Novel mechanisms of salt-sensitive hypertension

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A high dietary sodium-consumption level is considered the most important lifestyle factor that can be modified to help prevent an increase in blood pressure and the development of hypertension. Despite numerous studies over the past decades, the pathophysiology explaining why some people show a salt-sensitive blood pressure response and others do not is incompletely understood. Here, a brief overview of the latest mechanistic insights is provided, focusing on the mononuclear phagocytic system and inflammation, the gut–kidney axis, and epigenetics. The article also discusses the effects of 3 types of novel drugs on salt-sensitive hypertension—sodium–glucose cotransporter 2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and aldosterone synthase inhibitors. The conclusion is that besides kidney-centered mechanisms, vasoconstrictor mechanisms are also relevant for both the understanding and treatment of this blood pressure phenotype.

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A high dietary sodium-consumption level is considered the most important lifestyle factor that can be modified to help prevent an increase in blood pressure (BP) and the development of hypertension.[1] These BP effects relate specifically to sodium chloride (salt), but not necessarily to other sodium-containing salts.[2] Guidelines of the World Health Organization recommend limiting sodium consumption to <2 g/d (i.e., salt < 5 g/d) in order to improve BP control and associated cardiovascular outcomes in the general population.[1] Intriguingly, dietary sodium restriction does not improve BP control in everyone, and sometimes it even increases BP.[3] The change in BP following sodium loading also shows great variability, and this response can be used to discriminate salt-sensitive (SS) individuals from salt-resistant individuals in whom BP does not increase after the sodium load (Figure 1).[4] Several factors that increase salt-sensitivity have been identified, including aging, female sex, unhealthy lifestyle (e.g., overweight and a potassium-poor diet), a history of low birth weight or small gestational age, African descent, low-renin status, sympathetic hyperactivity, epithelial sodium-channel variants, and comorbidities such as hypertension, insulin-resistance, or chronic kidney disease

Editor's Note

Salt-sensitive hypertension is a long-known subcategory of arterial hypertension. The effect of dietary salt intake on blood pressure in the general population remains a hot topic. The authors of this review address novel, recently identified mechanisms that explain why some people are sensitive to high-salt diets, whereas others are not, including the role of inflammation, an implication of the gut–kidney axis, and several epigenetic modifications. The review ends with a discussion of the effects of new drugs on salt-sensitive hypertension, paving the way to new treatment possibilities.

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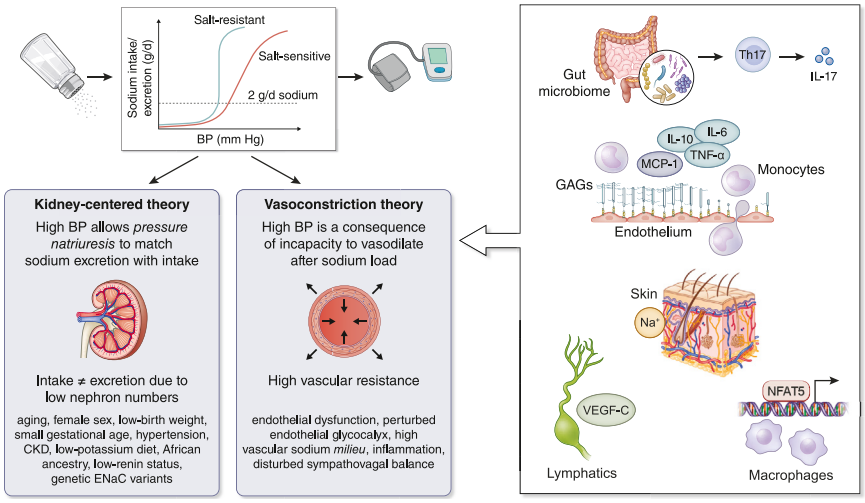

Figure 1 | Old and new concepts explaining salt sensitivity. The graph shows the natriuresis-pressure curves of both salt-resistant (i.e., no association between blood pressure [BP] and a wide range of sodium intake) and salt-sensitive individuals (i.e., tilted and right-shifted curve). According to the kidney-centered view, higher BP allows the matching of intake with urine excretion in conditions of impaired sodium-excreting capacity by the kidney. According to the vasoconstriction view, high BP is the result of expanded extracellular fluid volume combined with incapacity to reduce vascular resistance by arteriolar vasodilation. New players linked to salt sensitivity are summarized in the box on the right. Most studies indicate that these players interact in the association between BP and vasodysfunction during high–sodium level conditions. CKD, chronic kidney disease; ENaC, epithelial Na^+-channel; GAG, glycosaminoglycan; IL, interleukin; MCP, monocyte chemoattractant protein; NFAT, nuclear factor of activated T cell; Th17, T helper 17; TNF, tumor necrosis factor; VEGF-C, vascular endothelial growth factor C.

