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CKJ REVIEW

Epigenetic mechanisms of salt-sensitive hypertension

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ABSTRACT

Salt-sensitive hypertension (SSH) is a complex and heterogeneous phenotype characterized by an abnormal blood pressure response to dietary salt intake. While genetic factors have been extensively explored, emerging evidence highlights the pivotal role of epigenetic mechanisms (DNA methylation, histone modifications and non-coding RNAs) in modulating gene expression without altering the DNA sequence. These modifications respond dynamically to environmental stimuli such as diet, aging, stress and prenatal conditions, contributing to both the development and progression of SSH. This review summarizes current knowledge on the epigenetic regulation of genes involved in sodium handling, vascular tone and inflammation, focusing on pathways such as the renin–angiotensin–aldosterone system, the Klotho–Wnt5a–RhoA axis and the influence of the intrauterine environment. Special attention is given to transgenerational epigenetic inheritance and aging-related changes, as well as the reversibility of some epigenetic marks through lifestyle interventions such as salt restriction and physical activity. Understanding the interplay between environmental exposures and epigenetic regulation offers a new frontier for precision medicine in hypertension, but despite the promising findings, SSH-specific human data remain limited and a unifying epigenetic signature distinguishing SSH from other hypertensive phenotypes has yet to be defined. Further longitudinal studies and biomarker discovery efforts are needed to translate these insights into personalized preventive and therapeutic strategies.

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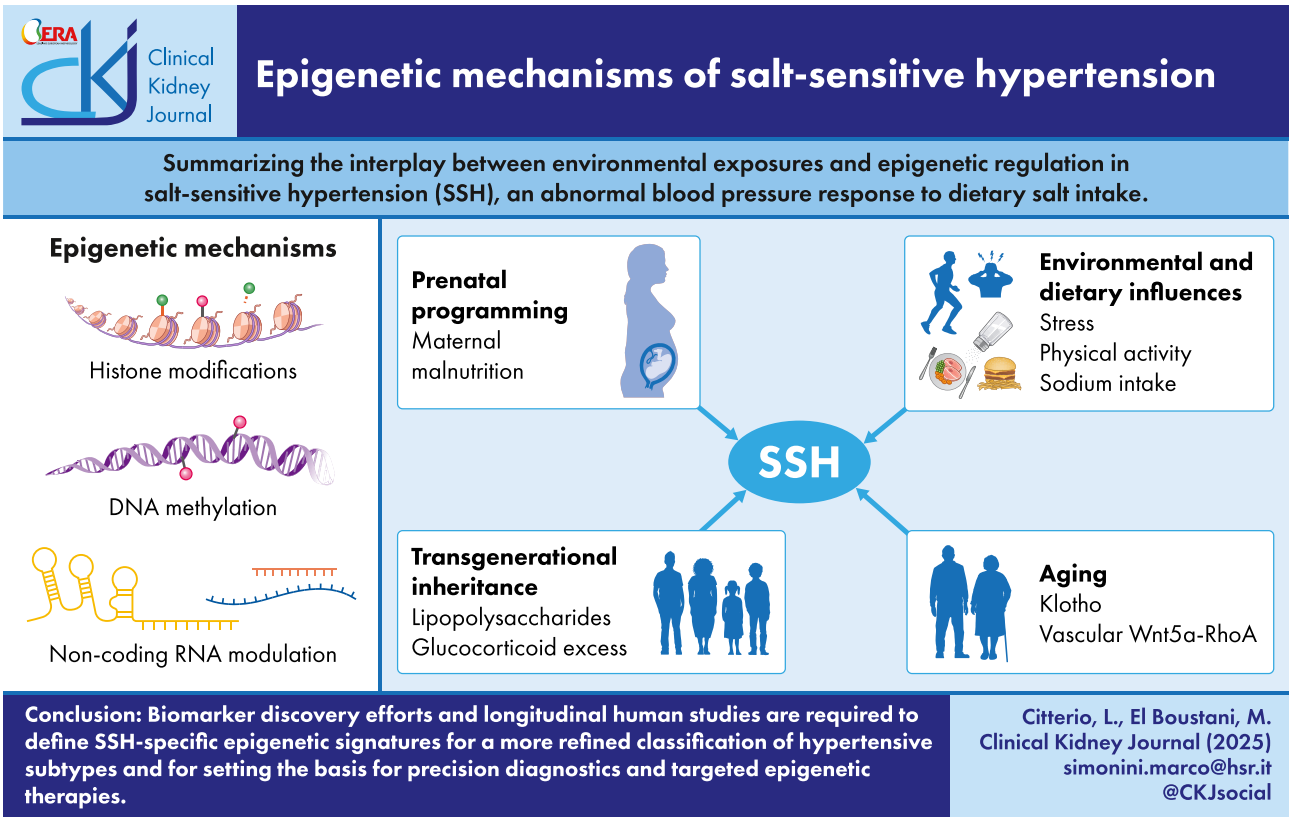
GRAPHICAL ABSTRACT



Keywords: ageing, environment, epigenetics, salt-sensitive hypertension, transgenerational inheritance

INTRODUCTION

Hypertension is a chronic condition characterized by persistently elevated blood pressure (BP) and represents a major risk factor for cardiovascular diseases such as stroke, myocardial infarction and heart failure. Among its various forms, salt-sensitive hypertension (SSH) is defined by a significant increase in BP in response to increased dietary salt intake. This phenotype arises from a complex interplay between genetic predisposition and environmental factors, including diet, aging and lifestyle adaptations [1].

While genetic factors have been extensively studied, emerging evidence suggests that epigenetic modifications also play a crucial role in the development and progression of SSH [2]. Epigenetics involves heritable changes in gene expression that do not alter the DNA sequence itself. This includes DNA methylation, histone modifications and non-coding RNA regulation. These mechanisms are dynamic and can be influenced by environmental factors, leaving enduring molecular 'marks' that affect physiological responses [3].

A key player in BP regulation is the renin–angiotensin–aldosterone system (RAAS), which modulates sodium balance and vascular tone. In SSH individuals, the RAAS becomes dysregulated in response to sodium intake, impairing sodium excretion and promoting water retention. This maladaptive response contributes directly to elevated BP levels in people with SSH [4].

This review aims to provide a comprehensive overview of the epigenetic mechanisms involved in SSH, focusing on how environmental stimuli modulate gene expression through epigenetic alterations. We examine current findings on DNA methylation, histone modifications and non-coding RNA regulation to point out novel insights in identifying markers and potential therapeutic targets.

EPIGENETIC MECHANISMS

Epigenetic regulation involves DNA methylation, histone modifications and non-coding RNAs (Fig. 1). These mechanisms regulate gene expression without altering the underlying DNA sequence. They can influence specific gene activation or silencing and they play a vital role in cellular differentiation, development and response to environmental stimuli. Thus they influence cellular phenotype and subsequently pathophysiological conditions including SSH.

