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REVIEW ARTICLE

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Evaluation of the pathophysiological mechanisms of salt-sensitive hypertension

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Abstract

The currently available data have indicated that dietary salt is directly correlated with blood pressure (BP) and the occurrence of hypertension. However, the salt sensitivity of BP is different in each individual. Genetic factors and environmental factors influence the salt sensitivity of BP. Obesity, stress, and aging are strongly associated with increased BP salt sensitivity. Indeed, a complex and interactive genetic and environmental system can determine an individual's BP salt sensitivity. However, the genetic/epigenetic determinants leading to salt sensitivity of BP are still challenging to identify primarily because lifestyle-related diseases, including hypertension, usually become a medical problem during adulthood, although their causes may be attributed to the earlier stages of ontogeny. The association between distinct developmental periods involves changes in gene expression, which include epigenetic phenomena. The role of epigenetic modification in the development of salt-sensitive hypertension is presently under investigation. Recently, we identified aberrant DNA methylation in the context of prenatally programmed hypertension. In this review, we summarize the existing knowledge regarding the pathophysiological mechanisms of salt-sensitive hypertension. Additionally, we discuss the contribution of epigenetic mechanisms in the development of salt-sensitive hypertension.

Keywords Blood pressure · Epigenetics · Hypertension · Salt-sensitive Hypertension

Introduction

Hypertension is one of the most common diseases in humans [1] and one of the most well-known major risk factors for cardiovascular disease (CVD) and stroke [2]. Epidemiological evidence of the relationship between sodium intake and blood pressure (BP) has been obtained via cross-sectional studies [3–5], and clinical interventional studies have revealed the effects of changes in sodium intake [6–8]. However, the salt sensitivity of BP differs among individuals. Patients with essential hypertension are classified into two groups according to BP response to a high-salt diet: salt-sensitive hypertensive and nonsalt-sensitive hypertensive [9, 10]. Guyton et al. demonstrated that an impaired pressure–natriuresis curve results in salt-sensitive hypertension [11], and accumulating evidence has validated the hypothesis that BP salt sensitivity is critically dependent on renal sodium handling. Not only genetic factors but also nutritional and environmental factors such as obesity, stress, and aging are involved in the development of salt-sensitive hypertension.

The prevalence of obesity has increased over the past several decades. Obesity, particularly visceral obesity, is closely related to hypertension [12, 13]. The risk of hypertension markedly increases in proportion with the amount of excess weight [14]. Obesity is strongly linked to the risk of mortality [15] because such a condition is highly associated with the incidence of type 2 diabetes mellitus, dyslipidemia [16], stroke, and CVD [17]. Although sodium intake has been associated with obesity through energy intake, it is a potential risk factor for obesity independent of energy intake [18].

Moreover, daily sodium intake proportionally increases with the increase in hypertension and obesity incidence [19]; thus, a direct association was observed between sodium intake and body fat mass [18, 20]. In addition to the

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strong association between sodium intake and body fat, obese adolescents had higher salt sensitivity of BP than nonobese adolescents [21, 22]. A positive relationship was observed between the salt sensitivity of BP and the risk factors for metabolic syndrome, including large waist circumference, hypertriglyceridemia, hypertension, and hyperglycemia, in patients with metabolic syndrome [22]. These studies indicate that salt sensitivity in obese participants is affected by obesity-related metabolic disorders.

Not only genetic factors but also nutritional and environmental factors such as malnutrition and various stresses during the fetal and postnatal stages are involved in the development of lifestyle-related diseases, including hypertension. Remarkably, twins with identical genetic backgrounds do not develop the same diseases in life [23]. In the 2000s, the associations between these environmental factors, the development of lifestyle-related diseases and epigenetics, including DNA methylation, histone modification, miRNA, and long noncoding RNA, has attracted attention. Epigenetics refers to the control mechanism of gene expression that activates or inactivates genes without changing their DNA sequences and results in transmitting the memory of cells to the next generation. A large-scale clinical study concluded that the differences in the pattern of DNA methylation and histone acetylation occur with aging [24] and that these changes are caused by differences in epigenetic memory due to environmental factors, although genetic factors almost do not change throughout life.

