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# Emerging New Insights Based on Pathogenesis of Distinct Hypertension Inducing Models on Rodents: A Review

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**ABSTRACT**

Hypertension is a major global health challenge and a leading risk factor for cardiovascular, cerebrovascular and renal disorders. Owing to its asymptomatic nature it is often termed a “silent killer” with organ damage becoming evident only at advanced stages. Experimental animal models play a crucial role in understanding the complex pathophysiology of hypertension and in evaluating novel therapeutic strategies. This review comprehensively summarizes the mechanistic basis of commonly employed in vivo hypertension-inducing models in rodents, including angiotensin II–induced hypertension, monocrotaline-induced pulmonary arterial hypertension, deoxycorticosterone acetate (DOCA)-salt hypertension, high-salt diet–induced hypertension, fructose-induced hypertension, stress-induced hypertension, and L-NAME-induced nitric oxide–deficient hypertension. These models mimic diverse pathological features such as sympathetic overactivation, endothelial dysfunction, oxidative stress, inflammation, vascular remodeling, impaired baroreflex sensitivity, and renal sodium retention. Additionally, emerging pathogenic contributors, including altered hepatic flavin monooxygenase (FMO3) activity, elevated plasma trimethylamine-N-oxide (TMAO) levels, nucleus tractus solitarius (NTS) dysfunction, and pro-inflammatory cytokine activation in spontaneously hypertensive rats, are discussed. Understanding the molecular, neural, and metabolic pathways involved in these models provides valuable insight into hypertension progression and highlights potential biomarkers and therapeutic targets. This consolidated overview supports the rational selection of experimental models for antihypertensive drug discovery and translational cardiovascular research.

## 1. Introduction

Hypertension represents one of the most prevalent and challenging non-communicable diseases worldwide and remains a primary contributor to global morbidity and mortality [1]. It is a major etiological factor for a wide spectrum of cardiovascular, cerebrovascular, and renal complications, including heart failure, myocardial infarction, stroke, and chronic kidney disease [2]. Due to its largely asymptomatic progression during early stages, hypertension is often described as a "silent killer," with irreversible target organ damage becoming clinically apparent only at advanced stages [3]. Persistent elevation of arterial blood pressure induces structural and functional alterations in the heart, vasculature, kidneys, and central nervous system, thereby accelerating disease progression and increasing mortality risk [8,9]. Clinically, hypertension is classified based on systolic and diastolic blood pressure measurements. A sustained blood pressure of ≥140/90 mmHg is considered stage 2 hypertension, while readings exceeding 180/120 mmHg constitute a hypertensive crisis, necessitating immediate medical intervention [4]. Despite extensive clinical research and the availability of multiple antihypertensive drug classes, optimal blood pressure control remains inadequate in a significant proportion of patients, underscoring the need for deeper mechanistic insights and novel therapeutic strategies.

Hypertension is a multifactorial disorder involving complex interactions among genetic predisposition, neurohumoral dysregulation, metabolic imbalance, endothelial dysfunction, renal sodium handling, oxidative stress, inflammation, and altered autonomic control [5]. The heterogeneity of its pathogenesis poses a major challenge to translational research, making experimental animal models indispensable for dissecting disease mechanisms and evaluating potential pharmacological interventions. Rodent models of hypertension have been extensively employed to replicate distinct etiological and pathological aspects of the human condition. These models include angiotensin II–induced hypertension, deoxycorticosterone acetate (DOCA)-salt–induced hypertension, monocrotaline-induced pulmonary arterial hypertension, nitric oxide synthase inhibition–mediated hypertension (L-NAME model), dietary models such as high-salt and fructose-induced hypertension, and stress-induced hypertension [6]. Each model reproduces specific features of hypertensive pathology, including sympathetic nervous system overactivation, vascular remodeling, endothelial dysfunction, impaired baroreflex sensitivity, renal dysfunction, and neuroinflammation.[7] In addition to classical mechanisms, recent studies have identified emerging pathogenic contributors that offer novel perspectives on hypertension development. Alterations in hepatic flavin monooxygenase 3 (FMO3) activity and elevated circulating levels of trimethylamine-N-oxide (TMAO) have been implicated in vascular inflammation, oxidative stress, and blood pressure dysregulation [8]. Furthermore, dysfunction of central autonomic regulatory regions such as the nucleus tractus solitarius (NTS) and paraventricular nucleus (PVN), along with enhanced pro-inflammatory cytokine signaling and synaptic plasticity changes in spontaneously hypertensive rats, highlight the critical role of neuroimmune and neurohumoral pathways in hypertension pathogenesis [9-10].

