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Epigenetic Regulation in Hypertension: Mechanistic Insights and Environmental Influences

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Abstract:

Hypertension is a leading global cause of cardiovascular, renal, and cerebrovascular morbidity. Beyond classical genetic and environmental determinants, accumulating evidence highlights epigenetic regulation as a key contributor to blood pressure control and vascular pathology. Epigenetic mechanisms including DNA methylation, histone post-translational modifications, and non-coding RNAs govern gene expression without altering the underlying DNA sequence, thereby linking environmental and physiological stimuli to stable transcriptional changes. Aberrant epigenetic signatures have been identified in vascular, renal, and endocrine tissues integral to blood pressure regulation, influencing pathways that mediate vascular tone, sodium handling, oxidative stress, and inflammation. Among these, differential methylation and histone modification of renin angiotensin aldosterone system (RAAS) genes, including *AGT*, *REN*, *ACE*, and *AT1R*, have been shown to promote sustained activation of vasoconstrictive and sodium-retentive signaling cascades. Chronic exposure to a high-salt diet (HSD) represents a potent environmental modifier of this epigenetic landscape. Excess dietary sodium can alter CpG methylation patterns, histone acetylation states, and microRNA profiles across multiple tissues, leading to enhanced RAAS activity and vascular dysfunction. These HSD-induced alterations often persist despite subsequent sodium normalization, reflecting an enduring "epigenetic memory" of dietary stress that contributes to salt-sensitive hypertension. Understanding how HSD and other environmental

factors reprogram RAAS-related gene networks through epigenetic mechanisms provides critical insight into the molecular basis of hypertension. Moreover, these findings open new avenues for therapeutic intervention utilizing DNA methyltransferase and histone deacetylase inhibitors, as well as RNA-based precision therapies aimed at reversing the maladaptive epigenetic imprint underlying chronic blood pressure elevation.

Keywords: Hypertension; epigenetics; DNA methylation; histone modifications; high-salt diet.

Introduction:

Hypertension remains a leading global health concern, affecting over one billion individuals and contributing significantly to cardiovascular, renal, and cerebrovascular morbidity and mortality[1-4]. Despite the availability of effective antihypertensive therapies, blood pressure control remains suboptimal in a large proportion of patients, underscoring the need to better understand the underlying mechanisms of disease pathogenesis[5]. While genetic and environmental factors have long been implicated in hypertension, they do not fully explain its complex and variable presentation[6].

Epigenetics has emerged as a key regulatory layer influencing gene expression in complex, multifactorial diseases like hypertension[7]. Epigenetic mechanisms including DNA methylation, histone post-translational modifications, and non-coding RNAs such as microRNAs and long non-coding RNAs allow for dynamic regulation of gene activity in response to environmental and physiological stimuli[8-11]. These processes do not alter the underlying DNA sequence but can heritably influence gene expression, particularly in vascular and renal tissues relevant to blood pressure control[12].

Among these mechanisms, DNA methylation remains one of the most extensively studied in the context of hypertension[8, 13-15]. Typically occurring at CpG dinucleotides within gene promoters, methylation is associated with transcriptional repression, whereas hypomethylation may promote gene activation[13, 16, 17]. Alterations in DNA methylation have been linked to dysregulated expression of genes involved in vascular tone, renal sodium handling, inflammation, and hormonal signaling[18]. However, emerging evidence also highlights the importance of histone modifications and non-coding RNAs as integral components of this regulatory network.

Histone modifications such as acetylation, methylation, and phosphorylation are central to chromatin remodeling and gene accessibility[19]. In hypertensive models, aberrant histone acetylation patterns have been observed in vascular and renal tissues, contributing to dysregulated expression of vasoactive genes and inflammatory mediators[20]. Non-coding RNAs, particularly microRNAs, further modulate gene networks by repressing target mRNAs involved in blood pressure regulation, oxidative stress, and endothelial function[21].

Together, these epigenetic processes orchestrate a multilayered control system that responds to external cues such as aging, stress, and dietary factors[22]. Of particular interest is the effect of a high-salt diet (HSD), which has been shown to reprogram epigenetic signatures across multiple organs, including the kidney, vasculature, and brain[18]. These changes converge on key hypertensive pathways, notably the renin-angiotensin-aldosterone system (RAAS), promoting sustained hypertension and vascular damage[23].

This review aims to synthesize current knowledge on the role of epigenetic regulation in hypertension, with emphasis on RAAS-related gene networks and the modifying effects of HSD.

Special attention is given to the interplay between methylation and other regulatory layers in mediating long-term changes in blood pressure homeostasis.

1. Epigenetic Mechanisms: Epigenetics refers to the study of heritable and reversible changes in gene expression that occur without altering the underlying DNA sequence[24]. These modifications influence cellular function and development, crucial in both normal physiological processes and disease progression[25]. Epigenetic changes are highly dynamic and can be influenced by various internal and external factors, including stress, nutrition, aging, environmental toxins, and lifestyle choices such as diet and exercise[26]. Exposure to these stimuli can lead to alterations in epigenetic patterns, affecting gene activity and contributing to conditions such as cancer, cardiovascular diseases, and hypertension [8]. The different types of epigenetic regulations involved in hypertension include DNA methylation, histone modifications, non-coding RNAs, and chromatin remodeling [27].