In this review, we summarize the existing knowledge about the pathophysiological mechanisms of salt-sensitive hypertension, including a discussion from the perspective of epigenetic mechanisms.

Obesity and salt-sensitive hypertension

Mechanism underlying obesity-related hypertension

Obese adolescents are reported to have higher BP salt sensitivity than nonobese adolescents [21, 22]. Obese individuals present with extracellular fluid volume expansion and increased blood flow in numerous tissues [25]. In the early phase of obesity, a high glomerular filtration rate and renal blood flow increase renal sodium reabsorption. With prolonged hypertension, glomerular hyperfiltration and neurohumoral activation lead to severe hypertension, glomerular injury, and impaired renal sodium excretion capacity, thereby resulting in the gradual loss of nephron and kidney function. Considering that salt-sensitive hypertension in obese individuals is solely attributed to impaired renal-pressure natriuresis [26], obese individuals require a higher BP than nonobese individuals to maintain sodium balance. The underlying factors that induce impaired sodium excretion in the kidneys include the physical compression of the kidney due to increased visceral fat, the renin–angiotensin system (RAS), the aldosterone/mineralocorticoid receptor (MR) system, and the activation of the sympathetic nervous system (SNS) [27]. Furthermore, obese individuals present with metabolic disorders, such as hyperinsulinemia, glucose intolerance, dyslipidemia, and inflammation, which influence each other, leading to renal sodium reabsorption and renal injury.

Renin–angiotensin system

The activation of RAS is closely associated with the development of obesity-induced hypertension [27, 28]. Despite sodium retention, RAS activation occurs in obese individuals who often have mild-to-moderate increases in plasma renin activity, angiotensinogen (Agt) level, angiotensin-converting enzyme (ACE) activity, angiotensin II (AngII) level, and aldosterone level [29]. RAS activation in the context of obesity is elicited by multiple factors, including the compression of the kidneys by fat mass, increased SNS activation, and possibly the local RAS in adipose tissues [30], which contain all the components of the RAS, such as Agt, renin, ACE, and AngII receptor types 1 and 2, and can produce AngII [31]. In general, Agt is produced primarily in the liver; however, Agt secretion by adipose tissues is closely regulated in obese individuals [32]. Adipocyte-derived AngII has been considered important in the development of obesity-related hypertension. Yiannikouris et al. showed that a high-fat diet induced an increase in BP only in wild-type littermates, whereas no increase was observed in adipocyte Agt-deficient mice, although both gained weight and had similar amounts of fat mass [33]. Moreover, plasma Agt protein levels were comparable in these two types of mice; however, the plasma AngII level increased only in wild-type littermates. These results indicated that adipose tissue can be a major source of AngII in the development of obesity-related hypertension, and whether adipocyte-derived Agt or AngII has more influence on BP regulation in the context of obesity remains to be elucidated.

Aldosterone–MR pathway

Several investigators have reported that an excessive amount of aldosterone is often observed in the context of obesity and indicates the involvement of aldosterone in the pathogenesis of obesity-related hypertension [34, 35]. Weight loss considerably decreases plasma aldosterone concentrations (PACs) [36, 37], indicating that severe obesity may cause hyperaldosteronism. Moreover, several studies have shown a strong association between hyperaldosteronism and hypertension in individuals with obesity

