Current Understanding of Pressure Natriuresis

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Pressure natriuresis refers to the concept that increased renal perfusion pressure leads to a decrease in tubular reabsorption of sodium and an increased sodium excretion. The set point of blood pressure is the point at which pressure natriuresis and extracellular fluid volume are in equilibrium. The term "abnormal pressure natriuresis" usually refers to the expected abnormal effect of a certain level of blood pressure on sodium excretion. Factors that cause abnormal pressure natriuresis are known. Sympathetic nerve system, genetic factors, and dietary factors may affect an increase in renal perfusion pressure. An increase in renal perfusion pressure increases renal interstitial hydrostatic pressure (RIHP). Increased RIHP affects tubular reabsorption through alterations in tight junctional permeability to sodium in proximal tubules, redistribution of apical sodium transporters, and/or release of renal autacoids. Renal autocoids such as nitric oxide, prostaglandin E2, kinins, and angiotensin II may also regulate pressure natriuresis by acting directly on renal tubule sodium transport. In addition, inflammation and reactive oxygen species may mediate pressure natriuresis. Recently, the use of new drugs associated with pressure natriuretic mechanisms, such as angiotensin receptor neprilysin inhibitor and sodium glucose co-transporter 2 inhibitors, has been consistently demonstrated to reduce mortality and hypertension-related complications. Therefore, the understanding of pressure natriuresis is gaining attention as an antihypertensive strategy. In this review, we provide a basic overview of pressure natriuresis to the target audience of nephrologists.

Key Words: Blood pressure, Hypertension, Kidney, Pressure natriuresis, Sodium excretion

INTRODUCTION

The relationship between renal perfusion and sodium excretion has long been considered crucial for blood pressure (BP) homeostasis. Pressure natriuresis (PN) refers to an increase in sodium excretion when the renal perfusion pressure increases[1-3]. When renal arterial pressure rises, the kidneys respond by increasing sodium excretion and decreasing the amount of extracellular fluid to maintain normal sodium balance and systemic arterial pressure. Therefore, the set point of BP is the point at which PN and extracellular fluid volume are in equilibrium. When the pressure-natriu-

retic response is impaired, BP is uncontrolled, making hypertension a disease of the kidney. Thus, abnormal PN refers to an abnormal effect of a certain level of BP on sodium excretion.

Salt sensitivity, characterized by significant changes in BP in relation to the sodium content of the diet, is associated with hypertension. In salt-sensitive patients, the slope of the pressure-natriuretic relationship is less steep and shifts to the right[4]. As a result, the response of the BP to changes in sodium intake is greater, that is, the salt sensitivity increases. Therefore, higher BP levels are required to increase sodium excretion and maintain sodium balance.

Recently, the use of new drugs associated with pressure-

natriuretic mechanisms has consistently been demonstrated to reduce mortality and hypertension-related complications. Therefore, the understanding of PN is gaining attention as an antihypertensive strategy. This review aims to provide a basic overview of PN to the target audience of nephrologists.

What is Salt Sensitivity in a Clinic?

Kawasaki et al. first suggested that BP responses to changes in salt intake vary[5]. Later, Weinberger et al. recognized the heterogeneity of BP responses to salt and proposed the concept of salt sensitivity[6]. Houston reported that high BP treatment with moderate sodium restriction of 70 mmol/day was effective, especially in patients with known salt-sensitive hypertension[7].

Salt sensitivity refers to a physiological characteristic present in humans, whereby BP changes in parallel with changes in salt intake. It can be caused by a failure of the natriuretic mechanism or other factors, including age, sex, and comorbidities. High sodium intake also accelerates the prevalence of salt-sensitive hypertension. The incidence of salt sensitivity is estimated to be 51% in hypertensive patients and 26% in normotensive individuals[6]. BP responses to dietary salt intake vary between individuals with high BP and those with normal BP. Salt-sensitive patients show sharp changes in BP with acute or chronic salt depletion or repletion. As described above, the slope of the pressure-natriuretic relationship is less steep and shifted to the right in salt-sensitive patients (Fig. 1)[4]. Therefore, higher BP levels are required to maintain sodium balance.