DNA methylation

DNA methylation involves adding a methyl group to the 5-carbon of cytosine residues in DNA, typically within CpG dinucleotides, which are regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide, occurring with high

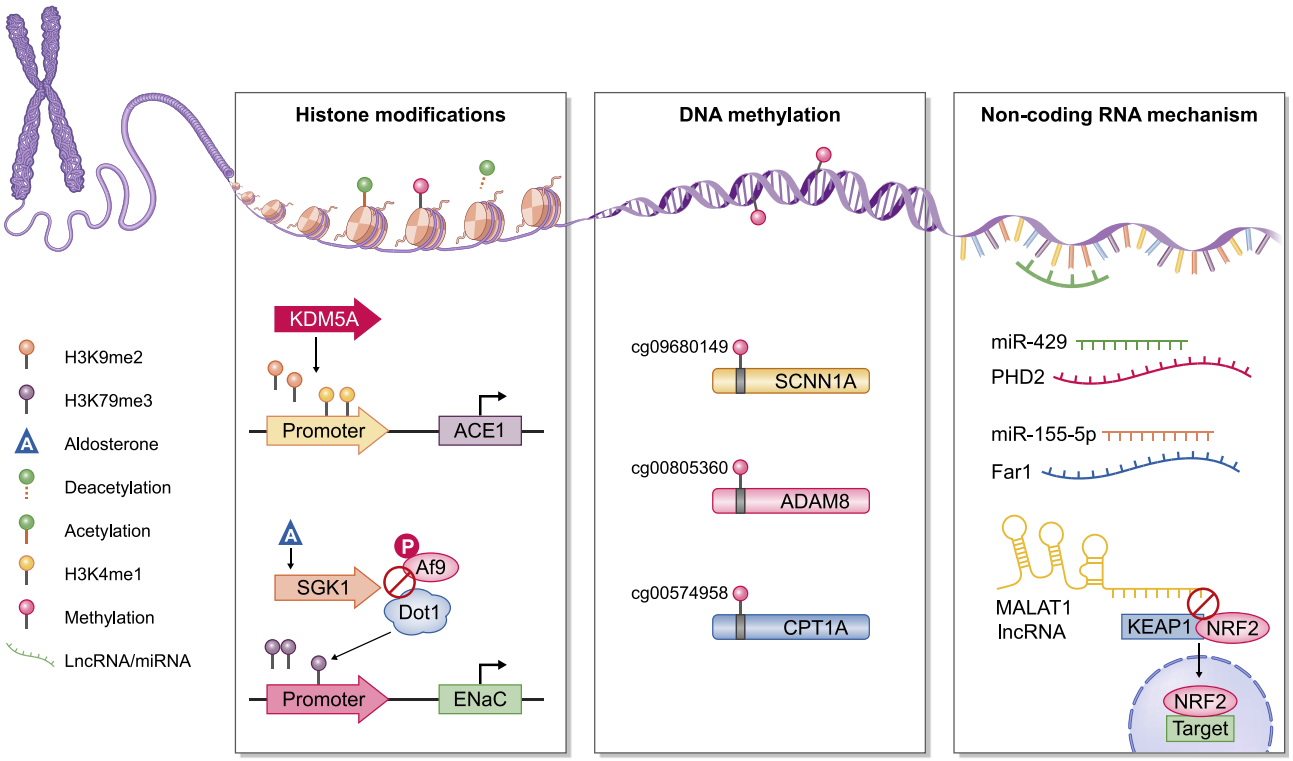


Figure 1: Mechanisms of epigenetic regulation in SSH: histone modifications, DNA methylation and non-coding RNA modulation. Histone modifications: KDM5A induces H3K4me1 enrichment and H3K9me2 depletion at the ACE1 promoter, leading to ACE1 upregulation. Aldosterone-activated SGK1 disrupts Af9-Dot1a interaction, reducing H3K79me3 at the ENaC promoter, resulting in ENaC upregulation. DNA methylation: the cg09680149 site is associated with SCNN1A, cg00805360 with ADAM8 and cg00574958 with CPT1A, thus influencing expression of these genes in hypertension. Non-coding RNA (miRNA/lncRNA) modulation: miR-429 impairs PHD2 mRNA expression, miR-155-5p decreases Far1 levels and lncRNA MALAT1 modulates the Keap1-Nrf2 antioxidant pathway in hypertension. ACE1: angiotensin-converting enzyme 1; ADAM8: metallopeptidase domain 8; CPT1A: carnitine palmitoyltransferase 1A; ENaC: epithelial sodium channel; Far1: fatty acyl CoA reductase 1; KDM5A: lysine-specific demethylase 5A; H3K4me1: histone H3 lysine 4 methylation; H3K9me2: histone H3 lysine 9 dimethylation; H3K79me3: histone H3 lysine 9 trimethylation; lncRNA: long non-coding RNA; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; miRNA: microRNA; PHD2: prolyl-hydroxylase 2; SCNN1A: SGK1: serum/glucocorticoid regulated kinase 1.

frequency in genomic regions called CpG islands. This modification by specific DNA methyltransferase occurs in gene promoter regions, usually resulting in the suppression of gene transcription [5]. DNA methylation patterns are established during development and are generally stable, although they can be altered by environmental factors such as diet, stress and aging.

Environmental changes beginning in intrauterine and extending into postnatal life may also lead to alterations in DNA methylation patterns and subsequently gene expression, predisposing to hypertension in adulthood. These methylation signatures are both cell-type and tissue specific [3]. Environmental factors and pathological conditions could leave an epigenetic mark on DNA. Mapping changes in de novo DNA methylation and demethylation in response to various factors opens new avenues for diagnostic and preventive approaches in hypertension [6].

In the context of SSH, aberrant DNA methylation has been implicated in the dysregulation of genes involved in BP regulation. For instance, hypermethylation of genes that suppress inflammation or oxidative stress can create a pro-hypertensive state, contributing to the development of SSH [7].

The Dahl SS rat, bearing naturally occurring mutations in genes coding for the RAAS, demonstrates various profiles of DNA methylation in the outer medulla of kidneys when fed a high salt diet [8]. A human study showed CpG sites (cg09680149, cg00805360 and cg00574958) closely linked to the regulation of gene expression, playing key roles in BP variation in response to salt intake (Fig. 1). The cg09680149 site is associated with the human *SCNN1A* gene, which encodes the alpha subunit of the epithelial sodium channel (ENaC). The ENaC is crucial for maintaining salt and water balance in the body by enabling sodium ion flow across high-resistance epithelia. The cg00805360 at metallopeptidase domain 8 (*ADAM8*) gene plays a crucial role in the regulation of endothelial-to-mesenchymal transition, involving BP regulation and leading to cardiac fibrosis in response to angiotensin II infusion. Finally, methylation levels at cg00574958, linked to the human *CPT1A* gene or carnitine palmitoyltransferase, essential in the beta oxidation of long-chain fatty acids, show a significant correlation with systolic BP levels [9].

Histone modifications

Histone proteins are essential components of chromatin, around which DNA is wound. Post-translational modifications of histones, such as acetylation, methylation, phosphorylation and ubiquitination, can alter chromatin structure and regulate gene expression. These modifications are reversible and can either promote or repress transcription depending on the specific modification and its location.