[38, 39]. In contrast, Goodfriend et al. reported that PAC was positively associated with the amount of visceral adipose tissues but inversely correlated with insulin sensitivity [40], indicating that a fat-derived substance contributes to the excess amount of aldosterone in individuals with visceral obesity. Ehrhart-Bornstein et al. verified that adipocyte secretory products directly stimulate aldosterone secretion in human adrenocortical cells [41], indicating that unknown aldosterone-releasing factors (ARFs) exist and might explain the direct association between obesity and hypertension. The candidate ARFs include 12, 13-epoxy-9-oxo-10(trans)-octadecanoic acid [42], an oxidized fatty acid product; complement C1q TNF-related protein [43]; and leptin [44]. Nagase et al. showed that the serum PACs are higher in obese spontaneously hypertensive rats (SHRs), a rat model of metabolic syndrome, and that the aldosterone secretagogue activity in the adipocytes of obese SHRs was significantly higher than that in the adipocytes of nonobese SHRs [45]. Moreover, in obese SHRs, salt loading increases BP and aggravates cardiorenal injury, which are inhibited by MR antagonist treatment [46, 47]. Salt-induced MR activation in obese SHRs may result from the inadequate suppression of PACs, which are maintained at appropriate levels after the feedback from a high-salt diet in normal rats and lean SHRs as a result of negative feedback inhibition by the endogenous RAS. Thus, the lack of negative feedback regulation of aldosterone secretion may contribute to the development of salt-sensitive hypertension and cardiorenal injury in obese SHRs.

Sympathetic nervous system activity

Increased SNS activity contributes to obesity-related hypertension [25]. Several studies have shown increased SNS activity in animal models of obesity [48, 49] and obese human participants [50, 51]. The administration of α/β-adrenergic blockers reduces SNS activity and obesity-related hypertension [52]. Furthermore, obese hypertensive patients and animals often present with both salt sensitivity of BP and increased SNS activity, particularly in the kidney [53, 54], indicating that renal SNS activation is an important factor influencing salt sensitivity of BP. Increased renin secretion, reduced renal blood flow, and increased renal tubular reabsorption are considered the main modulators of antinatriuretic effects via renal SNS activation [55]. Regarding noradrenaline-induced tubular sodium reabsorption, the stimulation of β-adrenergic receptors leads to the activation of the thiazide-sensitive sodium chloride cotransporter (NCC) [56], possibly via the serine–threonine protein kinase WNK4-OSR1 pathway in the distal tubule [57]. WNK kinases are regulated by changes in dietary sodium intake via effects on the circulating RAS and SNS, thereby influencing NCC activity [56, 58]. Increased endogenous AngII in the context of a low-salt diet is involved in NCC activation in an STE20/SPS-1-related proline/alanine-rich kinase-dependent manner [59, 60]. Aldosterone promotes the dietary salt-mediated increase in NCC activity via the WNK4-extracellular signal-regulated kinase 1/2 signaling pathway [61]. SNS overactivity increases NCC activity, both dependently and independently of the renin–angiotensin–aldosterone system (RAAS) [56]. Thus, SNS overactivity along with AngII or aldosterone in the context of obesity is responsible for salt-sensitive hypertension.

Rac1-induced MR activation in salt-sensitive hypertension

The circulating level of aldosterone is counterbalanced by changes in dietary sodium intake via the circulating RAS, resulting in the maintenance of sodium homeostasis and normal BP. Several factors, including reactive oxygen species [62], cAMP-dependent protein kinase A [63], and ubiquitin carrier protein 9 [64], modulate MR activation in a ligand-independent manner in various cells and tissues. Recently, Rac1, a Rho family small GTPase, was found to be a ligand-dependent and ligand-independent modulator of MR activation [65]. Moreover, this study showed that RhoGDP dissociation inhibitor (RhoGDI) α-knockout (KO) mice, an animal model of Rac1 activation in the kidney, had salt-sensitive hypertension and massive proteinuria along with MR activation in the kidney, despite the lack of changes in circulating aldosterone levels [65]. These abnormalities in RhoGDIα-KO mice were inhibited by Rac1 inhibition with NSC23766 and selective MR blockade by eplerenone along with the attenuation of MR activation, indicating that Rac1 is an upstream regulator of MR activity.

In Dahl-S rats, salt loading increases Rac1 activity in the kidneys, which is associated with MR activation and upregulation of the MR target gene serum and glucocorticoid-regulated kinase (Sgk1) expression, leading to sodium retention and hypertension [66]. However, treatment with the Rac1 inhibitor NSC23766 not only decreased MR activation but also suppressed the increase in BP induced by salt loading, which was as effective as treatment with eplerenone, an MR blocker. In contrast, Rac1 and MR activities were reduced by salt loading in Dahl salt-resistant and normotensive rats, which resulted in a normal BP. Thus, Rac1 is a determinant of both MR activation and salt sensitivity [66].