In this context, a comprehensive understanding of the mechanistic basis underlying distinct hypertension-inducing rodent models is essential for rational model selection, accurate interpretation of experimental outcomes, and successful translation of preclinical findings into clinical therapeutics. This critical review aims to consolidate current knowledge on classical and emerging rodent models of hypertension, emphasizing their molecular,

neural, and metabolic pathogenic mechanisms, and to highlight novel biomarkers and therapeutic targets relevant to antihypertensive drug discovery and translational cardiovascular research.

| BLOOD PRESSURE CATEGORY | SYSTOLIC mm Hg (upper number) | | DIASTOLIC mm Hg (lower number) |
|---|---|---|---|
| NORMAL | LESS THAN 120 | and | LESS THAN 80 |
| ELEVATED | 120-129 | and | LESS THAN 80 |
| HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1 | 130-139 | or | 80-89 |
| HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2 | 140 OR HIGHER | or | 90 OR HIGHER |
| HYPERTENSIVE CRISIS (consult your doctor immediately) | HIGHER THAN 180 | and/or | HIGHER THAN 120 |

**Figure-1: categorization of hypertension according to stages and risk level**

## 2. Pathogenesis *of In-Vivo Inducing Models*

### (a) Angiotensin-II Induced hypertension in rats

Angiotensin II (Ang II) plays a central role in the homeostatic regulation of arterial blood pressure and body fluid balance and is a key effector peptide of the renin–angiotensin system (RAS) [11]. Experimental administration of Ang II in rats is a well-established model for studying hypertension, as it closely replicates several hemodynamic, neural, and molecular features observed in human hypertensive pathology. Upon binding to angiotensin type-1 ($AT_1$) receptors, Ang II activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, leading to enhanced production of reactive oxygen species (ROS) in multiple tissues, including the vasculature, kidneys, and central nervous system [12,13]. Elevated ROS levels contribute to oxidative stress–mediated endothelial dysfunction and impair nitric oxide bioavailability, thereby promoting sustained vasoconstriction. In the central nervous system, Ang II–induced oxidative stress has been shown to reduce baroreflex sensitivity, which further exacerbates sympathetic overactivity and blood pressure elevation [14]. Beyond its well-characterized direct vasoconstrictor action (Figure-2a), Ang II indirectly increases peripheral vascular resistance through both central and peripheral mechanisms that enhance sympathetic nervous system activity. Centrally, Ang II acts on cardiovascular regulatory regions to augment sympathetic outflow, while peripherally it facilitates neurotransmitter release from sympathetic nerve terminals. Additionally, Ang II stimulates aldosterone secretion from the adrenal cortex and directly influences renal tubular function, resulting in increased sodium and water reabsorption and subsequent volume expansion [15]. Ang II also modulates prostaglandin synthesis, thereby altering vasomotor tone and renal hemodynamics it Changes in prostaglandin-mediated signaling affect vascular constriction, renal sodium handling, tissue production, plasma concentration, and urinary excretion of vasoactive mediators, collectively contributing to the development and maintenance of hypertension [16]. Thus,

the Ang II–induced hypertension model provides valuable insights into the interplay among oxidative stress, neurohumoral activation, renal dysfunction, and vascular remodeling in hypertensive disease progression.