Histone acetylation, mediated by histone acetyltransferases, typically relaxes chromatin structure, allowing gene

transcription. Conversely, histone deacetylation, mediated by histone deacetylases (HDACs), leads to chromatin condensation and gene repression. Histone methylation can have varying effects depending on the residue modified (e.g. lysine or arginine) and the degree of methylation (mono-, di- or tri-methylation) [7].

HDACs have been particularly implicated in the pathogenesis of SSH. Inhibition of HDACs has been shown to reduce BP in salt-sensitive animal models by promoting the expression of genes that counteract the effects of high sodium levels. For example, HDAC inhibition enhances the expression of nitric oxide synthase (NOS), promoting nitric oxide (NO) production, which leads to vasodilation and reduced BP [10]. Additionally, HDAC inhibitors downregulate pro-inflammatory genes, reducing vascular inflammation and improving endothelial function [11].

Histone methylation also plays a crucial role in BP regulation. A dietary intervention in 339 Chinese subjects compared salt-sensitive and salt-resistant individuals. In salt-sensitive subjects on a high-salt diet, serum H3K4me1 levels and those of Set7 methyltransferase were significantly increased, whereas no changes were detected in salt-resistant individuals [12].

Aberrant histone modifications, in general, may lead to the dysregulation of genes involved in vascular tone, sodium handling and inflammation, thus contributing to increased BP. Targeting histone-modifying enzymes has emerged as a potential therapeutic strategy for managing SSH. In the RAAS, angiotensin-converting enzyme 1 (ACE1) catalyses angiotensin I to angiotensin II. A high tissue-specific expression of ACE1 has been reported in the spontaneously hypersensitive rat (SHR) compared with the normotensive rat. An enrichment of histone H3 at lysine 4 trimethylation (H3K4me3) and a reduced level of the repressive histone H3 lysine 9 dimethylation (H3K9me2) have been observed at the promoter region of ACE1 following KDM5A demethylase binding in the adrenal gland, heart and kidney [13].

Lysine methyltransferase enzymes are responsible for catalysing the addition of methyl groups to lysine residues on histones. Lysine methyltransferases also regulate aldosterone and its mineralocorticoid receptor (MR) in response to enhanced angiotensin II stimulation. Aldosterone, upon binding to the MR in the cortical collecting duct of the kidney, activates ENaC and promotes the reabsorption of sodium ions. This mechanism contributes to hypertension by increasing fluid retention and consequently blood volume. Aldosterone-activated SGK1 blocks the interaction of Af9 and Dot1a and the Af17-mediated inhibition of Dot1a, resulting in reduced H3K79me3 at the promoter of ENaC and hence upregulation of ENaC in the mouse inner medullary collecting duct cell line (Fig. 1) [14, 15].

Non-coding RNAs

Non-coding RNAs (ncRNAs) are a diverse class of RNA molecules that do not encode proteins but play critical roles in regulating gene expression. The two main types of ncRNAs involved in epigenetic regulation are microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) [16]. miRNAs are small RNA molecules (≈22 nucleotides in length) that regulate gene expression by binding to the 3′ untranslated region of target mRNAs, leading to mRNA degradation or translational repression. miRNAs can influence various physiological processes, including BP regulation, by modulating the expression of genes involved in sodium handling, vascular function and inflammation. lncRNAs are longer RNA molecules (>200 nucleotides) that can interact with DNA, RNA or proteins to modulate gene expression. lncRNAs can act as scaffolds, guides, decoys or regulators of chromatin structure, playing a role in the epigenetic regulation of genes involved in SSH.

Several miRNAs have been identified as key regulators of gene expression in SSH. For instance, high salt-induced upregulation of miR-429 was impaired in the renal medulla of Dahl S rats, inducing mRNA decay of HIF prolyl-hydroxylase 2 (PHD2) (Fig. 1); the correction of the impaired miR-429 response successfully restored the PHD2-associated adaptive activation of antihypertensive genes in response to high salt intake, thus improving pressure natriuresis, promoting sodium excretion and reducing sodium retention after extra sodium loading, thereby attenuating SSH [17]. Similarly, in hypertensive Sprague Dawley rats, miR-155-5p revealed its potential role in the regulation of the occurrence and development of vascular endothelial dysfunction in hypertension [18]. Moreover, the overexpression of miR-155-5p was shown to significantly decrease fatty acyl CoA reductase 1 (Far1) levels, a peroxisomal enzyme essential for the synthesis of ether lipids, and increase reactive oxygen species (Fig. 1). Mechanistic investigations indicated that circular RNA derived from the *Nr1h4* gene (circNr1h4) acts as a competing endogenous RNA for miR-155-5p, leading to regulation of its target gene *Far1*. Lu *et al.* [19] demonstrated that circNr1h4, downregulated in renal injury, may help control Far1 by binding to miR-155-5p in hypertensive kidney injury, revealing the causes of deoxycorticosterone acetate salt-induced kidney damage.

The role of lncRNAs in SSH is less well characterized, but emerging evidence suggests that they may act as important regulators of epigenetic modifications. For example, lncRNA MALAT1 interacts with chromatin-modifying enzymes (Fig. 1), affecting the expression of genes involved in vascular tone and BP regulation [20]. The Nrf2 inhibitor, Keap1, associated with increased oxidative stress, is elevated in hypertension while sodium induces MALAT1 expression by promoting Sp1 transcription factor binding. Therefore, silencing MALAT1 prevents sodium-induced Keap1 upregulation, allowing Nrf2 to translocate to the nucleus and activate antioxidant genes [21].

At the human level, miRNAs represent the most studied non-coding RNAs in the pathogenesis of SSH. Circulating levels of miR-361-5p and miR-362-5p were significantly reduced in salt-sensitive individuals compared with salt-resistant controls, with miR-361-5p demonstrating strong diagnostic potential [22]. Urinary exosomal miRNome profiling further identified 45 urinary exosomal miRNAs as discriminative markers between salt-sensitive and non-salt-sensitive phenotypes in Caucasian subjects [23]. In another study, genetic variants in miRNA loci, such as miR-3620-5p and miR-210-3p, have been associated with long-term BP responses to dietary salt in large population cohorts [24]. Moreover, miR-214-3p, targeting endothelial nitric oxide synthase (eNOS) and modulating renal sodium handling, was upregulated in hypertensive human kidney biopsies [25]. These findings highlight the utility of miRNAs as both biomarkers and regulators of SSH, warranting further translational research.

Prenatal programming and SSH

The concept of foetal programming assumes that the environment in which a foetus develops can have long-lasting effects on its health (Table 1). Among environmental factors, maternal nutrition plays a pivotal role in shaping foetal development [26]. Epidemiological and experimental studies have shown that poor maternal nutrition, such as a low-protein diet during pregnancy,

Table 1: Summary of prenatal factors influencing epigenetic modifications leading to SSH.

Factor	Epigenetic modification	Gene(s) targeted	Outcome	Ref.
Poor maternal malnutrition	Increased DNA methylation	*AGTR1*, *AGTR2*	Increased renal sympathetic activity; negative regulation of AT2R protein levels	[27, 29]
Glucocorticoid exposure	Decreased histone methylation	*AGTR1*	Upregulated receptor expression	[27]
Low-protein diet	Global DNA methylation changes	Multiple	Heightened blood pressure	[27]

is associated with an increased risk of hypertension in the offspring [27, 28].