Notably, a randomized, double-blind, placebo-controlled clinical trial (EVALUATE) showed that eplerenone can decrease BP and residual albuminuria in patients with hypertensive chronic kidney disease who were treated with RAS inhibitors [67]. Moreover, in a post hoc analysis of the EVALUATE study, in the placebo group, urinary albumin

excretion significantly increased during the 1-year treatment period, despite treatment with RAS inhibitors, in patients with the highest salt intake (24-h urinary sodium excretion) of the three groups classified according to dietary sodium intake but not in those with the lowest salt intake, indicating salt-induced resistance to RAS inhibitors. Accordingly, the antialbuminuric effects of eplerenone were observed in patients with higher sodium intake but not in those with lower sodium intake, indicating that a high dietary sodium intake causes resistance to RAS inhibitors via salt-induced Rac1-MR activation in the kidney [68].

Emerging role of the intercalated cells of the kidney in sodium chloride handling and salt-sensitive hypertension

The RAAS plays an important role in the control of fluid homeostasis and BP by activating renal sodium chloride transport mechanisms. In the aldosterone-sensitive distal nephron, increasing evidence has shown that NCC in the distal convoluted tubule and the epithelial sodium channel in the principal cells of the connecting tubule (CNT) and the collecting duct (CD) plays an essential role in regulating sodium reabsorption and BP control.

Pendrin, which is encoded by SLC26A4, is a chloride–bicarbonate exchanger that is expressed specifically in the β-intercalated cells of the CNT–CD [69], and it regulates acid–base balance by excreting bicarbonate in the urine. In addition to its role in bicarbonate excretion, several studies have shown that pendrin and sodium-dependent chloride–bicarbonate exchangers promote chloride reabsorption [70, 71] and increase sodium reabsorption [70, 72–74]. With respect to the physiological role of pendrin in BP regulation, pendrin overexpression in intercalated cells results in salt-sensitive hypertension [75], whereas the acute deletion of pendrin lowers BP [76]. Shibata et al. identified a phosphorylation site in the ligand-binding domain of the MR at S843 (pMR-S843) that prevents ligand binding and MR signaling in intercalated cells [74]. Indeed, AngII upregulates pendrin expression [71, 74], which is associated with the dephosphorylation of pMR-S843, indicating the involvement of the MR–pendrin system in the sodium chloride reabsorption mechanism.

We recently found that pendrin expression does not increase until aldosterone binds to an MR that has been dephosphorylated by AngII, indicating that both AngII and aldosterone are indispensable for pendrin activation [77]. Furthermore, the BP of pendrin-KO mice was similar to that of wild-type mice fed a high-salt diet. However, the pendrin-KO mice had substantial hypotension compared with the BP of the wild-type mice fed a low-salt diet [77]. These results revealed that pendrin contributes to the maintenance of normal BP during RAAS activation under low-salt diet conditions [77]. Collectively, these results indicate that the abnormal activation of pendrin facilitates the development of salt-sensitive hypertension and that pendrin inhibitor can be a new therapeutic agent for salt-sensitive hypertension. However, further research must be conducted to validate such findings.

Dietary potassium intake and decreased BP

Dietary potassium has typically received less attention than sodium, possibly because the traditional body fluid model for BP control focuses on sodium homeostasis. The characteristics of the modern western diet—which is high in sodium and low in potassium—produce a biologic interaction with the kidneys, resulting in excessive sodium and insufficient potassium concentrations in the human body, leading to more focus on the balance between sodium and potassium.