Previous studies have reported that salt sensitivity is associated with increased cardiovascular disease incidence and decreased survival in both normotensive and hypertensive individuals[8,9]. Therefore, it is important to understand and suspect salt sensitivity when managing patients with hypertension. Salt sensitivity plays a significant role in the pathophysiology of BP, and although various diagnostic approaches have been proposed to date, there is no consensus on the diagnostic criteria. In addition, the exact mechanisms that explain this association are not yet elucidated. Recently, Titze et al. suggested that sodium can accumulate without accompanying water retention and that the
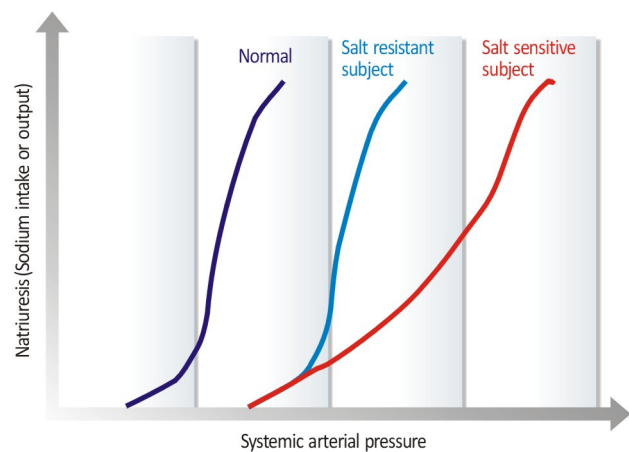

Fig. 1. The relationship between blood pressure and natriuresis. In salt-resistant subject, the pressure-natriuretic relationship shifts to the right without change in the slope. In salt-sensitive subject, the slope is declined and higher blood pressure levels are required to maintain sodium balance through increased sodium excretion.

skin is a major site for osmotically inactive sodium storage[10]. In addition, several studies suggested that the endothelial surface layer facing the blood stream may be another important non-osmotic sodium storage compartment[11-13]. These new concepts highlight that sodium homeostasis and salt sensitivity are associated with not only renal dysfunction but also endothelial dysfunction. Further studies are needed to assess the extent of alterations in the sodium buffering capacity of the skin interstitium and to develop therapeutic strategies to modulate endothelial dysfunction.

Mechanism of PN

It is well known that PN plays an important role in BP control. The mechanism of PN refers to the effect of arterial pressure on renal sodium excretion, and PN is mainly mediated by the inhibition of tubular sodium reabsorption[3]. Although neurological, hormonal and vascular factors have been the dominant regulators of arterial pressure, the exact mechanism of PN remains debatable[14,15].

As renal perfusion pressure increases, renal interstitial hydrostatic pressure (RIHP) increases (Fig. 2). Intrarenal mechanisms for decreased tubular reabsorption in response to an increase in renal perfusion pressure are associated with renal autacoids such as angiotensin II, nitric oxide, prosta-
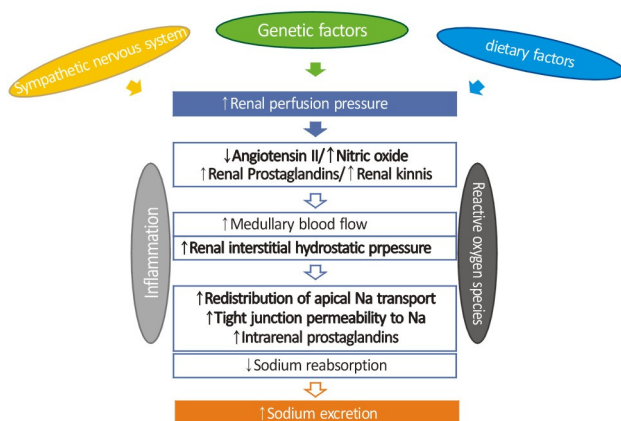
Fig. 2. The potential mechanism of pressure natriuresis.
Sympathetic nerve system, genetic factors, and dietary factors may affect an increase in renal perfusion pressure. An increase in renal perfusion pressure increases renal interstitial hydrostatic pressure (RIHP) through increases in nitric oxide, prostaglandin E2, and kinins, and decreases in intrarenal angiotensin II. An increase in RIHP without appreciable changes in total renal blood flow may be associated with an increase in renal medullary flow. Increased RIHP affects tubular reabsorption through alterations in tight junctional permeability to sodium in proximal tubules, redistribution of apical sodium transporters, and/or release of renal autacoids such as prostaglandin E2. Renal autocoids such as nitric oxide, prostaglandin E2, kinins, and angiotensin II may also regulate pressure natriuresis by acting directly on renal tubule sodium transport. In addition, inflammation and reactive oxygen species may mediate pressure natriuresis.

