Review Article

Mechanistic Issues in Salt Sensitive Hypertension

Prem Ratan Degawat
Consultant, Interventional Cardiology, *Department of Cardiology, Eternal Heart Care Centre and Research Institute, Jaipur, Rajasthan, India*
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ABSTRACT

Salt sensitivity is defined as rise in blood pressure (BP) by 5% or more from baseline after high salt diet than that during a low salt diet. The mechanism of salt sensitivity is multifactorial with a complex conceptual framework. Renin-angiotensin aldosterone system (RAAS) is crucial in maintaining sodium equilibrium in body. It has been reported that blunted renin response to salt depletion is responsible for salt sensitivity. Adrenal and sympathetic nervous system, through glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) pathways play a key role in salt sensitivity. Other mechanisms are endothelial dysfunction, hyperinsulinemia, CYP450 derived metabolites of arachidonic acid, kallikrein-kinin system, and impaired ion transport through the kidney. Recent studies have identified newer causative mechanism including sodium storage, vascular endothelial dysfunction, and innate immunity in salt sensitivity.

Keywords: Aldosteron, Blood pressure, Renin-angiotensin aldosterone system.

INTRODUCTION

Hypertension has complex pathophysiology determined by genetic and environmental factors. Dietary salt intake is one of the leading risk factor for hypertension. In developed countries the prevalence of hypertension is around 30% of world population due to recent increase in dietary salt intake.[1-3] Various clinical trials[4-9], animal studies[10-12], and observational studies[13-14] have shown causal relationship between dietary salt intake and hypertension. Multiple evidences suggest that blood pressure (BP) response to dietary salt intake vary considerably among individuals and this phenomenon is described as salt sensitivity of BP.[15-17] Although, there is no universal definition of salt sensitive hypertension it is arbitrarily defined as increase in BP of more than 5% or greater from baseline after high salt diet than that during low salt diet. Overall salt sensitivity have incidence around 51% in patients of hypertension and 26% in normotensive people.[17,18]

MECHANISMS OF SALT SENSITIVITY

Mechanism of salt sensitivity is multifactorial and most of conceptual framework is derived by work of Guyton and coworkers. Accordingly it is lack of regulation (clamping) between the natriuretic and anti-natriuretic mechanism of body (Figure 1).[19-22] Recent genetic research has identified newer causative mechanism including sodium storage, regulation of regional blood flows, vascular endothelial dysfunction, and innate immunity.[23,24]

Renin-angiotensin aldosterone system (RAAS) pathway:

RAAS is crucial in maintaining sodium excretion and equilibrium and is ultra-sensitive to change in body sodium level.[25,26] Parfrey and coworkers revealed that blunted renin response to salt depletion is the major cause of reduction in BP in salt sensitive hypertensive patients and this observation was supported by the fact that Salarasin reduce BP in preserved renin responsive and not in the blunted renin responsive.[27,28] They also showed that diminished renin, angiotensin-II, and aldosterone responses to salt depletion were more prominent in blacks than in whites and in hypertensive whites than in normotensive whites and observed greater BP decrease during salt depletion in blacks than in whites and in hypertensive compared with normotensive whites.[29,30] Various studies on salt sensitive BP have shown that in these patients renin response to salt depletion and salt loading is blunted and this established that blunted renin-angiotensin system is a phenotypic characteristic of salt sensitive BP.[31-35]

Local renal RAAS mechanism:

It has been revealed that local RAAS system at kidney also independently regulate sodium excretion.[36-37] It is observed by Crowley et al[38] that AT1 receptor in kidney is responsible for angiotensin II mediated hypertension though increased tubular sodium reabsorption, this may contribute to salt sensitive BP.