Nearly 100 years ago, dietary potassium was found to have a BP-lowering effect in humans [78]. Dietary interventions, particularly those based on sodium or potassium intakes, can reduce BP in humans [79–81]. The Dietary Approaches to Stop Hypertension diet, a US-based multicenter randomized controlled trial, showed that a high-potassium dietary intervention is associated with a significant decrease in mean BP regardless of sodium intake compared with the effects of a control diet [6]. A meta-analysis demonstrated that a higher potassium intake reduces BP in adults with hypertension [82]. A higher potassium intake was associated with a decrease in the occurrence of stroke, indicating that increased potassium intake may be beneficial for the prevention and control of elevated BP and the occurrence of stroke in most individuals. Furthermore, Yang et al. showed that a higher sodium-to-potassium ratio is associated with a significantly increased risk of CVD and all-cause mortality, and higher sodium intake was correlated with an increase in total mortality in the population in the US [83]. It is now clear that dietary potassium intake is inversely associated with BP [5]. The combined effects of low-sodium and high-potassium intake on BP and hypertension may be larger than those of either sodium or potassium alone [4, 6], indicating the importance of considering both sodium and potassium in dietary interventions.

Regarding the mechanism of reducing BP with dietary potassium intake, recent reviews have indicated the myriad and complex mechanisms underlying the effects of potassium on BP, which include effects on the SNS and vasculature [84]. Notably, Terker et al. recently showed that NCC is activated by dietary potassium deficiency, even with high sodium intake, thereby causing sodium retention and an increase in BP [85]. To some extent, this result explains the renal mechanism that promotes sodium excretion by

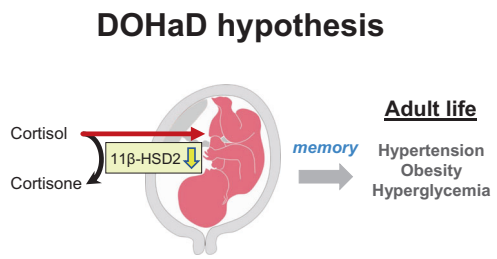

Fig. 1 Developmental origins of health and disease (DOHaD) hypothesis. Decreased 11-β-dehydrogenase type 2 (11β-HSD2) activity due to placental dysfunction caused fetal exposure to excess glucocorticoid levels, leading to low birth weight and eventually permanent hypertension, obesity, and diabetes in adulthood

potassium intake. Consistently, the antihypertensive effect of dietary potassium is greater in association with higher sodium intake than with lower sodium intake [79]. This result supports the hypothesis that the hypotensive effect is mainly due to natriuresis [86].

Role of epigenetics in salt-sensitive hypertension

Fetal malnutrition and salt-sensitive hypertension

The idea that cardiac and metabolic disease can have intrauterine origins, referred to as the developmental origins of health and disease (DOHaD) (Fig. 1), was initially based on an early epidemiological study of prenatal nutrition and late-onset coronary heart disease, which was published by Barker et al. in the late 1980s [87]. Even to date, the incidence of insufficient nutrition is high worldwide. However, the detailed mechanism by which low birth weight leads to lifestyle-related diseases in adults has not been fully elucidated.

We recently revealed that maternal malnutrition, causing prenatal exposure to excessive glucocorticoid levels, induced adverse metabolic programming, leading to salt-sensitive hypertension in the offspring [88]. The plasma cortisol concentration moderately increases in normal pregnant mothers. However, the fetus is not exposed to high cortisol levels because 11-β-dehydrogenase type 2 (11β-HSD2) converts cortisol to cortisone, an inactive metabolite, in the placenta. However, placental 11β-HSD2 activity is decreased by placental dysfunction in pregnant rats receiving a low-protein diet and results in exposure to high cortisol levels (corticosterone in rodents) in the fetus. In the offspring of pregnant rats receiving a low-protein diet or dexamethasone, a synthetic placenta-permeable glucocorticoid, the mRNA expression of angiotensin receptor type 1a (AT1a) in the paraventricular nucleus of the hypothalamus was upregulated and DNA methyltransferase 3a (Dnmt3a) expression, the binding of Dnmt3a to the AT1a gene, and DNA demethylation decreased. The upregulation of AT1a induced by DNA demethylation remains a memory in adulthood; in turn, the overproduction of reactive oxygen species due to increased AT1a activity causes salt-sensitive hypertension via renal sympathetic overactivity [54, 89]. Thus, the epigenetic modulation of hypothalamic angiotensin signaling contributes to the development of the salt-sensitive hypertension induced by excess prenatal glucocorticoid levels in the offspring of mothers who are malnourished during pregnancy [88]. These results validated the DOHaD hypothesis via epigenetic mechanisms. Understanding the role of epigenetic modifications in prenatal programmed hypertension sheds light on how the system could be targeted to prevent and treat such conditions in the future.