(CKD).[4,5] The clinical significance of the SS BP phenotype is emphasized by its link with increased cardiovascular risk and mortality, and with intermediate kidney outcomes, such as proteinuria.[6,7] Nevertheless, despite numerous studies over the past 50 years, the pathophysiology explaining why some show an SS BP response, and others show a salt-resistant BP response, is incompletely understood. Here, a brief overview of the latest mechanistic insights and therapeutic options is provided.

Abandonment of the concept of the kidney as the sole key driver central to salt sensitivity?

According to traditional concepts, sodium homeostasis is responsible for a stable *milieu intérieur* and is a key factor for BP control.[8] In SS individuals, a high level of sodium consumption is expected to lead to sodium accumulation and concurrent extracellular fluid volume expansion, at the cost of a BP increment (Figure 1).[8] Meticulously performed sodium-balance studies in humans, however, have shown that the association between sodium and BP is more complex.[9] The prevailing 2-compartment view on sodium homeostasis, in which body water is divided over the intra- and extracellular fluid space, has been revised due to the reappraisal of a third compartment, the interstitium, in which sodium can accumulate without concurrent water retention.[9] Subsequent studies have shown that tissue sodium accumulation—in the skin, muscles, and endothelial glycocalyx—relates to SS conditions, including diabetes, hypertension, and CKD.[9] Increased tissue sodium accumulation, facilitated by negatively charged polymeric disaccharides called glycosaminoglycans, was associated with impaired vasodilatation in response to high levels of sodium, much in keeping with experimental observations showing that salt sensitivity is caused merely by sodium-induced increases in vascular resistance rather than expansion of extracellular fluid volume and cardiac output.[8,9] Besides tissue sodium accumulation, the autonomic nervous system plays a pivotal role in decreased arteriolar vasodilatory capacity upon sodium loading.[10] Yet, in patients with diabetes, the BP increase after a 7-day high-salt diet was not associated with systemic vascular resistance or extracellular fluid volume expansion.[11] Rather, in these patients, a central role for skin macrophages and the dermal lymphatic system was apparent,[12] which is in line with previous rat experiments.[13] In these studies, tonicity-responsive enhancer-binding protein (also known as nuclear factor of activated T cells) mediated vascular endothelial growth factor–C signaling in macrophages in response to increased tissue sodium storage, and caused salt-induced hypertension.[13] An incapacity to expand the tissue lymph capillary network after excessive sodium intake (8% saline) was strongly associated with the sodium-induced BP response.[13] Subsequent studies revealed that sodium increases monocyte interleukin (IL)-6 production and C-C chemokine receptor type 2 receptor expression. This upregulates tissue monocyte infiltration and plasma monocyte chemoattractant protein-1 and explains the higher skin proinflammatory macrophage densities that are seen after a high-sodium diet.[14] *In vitro*, macrophages demonstrate a predominantly proinflammatory phenotype upon high-sodium exposure, characterized by secretion of IL-6 and tumor necrosis factor-α, although IL-10 secretion is enhanced as well.[14] Given the observations from animal studies that BP