glandins, and renal kinins[16,17]. The renin-angiotensin system (RAS) is one of the most potent modulators of PN and consequently long-term BP control. Angiotensin II is a sodium-retaining hormone that acts through angiotensin I or II receptors and substantially alters PN, medullary flow, and RIHP[18,19]. An increase in renal perfusion pressure may mediate a decrease in sodium reabsorption by decreasing intrarenal angiotensin II and retracting sodium transport or reducing medulla vascular resistance. On the other hand, when renal perfusion pressure increases, nitric oxide, prostaglandin E2, and kinins are released. The increase in renal perfusion pressure enhances nitric oxide production, which directly inhibits tubular sodium reabsorption and indirectly increases medullary blood flow and RIHP. Therefore, the mechanism by which RIHP increases without changes in renal blood flow may be related to an increase in renal medullary flow as a result of a decrease in renal medullary vascular resistance

by nitric oxide. Although the exact mechanism by which RIHP affects tubular reabsorption is uncertain, it may be related to alterations in junctional permeability to sodium in proximal tubules, re-distribution of apical sodium transporters such as sodium/proton exchanger isoform 3 and the soium-phosphate co-transporter, and release of renal autacoids such as prostaglandin E2[20]. In addition, prostaglandin inhibition attenuates the natriuresis of elevated RIHP[21].

Abnormal PN

Preventing an increase in RIHP in response to an increase in renal perfusion pressure significantly attenuates PN. The term "abnormal PN" usually refers to the expected abnormal effect of a certain level of BP on sodium excretion. In other words, abnormal PN is defined as the presence of increased BP in the normal state of sodium balance. In hypertension, the PN mechanism is abnormal because sodium excretion is the same as that in normotension despite increased BP. In salt-sensitive subjects, the pressure-natriuretic relationship shifts to the right, and higher BP levels are required to maintain sodium balance through increased sodium excretion. Additionally, the combined effects of transient increases in BP, oxidative stress, inflammation, and local vasoconstriction can lead to pressure-natriuretic disorders. Abnormal PN can also be induced in many situations, including chronic kidney disease, salt retention, high salt intake, renal nerve activation, renal nitric oxide deficiency, adverse effects of medications on the kidneys, and ineffective diuretic usage.

Autoimmunity and hypertension

It has been suggested that T lymphocytes infiltrating the kidneys and arteries may play a role in improving BP. Heat shock protein (HSP) has been found to be overexpressed in target organs in several animal models of hypertension. Autoimmune reactivity to HSP70 in the kidney impairs PN and plays an important role in the pathogenesis of salt-sensitive hypertension[22].

Other perspectives on the etiology and pathogenesis

Recently, with increasing interest in the complex integrated mechanisms of salt sensitivity and PN, new insights

into the renal processing of sodium and salt sensitivity of BP have been presented from various perspectives[23].

1) Genetics

Many studies have been conducted to identify genes and single nucleotide polymorphisms (SNPs) that affect BP[24]. Although it is challenging to identify specific genes or markers for salt sensitivity in BP, previous studies have reported that SNPs in the sodium-bicarbonate co-transporter gene (SLC4A5) and SH2B adapter protein 3 genes are associated with salt-sensitive hypertension[25,26]. Recently, new evidence for BP-related genetic variations has been reported[27-29]. However, these studies failed to determine the salt sensitivity and molecular mechanisms of BP in test subjects.

It is clear that multiple genes influence BP and salt sensitivity; however, the evidence and precise mechanisms are limited. Therefore, further studies are needed to complement the understanding of hypertension and salt sensitivity from a genetic perspective.