1.1 DNA Methylation and Hypertension:

DNA methylation is a key epigenetic mechanism that regulates gene expression without altering the DNA sequence[28]. It typically involves the addition of a methyl group ($–CH_3$) to the cytosine base of DNA at CpG dinucleotides, a reaction catalyzed by DNA methyltransferases (DNMTs) such as DNMT1, DNMT3A, and DNMT3B[29]. When this modification occurs in gene promoter regions, it often represses transcription by blocking the access of transcription factors and other regulatory proteins[16]. DNA methylation plays a critical role in essential biological processes, including X-chromosome inactivation, genomic imprinting, and the silencing of transposable elements[29]. Abnormal methylation patterns either excessive (hypermethylation) or insufficient (hypomethylation) have been linked to a variety of diseases, such as cancer, neurodegenerative

disorders, autoimmune conditions, and importantly, hypertension[17, 30, 31]. Altered methylation patterns in specific genes involved in key biological pathways such as RAAS, the sympathetic nervous system (SNS), and the renal sodium retention system contribute to the pathogenesis of hypertension[32]. The hypomethylation of the angiotensin type 1A (AT1a) receptor gene, a key component of the RAAS, leads to its increased expression, which is associated with hypertension[33]. Conversely, hypermethylation of the AT1b receptor gene affects expression of the AT1b receptor, not the secretion of angiotensin itself[34]. It is important to note that this type of regulation, if it exists, only occurs in rodents since humans do not express AT1b[35]. Hypomethylation of the angiotensin-converting enzyme (ACE) gene led to increased expression, which contributed to dysregulated blood pressure control[36]. Another key enzyme, 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2), which regulates renal sodium reabsorption, exhibits altered methylation in hypertensive patients, linking mineralocorticoid excess to salt sensitivity[37]. Genome-wide methylation studies have further shown that overall methylation levels are reduced in individuals with hypertension. Specific genes such as *Sulf1*, *Prcp* and *Abcg4* which influence vascular tone and blood pressure control, are differentially methylated in these patients[32, 38]. These epigenetic alterations not only disrupt vascular function and promote inflammation but also represent promising targets for novel therapeutic interventions aimed at reversing aberrant methylation patterns in hypertension[39].

1.2 Histone Modifications and Hypertension:

Histone modifications represent another major epigenetic mechanism regulating gene expression by influencing chromatin structure and accessibility[40]. These post-translational modifications occur on specific amino acid residues of histone proteins and include acetylation, methylation, phosphorylation, and ubiquitination[41]. The pattern and type of these chemical changes determine

how tightly DNA is wound around histones, thereby regulating accessibility to transcriptional machinery[42]. For instance, transcriptional activity is the primary cause of histone acetylation, which is catalyzed by histone acetyltransferases (HATs)[43]. Whereas transcriptional repression is linked to histone deacetylation, which is catalyzed via histone deacetylases (HDACs)[44]. Emerging evidence links aberrant histone modifications to the development of several chronic inflammatory diseases, including atherosclerosis, hypertension, type 2 diabetes, alzheimer's disease, psoriasis, asthma, chronic lung disorders, and inflammatory bowel disease[45]. In the context of hypertension, histone modifications affect the expression of genes that regulate vascular tone and blood pressure[20]. For instance, ACE is upregulated by increased histone acetylation (H3Ac) and trimethylation at histone H3 lysine 4 (H3K4me3), both markers of transcriptional activation[46]. Simultaneously, a reduction in demethylation at H3K9 (H3K9me2) a repressive mark also contributes to increased ACE expression, thereby enhancing RAAS activity[47]. The inflammatory mediator NLRP3 undergoes H3K9 acetylation (H3K9Ac), which enhances its transcription and contributes to inflammation-driven hypertension[48, 49]. NOS3 (eNOS) is regulated by multiple histone modifications (H3K9Ac, H4K12Ac, H3K4me2, H3K4me3), affecting nitric oxide production and endothelial vasodilation[50]. Additionally, Slc12a2 (NKCC1) expression is modulated by increased H3Ac and reduced H3K27me3, impacting ion transport and blood pressure regulation[51]. These histone modifications contribute to vascular dysfunction, inflammation, and dysregulation of blood pressure, making them promising epigenetic targets for therapeutic intervention in hypertension[52].

1.3 Non-coding RNAs and Hypertension:

Non-coding RNAs (ncRNAs) including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are a heterogeneous group of transcripts that play a key role in regulating the expression

of genes[53]. These ncRNAs influence mRNA stability and translation, thereby impacting cellular function. For example, lncRNAs can interact with the chromatin-modifying complexes, whereas miRNAs target the specific mRNAs for degradation or translational repression to regulate gene expression[54]. Recent studies highlight the pivotal role of ncRNAs in the development and progression of hypertension, particularly through regulation of vascular function, inflammation, and the RAAS[55].