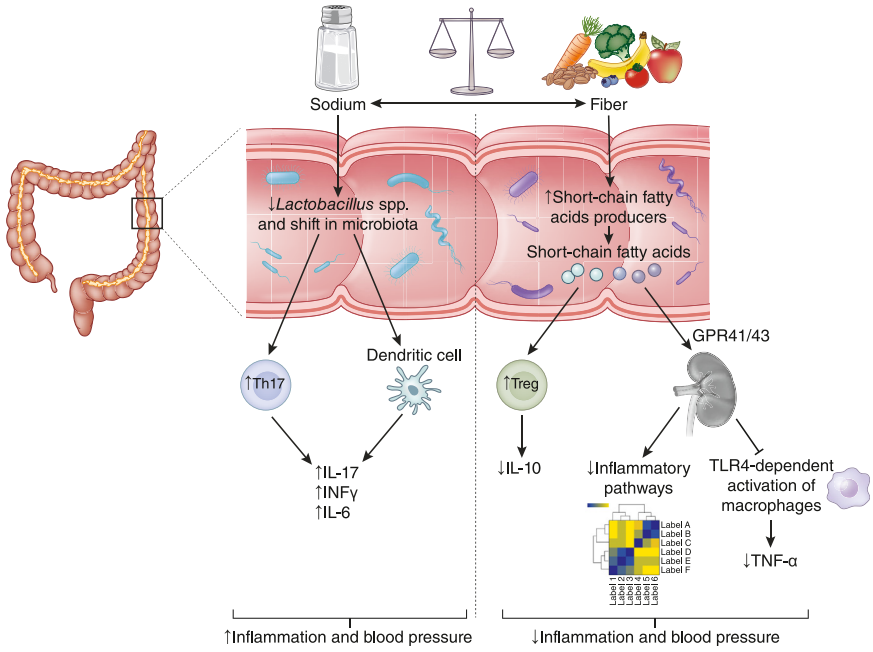

Figure 2 | The effect of sodium on the gut microbiome. Sodium modulates the composition of the gut microbiota, with a decrease in *Lactobacillus* species. Via production of metabolites and other unknown mechanisms, high-sodium intake activates dendritic cells and increases the population of T helper 17 (Th17) cells systemically. This leads to production of proinflammatory molecules such as interleukin 17 (IL-17), interferon γ (INFγ), and IL-6, which increase systemic and renal inflammation, and increase blood pressure. High-fiber intake reduces systemic inflammation and blood pressure by modulating the gut microbiota and increasing the production of short-chain fatty acids. These can increase the prevalence of T regulatory (Treg) cells, which produce anti-inflammatory cytokines such as IL-10. Short-chain fatty acids, via activation of the G-protein coupled receptors GPR41/43, reduce renal inflammatory pathways at the transcriptome level and block Toll-like receptor 4 (TLR4)–dependent activation of macrophages in the kidney. TNF-α, tumor necrosis factor-α.

increments depend on monocyte and macrophage depletion,[13] and the observations in patients with diabetes that disturbed skin macrophage influx links lymphatic density to salt sensitivity,[12] the mononuclear phagocytic system–derived inflammatory response should be considered a new key player in salt sensitivity.

Sodium, the gut–kidney axis, and inflammation

The large intestine is the main site of absorption of sodium; thus, a plausible possibility is that it may impact the gut microbiome and salt sensitivity (Figure 2), via both localized (i.e., intestinal) and systemic immune-dependent and -independent mechanisms.[15] The first evidence for this came from Dahl SS and salt-resistant rats, which have distinct microbiomes.[16] Studies using fecal microbiota transplantation are key to differentiating association from causation.[15] Indeed, a fecal microbiota transplantation from Wistar rats on a normal-sodium diet (0.49%) into Wistar rats on an excessive-sodium diet (8%) normalized BP, whereas the reverse fecal microbiota transplantation increased BP.[17] Moreover, germ-free mice that received a fecal microbiota transplantation from excessive sodium–fed mice had an exaggerated response to angiotensin II and higher plasma levels of proinflammatory cytokines (IL-6, IL-17) relative to normal sodium–fed recipients.[18] Excessive sodium intake increased intestinal inflammation, demonstrated as an accumulation of leukocytes, macrophages, and isolevuglandins in the colon, of both mice and humans.[18] A possibility is that the production of proinflammatory IL-17 and interferon γ with sodium is driven by intestinal dendritic cell activation via isolevuglandins. Furthermore, excessive sodium intake depleted *Lactobacillus murinus* in mice, resulting in a higher number of T-helper 17 (Th17) cells in the spleen and intestinal lamina propria, likely via indole-3-lactic acid.[19] Treatment with *Lactobacillus spp.* modestly decreased BP and the prevalence of Th17 cells in mice and healthy humans challenged with a high salt level.[19]