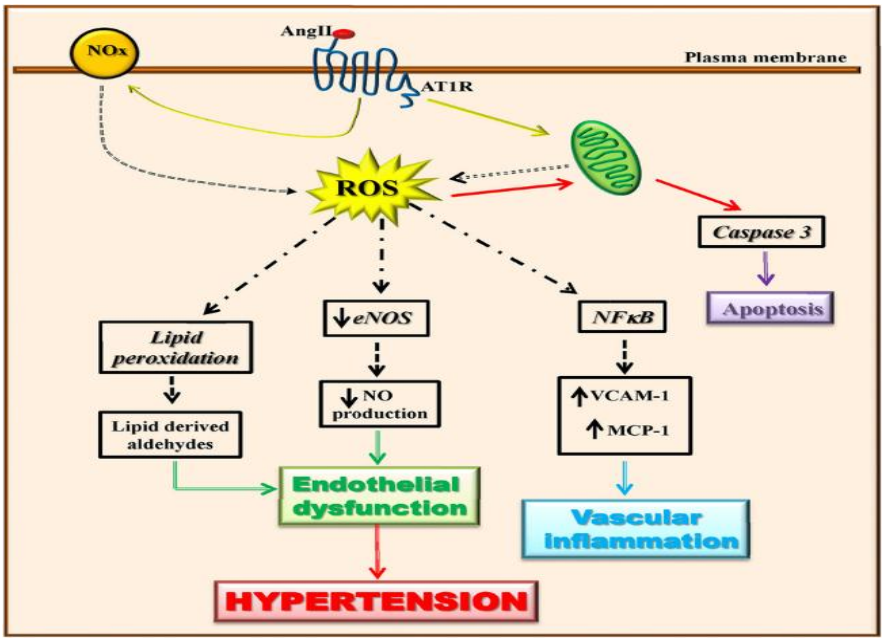


**Figure-2(a): Mechanism Based Angiotensin-II induced hypertension**

**(b) Monocrotaline Induced Pulmonary Arterial Hypertension in Rats**

To study Monocrotaline (MCT)-induced pulmonary arterial hypertension (PAH) is one of the most extensively studied and long-established experimental models for investigating PAH pathophysiology and evaluating potential therapeutic interventions, having been in use for over five decades [17]. This model reliably reproduces key pathological features of human PAH, including progressive pulmonary vascular remodeling, inflammation, elevated pulmonary arterial pressure, and right ventricular hypertrophy and failure. MCT is a pyrrolizidine alkaloid isolated from the plant *Crotalaria spectabilis*. Following systemic administration, MCT undergoes bioactivation in the liver by cytochrome P450 3A enzymes to form highly reactive toxic metabolites, primarily dehydromonocrotaline (DHM) and related pyrrolic intermediates [18]. These metabolites selectively target pulmonary vascular endothelial cells, leading to endothelial injury, increased vascular permeability, and subsequent initiation of inflammatory and proliferative responses within the pulmonary circulation (Figure-2b). Inflammation represents a central pathogenic feature of MCT-induced PAH, as evidenced by the marked infiltration of inflammatory cells and enhanced production of pro-inflammatory cytokines [19]. Experimental studies have demonstrated significant upregulation of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) following MCT administration, accompanied by activation of the nuclear factor kappa B (NF-κB) signaling pathway, which plays a pivotal role in sustaining inflammatory and proliferative vascular responses [20]. The progressive elevation of mean pulmonary arterial pressure (mPAP) observed in the MCT-PAH model occurs gradually and is primarily attributed to pulmonary vascular remodeling resulting from endothelial damage induced by MCT

toxic metabolites [21]. Structural changes include medial hypertrophy, adventitial thickening, and luminal narrowing of pulmonary arterioles, which collectively increase pulmonary vascular resistance. Pulmonary artery remodeling is therefore considered the principal determinant of the sustained rise in mPAP in this model [22]. Importantly, the temporal progression of inflammation and vascular remodeling in MCT-induced PAH provides a defined therapeutic window during which anti-inflammatory and antiproliferative interventions may effectively attenuate disease progression. Consequently, this model remains highly valuable for evaluating novel pharmacological strategies targeting inflammatory signaling pathways and vascular remodeling in PAH [23].