1.3.1 Key microRNAs in Hypertension: Importantly, miR-155 is downregulated in hypertensive patients, leading to increased AGTR1(angiotensin II type 1 receptor) expression and heightened vasoconstriction[56] while miR-143/145 controls vascular smooth muscle cell (VSMC) differentiation, with reduced expression contributing to arterial stiffness and hypertension[57]. In contrast, miR-21 is upregulated in hypertension, promoting VSMC proliferation and fibrosis through PTEN (Phosphatase and Tensin Homolog deleted on Chromosome 10) inhibition[58]. Among long non-coding RNAs, MALAT1 is associated with endothelial dysfunction and inflammation, driving vascular remodeling in hypertensive conditions, whereas H19 regulates RAAS by modulating ACE and AGTR1, influencing blood pressure[59]. Additionally, miR-126 plays a protective role by enhancing endothelial function and nitric oxide production, with its reduced levels linked to hypertension[60, 61]. These ncRNAs act as crucial regulators of gene expression, making them potential targets for therapeutic intervention in hypertension. Some of the key long non-coding RNAs (lncRNAs) related to hypertension include MALAT1 (metastasis-associated lung adenocarcinoma transcript 1)[62, 63], H19[64-66], LEENE (LncRNA that Enhances Endothelial Nitric Oxide Synthase Expression)[67, 68], MIAT (Myocardial Infarction–Associated Transcript)[69-71], and NORAD (Noncoding RNA Activated by DNA Damage)[72].

1.4 Chromatin Remodeling in Hypertension:

Chromatin remodeling plays a crucial role in the regulation of gene expression related to hypertension by altering the accessibility of transcription factors to DNA[73]. This process involves the dynamic modification of chromatin structure through ATP-dependent chromatin remodeling complexes (such as switch/sucrose nonfermentable (SWI/SNF); imitation switch (ISWI); chromodomain helicase DNA-binding (CHD); and inositol requiring 80 (INO80)), which either relax or condense chromatin to regulate gene transcription[74]. These complexes do not chemically modify histones but rather use energy from ATP hydrolysis to physically alter chromatin structure[75]. ATP-dependent chromatin remodeling complexes regulate gene expression by using ATP hydrolysis to reposition or restructure nucleosomes, altering DNA accessibility for transcription[20, 76]. SMARCA4 (BRG1) and SMARCA2 (BRM) are core subunits of the SWI/SNF (BAF) complex, which facilitate chromatin relaxation and gene activation. The CHD1-CHD8 proteins, belonging to the CHD (Chromodomain-Helicase-DNA-binding) family, play a role in nucleosome spacing and transcriptional regulation. Similarly, ISWI (SMARCA1, SMARCA5), part of the ISWI complex, is responsible for nucleosome assembly and overall chromatin organization. Additionally, INO80 and SRCAP, components of the INO80 complex, are crucial for DNA repair, replication, and transcription regulation[20, 75, 76]. These remodeling complexes coordinate to dynamically reorganize chromatin in response to physiological and environmental signals, enabling precise control of gene expression[77]. In the context of hypertension, chromatin remodeling contributes to the regulation of genes involved in vascular tone, inflammation, and renal sodium handling. Importantly, dysregulation of chromatin remodeling complexes has been associated with several diseases, including hypertension, cancer, and neurodegenerative disorders[78]. Aberrant chromatin remodeling can lead to inappropriate activation or silencing of critical genes, thereby contributing to disease progression. Consequently, components of these

complexes represent potential therapeutic targets for modulating gene expression in hypertensive and other pathological states[79].

Recent studies have demonstrated that chromatin remodeling responses to oxidative stress are highly dependent on the cell type, the specific microenvironment, and the organism[80]. These epigenetic outcomes are not uniform, as demonstrated by opposing outcomes like heterochromatin loss in neurotoxicity versus protective stabilization in other cancer cells. Further, oxidative stress influences gene expression through various mechanisms, including direct chemical modification of histone proteins by reactive species and the modulation of chromatin modifier activity, such as the inhibition of iron-dependent demethylases. Resolving neuronal subtype specificity and understanding the selective roles of chromatin remodelers in specific gene networks are necessary to grasp how these processes link DNA damage to differential epigenetic reprogramming[80-83].

2. Factors influencing Epigenetic Modifications:

Hypertension is a complex and multifactorial condition influenced by both genetic predisposition and environmental exposures. Epigenetic mechanisms-including DNA methylation, histone modifications, and chromatin remodeling-play a pivotal role in modulating gene expression pathways involved in vascular function, inflammation, and the RAAS. These epigenetic changes are dynamic and responsive to various intrinsic and extrinsic stimuli, thereby contributing to the development and progression of hypertension[84] (**Fig.2**).

2.1 Genetic Background:

Genetic variations influence epigenetic modifications in hypertension[85]. Polymorphisms in DNA methyltransferases (DNMTs), histone-modifying enzymes, and chromatin remodelers can affect gene regulation related to blood pressure control[86]. For instance, mutations in DNMT3A and

DNMT3B lead to aberrant methylation of ACE and AGTR1, altering RAAS activity and increasing vasoconstriction. Similarly, mutations in chromatin remodelers such as SMARCA4 (BRG1) can affect vascular smooth muscle cell (VSMC) function, contributing to arterial stiffness[87, 88]. These findings highlight how genetic background shapes the epigenetic landscape contributing to hypertension.