These studies did not measure[19] or detect[18] changes in kidney function or inflammation. However, other evidence suggests the existence of a gut–kidney axis that prevents and drives kidney inflammation. For example, interventions using fermentable fiber (which is digested by the microbiota) or direct treatment with short-chain fatty acids (SCFAs; produced by the microbiota during fiber fermentation) shifted the kidney transcriptome, with changes in inflammatory pathways such as IL-1β signalling.[20] SCFAs reach the systemic circulation, where they reduce BP in hypertensive animals[20–22] and patients.[23] They may act via reducing hypertension-associated inflammatory mechanisms, such as by priming T cells to differentiate into anti-inflammatory T regulatory cells.[21,22,24] Alternatively, in the absence of SCFA-signaling via their G-protein–coupled receptors GPR41 and GPR43, the breakdown of the gut epithelial barrier allows passage of microbial-produced endotoxins such as lipopolysaccharides

from the luminal gut into the systemic circulation.[25] Lipopolysaccharide then binds to toll-like receptor 4 in macrophages, resulting in their migration to the kidney and the production of proinflammatory cytokines.[25] An interesting notion is that sodium intake and SCFA levels may be inversely related. In a randomized clinical trial, aimed at reducing sodium intake over 6 weeks, a significant increase occurred in circulating SCFA levels, which was associated with a BP decrease, particularly in women.[26] In mice[27] and a cohort study,[28] a high sodium level is associated with a reduction in abundance of bacteria associated with production of SCFAs. Regarding the therapeutic potential of SCFAs,[23] whether interventions with fermentable fiber and/or SCFAs can mitigate the detrimental interplay among sodium, gut microbiota, BP, and inflammation remains unclear.

Another relevant interaction is the role of potassium in the gut microbiome. A cohort study of 2833 healthy Chinese participants whose dietary information was collected as 3-day, 24-hour recalls reported associations between 30 specific microbial taxa and potassium, and 54 that had a sodium-to-potassium ratio with a q value < 0.1.[29] Many of these associations identified SCFA producers, such as *Ruminococcus spp.*, *Blautia*, and other bacteria from the *Lachnospiraceae* family.[29] Mice placed on a low-potassium diet for 28 days had increased markers of intestinal permeability and bacteria translocation from the gut to other sites (e.g., mesenteric lymph nodes).[30] An important point to consider is that certain types of food rich in fermentable fiber are also rich in potassium—for instance, green banana flour and beans—thereby being a confounding factor in some studies.

Epigenetic modifications and their association with the SS phenotype

Epigenetic mechanisms may play an important role in the development of SS hypertension. Epigenetic modifications via DNA methylation, histone modifications, microRNAs, or chromatin modifications respond to high-sodium intake by altering the expression of candidate genes, without changes in the underlying DNA sequence and their downstream signaling pathways, thus leading to SS hypertension.[31,32] DNA methylation, a major type of epigenetic modification, may exhibit stable, long-lasting effects. In Dahl SS hypertension, *de novo* DNA methylation in the renal medulla contributed to the development of sodium-induced hypertension.[31] Renal expression of DNA methyltransferase 3a was higher in excessive sodium (4%)–fed Dahl SS rats, whereas no difference occurred in DNA methyltransferase 3a expression between rat strains on the low-salt diet. Moreover, hypermethylation of differentially methylated regions was specific to the infiltrating kidney T cells of Dahl SS rats on high-sodium intake.[33] Inhibition of DNA methyltransferases blunted sodium-induced hypertension, associated with reduced immune-cell infiltration in the kidney, indicating that DNA methylation plays a functional role in SS hypertension.

Environmental factors (e.g., nutrition and stress) during pregnancy contribute to the development of SS hypertension through epigenetic mechanisms. Aberrant DNA methylation contributes to prenatal programmed hypertension in offspring (F1) of pregnant mothers receiving a low-protein diet. Angiotensin II type 1a (AT1a) receptor gene DNA was undermethylated in the hypothalamus of offspring on a low-protein diet. This undermethylation was associated with reduced DNA methyltransferase 3a expression and activity and, in turn, increased hypothalamic AT1a receptor activity, leading to SS hypertension through kidney sympathetic overactivity (Figure 3).[34] Prenatal lipopolysaccharide exposure induces transgenerational transmission of SS hypertension by histone modification.[35] H3K9me2 (an epigenetic modification to the DNA packaging protein histone H3) was downregulated in the kidneys of F4 and F5 offspring, and this