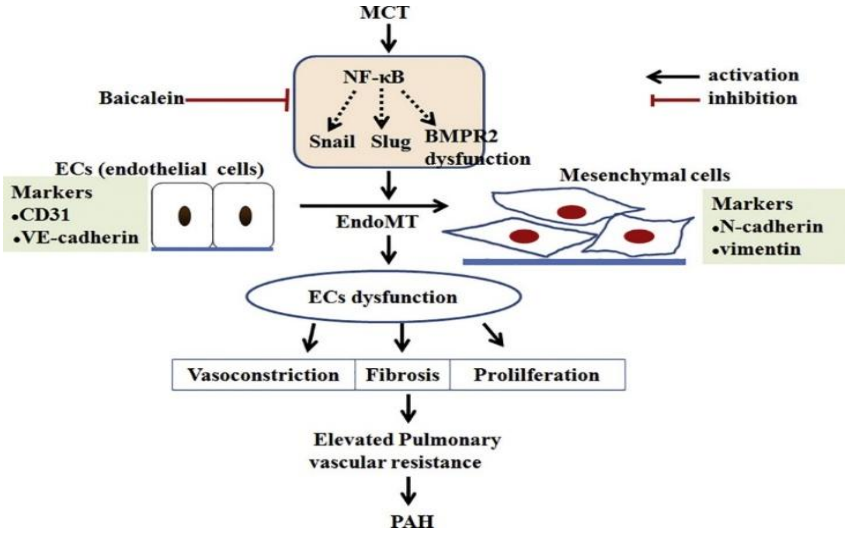


**Figure-2(b): Monocrotaline induced Pulmonary hypertension in rats**

**(c) DOCA Salt Induced Hypertension in rats**

Deoxycorticosterone acetate (DOCA)-salt hypertensive rat is one of the most widely employed experimental models for evaluating antihypertensive activity and studying mineralocorticoid-dependent hypertension [24]. Administration of DOCA in combination with a high-salt intake induces sustained hypertension characterized by marked sympathetic nervous system overactivation and neuroinflammation within central autonomic regulatory centers [25]. Enhanced sympathetic drive plays a critical role in both the initiation and maintenance of elevated blood pressure in this model. In addition, DOCA salt-treated rats exhibit increased salt consumption and enhanced renal sodium retention, leading to plasma volume expansion and the development of volume-dependent hypertension [26]. The model is largely independent of the renin–angiotensin system; however, antihypertensive agents such as angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors exert beneficial effects, primarily through attenuation of oxidative stress and improvement of vascular function. Inflammation is a key contributor to DOCA-salt hypertension, with activation of nuclear factor kappa B (NF-κB) triggering the production of pro-inflammatory mediators that promote vascular dysfunction and progressive renal injury, including glomerular damage [28]. Furthermore, oxidative stress, vascular remodeling, and chronic low-grade inflammation are mediated in part through toll-like receptor (TLR) signaling pathways, which amplify innate immune

responses and sustain hypertensive pathology [29]. Emerging evidence also highlights the protective role of anti-inflammatory lipid mediators such as Maresin-1, derived from the omega-3 polyunsaturated fatty acid docosahexaenoic acid (DHA), in attenuating inflammation and High dietary salt intake can induce sustained elevations in blood pressure even in animals without genetic predisposition, highlighting the critical role of environmental and metabolic factors in salt-sensitive hypertension [30]. The development of salt-dependent hypertension involves endogenous vasoactive mediators and complex alterations in vascular, renal, and metabolic regulatory pathways.

Sodium overload disrupts nitric oxide (NO) bioavailability and cytochrome P450 (CYP450)–dependent metabolic pathways, thereby modifying vascular reactivity and sensitivity to vasoactive substances [31]. In particular, alterations in the renal vascular bed play a pivotal role, as changes in medullary circulation influence tubular sodium reabsorption, renal excretion, and extracellular fluid volume, leading to volume-dependent increases in blood pressure [32].

Experimental evidence indicates that high salt intake modulates renal CYP450 activity, resulting in altered production of vasoactive eicosanoids and transport-inhibitory metabolites, whose biological effects depend on the magnitude of sodium consumption [33]. High-salt diets reduce renal production of 20-hydroxyeicosatetraenoic acid (20-HETE), an arachidonic acid metabolite generated by CYP450 enzymes, while increasing CYP2C isoform activity and Epoxyeicosatrienoic acid (EET) generation in the kidney. However, extra-renal 20-HETE production is increased in high-salt–fed hypertensive rats, contributing to vascular dysfunction, blood volume expansion, and sustained hypertension [34].

**(e) Fructose Induced hypertension in Rats**

Fructose-induced hypertension is increasingly recognized as a metabolically driven model that highlights the contribution of central autonomic dysregulation to blood pressure elevation. Chronic fructose consumption disrupts L-arginine-mediated glutamatergic signaling in nucleus tractus solitarius (NTS) neurons projecting to the caudal ventrolateral medulla, a key brainstem region involved in cardiovascular reflex control [35]. Electrophysiological studies have demonstrated a significant reduction in the baseline frequency of miniature excitatory postsynaptic currents (mEPSCs) in fructose-fed rats compared with controls, indicating impaired excitatory synaptic input [36]. While L-arginine exerts minimal effects on mEPSC amplitude-suggesting preserved postsynaptic sensitivity-it markedly increases mEPSC frequency under normal conditions, reflecting enhanced presynaptic glutamate release mediated by nitric oxide (NO) signaling [37]. This facilitatory effect of L-arginine is significantly blunted in fructose-fed rats, indicating compromised NO-dependent synaptic transmission. Collectively, these findings suggest that fructose intake reduces NO and glutamate production within the NTS, leading to impaired baroreflex sensitivity, heightened sympathetic outflow, and the subsequent development of hypertension [38].