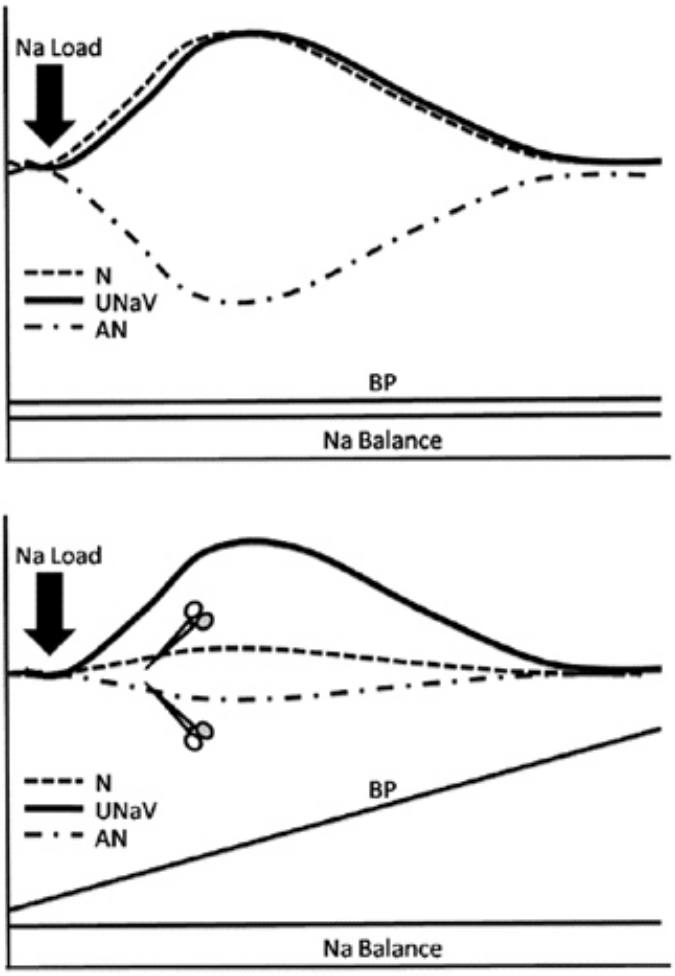

Figure 1: (a) Handling of a sodium load (Na load, arrow) by stimulation of natriuretic systems (N) and inhibition of antinatriuretic systems (AN); (b)The theoretical framework by which "clamping" of N, AN, or both at inappropriate levels (poorly stimulated N systems or poorly inhibited AN ones) leads to elevation of BP and pressure natriuresis.

Adrenal and sympathetic nervous system:

It has been revealed that sodium handling at proximal tubule and other segment including distal tubule plays significant key role in salt sensitive BP.[39] The adrenal hormones, aldosterone, and cortisol by acting on their receptors, the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) regulate homeostasis by sodium reabsorption in distal tubules. Studies have identified two novel pathways that are involved in abnormal handling of renal sodium excretion in distal tubules.[40,41]

Mineralocorticoid receptor activation pathway:

Dietary sodium intake regulates the plasma level of aldosterone by change in plasma level of RAAS so that homeostasis of sodium is maintained. In primary aldosteronism, increase tubular sodium reabsorption through MR receptor activation leads to salt-sensitive hypertension. In rodent model continuous infusion of aldosterone and salt loading mimics like primary aldosteronism and on low salt however aldosterone induced hypertension was abolished. This suggest that salt has a key role in aldosterone mediate activation of sodium absorption.[42] Studies in rodent models have shown that in obesity lack of feedback regulation of aldosterone by salt is abolished and this may cause salt-sensitive hypertension. In a study, resistant hypertensive obese patients responded well to spironolactone.[43-48] Three factors activate MR in a ligand independent manner: cAMP dependent protein kinase A reactive oxygen species, and a member of Rho-guanine triphosphate hydroxylase family named Rac1 identified by Shibata S et al.[49] Adrenal Rac1-MR-Sgk1-NCC/ENaC p (Rac1-mineralocorticoid receptor-glucocorticoid-inducible kinase 1-sodium chloride co-transporter/epithelial sodium channels pathway) activate MR receptor and regulate sodium homeostasis.

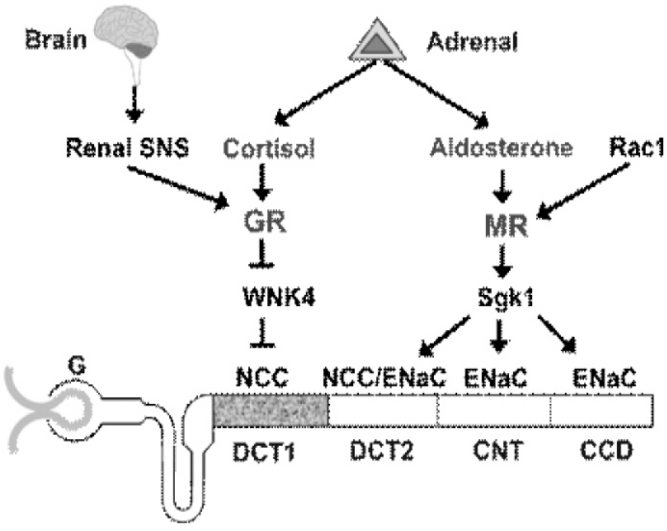

Figure 2: The adrenal glands and central renal SNSs are involved in the development of salt-sensitive hypertension.