During pregnancy, maternal malnutrition can lead to intrauterine growth restriction, which is a significant risk factor for the development of SSH. This condition frequently reflects compromised placental function and nutrient delivery, causing compensatory changes in foetal physiology and epigenetic alterations in gene expression, particularly in pathways related to BP regulation.

Epigenetic mechanisms such as DNA methylation and histone modifications are central to this programming. For example, DNA demethylation of the *AGTR1* gene, which encodes the angiotensin II type 1 receptor, has been observed in the hypothalamus of offspring born to rats fed a low-protein diet. This demethylation leads to AGTR1 overexpression, resulting in heightened sympathetic nervous system activity and increased arterial pressure [23].

Epigenetic modifications such as DNA methylation and histone modifications play a central role in the prenatal programming of SSH. These modifications influence the expression of genes that regulate BP, setting the stage for SSH development later in life. One key finding in the study of prenatal programming and SSH is the role of DNA methylation in regulating the expression of the *AGTR1* gene, which encodes angiotensin II receptor type 1a. Angiotensin II is a potent vasoconstrictor that plays a crucial role in BP regulation. In offspring of pregnant rats receiving a low-protein diet, increased DNA demethylation of the *AGTR1* gene during foetal development has been linked to its overexpression in the hypothalamus, leading to heightened sympathetic nervous system activity and increased BP [27]. Evaluation of renal AT2R methylation profiles in stroke-prone SHR offspring exposed to maternal protein restriction *in utero*, and in grand-offspring derived from protein restricted grand-dams during pregnancy, demonstrated that DNA methylation of the AT2R promoter region negatively regulated AT2R protein levels in offspring exposed to maternal protein restriction and post-weaning salt loading, an effect not seen in water-drinking conditions [29].

In addition to DNA methylation, histone modifications in the hypothalamus are also involved in the prenatal programming of SSH. For instance, prenatal exposure to glucocorticoids, which can occur due to maternal stress or malnutrition, has been shown to reduce histone methylation at specific loci in the hypothalamus. This reduction in histone methylation can lead to increased expression of genes that promote hypertension, such as the *AGTR1* gene [27]. Research in animal models, particularly rodents, has provided substantial evidence supporting the role of prenatal epigenetic modifications in SSH: offspring of pregnant rats subjected to a low-protein diet exhibit significant increases in BP when exposed to a high-salt diet postnatally, correlating with the observed epigenetic changes in genes such as *AGTR1* and those involved in renal sodium handling [27].

Moreover, analysis of epigenome-wide methylation patterns using umbilical cord blood DNA reported that large mother and child cohorts associate maternal nutritional imbalances with infant DNA methylation alterations and early vascular stiffness precursors to hypertension [30].

Transgenerational inheritance of SSH

Epigenetic inheritance refers to the transmission of epigenetic marks from one generation to the next, independent of changes in the DNA sequence. While most epigenetic marks are reset during gametogenesis, some can escape this reprogramming and be passed on to subsequent generations [31]. This process is particularly relevant in the context of SSH, where environmental factors experienced by one generation can predispose future generations to hypertension.

Numerous studies have provided evidence for the transgenerational inheritance of SSH (Table 2). Histone modifications, particularly those involving repressive marks such as H3K9me2, are also implicated in transgenerational epigenetic inheritance. These modifications can regulate gene expression in a manner that can be stable across generations. In SSH, histone modifications in genes involved in sodium handling and BP regulation are passed down through multiple generations, influencing the susceptibility of offspring to hypertension.

For instance, prenatal exposure to lipopolysaccharides (LPSs), which mimics bacterial infection, has been shown to induce epigenetic changes that are transmitted across multiple generations [32]. Offspring of LPS-exposed mothers exhibit increased BP in response to a high-salt diet. This phenotype is observed in subsequent generations even in the absence of further LPS exposure. Downregulation of the repressive histone mark H3K9me2 in the kidneys of offspring exposed to prenatal stress leads to increased Rac1 expression. The latter is a member of the Rho family of GTPases, which in turn activates MR signalling, thus promoting sodium reabsorption and contributing to SSH [32].

DNA methylation is generally stable and can be maintained across cell divisions. However, certain environmental factors can induce changes in DNA methylation patterns that are heritable. For example, prenatal exposure to malnutrition or stress can lead to altered DNA methylation in the germ cells, which can be transmitted to offspring.

Lysine-specific histone demethylase 1A (LSD1), an epigenetic regulator of gene transcription through the separation of methyl groups from Lys4 and Lys9 of histone H3, is modulated by dietary sodium intake as shown in mouse kidneys. Both a risk allele in the corresponding human *KDM1A* gene and LSD1 deficiency

Table 2: Key studies on transgenerational epigenetic inheritance in SSH.

Study	Epigenetic mechanism	Affected gene(s)	Generational impact	Ref.
LPS exposure in rodents	Histone modification (H3K9me2)	*Rac1*	SSH in F4 and F5 generations	[32]
Dietary high-salt intake	Histone methylation reduction (LSD1)	Various substrates	Increased SSH risk across generations	[33]
Glucocorticoid exposure	DNA demethylation	*AGTR1*	Increased renal sympathetic nerve activity and postnatal risk of SSH	[28]

(LSD1$^{+/-}$) in mice resulted in increased salt sensitivity of BP with aging and with the development of SSH in the elderly [33].

Exposition of the foetus to glucocorticoid excess, such as treatment with dexamethasone passing through the placenta or by a low-protein diet, can induce DNA demethylation, which is caused by downregulation of DNA (cytosine-5)-methyltransferase 3A (DNMT3A), and upregulates AGTR1 mRNA in the paraventricular nucleus of the hypothalamus. The resulting increase in angiotensin signalling in the hypothalamus leads to increased renal sympathetic nerve activity and the postnatal development of SSH [28].

These findings highlight the potential for environmental factors to induce heritable epigenetic changes that predispose future generations to SSH. The identification of specific epigenetic marks involved in this process could lead to the development of biomarkers for early detection and prevention of SSH in at-risk populations.

Aging and epigenetic regulation in SSH

Aging is a significant risk factor for the development of hypertension, including SSH. As individuals age, they experience a natural decline in the regulatory mechanisms that maintain BP within a healthy range. This decline is often accompanied by epigenetic changes that alter the expression of genes involved in BP control.

Klotho gene: epigenetic regulation and aging

The *Klotho* gene (*KL*) is a critical regulator of aging and has been associated with protection against several age-related diseases, including hypertension [34]. Klotho is primarily expressed in the kidneys, where it functions as an anti-ageing protein with multiple protective effects, including the regulation of calcium and phosphate homeostasis, suppression of oxidative stress and inhibition of the renin–angiotensin system [35, 36]. Deficiency of this protein causes SSH and renal damage by activating the CCR2-mediated inflammatory process in one-half of klotho-deficient mice, resulting in renal structural injury and renal functional impairment [37]. Moreover, a missense genetic variant in *KL* was found to be associated with SSH in naïve hypertensive patients who underwent an acute salt load. In particular, circulating a-klotho levels were mainly related to diastolic BP changes at the end of a salt load and to eGFR as an expression of kidney aging [38].