2.2 Environmental Exposures:

Environmental factors such as air pollution, heavy metals (e.g., lead and cadmium), and cigarette smoking contribute to the development of hypertension through epigenetic alterations[89]. Exposure to fine particulate matter ($PM_{2.5}$) has been shown to cause global DNA hypomethylation, along with gene-specific hypermethylation particularly of genes critical to endothelial function, such as NOS3 (endothelial nitric oxide synthase)[90]. These changes result in decreased nitric oxide production and impaired vasodilation[91]. Likewise, exposure to heavy metals disrupts histone acetylation patterns, leading to upregulated expression of pro-inflammatory genes, which in turn contributes to vascular dysfunction and elevated blood pressure[92, 93]. These data underscore the mechanistic link between environmental toxicity and epigenetic dysregulation in hypertensive disease.

2.3 Aging:

Aging is a significant risk factor for hypertension and is closely associated with epigenetic drift characterized by global DNA hypomethylation and gene-specific hypermethylation of regulatory elements[94]. In hypertensive individuals, aging leads to hypermethylation of the 11β-HSD2 gene, resulting in decreased expression of the enzyme and subsequent mineralocorticoid excess and sodium retention, which contribute to elevated blood pressure[95]. Furthermore, age-related histone

modifications such as reduced trimethylation of histone H3 at lysine 9 (H3K9me3) and acetylation of histone H4 at lysine 16 (H4K16ac) are implicated in endothelial dysfunction by promoting oxidative stress and inflammatory responses[96, 97]. Collectively, these findings indicate that age-dependent remodeling of the epigenome accelerates vascular and renal alterations underlying hypertension.

2.4 Oxidative Stress and Inflammation:

Oxidative stress and chronic inflammation are key drivers of hypertension. Reactive oxygen species (ROS) modify epigenetic landscapes by oxidizing 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC), leading to passive DNA demethylation. Inflammatory cytokines such as TNF-α and IL-6 induce histone acetylation (H3K9Ac) at pro-inflammatory genes like Nlrp3, promoting vascular inflammation and endothelial dysfunction[98]. Chromatin remodeling enzymes, particularly CHD and ISWI family members, are also dysregulated in hypertension, leading to altered nucleosome positioning and aberrant gene expression[99].

2.5 Diet and Nutrition:

Dietary components play a crucial role in modulating epigenetic regulation associated with hypertension. High dietary salt intake has been shown to increase DNA methyltransferase (DNMT) activity, resulting in hypermethylation of anti-inflammatory genes and contributing to endothelial dysfunction[18]. In contrast, diets rich in methyl donors such as folate, vitamin B12, and choline support proper DNA methylation and may help reverse aberrant gene silencing observed in hypertensive individuals[100]. Additionally, polyphenols such as resveratrol, curcumin, and epigallocatechin gallate (EGCG) from green tea have demonstrated the ability to inhibit histone deacetylases (HDACs), thereby enhancing histone H3 lysine 9 acetylation (H3K9Ac) at genes

involved in the regulation of vascular tone and blood pressure[101]. These findings demonstrate how diet modulates epigenetic regulation and contribute to hypertension risk through both adverse and protective mechanisms.

3. Renin-Angiotensin-Aldosterone System (RAAS): Dietary Salt and Epigenetic Regulation

The renin-angiotensin-aldosterone system (RAAS) is a key regulator of blood pressure, electrolyte balance, and vascular resistance (**Fig.1**). Epigenetic modifications in RAAS genes have emerged as important contributors to hypertension, especially under dietary stress conditions such as chronic high-salt diet (HSD) exposure[18]. HSD has been shown to reprogram the vascular epigenome, particularly through alterations in DNA methylation, histone post-translational modifications, and non-coding RNA expression[102]. These molecular changes impact gene expression patterns in key components of the RAAS, leading to enhanced hormonal signaling, vascular dysfunction, and the development of salt-sensitive hypertension[18].

Chronic HSD intake has been associated with hypomethylation of the human angiotensinogen (AGT) promoter, especially in individuals or mouse models carrying the -6A haplotype[103]. This epigenetic modification enhances AGT gene transcription and leads to elevated production of angiotensin II[104, 105]. Transgenic mouse models expressing human AGT and human renin develop salt-sensitive hypertension that is further exacerbated by epigenetic activation of RAAS components[106]. Renin (REN), the rate-limiting enzyme in the pathway, may also be influenced by chromatin remodeling and the methylation status of its promoter region, although data in this area are still emerging[59].

The ACE, which converts angiotensin I to the potent vasoconstrictor angiotensin II, shows increased transcription under HSD conditions due to histone acetylation at its promoter region[15,

[32]. Angiotensin II exerts most of its physiological and pathological effects through AT1R[107]. Epigenetic studies reveal that hypomethylation and histone acetylation at the AGTR1 promoter increase receptor expression, thereby amplifying the downstream signaling cascade responsible for vasoconstriction, sodium retention, and vascular remodeling[108].

Aldosterone synthase (CYP11B2), which catalyzes the final step in aldosterone biosynthesis, is also regulated by epigenetic marks[109]. Increased HSD enhances CYP11B2 transcription in the adrenal cortex through demethylation of promoter CpG islands and recruitment of transcriptional co-activators[110]. This leads to heightened aldosterone production, which contributes to sodium retention, fluid overload, and maintenance of elevated blood pressure in salt-sensitive individuals[111].