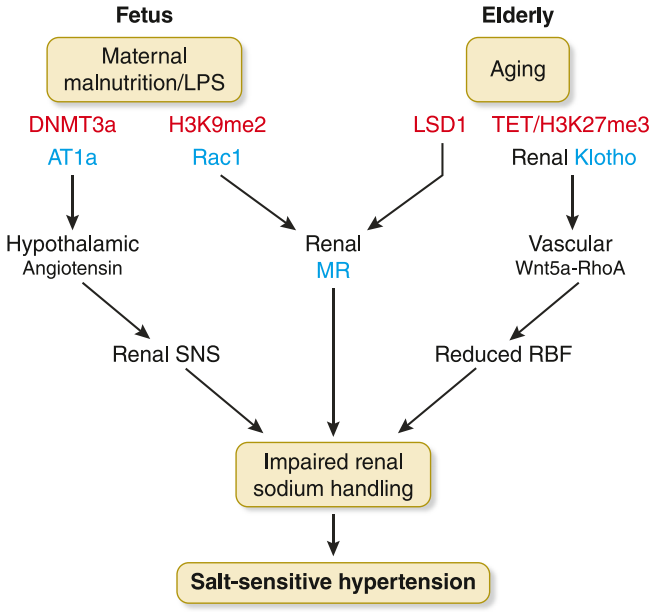

Figure 3 | Epigenetic modulations of salt-sensitive hypertension in the fetus and the elderly. Maternal malnutrition during pregnancy induces upregulation of angiotensin receptor 1a (AT1a) receptor gene by aberrant DNA methylation, and increased AT1a receptor activity in the hypothalamus develops prenatally programmed hypertension through renal sympathetic overactivity. Maternal lipopolysaccharide (LPS) exposure during pregnancy induces upregulation of Ras-related C3 botulinum toxin substrate 1 (Rac1) through histone modification across generations, resulting in sodium-induced activation of the Rac1–mineralocorticoid receptor (MR) pathway in the kidney and the development of salt-sensitive hypertension in F4 and F5 offspring. Lysine-specific histone demethylase-1 (LSD1) deficiency modifies the age effect on blood pressure salt sensitivity and develops salt-sensitive hypertension by a ligand-independent activation of MR. Aging induces Alpha-Klotho anti-aging protein (Klotho) deficiency in the kidney by aberrant DNA methylation and histone modification of the Klotho gene, and reduced circulating Klotho levels activate the vascular Wingless-related integration site 5a-Ras homolog family member A (Wnt5a-RhoA) pathway and vasoconstriction, developing salt-sensitive hypertension through decreased renal blood flow (RBF) and impaired renal sodium handling. DNMT3a, DNA methyltransferase 3 alpha; H3K9me2, histone H3 dimethyl Lys9; H3K27me3, histone H3 trimethyl Lys27; SNS, sympathetic nervous system; TET, ten-eleven translocation.

was accompanied by reduced recruitment of H3K9me2 to the Ras-related C3 botulinum toxin substrate 1 (Rac1) promoter. Given that Rac1 is a potent activator of mineralocorticoid receptor (MR) signal transduction, sodium-induced activation of the Rac1–MR pathway leads to SS hypertension through impaired kidney sodium handling (Figure 3).[35,36]

During the past few decades, the relationship among genes, epigenetic regulation, and age has been the focus of extensive research. Lysine-specific histone demethylase-1 (LSD1) is an epigenetic regulator of gene transcription that removes methyl groups from Lys4 and Lys9 of histone H3. LSD1 expression is modulated by dietary sodium intake; a high-sodium diet decreases the protein expression of LSD1 in mouse kidney. An LSD1 risk allele in humans and LSD1 deficiency ($LSD1^{+/-}$) in mice led to increased salt sensitivity with aging and the development of SS hypertension in the elderly.[37,38] $LSD1^{+/-}$ mice on high-sodium intake have hypertension, increased urinary potassium excretion, and increased levels and activation of MR, despite having reduced urinary aldosterone excretion. Treatment with the MR antagonist eplerenone improved hypertension and kaliuresis in these mice, suggesting that ligand-independent activation of MR is the underlying cause of this LSD1 deficiency–mediated phenotype.[38] According to the molecular mechanism by which LSD1 deficiency induces overactivation of the MR pathway, LSD1 has been postulated to act as a transcription repressor at H3K4 of the gene encoding MR, which can activate MR independently of aldosterone (Figure 3).