The age-related decline in circulating klotho levels is well known and could be due to increased methylation of the promoter region in the *KL* gene. The reduced levels of this protective circulating protein [39] enhanced levels of pro-inflammatory markers such as interleukin-10, tumour necrosis factor and nuclear factor kappa B levels in the blood of patients with atherosclerotic vascular disease [40]. In turn, the epigenetic change associated with decreased levels of circulating soluble klotho may contribute to the development of SSH. Advantageously, the epigenetic modification of DNA is generally lifestyle related, meaning that the age-associated increased methylation of *KL* and the related decrease in circulating klotho can be attenuated.

In addition to DNA methylation, histone modifications also play a role in the regulation of klotho expression. For example, upregulation of histone H3K27me3, a repressive mark, has been observed in the *KL* promoter in aged kidneys. This modification further reduces klotho expression, exacerbating the decrease in renal function and increasing the risk of SSH [41] (Table 3).

Wnt5a–RhoA pathway in vascular aging

The Wnt5a–RhoA pathway is a non-canonical signalling pathway that has been implicated in the regulation of vascular function and BP. Under normal conditions, Wnt signalling is tightly regulated, but in the absence of sufficient klotho, such as in aged mice and young heterozygous klotho-knockout mice, this pathway becomes dysregulated, leading to increased RhoA activity. RhoA is a small GTPase that plays a critical role in regulating vascular tone by controlling the contractility of smooth muscle cells. In these mice, high salt increased BP and was associated with increased vascular expression of Wnt5a and p-MYPT1, which indicates RhoA activity. Increased RhoA activity in the vasculature leads to enhanced vasoconstriction, reduced renal blood flow and increased peripheral resistance, all of which contribute to the development of SSH [42] (Table 3). The dysregulation of the Wnt5a–RhoA pathway in aged individuals is partly due to epigenetic modifications that alter the expression of genes involved in this signalling cascade. Increased DNA methylation of genes that inhibit RhoA activity can lead to unchecked RhoA signalling, promoting vascular dysfunction and hypertension.

Clinical implications of aging-associated epigenetic changes

The epigenetic changes associated with aging have significant clinical implications for managing SSH. Understanding how these changes contribute to the development of hypertension in the elderly could lead to new therapeutic strategies aimed at reversing or mitigating these epigenetic alterations. Targeting the epigenetic regulation of the *KL* gene or the Wnt5a–RhoA pathway could provide novel approaches to treating SSH in aging populations. For example, therapies that reduce DNA

Table 3: Comparative analysis of epigenetic changes in subsets of different ages with SSH.

Age group	Epigenetic change	Affected gene	Pathway activation	Clinical outcome	Ref.
Aged mice tissues	DNA methylation	*KL*	Increased Wnt5a–RhoA activation	Vascular tone and SSH	[42]
Aged adults	DNA methylation	*KL*	Enhanced levels of pro-inflammatory markers	Elevated BP and SSH	[37, 39]
Aged kidneys	Histone modification	*KL*	H3K27me3 upregulation	Kidney cell aging	[41]

methylation of *KL* promoter or inhibit RhoA activity could help restore normal BP regulation in aged individuals.

Furthermore, identifying epigenetic biomarkers associated with aging-related SSH could enable earlier detection and intervention. Measuring DNA methylation levels of the *KL* gene or other key genes involved in BP regulation could help identify individuals at risk of developing SSH, allowing for personalized treatment strategies [28].

Environmental and dietary influences

Environmental factors and lifestyle choices are known to have a profound impact on the development and progression of many chronic diseases, including hypertension. In SSH, environmental influences, including dietary sodium intake, stress and physical activity, play pivotal roles in modulating epigenetic mechanisms that regulate BP. These environmental factors act as converging epigenetic modulators on common pathways regulating BP, including the RAAS, tubular sodium transport and vascular inflammation. Thus diet, stress, microbiota and physical activity are not separate mechanisms, but parts of a single pathogenic network in SSH [43]. Emerging evidence also links gut microbiota composition to epigenetic modifications affecting vascular tone and immune responses, suggesting a potential contributory role in SSH pathogenesis [44]. Gut microbiota influence various bioactive molecules and their pathways are controlled by nutritional and lifestyle factors, including salt, thus modulating cardiovascular dynamics and their pathogenesis, predisposing to hypertension [45]. Understanding how these factors influence the epigenome offers valuable insights into the development of effective, individualized strategies for preventing and managing SSH.

Dietary sodium intake and epigenetic modifications

One of the most critical environmental factors influencing epigenetic regulation in SSH is dietary sodium intake. In individuals with SSH, BP responds more significantly to changes in dietary salt intake. In particular, the acute saline test classified a naïve hypertensive cohort into three main groups, each ≈30% of individuals: salt resistant, during which BP displayed either no substantial variation was observed; salt sensitive, with an increase in BP; and inverse salt sensitive, with a paradoxical decrease in BP. Salt sensitivity and inverse salt sensitivity appear to be equivalent risk factors for CV events [46].

High dietary sodium intake is associated with adverse epigenetic changes in genes that regulate sodium transport and BP. Specifically, it has been shown to induce DNA methylation changes in key genes involved in renal sodium handling, such as those composing ENaC and Na^+/K^+-ATPase. These genes are crucial for sodium reabsorption in the kidneys, and their upregulation due to methylation variation at CpG1 and CpG2 can lead to increased sodium retention, fluid overload and ultimately higher BP [47].

Studies in animal models of SSH have demonstrated that high-sodium diets lead to hypermethylation of specific CpG sites in the promoters of genes involved in sodium transport. This epigenetic modification results in upregulation of these genes [48], leading to enhanced sodium reabsorption in the kidneys and subsequent increases in BP. Sodium restriction significantly also affects DNA methylation in T cells and arterioles, some of which are associated with BP in hypertensive subjects [49]. In addition to DNA methylation, high sodium intake has been linked to histone modifications that regulate chromatin structure and gene expression. For instance, histone acetylation in the promoters of genes involved in sodium transport is often reduced in response to excessive sodium intake, leading to tighter chromatin and reduced expression of sodium-excreting proteins, thus exacerbating sodium retention and hypertension. Moreover, epigenetic regulation of RAAS components, such as renal and vascular HSD11B2, is an important pathogenetic mechanism for SSH.

Stress and lifestyle factors

Beyond dietary factors, stress and lifestyle choices such as physical activity also significantly influence epigenetic regulation in SSH. Chronic stress, in particular, has been implicated in the development of hypertension through its effects on the hypothalamic–pituitary–adrenal (HPA) axis, sympathetic nervous system activation and epigenetic dysregulation of genes involved in BP control [50].

Chronic psychological stress has been shown to induce both DNA methylation changes and histone modifications, contributing to the dysregulation of genes that control BP. The persistent activation of the stress response through the HPA axis leads to the release of glucocorticoids, which can alter the epigenetic landscape in key tissues such as the brain, kidneys and cardiovascular system. Specifically, chronic stress has been associated with increased DNA methylation of genes involved in the negative feedback regulation of the HPA axis, such as the *glucocorticoid receptor* (*GR*) gene. Increased methylation of the *GR* gene promoter can reduce its expression, leading to prolonged activation of the stress response and increased sympathetic nervous system activity. This, in turn, contributes to elevated BP, particularly in predisposed individuals [51].