**(f) Stress Induced Hypertension in Rats**

Chronic exposure to stressors such as immobilization, social defeat, or overcrowding induces sustained activation of hypothalamic nuclei, particularly the paraventricular nucleus (PVN), which plays a central role in cardiovascular and autonomic regulation [39]. Persistent PVN activation enhances sympathetic nervous system outflow, leading to increased release of norepinephrine (NE) and epinephrine (E) from sympathetic nerve terminals and the adrenal medulla. These catecholamines elevate arterial blood pressure by increasing heart rate, cardiac output, and peripheral vasoconstriction [40]. Stress also activates

the hypothalamic–pituitary–adrenal (HPA) axis, characterized by increased hypothalamic corticotropin-releasing hormone (CRH) secretion, followed by adrenocorticotropic hormone (ACTH) release from the anterior pituitary. This cascade results in elevated glucocorticoid levels-corticosterone in rodents and cortisol in humans. Sustained corticosterone exposure promotes sodium and water retention, enhances vascular reactivity, and induces metabolic disturbances such as insulin resistance, all of which contribute to the development and maintenance of hypertension [41].

**(g) L-NAME Induced hypertension in Rats**

L-NAME (N-G-Nitro-L-Arginine Methyl Ester) is a non-specific nitric oxide synthase (NOS) inhibitor that blocks the production of nitric oxide (NO) a critical vasodilator[42] Chronic administration of L-NAME induces hypertension, oxidative stress, endothelial dysfunction, and target organ damage in rats, mimicking aspects of human essential and secondary hypertension.NO is synthesized from L-arginine by NOS enzymes (eNOS in the endothelium, nNOS in neurons, iNOS in immune cells) L-NAME competitively inhibits NOS, leading to decrease Nitric oxide (NO) production, Loss of endothelium-dependent vasodilation, Increase Vascular tone and resistance, Immediate increase in mean arterial pressure (MAP) NO normally maintains vascular homeostasis [43]. Its absence leads to systemic vasoconstriction. NO deficiency impairs endothelial-dependent relaxation of blood vessels [44]. There's a reduction in bioavailability of vasodilators (like NO and prostacyclin) and an increase in vasoconstrictors (like endothelin-1 and thromboxane A2) [45]. L-NAME causes accumulation of superoxide anions ($O_2^-$) due to uncoupled NOS activity. Superoxide reacts with NO to form peroxynitrite ($ONOO^-$), a reactive nitrogen species that raises oxidative stress and lowers NO levels even more. ROS stimulate redox-sensitive transcription Collectively, these findings indicate that hypertension may be influenced by coordinated alterations in FMO3 and GRK expression, potentially arising from disrupted amine metabolism and dysregulated receptor signaling. This pathway represents a novel metabolic-signaling interface with potential relevance for biomarker identification and therapeutic targeting in hypertension [51].

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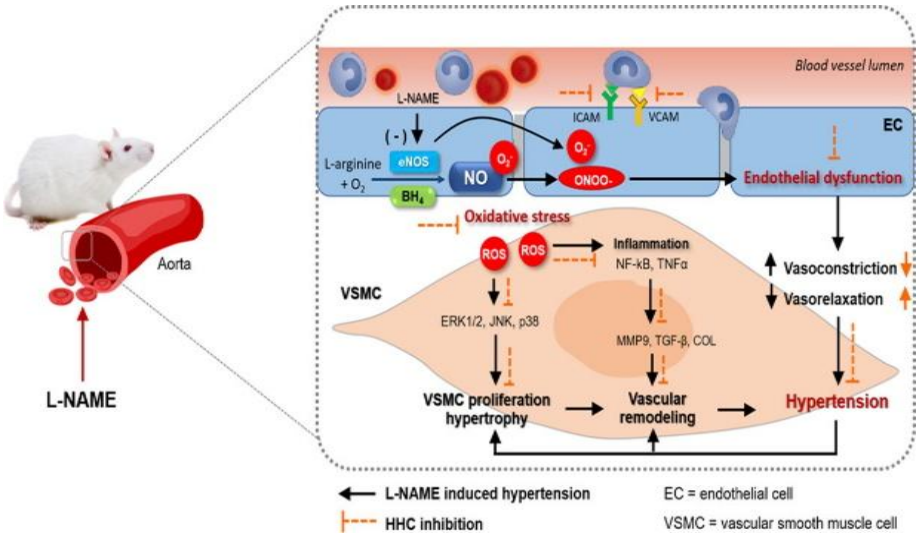