Beyond canonical RAAS components, HSD also affects intersecting pathways involved in vascular inflammation, oxidative stress, and fibrosis[112]. The transcription factor NRF2 (*NFE2L2*), which governs antioxidant defense genes such as HO-1 and SOD2 is often epigenetically silenced in salt-sensitive models[113]. Histone deacetylation and promoter methylation reduce NRF2 expression, impairing cellular redox balance and enhancing oxidative stress[114]. Similarly, pro-inflammatory cytokines such as IL-6 and TNF-α show enhanced expression through increased H3K9 acetylation, contributing to vascular inflammation and endothelial dysfunction[115].

TGF-β1 and endothelin-1 (EDN1), both implicated in vascular remodeling and fibrosis, also exhibit increased expression in HSD-fed models[116, 117]. This upregulation is due to promoter demethylation and enrichment of activating histone marks. These genes, regulated by both RAAS and salt-sensitive epigenetic mechanisms, mediate vascular hypertrophy, arterial stiffening, and long-term end-organ damage. Inflammatory mediators such as MCP-1 (CCL2; Chemokine (C-C

motif) ligand 2) and IL-6 are also upregulated in this context, with increased H3K9 acetylation and hypomethylation promoting their sustained transcription[118-120].

At the post-transcriptional level, HSD affects microRNAs that regulate RAAS signaling[121]. Downregulation of miR-155 under HSD conditions leads to increased AT1R mRNA translation, enhancing angiotensin II signaling[122]. miR-132 and miR-181a which normally suppress components of the RAAS and inflammatory response, are also downregulated in salt-loaded animals and hypertensive humans[123, 124]. The net effect of these alterations is sustained activation of the RAAS pathway and chronic vascular inflammation, perpetuating a hypertensive state.

The compensatory renin-angiotensin system (RAS), also called the counter-regulatory RAS, is a protective pathway that releases beneficial peptides (Angiotensin-1-7) to counteract the harmful effects of the classic RAS, which typically causes vasoconstriction, inflammation, and tissue damage in conditions like heart failure. Functioning as an innate protective response, this system helps support tissue recovery and maintain physiological stability [125, 126].

Taken together, these findings reveal a complex and integrated epigenetic network through which HSD reprograms gene expression across multiple physiological pathways[18]. Understanding these gene-specific modifications offers novel therapeutic strategies for targeting salt-sensitive hypertension via epigenetic modulation, including demethylating agents, histone modification inhibitors, and miRNA mimetics[18, 78].

3.2 High Salt Intake and Gene Regulation in RAAS: Dietary salt modulates the expression of key genes involved in RAAS. Studies have shown that high salt intake can downregulate AT1R gene expression, reducing the sensitivity to angiotensin II and thus modulating vasoconstriction and sodium retention[127]. Additionally, epithelial sodium channels (ENaC) in the kidney, regulated

by aldosterone, are also affected. High salt intake reduces aldosterone, leading to decreased ENaC expression and reduced sodium reabsorption[128].

Furthermore, emerging evidence points to epigenetic regulation in this context. High salt can induce DNA methylation and histone modification changes, leading to long-lasting alterations in the expression of RAAS components and contributing to persistent hypertension[59]. Epigenetic studies demonstrate that DNA demethylation of the AGT promoter, particularly in the presence of the *hAGT* -6A haplotype, allow for transcription factors like USF1, STAT3, and HNF-1α to bind, leading to increased *hAGT* expression[59]. Furthermore, histone acetylation at pro-inflammatory RAAS target genes such as *Nlrp3* and *Mcp-1* promotes vascular inflammation, while lncRNAs such as MALAT1 and H19 modulate ACE and AT1R expression, further integrating RAAS dysregulation with endothelial dysfunction[59]. This salt-induced epigenetic reprogramming helps explain why hypertension remains sustained even after dietary sodium reduction.

In summary, while high salt intake normally suppresses systemic RAAS activity to prevent hypertension, this suppression is inadequate in salt-sensitive individuals[129, 130]. Additionally, local (tissue-specific) RAAS activity may persist or even increase despite high salt intake, further promoting vascular resistance, oxidative stress, endothelial dysfunction, and elevated blood pressure[131]. Understanding these interactions provides a foundation for developing targeted therapies for salt-sensitive hypertension.

3.3 Novel Target Genes and Pathways Implicated in the Pathogenesis of Hypertension in Response to High Salt Diet: Comprehensive transcriptomic profiling has revealed novel genes and signaling pathways responsive to chronic high-salt-diet (HSD) exposure, providing deeper insight into the molecular mechanisms driving hypertension[132]. Whole-transcriptome RNA

sequencing of liver and kidney tissues from hypertensive transgenic (TG) mice identified distinct gene-expression patterns that link dietary sodium excess to vascular, renal, and metabolic dysfunction[103, 104].