2) Inflammation

Inflammatory cytokines are known to be elevated in patients with hypertension[30]. Various inflammatory mediators, such as recombination activating gene-1, interleukin (IL)-17A, interferon-gamma, and IL-1β, affect renal sodium transporters, sodium handling, and BP[31]. However, the role of inflammation in the salt sensitivity of BP has not been investigated in humans. There have been several animal studies on salt-sensitive hypertension, which is characterized by renal inflammation[32-35]. These studies suggest that renal immune cell infiltration and inflammatory cytokines influence renal sodium handling and promote salt-sensitive hypertension. They also showed that the suppression of renal immune cell infiltration promotes sodium homeostasis and normotension. Based on these studies, further investigations are needed for treating patients with salt-sensitive hypertension.

3) Dietary Intake

Dietary potassium levels affect sodium reabsorption by modulating the activity of sodium chloride cotransporters and epithelial sodium channels in the distal nephron, and a low potassium diet is associated with elevated BP and salt-sensitive hypertension[36]. Dietary fructose intake is also associated with BP[37]. An *in vivo* salt resistance study by Cabral et al. showed that dietary fructose supplementation before and during increased dietary salt intake induces the development of salt-sensitive hypertension[38]. Therefore, low potassium intake and high fructose and sodium intake promote the prevalence of salt-sensitive hypertension by modulating renal sodium transporter activity and expression, which induces renal sodium retention.

4) Reactive Oxygen Species (ROS)

Nitric oxide and ROS reciprocally alter PN, and this relationship in the kidneys is associated with hypertension[39]. Elevated renal ROS production may contribute to salt-sensitive hypertension by reducing sodium transport and filtration in the kidney, thereby promoting sodium retention. In addition, ROS may play an important physiological role in promoting renal excretion of sodium and maintaining salt resistance[40].

5) Sympathetic Nervous System (SNS)

Activated SNS by the effects of angiotensin II stimulates renal sodium reabsorption and elevates BP. Recent studies have reported that salt-sensitive hypertension is driven by an increased renal sympathetic release of norepinephrine[41]. However, there is a debate on the direct effects of sympathetic outflow. The effect of systemic and local release of norepinephrine on the regulation, expression, and activity of the sodium chloride cotransporter requires further investigation.

New Drugs for restoring Abnormal PN

Angiotensin receptor neprilysin inhibitor (ARNI) and sodium glucose co-transporter 2 (SGLT2) inhibitors are known to be involved in the mechanism of PN and continue to report promising results. Although their pharmacological effects are not well clear, they are widely used for controlling BP and improving long-term clinical outcomes. For practical clinical application, it is necessary to understand the basic

concepts of PN and these drugs.

1) ARNI

ARNIs are an emerging cardiovascular agents characterized by their dual action on the major regulators of the cardiovascular system, including the RAS and the natriuretic peptide system. Neprilysin is an endopeptidase responsible for the breakdown of the main natriuretic peptides: atrial natriuretic peptide, B-type natriuretic peptide, and C-type natriuretic peptide. Receptors of these natriuretic peptides generate cyclic guanosine monophosphates, which contribute to the regulation of systemic homeostasis and metabolism, including vasodilation, increased renal perfusion, natriuresis, antihypertrophic and antifibrotic actions, and reduced water and salt intake[42-46]. The dual effect of ARNI and angiotensin receptor blockade significantly affects the natriuretic peptide axis through its vasodilatory and natriuretic properties, along with inhibitory effects on endothelin, vasopre ssin, sympathetic activity, and renin-angiotensin-aldosterone system.

The key mechanism of the BP-lowering effect of ARNI is natriuresis[47,48]. Wang et al. conducted a trial to investigate the mechanisms of ARNI in lowering BP in salt-sensitive hypertensive patients[49]. They found that ARNI treatment increased 6- and 24-hour cumulative sodium excretion and urine excretion and had a BP-lowering effect. The authors suggested that the vasodilatory effect of natriuretic peptides could reset sodium and water homeostasis and prevent sustained natriuresis and diuresis in these patients. Through this mechanism, ARNI increases natriuresis despite the hypotensive effect, and the slope of PN becomes stiffer, which is likely to convert the salt-sensitive subjects shown in Fig. 1 to a salt-resistant direction. Although the rationale for approval of heart failure is based on the improvement of hard outcome indicators in patients with heart failure, changes in volume and functional parameters of echocardiography through improvement of BP and natriuresis are mentioned as major mechanisms. In addition to heart failure, the pressure-natriuretic curve is expected to change under the influence of ARNI in diseases with various abnormal pressure natriuretic responses such as hypertension, chronic kidney disease, and resistant hypertension. Further results

exploring the biologic effects of ARNI therapy on these disease are still pending.