**Figure: - 2(g): L-NAME Mechanism inducing hypertension in rats**

## 3. Additional Pathogenesis involved in inducing hypertension in rodents

### (a) Liver FMO and Plasma TMAO Levels in Strain Rats

Flavin-containing monooxygenases (FMOs) are essential enzymes that catalyze the oxidation of a wide range of endogenous and exogenous amines. Flavin monooxygenase 3 (FMO3) converts trimethylamine (TMA), a metabolite produced by gut microbial metabolism, into trimethylamine N-oxide (TMAO), a circulating biomarker associated with cardiovascular disease risk [47]. Emerging evidence suggests that altered FMO expression contributes to elevated blood pressure in experimental models of hypertension. The diet-sensitive TMA-FMO3-TMAO pathway has been implicated in hypertension, as demonstrated by significantly increased hepatic FMO3 mRNA expression and elevated plasma TMAO levels in spontaneously hypertensive rats [48] (Figure-3a). In addition to its metabolic role, FMO3-TMAO signaling influences cellular pathways involving G-protein–coupled receptors (GPCRs), non-GPCR receptors, and intracellular substrates in target organs such as the kidney, heart, and vasculature. G-protein-coupled receptor kinases (GRKs), particularly the non-retinal isoforms GRK2-GRK6, are key regulators of GPCR signaling and blood pressure homeostasis [49]. Abnormal GRK expression and activity have been reported in both human and animal models of hypertension [50]. Although GRK1 and GRK7 are predominantly retinal isoforms, their ectopic hepatic expression may also contribute to the hypertensive phenotype observed in spontaneously hypertensive rats. Collectively, these findings suggest that hypertension may be influenced by coordinated alterations in FMO3 and GRK expression, potentially arising from impaired amine metabolism and dysregulated receptor signaling pathways [51].