Ingenuity Pathway Analysis (IPA) of HSD-treated liver tissue of Hap-I (-6A) TG mice revealed several hypertension-associated genes, including *Epas1, Ece1, Ednra, Ednrb, Fhit, Fhl1, Gata4, Gbe1, Gucy1a1, Hfe, Mme, Npr3, Pde3a, Pparg, Psma6, Smad7, Topbp1, Adamts5, Adra1a, Ar, Atxn2, Bmp4,* and *Cav1*[104]. Among these, *Fhit, Hfe,* and *Psma6* were found to be downregulated, while all other genes were upregulated, suggesting complex transcriptional shifts related to blood pressure regulation in response to dietary salt[104]. IPA also identified alterations in the expression of hypertension-related genes in the kidney of Hap-I (-6A) TG mice[104]. These genes include *Ciart, Cndp1, Cyp3a5, Cyp4a11, Dlg2, Fabp1, Fgb, Gabrb3, Gstp1, Il12B, Il1b, Kcnj2, Kcnma1, Mt-rnr2, Myh6, Nqo1, Ptger3, Ren, Serpina3, Tnnt2, Ttn, Alb, Angpt2, Aplnr, Arg2, Atp4a, Ccng1 and Chn2*[104]. The following genes (*Ciart, Cndp1, Cyp4a11, Gstp1, Kcnj2, Nqo1, Angpt2, Aplnr, and Arg2*) were found to be upregulated, whereas all the remaining genes were found to be downregulated[104].

Transcriptome analysis in liver from HSD-treated Hap-I TG mice identifies several novel pathways that may be involved in the pathogenesis of hypertension[103, 104]. These include PI3-AKT signaling pathway, AMPK signaling pathway, TGF-beta signaling pathway, metabolic pathway, type 2 diabetes mellitus pathway, insulin signaling pathway, regulation of lipolysis in adipocytes, renin-angiotensin system, hypertrophic cardiomyopathy, JAK-STAT signaling pathway and insulin resistance pathways[104]. Further transcriptome analysis in the kidney from HSD-treated Hap-I TG mice identifies several novel pathways that may be involved in the pathogenesis of hypertension[104]. These include the NF-kappa beta signaling pathway, steroid hormone

biosynthesis pathway, cytokine-cytokine receptor interaction pathway, PPAR signaling pathway, type I diabetes mellitus pathway, JAK-STAT signaling pathway, ECM-receptor interaction pathway, renin-angiotensin system, MAPK signaling pathway and insulin secretion pathway[104]. Collectively, these findings indicate the HSD triggers systemic transcriptional reprogramming that integrates inflammatory, metabolic, and hormonal mechanisms contributing to sustained hypertension[132].

This systems-level evidence highlights hypertension as a disorder emerging from convergent epigenetic and transcriptomic perturbations[133]. Identification of these pathway networks provides a foundation for precision-epigenetic interventions-targeting both canonical RAAS genes and newly recognized signaling nodes involved in salt-induced hypertension[104, 132].

Emerging Therapeutic Interventions:

Evolving strategies for treating hypertension have increasingly focused on targeting epigenetic mechanisms[134]. Some DNA methyltransferase (DNMT) inhibitors, such as azacitidine and decitabine, which were originally approved for use in myelodysplastic syndrome (MDS), have shown potential in reducing inflammatory responses and improving vascular functions in atherosclerosis[135, 136]. Certain histone deacetylase (HDAC) inhibitors, which generally have been used for treating neurodegenerative diseases, may indirectly lower blood pressure regulation through neural pathways, as shown in hypertensive animal models[20]. Other epigenetic regulators, including histone acetyltransferases (HATSs), histone methyltransferases (HMTs), and bromodomain and extra-terminal domain (BET) proteins, are also under exploration as therapeutic targets[20, 137-139]. Moreover, microRNAs (miRNA) such as miR-505, miR-182–5p, and miR-126–3p have been identified as biomarkers and potential therapeutic targets for hypertension[140-142].

Studies have also shown that manipulating specific miRNAs can influence the response to antihypertensive drugs like candesartan and beta-blockers[10, 143]. Antagomirs, chemically modified oligonucleotides, are being developed to silence pathogenic miRNAs and mitigate fibrosis in hypertension-related organs[10, 11]. Present challenges include achieving tissue-specific drug delivery while minimizing off-target effects as well as deciphering mechanisms between epigenetics and other regulatory pathways in hypertension[14, 15]. Current efforts aim to leverage circulating DNA methylation patterns and miRNA profiles to enable personalized treatment strategies through precision medicine, such as nano particle-mediated drug delivery systems[144] (**Table.1**). It is important to note that these epigenetic therapies are not common treatments for hypertension due to lack of their specificity.

Epigenetic Mechanism	Key Targets	Physiological/Phenotypic Outcome	Therapeutic Targets	
DNA Methylation				Ref
Global DNA hypomethylation	Leukocytes, Vascular endothelial cells, Renal tissues	Increased hypertension severity, Vascular inflammation, Endothelial dysfunction	DNA methyltransferases (DNMT1, DNMT3A/B), TET enzymes	145-148
Gene-specific promoter methylation	AGT, ACE, AGTR1, AT1a (hypothalamus, kidney, vasculature)	RAAS overactivation, Enhanced sympathetic tone, Salt-sensitive hypertension	DNMTs, TETs, Transcription factor-CpG interactions	47, 59, 104, 148-150