Glucocorticoid receptor activation pathway:

Another key factor that regulates the sodium reabsorption is renal sympathetic nervous system (SNS) by GR receptor. Rodent study has revealed that renal SNS activity is increased by salt loading and this is responsible for salt sensitive hypertension by reduced renal flow, increased renin secretion, and increased tubular reabsorption.[50,51] In obese hypertensive patients and animals, increased SNS activity in kidney is responsible for SSBP and renal denervation not only reduce BP in resistant hypertension but obese patients also respond positively.[52-54] However, it remains unclear how increased SNS activity in the kidney enhances tubular sodium reabsorption and leads to the development of salt-sensitive hypertension.

Thus, the control of renal sodium regulation and BP maintenance is primarily regulated by NCC (sodium chloride co-transporter). NCC activation is responsible for salt-sensitive hypertension in rodent models through two novel pathways: the Rac1-MR-Sgk1-NCC and beta adrenergic recpetor-GR-WNK4-NCC pathways. Sodium reabsorption is increased by an abnormal Rac1-MR pathway through activation of NCC in the DCT2 segment in addition to activation of epithelial sodium channels (ENaCs) in the DCT2, connecting tubule and cortical collecting duct segments, whereas an aberrant b-AR-GR-WNK4 pathway activates NCCs in the DCT1 segment (Figure-2).[48,55] This mechanism is identified in animals and is synonymous to the mechanism found in human salt sensitive BP.[56] These two pathways can be a potential target for therapeutic management of salt sensitive BP and cardiorenal injury.

Endothelin system and endothelial dysfunction:

Normally urine endothelin correlate negatively with BP in normal as well as hypertensive subjects but positively with sodium excretion during a salt load, and in salt sensitive hypertensive patients. Salt sensitive hypertensives have diminished levels of urinary endothelin, which may contribute to their impaired natriuresis in response to a salt load.[57]

Endothelium, by secreting both vasodilating and vasoconstrictive substance, regulate vascular tone and blood pressure. The main vasodilating substances are nitric oxide (NO) and prostacyclin.[58] In clinical studies it has been revealed that in salt sensitive hypertensive patients, nitric oxide production is defective that contributes to salt sensitive BP.[59] In response to salt loading, NO secretion is increased from kidney and peripheral vascular endothelium for the regulation of BP and sodium balance.[60] Normotensive salt sensitivity in black populations is associated with an increase in plasma asymmetric dimethyl arginine, an endogenous competitive inhibitor of endothelial NO synthase, which in turn inhibits vasodilation. Studies have shown higher concentrations of asymmetric dimethyl arginine, lower availability of NO, and an increase in BP in the study population after 7 days of a high-salt diet.[61-63] A similar situation may occur in patients with type 2 diabetes mellitus who have microalbuminuria. They are more salt sensitive than those without microalbuminuria and exhibit lower urinary excretion of NO.[64] Abnormality in NO production may be present in salt sensitive subjects. For example, salt sensitive blacks shows greater BP reduction and smaller increase in renal blood flow when given intravenous l-arginine compared with salt resistant or normotensive subjects. This NO deficit may be responsible for their endothelial dysfunction, which in turn may contribute to salt sensitive BP by impeding vasodilation after a salt load.[65]

Atrial natriuretic peptides (ANP):

ANP is secreted by atrial myocytes, has diuretic, natriuretic, and hypotensive property. It influence glomerular filtration rate and inhibit aldosterone secretion by adrenocortical cells.[66] Campese et al[67] have shown that on high-salt intake, plasma levels of atrial natriuretic peptide were lower in salt-sensitive black patients than in their salt-resistant black. High salt intake did not cause any changes in plasma levels of atrial natriuretic peptide in hypertensive white patients, suggesting that decreased secretion of atrial natriuretic peptide is a potential cause of salt sensitivity in black populations. These observations clarify the fact that deficiency in ANP expression is responsible for salt sensitive hypertension.

Hyperinsulinemia:

It has been revealed that normotensive and hypertensive salt-sensitive subjects and hypertensive rat strains are more insulin resistant compared to salt resistant subject independent of BP.[68,69] However it is still not clear that the stimulatory effect of insulin on tubular sodium reabsorption, sympathetic activity, or vascular remodelling

contributes to the development of salt-sensitive hypertension. However, insulin levels accentuate the effect of risk alleles of CYP4A11 in determining salt-sensitivity in humans.[70]

CYP450-derived metabolites of arachidonic acid:

Two major metabolite of arachidonic acid 20 hydroxyl eicosatetraeonic acid (20-HETE) and epoxy eicosatrienoicacids (EETs) are vasoconstrictor and vasodilator respectively. These are natriuretic agents in different parts of the renal tubule acting on different transporters. It has been observed that reduced synthesis of 20-HETE associated with salt-sensitivity in rats.[71-72] Salt sensitive subject don't have reduced 20-HETE but have reduced EETs during low salt intake compared to salt resistant subjects.[73,74]