Epigenetics and salt-sensitive hypertension in adults

Regarding the association between BP and epigenetics, BP changes have been associated with DNA methylation in human genome-wide studies. The level of DNA methylation, particularly that of CpG islands (clusters of CpG sites) located in promoter regions, is thought to be deeply correlated with the level of gene transcription activity. Richard et al. analyzed the cross-sectional associations between systolic and diastolic BP and blood-derived genome-wide DNA methylation in 17,010 individuals of European, African-American, and Hispanic ancestry and identified 13 replicated CpG sites associated with BP [90]. Kato et al. identified sentinel BP single nucleotide polymorphisms (SNPs) enriched for the association with DNA methylation at multiple nearby CpG sites in up to 320,251 individuals of East Asian, European, and South Asian ancestry [91].

Pojoga et al. reported that mice with heterozygous knockout of lysine-specific demethylase-1 (LSD1, Kdm1a), which induces histone H3 lysine 4 (H3K4) or H3K9 demethylation, had salt-sensitive hypertension associated with enhanced vascular contraction despite the suppressed RAAS and reduced relaxation via NO-cGMP pathway, indicating the functional role of LSD1 in the development of salt-sensitive hypertension [92]. Moreover, Williams et al. demonstrated the association between SNPs in *LSD-1* and salt sensitivity of BP in cohort studies of hypertensive humans of African and Mexican-American descent [93]. In humans carrying these SNPs, as in the case of heterozygous knockout of *LSD1*, the fluid volume was excessive despite the decreased plasma aldosterone levels, indicating the importance of the loss of function of LSD-1 in the development of salt-sensitive hypertension. Lee et al. showed that treatment with the histone deacetylase (HDAC) inhibitor valproic acid attenuated salt-sensitive hypertension in deoxycorticosterone acetate-salt (DOCA-salt)-induced

hypertensive rats and reduced the expression of MR target genes in accordance with the decreased recruitment of MR and RNA polymerase II on the promoters of target genes. These results indicate that HDAC inhibition attenuates the transcriptional activity of MR through its acetylation and prevents the development of hypertension in DOCA-salt-induced hypertensive rats [94]. Liu et al. showed that intrarenal administration of anti-DNA methyltransferase 3a/ten–eleven translocase 3 GapmeRs, which induces DNA demethylation, attenuated salt-induced hypertension in Dahl-S rats [95]. In addition, the genes differentially expressed in response to GapmeRs were involved in the regulation of metabolism and inflammation, indicating that DNA de novo demethylation in the kidney plays a significant role in the development of salt-sensitive hypertension in Dahl-S rats.

Salt-sensitive hypertension in older participants

Life expectancy is continually increasing in developed countries worldwide [96], leading to an ever-increasing representation of older adults (i.e., individuals aged >65 years) in the population. Older individuals have higher salt sensitivity of BP than younger individuals [97, 98], which is associated with a decline in renal function with age [99, 100]. The increased salt sensitivity in older individuals affects diurnal fluctuations in BP [101], which causes an increase in the risk for stroke and therefore requires active treatment [102]. BP increases with age in individuals in most modern countries [103]. However, BP elevation associated with aging is not observed in the Yanomami people, who have a nonsalt culture [104], indicating that dietary salt is indispensable for BP elevation induced by aging and the development of hypertension in aged people. Numerous clinical studies have shown that BP in older individuals with hypertension is reduced by sodium restriction [7, 105].

For example, in the Trial of Nonpharmacologic Interventions in the Elderly, urinary sodium excretion was reduced by 2–3 g/day over a period of 2 years based on the guidelines of dietary sodium reduction, and this difference resulted in a lower BP increase in the experimental group than in the control group after the discontinuation of antihypertensive drugs [7]. Thus, a decrease in BP can be expected in older individuals with hypertension as a result of sodium reduction. However, excessive sodium reduction may also cause dehydration and hypotension. Thus, aged people not only show impaired renal function of urinary sodium excretion but also a reduced ability to conserve sodium in the body during acute salt restriction.