Hypermethylation of sodium-handling genes	11β-HSD2, ENaC regulators	Mineralocorticoid excess, Renal sodium retention, Salt sensitivity	DNMTs, Mineralocorticoid pathway components	20, 37, 145
Histone Modifications				
Histone acetylation	ACE, AGTR1, NLRP3, MCP-1, NET promoters	Increased RAAS signaling, Sympathetic nervous system activation, Vascular inflammation	Histone acetyltransferases (HATs), Histone deacetylases (HDACs)	20, 47, 148, 150, 151
Histone methylation	H3K4me3, H3K9me2/3, H3K27me3 at ENaC, NOS3, Inflammatory genes	Altered sodium transport, Impaired nitric oxide signaling, Endothelial dysfunction	Histone methyltransferases (HMTs); Histone demethylases (HDMs)	20, 150, 152
Non-coding RNAs				
microRNAs (miRNAs)	miR-155, miR-21, miR-143/145, miR-126, miR-150	Dysregulated RAAS signaling, VSMC phenotypic switching, Fibrosis, Endothelial dysfunction	miRNA-mRNA interactions, Dicer/Argonaute machinery	56-58, 61
Long non-coding RNAs (lncRNAs)	MALAT1, H19, LEENE, MIAT, GAS5, NORAD	Vascular remodeling, Oxidative stress, Inflammation, Altered eNOS expression	lncRNA-chromatin modifier complexes, RNA-binding proteins	60, 62, 67, 71, 72
Chromatin Remodeling				

ATP-dependent chromatin remodeling	SWI/SNF (BRG1/SMARCA4), CHD, ISWI complexes	Aberrant gene accessibility, VSMC phenotypic switching, Vascular fibrosis	Chromatin remodeler ATPase subunits	75, 76, 88

Limitations and uncertainties of current research: Recent observations suggest that epigenetic biomarkers such as DNA methylation and miRNAs could be integrated into clinical care to revolutionize personalized medicine[153]. These epigenetic markers function by refining risk stratification, predicting the future onset of diseases like cancer or cardiovascular abnormalities in diabetic patients, often before symptoms appear, and capturing the influence of environment and lifestyle[154]. Furthermore, they are crucial for therapeutic decision-making, as they can predict a patient's response to targeted drugs, uncover distinct disease subtypes, and allow to monitor treatment effectiveness and the development of drug resistance[155]. Finally, while technologies like next-generation sequencing are enabling these advances, challenges remain concerning the need for large-scale clinical validation and standardization of data analysis[156].

To transform epigenetics of hypertension from correlation to proven causality and clinical application involves complex process[133]. It involves a rigorous longitudinal study to chronologically map when specific epigenetic changes occur relative to disease onset, coupled with mechanistic experiments (such as using CRISPR or enzyme inhibitors) to prove how these changes directly affect blood pressure regulation[145]. To translate these findings, the strategy emphasizes integrating GWAS with epigenomics to connect genetic risk, environmental factors, and molecular changes that drive hypertension[157]. Finally, the goal is to develop personalized medicine approaches through the identification of epigenetic biomarkers for diagnosis and the

creation of novel drugs that target epigenetic enzymes (DNMTs or HDACs) to potentially reverse detrimental gene expression patterns [12, 158-162].

It is important to note the limitations and uncertainties of current research, especially in human studies. The limitations and uncertainties of current research in human hypertension studies primarily stem from methodological challenges, the complex nature of the disease, and difficulties in establishing causality[145, 157, 161]. The key limitations include tissue specificity, causality vs. consequence, polygenic and multifactorial complexity, limited functional validation, translational & methodological hurdles[133, 157]. Epigenetic changes are highly tissue specific[163]. Human studies mostly rely on easily available tissues like whole blood or peripheral blood mononuclear cells, rather than the primary effector tissues such as kidneys, blood vessels and adrenal glands[164]. The utility and relevance of blood-derived methylation status for understanding the hypertension pathogenic mechanisms in target organs remain uncertain[145]. A major challenge is showing whether identified epigenetic changes are a cause of hypertension or simply a consequence of hypertension or associated risk factors (like obesity, smoking, or inflammation)[133]. The complex interplay with environmental factors makes it challenge to establish a clear causal link in observational human studies[145]. Hypertension is a complex, polygenic disease influenced by various genetic and environmental factors[165]. This complexity makes it difficult to pinpoint the exact epigenetic mechanisms involved in a general population, as findings can be heterogeneous across different studies and ancestry groups[166, 167]. While associations are identified, functional follow-up studies are needed to unravel the precise molecular mechanisms at specific sites[168]. Validating the functional role of specific epigenetic modifications in a whole organism, particularly in humans in vivo, is technically challenging[169]. Findings from animal models, while valuable for mechanistic insight, are not always directly transferable to the humans due to species

variation[170]. There is a lot of heterogeneity in research methods, with some studies focusing on single CpG sites while largely omitting analysis of differentially methylated regions or the integration of other epigenetic layers like histone modifications and ncRNAs[171].

Other limitations include lack of longitudinal data, confounding factors such as genetic variation, and lifestyle factors, which can all influence epigenetic changes and hypertension [172-176]. Future research must aim to address these limitations using multi-omics platforms, integration of different epigenetic layers, and correct methods for targeted epigenetic editing to assist translate biological insights into clinical benefits[177, 178].

Conclusions and Perspectives: This review underscores the pivotal role of epigenetic mechanisms including DNA methylation, histone modification, chromatin remodeling, and non-coding RNAs in the development and persistence of hypertension. These mechanisms serve as dynamic mediators linking genetic susceptibility, environmental exposures, and lifestyle factors to altered gene expression in vascular, renal, and endocrine tissues.