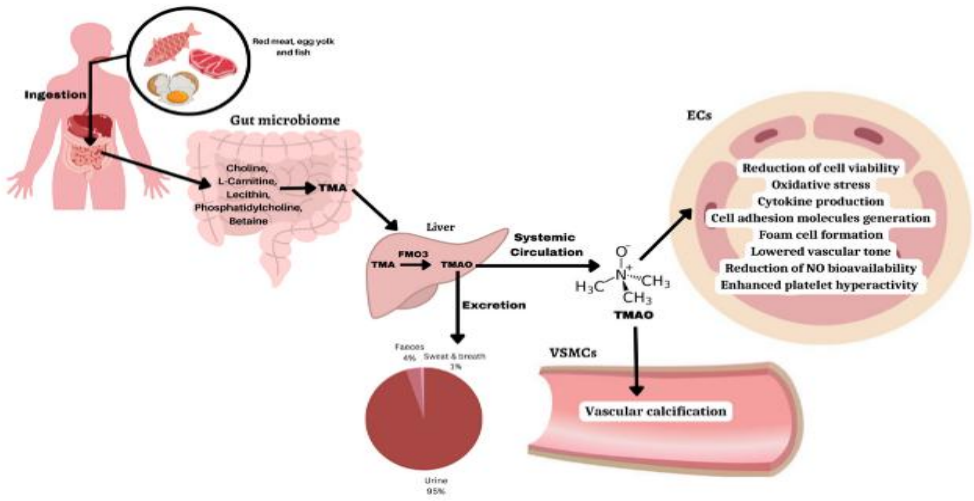


**Figure:3a- TMAO and FMO in Cardiovascular diseases**

**(b) Nucleus Tractus Solitarius (NTS) in Autonomic Regulation**

The nucleus tractus solitarius (NTS), located in the dorsomedial medulla oblongata, serves as a primary integrative center for autonomic reflexes involved in cardiovascular regulation. It receives afferent input from arterial baroreceptors and chemoreceptors and plays a critical role in modulating sympathetic and parasympathetic outflow to maintain blood pressure homeostasis. Fructose-fed rat models are frequently employed to investigate NTS-mediated autonomic dysfunction and metabolic disturbances while minimizing confounding factors such as overt diabetes, obesity, and severe hypertension [52]. Experimental stimulation of the NTS with L-glutamate mimics baroreflex activation in spontaneously hypertensive rats, resulting in reductions in arterial blood pressure and sympathetic nerve activity. Conversely, electrolytic lesions of the NTS in both humans and experimental animals lead to enhanced sympathetic vasomotor tone and impaired baroreflex control of blood pressure and heart rate [53]. The neural projection from the NTS to the caudal ventrolateral medulla (CVLM) constitutes a key pathway mediating baroreflex-dependent cardiovascular regulation. Integrity of the NTS-CVLM axis is essential for maintaining autonomic balance and stable arterial pressure. Disruption or neuronal dysfunction within this pathway diminishes baroreflex sensitivity and may contribute to sustained sympathetic activation, thereby promoting the development and progression of hypertension and related cardiovascular disorders [54].

**(c) Proinflammatory cytokines in Spontaneously Hypertensive Rats**

Inflammation is increasingly recognized as a critical contributor to the pathogenesis and progression of hypertension. In spontaneously hypertensive rats (SHRs), elevated circulating and tissue levels of pro-inflammatory cytokines correlate with disease severity. Cytokines with strong predictive relevance include interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), all of which have been shown to increase proportionally with rising blood pressure [55]. These mediators promote endothelial dysfunction, vascular remodeling, and enhanced sympathetic activation, thereby sustaining hypertensive pathology. Antihypertensive therapies such as angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors

exert beneficial effects in part by reducing oxidative stress and alleviating chronic tissue hypoxia, highlighting the close interplay between inflammatory and redox pathways in hypertension [56]. In addition, non-pharmacological interventions such as regular moderate-intensity exercise have been shown to attenuate inflammatory burden and are well tolerated in rats with developing hypertension [57]. Specialized pro-resolving lipid mediators (SPMs) have emerged as important modulators of inflammation in cardiovascular disease. Maresin-1 (MaR1), derived from the omega-3 polyunsaturated fatty acid docosahexaenoic acid (DHA), has demonstrated protective effects in multiple experimental models by promoting resolution of inflammation and improving vascular function [58]. At the molecular level, activation of nuclear factor kappa B (NF-κB) initiates an inflammatory cascade that amplifies cytokine production and, with progression of glomerular injury, markedly exacerbates hypertension. Toll-like receptors (TLRs) further serve as key upstream mediators linking oxidative stress, chronic low-grade inflammation, and vascular remodeling. Collectively, these findings provide strong evidence that inflammatory cytokines and lipid-derived mediators play a central role in hypertension development and represent potential therapeutic targets [59].

**Conclusion**

Progress in cardiovascular disease control requires understanding of the pathogenesis of the disease and testing of potential therapies, models for experimental hypertension are useful resources for researching the pathophysiology of chronic hypertension and its effects. These include a variety of rodent models, especially those are Inducing or genetically inclined to mimic particular pathophysiological characteristics which is Associated with inducing models like Angiotensin-II, Monocrotaline, Fructose, L-NAME, DOCA-salt, and Stress induced model used to test anti-hypertensive drug in hypertensive animals. Conversely, a pathogenesis-based mechanism proceeds through the stages that lead to hypertension. Research into the mechanism and creation of novel treatment drugs or targets for hypertension can be accelerated by the creation of new models and findings that take into account recent developments in the pathophysiology condition. Its continuous applicability in molecular research and preclinical pharmacological screening highlights its usefulness until better clinically reflective models are developed. The creation of new therapeutic targets with consequences for human health is still guided by the translational reliability of based investigations. Simulating drug-receptor dynamics, optimizing candidate compounds, and accurately predicting pharmacodynamic responses are all made possible by the integration of computational innovations like molecular docking, in silico pharmacokinetic modelling, and AI-driven target prediction. The complex etiology of hypertension can be better understood by researchers by utilizing state of the art computational platforms and continuously improving experimental models. Therefore, we feel to justified in adopting the affirmative stance that an excellent laboratory counter part of essential hypertension until a better experimental model becomes available. In addition to offering safer and more focused treatment options, this strategy is a significant step in reducing the worldwide burden of hypertension and ushering in a new era of individualized and predictive cardiovascular care.

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