Stress can also lead to changes in histone modifications that alter the expression of genes involved in BP regulation. Chronic stress has been shown to increase histone acetylation at stress-responsive genes, promoting their overexpression. This can exacerbate the effects of stress on BP by enhancing the sensitivity of the cardiovascular system to stress-related stimuli [51].

Impact of physical activity on epigenetic modifications

Conversely, physical activity is a positive lifestyle factor that has been shown to induce beneficial epigenetic changes that can help counteract the effects of stress and high sodium intake. Regular exercise can influence gene expression by modifying DNA methylation patterns and histone acetylation, promoting

Table 4: Translational potential of epigenetic and lifestyle interventions in SSH.

Intervention	Evidence in SSH (human)	Evidence in SSH (animal models)	Translational potential
Dietary sodium reduction	Strong—multiple clinical and population-based studies demonstrate BP improvement in SSH individuals	Strong—consistent reduction of BP and reversal of adverse epigenetic marks	High—immediately applicable, low risk
Physical activity	Moderate—observational studies and small trials suggest BP improvement and endothelial benefits	Strong—improves NO bioavailability and beneficial histone/DNA methylation changes	Medium—feasible as adjunct therapy
Epigenetic drugs (e.g. HDAC inhibitors)	Limited—preliminary or indirect evidence from non-SSH hypertension studies	Strong—BP lowering and anti-inflammatory effects in SSH models	Low–medium—needs safety, specificity and delivery optimization
Microbiota modulation (e.g. probiotics, dietary fibre)	Limited—few human SSH-specific studies, mostly associative	Moderate—some BP and epigenetic improvements in animal models	Experimental—requires mechanistic validation and trials

the expression of protective genes involved in cardiovascular health and BP regulation [52].

Physical activity has been associated with reduced DNA methylation of anti-inflammatory genes and genes involved in NO production, such as eNOS. By promoting NO production, exercise helps to improve endothelial function, reduce vascular resistance and lower BP, particularly in individuals with SSH. Exercise has also been shown to increase histone acetylation in the promoters of genes that protect against hypertension. This epigenetic modification leads to a more open chromatin structure, facilitating the transcription of genes involved in antioxidant defence and vascular relaxation [53].

Challenges and opportunities in targeting epigenetic modifications

One of the most promising aspects of epigenetic regulation is its potential reversibility. Several studies have shown that reducing dietary sodium intake can reverse some of the adverse epigenetic modifications induced by high sodium consumption, underscoring the importance of dietary interventions in managing SSH [54]. In both human and animal studies, sodium restriction has been shown to reverse the DNA methylation changes in genes involved in sodium transport and vascular vessels. This leads to reduced expression of sodium-retaining genes and helps normalize BP [49, 55]. Importantly, tissue-specific changes in DNA methylation have been observed following sodium restriction, suggesting that targeted epigenetic therapies could potentially complement dietary interventions. While sodium restriction can reverse some epigenetic changes, the concept of 'epigenetic memory' suggests that previous high-sodium exposures may leave a lasting imprint on the epigenome [56]. Experimental data show that high sodium intake may remain predisposed to SSH, even after reducing sodium intake, due to persistent epigenetic marks. Further research is needed to understand the long-term effects of sodium restriction on the epigenome and BP regulation.

While epigenetic therapies show promise, several challenges are associated with their development and implementation. Recent advances in epigenetic editing technologies present a transformative opportunity for precise, reversible and on-demand therapeutic interventions in cardiovascular diseases, including SSH. However, the successful translation of these innovations into clinical practice relies on overcoming critical challenges, particularly in delivery efficiency, target specificity, long-term safety and ensuring equitable access across populations [57]. Indeed, one of the main challenges is the need for specificity. Epigenetic modifications can affect multiple genes and pathways, and systemic administration of epigenetic drugs may lead to off-target effects or unintended consequences. Hence, substantial doubts remain about the feasibility of direct interventions on specific targets and their long-term efficacy.

Instead, interventions involving lifestyle modification may be more practical. High sodium intake and chronic stress can induce harmful epigenetic changes, but physical activity and dietary modifications can help reverse these changes and promote cardiovascular health. An integrated approach to SSH management, including dietary sodium restriction, stress reduction techniques (such as mindfulness or cognitive behavioural therapy) and regular physical activity, can have synergistic effects on the epigenome. This holistic approach not only helps reduce BP but also promotes long-term cardiovascular health by addressing the root causes of epigenetic dysregulation.

The translational potential of both lifestyle modifications and emerging epigenetic-targeted interventions in SSH is heterogeneous. Table 4 summarizes the current level of evidence in SSH-specific human studies and animal models, together with an assessment of their feasibility and readiness for clinical application. While lifestyle strategies such as sodium restriction and physical activity are immediately implementable and supported by strong or moderate evidence, pharmacological and microbiota-based approaches remain largely experimental and require further validation in well-designed human trials.

SSH-specific limitations

While this review presents multiple epigenetic findings in the context of SSH, it is important to note that most of the available data are derived from general models of hypertension or from experimental paradigms that overlap with SSH. Nevertheless, many epigenetic studies in animal models increasingly

highlight that specific epigenetic alterations uniquely characterize the development of SSH.

Although human-specific studies on SSH are limited, ongoing research paves the way for future breakthroughs. Advancing this field requires well-designed longitudinal human studies to define SSH-specific epigenetic signatures. Researchers could move toward a more refined classification of hypertensive subtypes and set the basis for precision diagnostics and targeted epigenetic therapies.

CONCLUSION

This review has explored the multifaceted role of epigenetics in the development and progression of SSH. From prenatal programming to transgenerational inheritance and the impact of aging, epigenetic mechanisms offer a deeper understanding of SSH. The interaction between environmental factors and genetic predispositions, mediated by epigenetic modifications, underscores the complexity of hypertension as a condition that cannot be fully explained by genetics alone.

Future research should focus on further elucidating the specific epigenetic changes that contribute to SSH by investigating the role of epigenetic biomarkers in predicting individual salt sensitivity and considering the feasibility of targeted epigenetic therapies. The development of epigenetic therapies, coupled with lifestyle interventions, holds promise for improving the management of hypertension, particularly in individuals with a heightened sensitivity to salt. Additionally, the identification of epigenetic biomarkers could enable earlier detection and more personalized treatment strategies, ultimately reducing the global burden of hypertension. The integration of epidemiology, molecular biology and clinical trials is the necessary step to define an SSH-specific epigenetic signature. This road map, supported by emerging epigenetic editing technologies and population-based studies, has the potential to transform SSH management from a reactive approach to a preventive and personalized strategy.

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AUTHORS' CONTRIBUTIONS

M.S., C.L. and P.M. were responsible for conception of the work and revised the manuscript. M.S., L.C. and M.E.-B. were responsible for the acquisition and analysis of data. L.C. and M.E.-B. wrote the manuscript.