There is growing interest in the relationship between aging and epigenetics. A large-scale clinical study showed that differences in the pattern of DNA methylation and histone acetylation occur with aging [24]. The Klotho gene was originally identified as a putative aging-suppressor gene in mice that extended lifespan when overexpressed and caused multiple premature aging phenotypes when disrupted [106, 107]. The Klotho levels in both kidney and blood decrease with age [108, 109]. At the age of 70 years, the serum level of Klotho is only approximately half of what it was at the age of 40 years [110].

Regarding the regulatory mechanism of the Klotho gene by epigenetics, Chen et al. showed that the DNA of the Klotho gene was methylated in the kidney of aged mice, which was associated with the decreased expression of this gene. However, treatment with DNA demethylase activator decreased the methylation of the Klotho gene in the kidneys, which was associated with the reversal of the decreased Klotho levels in both kidneys and serum and resulted in a significant reduction in BP [111]. These results indicate that the aging-related decrease in soluble Klotho levels is regulated by epigenetic mechanisms. However, further studies are necessary to validate how Klotho deficiency is involved in aging-associated salt-sensitive hypertension.

Conclusions

This review focused on the pathophysiological mechanisms underlying the development of salt-sensitive hypertension, which include epigenetic mechanisms. Nutritional and environmental factors during the fetal (malnutrition during pregnancy) and postnatal (obesity or aging) stages are significantly associated with the development of salt-sensitive hypertension. First, malnutrition during pregnancy causes prenatal programmed hypertension. Aberrant DNA methylation via exposure to high glucocorticoid levels in the fetal hypothalamus remains a memory in adulthood, and the resultant upregulation of certain genes facilitates the development of salt-sensitive hypertension and obesity. Second, obesity causes salt-sensitive hypertension via either the excess amount of aldosterone and Rac1-MR activation or sympathetic overactivity during childhood and middle adulthood. Third, aging is often associated with the increasing incidence of hypertension due to the increased salt sensitivity of BP. The decrease in circulating soluble Klotho levels, which is mediated by DNA methylation, induces salt-sensitive hypertension in older individuals. Thus, epigenetics plays an important role in the development of salt-sensitive hypertension throughout life—from the fetal stage to the elderly stage (Fig. 2). Despite recent advances in the development of molecular mechanisms of salt-sensitive hypertension, including epigenetics, not all mechanisms have been elucidated. Thus, decreased sodium intake is important to prevent the development of hypertension. Further developments in this

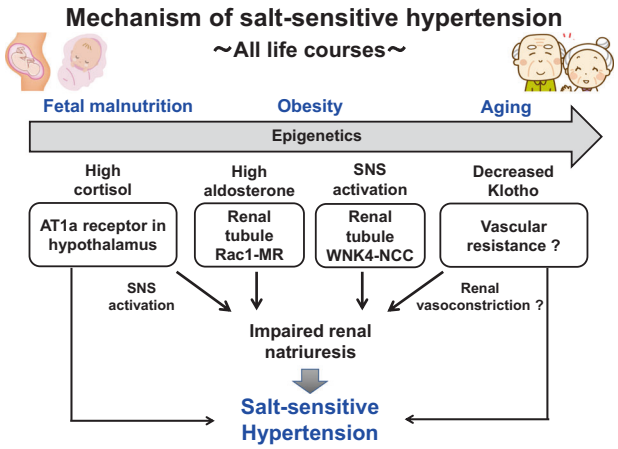

Fig. 2 Mechanism of salt-sensitive hypertension. Epigenetics plays an important role in the development of salt-sensitive hypertension, from the fetal stage to the elderly stage. *AT1a*, angiotensin receptor type 1a; *MR*, mineralocorticoid receptor; *NCC*, sodium chloride cotransporter; *SNS*, sympathetic nervous system

field will not only lead to a precise understanding of salt-sensitive hypertension but also contribute to the identification of new therapeutic targets that might complement existing therapies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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