhibition, thereby supporting both efficacy and safety assessments of novel agents. In the near future, integration of molecular and genetic insights with innovative therapeutic paradigms may enable effective control of uncomplicated hypertension. Nevertheless, sustained blood pressure reduction and long-term cardiovascular risk mitigation necessitate strategies that prevent compensatory adaptations and employ multimodal therapeutic regimens. Ongoing research must also elucidate the interplay between environmental exposures, epigenetic regulation, and disease pathophysiology to refine preventive and therapeutic approaches. Ultimately, addressing the global burden of hypertension requires a multidisciplinary framework that unites molecular biology, pharmacology, and clinical medicine. The development of advanced experimental models, novel pharmacological agents, and individualized treatment strategies holds promise for reducing hypertension prevalence worldwide, thereby improving long-term patient outcomes and quality of life.

Ethical Considerations

Not applicable.

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Conflict of Interest

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None.

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