DATA AVAILABILITY STATEMENT

All data are available in the article.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Bailey MA, Dhaun N. Salt sensitivity: causes, consequences, and recent advances. *Hypertension* 2024;**81**:476–89. https://doi.org/10.1161/HYPERTENSIONAHA.123.17959
2. Liu P, Liu Y, Liu H *et al*. Role of DNA de novo (de)methylation in the kidney in salt-induced hypertension. *Hypertension* 2018;**72**:1160–71. https://doi.org/10.1161/HYPERTENSIONAHA.118.11650
3. Moore LD, Le T, Fan G. DNA methylation and its basic function. *Neuropsychopharmacology* 2013;**38**:23–38. https://doi.org/10.1038/npp.2012.112
4. te Riet L, van Esch JHM, Roks AJM *et al*. Hypertension. *Circ Res* 2015;**116**:960–75. https://doi.org/10.1161/CIRCRESAHA.116.303587
5. Mattei AL, Bailly N, Meissner A. DNA methylation: a historical perspective. *Trends Genet* 2022;**38**:676–707. https://doi.org/10.1016/j.tig.2022.03.010
6. Han X, Xue J, Gao S *et al*. Identification of potential diagnostic biomarkers for hypertension via integrated analysis of gene expression and DNA methylation. *Blood Press* 2024;**33**:2387025. https://doi.org/10.1080/08037051.2024.2387025
7. Stoll S, Wang C, Qiu H. DNA methylation and histone modification in hypertension. *Int J Mol Sci* 2018;**19**:1174. https://doi.org/10.3390/ijms19041174
8. Liu Y, Liu P, Yang C *et al*. Base-resolution maps of 5-methylcytosine and 5-hydroxymethylcytosine in Dahl S rats. *Hypertension* 2014;**63**:827–38. https://doi.org/10.1161/HYPERTENSIONAHA.113.02637
9. Hong X, Miao K, Cao W *et al*. Association between DNA methylation and blood pressure: a 5-year longitudinal twin study. *Hypertension* 2023;**80**:169–81. https://doi.org/10.1161/HYPERTENSIONAHA.122.19953
10. Kee HJ, Ryu Y, Seok YM *et al*. Selective inhibition of histone deacetylase 8 improves vascular hypertrophy, relaxation, and inflammation in angiotensin II hypertensive mice. *Clin Hypertens* 2019;**25**:13. https://doi.org/10.1186/s40885-019-0118-8
11. Wang Y, Jiao B, Hu Z *et al*. Critical role of histone deacetylase 3 in the regulation of kidney inflammation and fibrosis. *Kidney Int* 2024;**105**:775–90. https://doi.org/10.1016/j.kint.2024.01.010
12. Liao Y, Chu C, Yan Y *et al*. High dietary salt intake is associated with histone methylation in salt-sensitive individuals. *Front Nutr* 2022;**9**:857562. https://doi.org/10.3389/fnut.2022.857562
13. Lee H-A, Cho H-M, Lee D-Y *et al*. Tissue-specific upregulation of angiotensin-converting enzyme 1 in spontaneously hypertensive rats through histone code modifications. *Hypertension* 2012;**59**:621–6. https://doi.org/10.1161/HYPERTENSIONAHA.111.182428
14. Chen L, Wu H, Pochynyuk OM *et al*. Af17 deficiency increases sodium excretion and decreases blood pressure. *J Am Soc Nephrol* 2011;**22**:1076–86. https://doi.org/10.1681/ASN.2010121270
15. Ray A, Stelloh C, Liu Y *et al*. Histone modifications and their contributions to hypertension. *Hypertension* 2024;**81**:229–39. https://doi.org/10.1161/HYPERTENSIONAHA.123.21755
16. Esteller M. Non-coding RNAs in human disease. *Nat Rev Genet* 2011;**12**:861–74. https://doi.org/10.1038/nrg3074
17. Zhu Q, Hu J, Wang L *et al*. Overexpression of microRNA-429 transgene into the renal medulla attenuated salt-sensitive hypertension in Dahl S rats. *Am J Hypertens* 2021;**34**:1071–7. https://doi.org/10.1093/ajh/hpab089
18. Wang X, Han W, Zhang Y *et al*. Soluble epoxide hydrolase inhibitor t-AUCB ameliorates vascular endothelial dysfunction by influencing the NF-κb/miR-155-5p/eNOS/NO/iκb cycle in hypertensive rats. *Antioxidants* 2022;**11**:1372. https://doi.org/10.3390/antiox11071372