Alpha-Klotho (Klotho), an anti-aging protein, is mainly produced in the kidney, and is secreted into the blood. Circulating Klotho serves as a hormone and acts on distant organs. Klotho levels in the kidney and blood decrease with age. In the kidneys of aged mice with salt-induced hypertension, the Klotho gene is methylated by alteration of DNA demethylation with the ten-eleven translocation enzymes, resulting in reduced expression of Klotho.[39] Sodium loading under Klotho deficiency activates the vascular Wnt5a-RhoA noncanonical pathway, leading to the development of SS hypertension by vasoconstriction and reduced kidney blood flow.[40] Treatment of aged mice with the DNA demethylase activator compound H induced Klotho demethylation and reversed the age-related decrease in Klotho levels in both kidneys and blood, and resulted in significant BP reductions.[39] This finding suggests that Klotho deficiency owing to aberrant DNA methylation contributes to aging-associated hypertension in mice. In addition, H3K27me3 contributes to decreased Klotho expression in the kidneys of aged mice.[41] Taken together, epigenetic modulations including aberrant DNA methylation and histone modifications are involved in the development of SS hypertension induced by maternal malnutrition, lipopolysaccharide exposure in the fetus, and aging in the elderly (Figure 3).

Effects of new drugs on salt-sensitive hypertension

Expanding insight into the mechanisms of SS hypertension also helps explain the BP-lowering effects of recently introduced cardiovascular drugs (Figure 4).[42–50] We discuss below 3 of these drugs—sodium–glucose cotransporter 2 (SGLT2) inhibitors, nonsteroidal MR antagonists, and aldosterone synthase inhibitors (ASIs)—that have shown positive effects on SS hypertension in large randomized clinical trials.

SGLT2 inhibitors ("gliflozins") can improve cardiovascular and kidney outcomes in patients with CKD or heart failure with or without type 2 diabetes. Improvement of SS hypertension is one of the possible explanations for the beneficial effects of SGLT2 inhibitors. A systematic review showed that the antihypertensive effect of SGLT2 inhibitors is a class effect and that these drugs reduce 24-hour ambulatory systolic and diastolic BP by 3.76 mm Hg and 1.83 mm Hg, respectively.[51] A dedicated BP trial showed that 12-week treatment with empagliflozin in patients with type 2 diabetes receiving stable antihypertensive therapy reduced nighttime systolic BP (by 6.3 mm Hg), body weight, and natriuretic peptide levels, suggesting an effect on extracellular volume.[52] The BP-lowering effects of SGLT2 inhibitors are also consistently observed in animal models. In normal C57BL/6 mice, SGLT2 inhibition induced acute natriuresis that is mediated by the sodium–hydrogen exchanger 3 (NHE3) in the proximal tubule, and lowered BP, with a reduction in extracellular volume despite a higher level of renal renin expression.[42] SGLT2 inhibitors also can reverse the sodium-retaining tendency in diabetes, heart failure, or hypertension. In diabetic mice, empagliflozin increased the phosphorylation of NHE3 (indicating lower activity), an effect that was absent in nondiabetic mice.[42] Empagliflozin also upregulated the scaffolding protein membrane–associated protein 17, which may explain the SGLT2–NHE3 interaction.[43] SGLT2 and NHE3 also were both upregulated in a nondiabetic rat model of heart failure, and treatment with empagliflozin reversed this.[53] Another finding in diabetic mice is dysregulation of Kelch-like 3 in the distal convoluted tubule, which increases the activity of the sodium–chloride cotransporter.[54] This effect was reversible by ipragliflozin and suggests that SGLT2 inhibitors also can exert diuretic effects in the distal tubule. In a recent kidney biopsy study of patients with early-onset type 2 diabetes, SGLT2 inhibitors reduced the mammalian target of rapamycin complex 1 (mTORC1).[44] This finding is likely also relevant for SS hypertension in diabetes, as mTORC1 inhibition by rapamycin attenuates sodium-induced hypertension.[45] In Dahl SS rats on an excessive-sodium (4%) diet, dapagliflozin reduced BP and caused a left shift of the pressure-natriuresis curve (Figure 1), but it had no effect on the renin–angiotensin system or kidney sodium transporters, including NHE3 and the sodium–chloride cotransporter.[46] In another study using the same model, SGLT2 inhibitors reduced salt-induced vasoconstriction by inhibiting vascular cytoplasmic calcium increase; this effect was mediated by transient receptor potential channel 3 and sodium–calcium exchanger 1.[55] In addition to effects on kidney sodium transport and vascular tone, SGLT2 inhibitors may exert their effects also by inhibiting the sympathetic nervous system. In a mouse model of