2) SGLT2 Inhibitor

Excessively filtered glucoses are reabsorbed in the proximal tubule of the kidney via SGLT, increasing sodium reabsorption. SGLTs are located on the luminal surface of the proximal tubule epithelium and transport glucose into the cells against a concentration gradient by cotransporting sodium and glucose[50]. It is known that the reabsorption of glucose and sodium through SGLT2 is enhanced in diabetic patients. SGLT2 inhibitor, novel antidiabetic drugs, lower plasma glucose levels by blocking reabsorption of glucose in the proximal tubule, thus leading to excretion of glucose and sodium into the urine.

Initially, a diuretic effect of SGLT2 inhibitor was assumed to be from a mild osmotic diuresis from glycosuria. In addition to glycosuria, as sodium reabsorption in the proximal tubule decreases, distal sodium delivery increases. This signal enhances tubuloglomerular feedback through the macula densa, thereby constricting the afferent arteriole and reducing glomerular hyperfiltration. It significantly lowers the glomerulus pressure, preserving glomerular filtration rate in the long run. This mechanism has a protective effect on the kidneys. Thus, the effects of the SGLT2 inhibitor may affect the pressure natriuretic curve through increased natriuresis, BP reduction and weight loss, as well as glycemic control. Like ARNI, SGLT2 inhibitor can make the slope of the PN curve in Fig. 1 stiffer and left-shifted.

Sympathetic nerves innervate the proximal tubules of the kidney and hyperactivity of SNS plays an important role in the pathophysiology of arterial hypertension. Recent study of Scheen et. al suggested that SGLT2 inhibitor can lower arterial BP as well as improve glucose control by inducing natriuresis. The mechanism of the diuretic effect of SGLT2 inhibitor is different from that of other conventional diuretics. SGLT2 inhibitors reduce arterial blood pressure without significantly increasing heart rate, suggesting attenuation of SNS activity. This effect may contribute to the improvement of the PN curve[51-53].

Several studies in diabetic patients have reported that the SGLT2 inhibitors lower cardiovascular mortality and slow

the progression of chronic kidney disease[54-57].

Recent study of Wiviott et al. reported that treatment with dapagliflozin significantly reduced the rates of cardiovascular outcomes and adverse renal outcomes in patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease[55]. The current guideline of Kidney Disease: Improving Global Outcomes recommends the use of both metformin and SGLT2 inhibitor for most patients with type 2 diabetes, chronic kidney disease, and an estimated glomerular filtration rate ≥ 30 ml/min per 1.73 m^2.

Even though the SGLT2 inhibitors were introduced as type 2 diabetes management drugs, recent study of Heerspink et al. indicated a clear benefit in non-diabetic chronic kidney disease management[58]. It showed that dapagliflozin results in beneficial effects on renal function and mortality among patients with chronic kidney disease, irrespective of diabetes mellitus status. Since these results cannot be explained by the hypoglycemic effect alone, the improvement of the PN through a decrease in sodium reabsorption and BP is considered as the key mechanism. Recently, the United States Food and Drug Administration (FDA) and the Korean FDA approved the use of SGLT2 inhibitor for non-diabetic kidney disease, and its use is expected to increase further.

CONCLUSIONS

Hypertension is a risk factor for chronic kidney failure, and BP control is important. PN is crucial for the long-term control of arterial pressure and extracellular fluid volume. This means that a decrease in renal perfusion pressure increases tubular reabsorption of sodium and a decrease in sodium excretion. In salt-sensitive patients, the pressure-natriuretic relationship is altered, and higher BP levels are required to achieve increased sodium excretion. Recently, various studies have reported genetic approaches to the mechanism of PN and salt sensitivity. New drugs related to PN have also emerged and are gaining attention. Further studies are needed to understand the mechanism of PN in salt-sensitive hypertension.

Conflict of Interest

Each author certifies that he has no commercial associa-tions (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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