19. Lu C, Chen B, Chen C *et al*. CircNr1h4 regulates the pathological process of renal injury in salt-sensitive hypertensive mice by targeting miR-155-5p. *J Cell Mol Med* 2020;**24**:1700–12. https://doi.org/10.1111/jcmm.14863
20. Xue Y-Z, Li Z-J, Liu W-T *et al*. Down-regulation of lncRNA MALAT1 alleviates vascular lesion and vascular remodeling of rats with hypertension. *Aging* 2019;**11**:5192–205. https://doi.org/10.18632/aging.102113
21. Khan MM, Kirabo A. Long noncoding RNA MALAT1: salt-sensitive hypertension. *Int J Mol Sci* 2024;**25**:5507. https://doi.org/10.3390/ijms25105507
22. Qi H, Liu Z, Liu B *et al*. micro-RNA screening and prediction model construction for diagnosis of salt-sensitive essential hypertension. *Medicine (Baltimore)* 2017;**96**:e6417. https://doi.org/10.1097/MD.0000000000006417
23. Gildea JJ, Carlson JM, Schoeffel CD *et al*. Urinary exosome miRNome analysis and its applications to salt sensitivity of blood pressure. *Clin Biochem* 2013;**46**:1131–4. https://doi.org/10.1016/j.clinbiochem.2013.05.052
24. Zhang X, Yao S, Wang Y *et al*. Associations of microRNA gene polymorphisms with salt sensitivity, longitudinal blood pressure changes, and hypertension incidence in the Chinese population. *J Clin Hypertens (Greenwich)* 2025;**27**:e70019. https://doi.org/10.1111/jch.70019
25. Liu Y, Usa K, Wang F *et al*. MicroRNA-214-3p in the kidney contributes to the development of hypertension. *J Am Soc Nephrol* 2018;**29**:2518–28. https://doi.org/10.1681/ASN.2018020117
26. Geurts AM, Mattson DL, Liu P *et al*. Maternal diet during gestation and lactation modifies the severity of salt-induced hypertension and renal injury in Dahl salt-sensitive rats. *Hypertension* 2015;**65**:447–55. https://doi.org/10.1161/HYPERTENSIONAHA.114.04179
27. Kawakami-Mori F, Nishimoto M, Reheman L *et al*. Aberrant DNA methylation of hypothalamic angiotensin receptor in prenatal programmed hypertension. *JCI Insight* 2018;**3**:e95625. https://doi.org/10.1172/jci.insight.95625
28. Kawarazaki W, Fujita T. Kidney and epigenetic mechanisms of salt-sensitive hypertension. *Nat Rev Nephrol* 2021;**17**:350–63. https://doi.org/10.1038/s41581-021-00399-2
29. Miyoshi M, Imakado Y, Otani L *et al*. Maternal protein restriction induces renal AT2R promoter hypomethylation in salt-sensitive, hypertensive rats. *Food Sci Nutr* 2021;**9**:1452–9. https://doi.org/10.1002/fsn3.2113
30. Murray R, Kitaba N, Antoun E *et al*. Influence of maternal lifestyle and diet on perinatal DNA methylation signatures associated with childhood arterial stiffness at 8 to 9 years. *Hypertension* 2021;**78**:787–800. https://doi.org/10.1161/HYPERTENSIONAHA.121.17396
31. Sales VM, Ferguson-Smith AC, Patti M-E. Epigenetic mechanisms of transmission of metabolic disease across generations. *Cell Metab* 2017;**25**:559–71. https://doi.org/10.1016/j.cmet.2017.02.016
32. Cao N, Lan C, Chen C *et al*. Prenatal lipopolysaccharides exposure induces transgenerational inheritance of hypertension. *Circulation* 2022;**146**:1082–95. https://doi.org/10.1161/CIRCULATIONAHA.122.059891
33. Krug AW, Tille E, Sun B *et al*. Lysine-specific demethylase-1 modifies the age effect on blood pressure sensitivity to dietary salt intake. *Age (Dordr)* 2013;**35**:1809–20. https://doi.org/10.1007/s11357-012-9480-0
34. Yang Z, Ma Y, Wang Y *et al*. The prognostic value of serum α-klotho in age-related diseases among the US population: a prospective population-based cohort study. *Prev Med Rep* 2024;**42**:102730. https://doi.org/10.1016/j.pmedr.2024.102730
35. Lindberg K, Amin R, Moe OW *et al*. The kidney is the principal organ mediating klotho effects. *J Am Soc Nephrol* 2014;**25**:2169–75. https://doi.org/10.1681/ASN.2013111209
36. Kale A, Sankrityayan H, Anders H-J *et al*. Epigenetic and non-epigenetic regulation of Klotho in kidney disease. *Life Sci* 2021;**264**:118644. https://doi.org/10.1016/j.lfs.2020.118644
37. Zhou X, Chen K, Lei H *et al*. Klotho gene deficiency causes salt-sensitive hypertension via monocyte chemotactic protein-1/CC chemokine receptor 2–mediated inflammation. *J Am Soc Nephrol* 2015;**26**:121–32. https://doi.org/10.1681/ASN.2013101033
38. Citterio L, Carpini SD, Lupoli S *et al*. Klotho gene in human salt-sensitive hypertension. *Clin J Am Soc Nephrol* 2020;**15**:375–83. https://doi.org/10.2215/CJN.08620719
39. Aczel D, Torma F, Jokai M *et al*. The circulating level of klotho is not dependent upon physical fitness and age-associated methylation increases at the promoter region of the klotho gene. *Genes* 2023;**14**:525. https://doi.org/10.3390/genes14020525
40. Martín-Núñez E, Pérez-Castro A, Tagua VG *et al*. Klotho expression in peripheral blood circulating cells is associated with vascular and systemic inflammation in atherosclerotic vascular disease. *Sci Rep* 2022;**12**:8422.
41. Han X, Sun Z. Epigenetic regulation of KL (klotho) via H3K27me3 (histone 3 lysine [K] 27 trimethylation) in renal tubule cells. *Hypertension* 2020;**75**:1233–41. https://doi.org/10.1161/HYPERTENSIONAHA.120.14642
42. Kawarazaki W, Mizuno R, Nishimoto M *et al*. Salt causes aging-associated hypertension via vascular Wnt5a under Klotho deficiency. *J Clin Invest* 2020;**130**:4152–66. https://doi.org/10.1172/JCI134431
43. Elgazzaz M, Lazartigues E. Epigenetic modifications of the renin–angiotensin system in cardiometabolic diseases. *Clin Sci (Colch)* 2021;**135**:127–42. https://doi.org/10.1042/CS20201287
44. O'Donnell JA, Zheng T, Meric G *et al*. The gut microbiome and hypertension. *Nat Rev Nephrol* 2023;**19**:153–67.
45. Mehta V, Nagu P, Inbaraj BS *et al*. Epigenetics and gut microbiota crosstalk: a potential factor in pathogenesis of cardiovascular disorders. *Bioengineering (Basel)* 2022;**9**:798. https://doi.org/10.3390/bioengineering9120798
46. Cuka E, Simonini M, Lanzani C *et al*. Inverse salt sensitivity: an independent risk factor for cardiovascular damage in essential hypertension. *J Hypertens* 2022;**40**:1504–12. https://doi.org/10.1097/HJH.0000000000003174
47. Zhong Q, Liu C, Fan R *et al*. Association of SCNN1B promoter methylation with essential hypertension. *Mol Med Rep* 2016;**14**:5422–8. https://doi.org/10.3892/mmr.2016.5905
48. Zhang W. Epigenetics of epithelial Na^+ channel-dependent sodium uptake and blood pressure regulation. *World J Nephrol* 2015;**4**:363–6. https://doi.org/10.5527/wjn.v4.i3.363
49. Kidambi S, Pan X, Yang C *et al*. Dietary sodium restriction results in tissue-specific changes in DNA methylation in humans. *Hypertension* 2021;**78**:434–46. https://doi.org/10.1161/HYPERTENSIONAHA.120.17351
50. Leistner C, Menke A. Hypothalamic–pituitary–adrenal axis and stress. *Handb Clin Neurol* 2020;**175**:55–64
51. Lee RS, Sawa A. Environmental stressors and epigenetic control of the hypothalamic-pituitary-adrenal axis. *Neuroendocrinology* 2014;**100**:278–87. https://doi.org/10.1159/000369585
52. Wu G, Zhang X, Gao F. The epigenetic landscape of exercise in cardiac health and disease. *J Sport Health Sci* 2021;**10**:648–59. https://doi.org/10.1016/j.jshs.2020.12.003

53. Chan Y, Fish JE, D'Abreo C *et al*. The cell-specific expression of endothelial nitric-oxide synthase. *J Biol Chem* 2004;**279**:35087–100. https://doi.org/10.1074/jbc.M405063200
54. Gupta DK, Lewis CE, Varady KA *et al*. Effect of dietary sodium on blood pressure. *JAMA* 2023;**330**:2258–66. https://doi.org/10.1001/jama.2023.23651.
55. Dasinger JH, Alsheikh AJ, Abais-Battad JM *et al*. Epigenetic modifications in T cells. *Hypertension* 2020;**75**:372–82. https://doi.org/10.1161/HYPERTENSIONAHA.119.13716
56. Liu N, Chen Y, Wang Y *et al*. The underlying mechanisms of DNA methylation in high salt memory in hypertensive vascular disease. *Sci Rep* 2024;**14**:925. https://doi.org/10.1038/s41598-024-51279-1
57. Chiapperino L, Habets M, Paneni F. Epigenetic editing in cardiovascular medicine: moving beyond the hype. *Nat Rev Cardiol* 2025;**22**:389–90. https://doi.org/10.1038/s41569-025-01143-0

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