The kallikrein-kinin system:

In this system, vasodilator bradykinin is produced by the enzyme kallikrein. Urinary kallikrein excretion was observed to be lower in salt-sensitive black individuals than in salt-sensitive white subjects. Further studies are required to elucidate how this system functions and how it may be associated with salt sensitivity in black subjects.[75]

Sodium and baroreceptors:

Baroreceptors located on arch of aorta and carotid sinus are stimulated upon increase in blood pressure, which results in reduction in sympathetic outflow to resistance arteries and heart; this ultimately reduce blood pressure to normal levels.[76,77] It is observed that these receptors are protecting in the effect of dietary sodium loading and have a key role in salt-sensitive hypertension.[78]

Impaired ion transport:

Kidney has a key role in regulation of ion transport and its thick ascending limb of Henle's loop where significant amounts of salt, instead water, are reabsorbed, a process mediated by an Na^+-K^+. $2Cl^-$ cotransporter and a sodium pump (Na-K ATPase).[79] Aviv et al[80] have observed that enhanced activity of the Na-K-2Cl cotransporter in the thick ascending limb of Henle's loop is the major factor contributing to the high prevalence of salt sensitivity in black populations. In studies, sodium pump activity is lower in black individuals but definitive association with salt sensitivity is not established.[81-82]

Salt sensitivity and immune system:

Recent research has revealed that transforming growth factor (TGF) has a key role in hypertension. Salt intake induce cutaneous lymphangiogenesis through tissue macrophages, this alter endothelial cell function and leads to increase secretion of NO, TGF. In endothelial dysfunction, reduced NO could not counter balance the TGF, and leads to hypertension.[83] Guzik et al found that recombi-nase-activating gene (RAG-1 -/ -) mice, which lack both T and B cells showed a blunted increase in BP and reduced vascular oxidative stress in response to desoxy corti-costerone acetate (DOCA) salt.[84] Observation also support a role for adaptive immunity and T cell function in the development of salt-sensitive hypertension.[85] Rudemiller et al[86] provided the evidence that the mutation of SH2B3 (LNK) significantly attenuated hypertension via immune cell function and renal injury in Dahl salt sensitive hypertensive rats. Role of immune function in hypertension is widely accepted, could be potential therapeutic target.

Sodium storage:

Recent studies have shown that non osmotic salt accumulation in the skin interstitium, the endothelial dysfunction caused by the deterioration of vascular endothelial glycocalyx layer, and the epithelial Na+ channel on the endothelial luminal surface (EnNaC) also play crucial role in storage of salt and salt sensitivity.[87]

Human genes and salt sensitivity:

Human genetics have an important role in ethnic difference in salt sensitivity. This accounts for interracial differences in the frequency of salt-sensitive HTN. Miller et al[88] observed that the change in BP between random-sodium and low sodium diets among white US families and they found a higher correlation in monozygotic pairs compared with sibling pairs: 0.72 for systolic BP (SBP), 0.62 for diastolic BP, and 0.68 for mean BP in monozygotic twins compared with 0.50, 0.33, and 0.36, respectively, for siblings. Svetkey et al[89] showed that 26% to 84% of the variability in mean arterial pressure and 26% to 74% of the variability in systolic BP response to sodium loading in black populations can be explained by genetic factors. The gene frequency of various gene polymorphisms of salt-sensitive HTN such as -3 subunit of G-protein (GNB3), angiotensinogen gene, alpha-adducin gene, aldosterone synthase gene promoter were in higher frequency in Japanese compared to Caucasians.[90] Various studies have

revealed that multiple genetic pathways have a crucial role in individuals salt sensitivity but molecular mechanism are still not fully elucidated.[91-93]

CONCLUSION

Salt sensitivity is independent risk factor for cardio-vascular disease. Even normotensive salt sensitive individuals are at high cardiovascular risk and lower survival rate, as BP eventually rises later in life with high salt diet. Studies have reported that salt sensitivity is associated with increased mortality risk and normotensive salt sensitive subjects had similar cumulative mortality as that of hypertensive patients.[94] Studies have also shown a strong relationship between salt sensitivity and insulin resistance leading to metabolic syndrome and cardio-vascular disease.[95-96] Salt sensitivity is a multifactorial entity with strong determinants are genetic factors, race, ethnicity, age, gender, body mass index, associated co-morbidities, and diet. The present review highlights the biochemical and genetic pathways of importance.

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Corresponding Author

Dr Prem Ratan Degawat, Consultant, Interventional Cardiology, Department of Cardiology, Eternal Heart Care Centre and Research Institute, Jagatpura Road, Jawahar Circle, Jaipur, Rajasthan, India. PIN-302017.

email: drpremratan@gmail.com