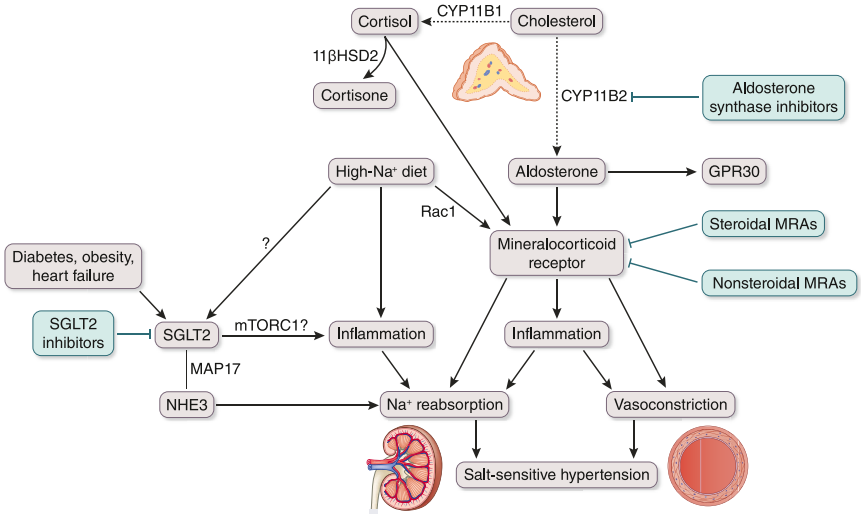

Figure 4 | New drugs targeting salt-sensitive hypertension. The figure focuses on 2 pathways that contribute to salt-sensitive hypertension and have been targeted recently by novel cardiovascular drugs (blue shading). The first pathway (left side) includes the sodium–glucose cotransporter 2 (SGLT2). SGLT2 is expressed in the kidney proximal tubule and is upregulated by diabetes, obesity, and heart failure. SGLT2 inhibitors improve cardiorenal outcomes in patients with chronic kidney disease and heart failure with or without diabetes. SGLT2 inhibitors also improve salt-sensitive hypertension, although whether a high-sodium (Na^+) diet by itself can upregulate SGLT2 is not clear. The acute natriuretic effect of SGLT2 inhibitors is mediated by sodium–hydrogen exchanger 3 (NHE3).[42] The interaction between SGLT2 and NHE3 is likely mediated by membrane-associated protein 17 (MAP17), a major scaffolding protein.[43] SGLT2 upregulation also promotes inflammation in kidney cells, which is likely mediated by the mammalian target of rapamycin complex 1 (mTORC1).[44] Both activation of mTORC1 and inflammation in general can further stimulate Na^+ reabsorption.[45] SGLT2 inhibitors may also improve salt-induced vasoconstriction (not depicted).[46] The second pathway (right side) includes the mineralocorticoid receptor (MR). The MR can be activated by its ligands aldosterone and cortisol. In the presence of 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2), however, cortisol is rapidly converted to inactive cortison. A high-Na^+ diet by itself can also activate the MR through the small GTPase Ras-related C3 botulinum toxin substrate 1 (Rac1). MR activation leads to Na^+ reabsorption, vasoconstriction, and inflammation. Aldosterone can also activate the G protein-coupled receptor GPR30, which causes rapid effects on vascular contractility.[47] The effects of aldosterone and the MR can be inhibited by, respectively, aldosterone synthase inhibitors (ASIs) and mineralocorticoid receptor antagonists (MRAs). ASIs selectively block the enzyme aldosterone synthase (CYP11B2) but leave the homologous cortisol synthase (CYP11B1) unaffected.[48] In addition to the steroidal MRAs spironolactone and eplerenone, the nonsteroidal MRA finerenone has been developed. This drug has been shown to improve cardiorenal outcomes in patients with diabetes and chronic kidney disease and may cause hyperkalemia less often.[49,50]

neurogenic hypertension, chemical denervation reduced BP and SGLT2 protein expression. In turn, SGLT2 inhibition reduced BP, with accompanying reductions in kidney tyrosine hydroxylase, norepinephrine, and noticeably, expression of IL-6 and IL-10.[56] This study also suggests that improved vasorelaxation plays a role in the SGLT2 inhibition–induced BP effects,[22] whereas human data indicate that reduced tissue sodium storage may explain BP changes.[57] Together, these studies suggest that SGLT2 inhibitors improve SS hypertension by affecting nearly all factors, as summarized in Figure 1. Future studies should clarify whether SGLT2 inhibitors have a universal effect on these BP- and sodium homeostasis–related systems or whether the effects rather are selective and dependent on the underlying disease.