High-salt-diet (HSD) induced epigenetic remodeling further amplifies renin angiotensin aldosterone system (RAAS) dysregulation, inflammation, and oxidative stress, leading to sustained hypertension and end-organ damage. Epigenetic modifications in RAAS components, combined with transcriptomic evidence from liver and kidney, reveal complex interactions among metabolic, hormonal, and inflammatory pathways that collectively drive disease progression.

Although much progress has been made, significant gaps remain in defining causal relationships between specific epigenetic alterations and hypertensive phenotypes. Longitudinal and cell-type–specific studies are needed to determine whether these modifications are primary drivers or secondary responses to elevated blood pressure. Moreover, inter individual variability in

epigenetic signatures shaped by genetic polymorphisms, diet, and age complicates the development of universal therapeutic models.

Future directions should focus on integrating multi-omic approaches (epigenomics, transcriptomics, and metabolomics) with advanced analytical tools such as single-cell sequencing and spatial profiling. These technologies will enable precise mapping of tissue specific epigenetic reprogramming and uncover new regulatory nodes for intervention. Emerging tools like CRISPR/dCas9-based epigenetic editing offer exciting prospects for correcting disease-associated methylation or histone marks at specific genomic loci.

Ultimately, translating these mechanistic insights into precision-epigenetic therapies guided by circulating biomarkers and supported by targeted delivery systems, holds great promise for preventing, diagnosing, and treating hypertension in a personalized and durable manner.

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Figure Legends

Fig. 1 Illustration showing the renin angiotensin aldosterone (RAAS) pathway and its consequence of high blood pressure. This illustration depicts the RAAS cascade and its effects on blood pressure homeostasis. The pathway begins with renin release from the kidney, which converts angiotensinogen to angiotensin I, followed by conversion to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II acts on multiple target organs: (1) vascular smooth muscle, causing vasoconstriction; (2) adrenal cortex, stimulating aldosterone secretion; (3) posterior pituitary, promoting antidiuretic hormone (ADH) release; and (4) kidney, enhancing sodium and water reabsorption. These coordinated effects on vasoconstriction, fluid retention, and

increased blood volume collectively result in elevated blood pressure. Arrows indicate the sequential activation of pathway components and their downstream effects on target organs.

Fig. 2 Factors influencing epigenetic modifications and their role in the pathogenesis of hypertension. This schematic diagram illustrates the factors that influence epigenetic modifications, leading to hypertension. The left panel shows key factors affecting epigenetic mechanisms. The central panel depicts major epigenetic mechanisms. The right panel demonstrates how dysregulation of these modifications leads to hypertension. Arrows indicate directional flow from causative factors through epigenetic mechanisms to hypertension development.

Table 1

Epigenetic Mechanism	Key Targets	Physiological/Phenotypic Outcome	Therapeutic Targets	
DNA Methylation				**Ref**
Global DNA hypomethylation	Leukocytes, Vascular endothelial cells, Renal tissues	Increased hypertension severity, Vascular inflammation, Endothelial dysfunction	DNA methyltransferases (DNMT1, DNMT3A/B), TET enzymes	145-148
Gene-specific promoter methylation	AGT, ACE, AGTR1, AT1a (hypothalamus, kidney, vasculature)	RAAS overactivation, Enhanced sympathetic tone, Salt-sensitive hypertension	DNMTs, TETs, Transcription factor-CpG interactions	47,59, 104,148-150
Hypermethylation of sodium-handling genes	11β-HSD2, ENaC regulators	Mineralocorticoid excess, Renal sodium retention, Salt sensitivity	DNMTs, Mineralocorticoid pathway components	20,37, 145
Histone Modifications				
Histone acetylation	ACE, AGTR1, NLRP3, MCP-1, NET promoters	Increased RAAS signaling, Sympathetic nervous system activation, Vascular inflammation	Histone acetyltransferases (HATs), Histone deacetylases (HDACs)	20,47, 148,150, 151
Histone methylation	H3K4me3, H3K9me2/3, H3K27me3 at ENaC,	Altered sodium transport, Impaired nitric oxide	Histone methyltransferases	20,150, 152

	NOS3, Inflammatory genes	signaling, Endothelial dysfunction	(HMTs); Histone demethylases (HDMs)	
Non-coding RNAs				
microRNAs (miRNAs)	miR-155, miR-21, miR-143/145, miR-126, miR-150	Dysregulated RAAS signaling, VSMC phenotypic switching, Fibrosis, Endothelial dysfunction	miRNA-mRNA interactions, Dicer/Argonaute machinery	56-58,61
Long non-coding RNAs (lncRNAs)	MALAT1, H19, LEENE, MIAT, GAS5, NORAD	Vascular remodeling, Oxidative stress, Inflammation, Altered eNOS expression	lncRNA-chromatin modifier complexes, RNA-binding proteins	60,62,67, 71,72
Chromatin Remodeling				
ATP-dependent chromatin remodeling	SWI/SNF (BRG1/SMARCA4), CHD, ISWI complexes	Aberrant gene accessibility, VSMC phenotypic switching, Vascular fibrosis	Chromatin remodeler ATPase subunits	75,76,88

Table 1: Summary table of key epigenetic mechanisms & markers, physiological/phenotypical outcome, and therapeutic targets.