For decades, blocking the sodium-retaining effects of aldosterone via its MR has been possible with steroidal MR antagonists such as spironolactone and eplerenone. These drugs are, therefore, successfully used in treatment of conditions characterized by sodium retention, including resistant hypertension, heart failure, and CKD. Yet, their use is limited by hyperkalemia, which is the logical consequence of the fact that MR antagonism blocks sodium–potassium exchange. Moreover, spironolactone, in contrast to eplerenone, is nonselective, and can also bind to other steroid receptors, inducing gynecomastia.

Two recent developments may help overcome these issues. First, a nonsteroidal MR antagonist has been developed—finerenone—that is purported to exert the same beneficial effects as the classical MR antagonists, but with less hyperkalemia (Figure 4). Indeed, its cardio-renoprotective efficacy was shown in 2 large trials in patients with CKD and type 2 diabetes.[49,50] These beneficial effects occurred largely independently of BP, leading the authors to suggest that finerenone might act by improving myocardial, vascular, and kidney inflammation.[58] Yet, to what degree MR antagonism truly lowers tissue sodium content remains unclear.[59,60] Hyperkalemia during finerenone treatment still occurred, but given that head-to-head comparator studies versus spironolactone are lacking, the degree to which the frequency of hyperkalemia is reduced during finerenone treatment remains unclear. Finerenone is as potent as spironolactone, but it displays a lower level of lipophilicity and a higher level of polarity.[61] Assuming that these characteristics result in reduced kidney accumulation, the simplest explanation for the reduced frequency of hyperkalemia is diminished MR blockade at the level of the kidney. This diminished blockage

might also explain the modest BP-lowering effects of finerenone, at least when it is given at doses of up to 20 mg/d. An alternative explanation is that finerenone has differing effects on the interaction between the MR and its many cofactors.[62]

Second, selective ASIs are now becoming available (Figure 4). Previously, selective blocking of aldosterone synthase (CYP11B2) was difficult because it displays >93% homology with the enzyme-generating cortisol (CYP11B1). Baxdrostat, lorundrostat, and dexfadrostat are the first ASIs that can actually do this. Baxdrostat was shown to dose-dependently lower BP in patients with treatment-resistant hypertension, without affecting cortisol, while increasing serum potassium more frequently than placebo.[48] Here, an important point to emphasize is that MR antagonism upregulates renin, and thus would bring back the aldosterone level, as least partially, in an angiotensin II–dependent manner. ASI will prevent this ''aldosterone escape." Indeed, during baxdrostat treatment, the aldosterone level remained low, despite a rise in renin level. However, some caveats remain. Cortisol displays equal affinity for the MR, and the only reason that it does not activate this receptor (given its 1000-fold higher levels) is that 11ß-hydroxysteroid dehydrogenase-2 rapidly inactivates cortisol in the vicinity of the receptor. Nevertheless, when aldosterone is entirely absent (as it is in AS knockout mice), MR stimulation still occurs, presumably by cortisol and sodium/Rac1.[63] Furthermore, aldosterone also acts on non-MR, in particular GPR30.[47] This action will still occur during MR antagonism, but will no longer occur during ASI. Taken together, these findings indicate that MR antagonism blocks MR activation irrespective of its agonist (aldosterone or cortisol) but would facilitate activation of non-MR by aldosterone. ASI results in diminished MR and GPR30 activation by aldosterone, but it is unable to block MR activation by cortisol or sodium/Rac1.

Conclusion

The number of uncovered novel mechanisms that explain the SS BP phenotype seems overwhelming, complicating mutual connections of each element in a straightforward way. The current evidence indicates that besides kidney-centered mechanisms, vasoconstrictive mechanisms also are relevant for both the understanding and treatment of this BP phenotype. Recent uncovered players include the gut-microbiome, endothelium, non-osmotic sodium storage, skin, the mononuclear phagocytic and acquired immune system, and epigenetic modifications. Future studies will reveal the degree to which novel drugs interfere with these phenomena.

DISCLOSURE

All the authors declared no competing interests.

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