Impaired Pressure-Natriuresis

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Blood pressure is a heritable trait because hypertension occurs with a familial tendency. The heritability of sitting and standing blood pressure was estimated to be between 39% and 63% in twins and between 16% and 22% in families. Although the brain, kidneys, and blood vessels are major organs involved in regulating blood pressure and inducing hypertension, the kidneys have a unique relationship with blood pressure, suggesting that some genetic factors elevating or decreasing blood pressure exist in the kidney.

Keywords: inflammation ; pressure-natriuresis ; salt-sensitivity ; sodium ; vascular resistance

1. Genetic Susceptibility and Salt Sensitivity

Primary or essential hypertension has a genetic basis, although we do not know which specific genes cause it [1]. The inheritance of hypertension is believed to be polygenic. Over the past decade, genome-wide association studies have identified more than 1000 single nucleotide polymorphisms that are associated with hypertension [2]. Individual single nucleotide polymorphisms have only a small effect on blood pressure. However, when multiple single nucleotide polymorphisms occur simultaneously, the risk of hypertension can be assessed using a polygenic risk score (PRS) [3]. The PRS is a reliable predictor of early-onset hypertension, with a progressive impact. Individuals who fall within the highest 2.5% of PRS have an almost threefold increased risk of developing hypertension, while a low PRS offers protection against it [4].

As a result of previous extensive genetic studies on human hypertension, some single-gene mutations were discovered that may either increase or decrease blood pressure. These components are present throughout the segments of the nephron and are directly or indirectly involved in the regulation of renal sodium transport. In particular, the genes are located in the distal nephron and code for tubular sodium transport systems or proteins that belong to regulatory pathways [5]. Hypertension is caused by gain-of-function mutations of the epithelial Na^+ channel (ENaC) in Liddle syndrome. It is also caused by mutations in WNK4, WNK1, KLHL3, and CUL3, which increase the thiazide-sensitive Na^+-Cl^- cotransporter (NCC) activity in pseudohypoaldosteronism type II. Additionally, hypertension can be caused by a chimeric 11 β-hydroxylase/aldosterone synthase gene in glucocorticoid-remediable aldosteronism. On the other hand, hypotension is induced by loss-of-function mutations of the NCC in Gitelman syndrome, as well as loss-of-function mutations of Na^+-K^+-$2Cl^-$ cotransporter 2 (NKCC2), the renal outer medullary potassium channel (ROMK), or the ClC-Kb chloride channel in Bartter syndrome. Although monogenic hypertension is very rare, these single-gene mutations have provided insight into the role of renal sodium handling in the development of hypertension.

Salt sensitivity of blood pressure is characterized by an increase in blood pressure following salt loading or a decrease in blood pressure following salt depletion. It is a trait observed in both humans and animals [6], and it can be identified in half of the hypertensive population and one-fourth of normotensive subjects [7]. Reseasrchers believe that salt sensitivity can be attributed to genetic susceptibility. According to Manosroi and Williams [8], 18 genes were found to be associated with salt-sensitive hypertension. These genes may account for approximately 50% of the population with primary hypertension. However, only eight genes were found to be associated with lower renin levels. Validation and further characterizations are necessary.

From the lessons learned from monogenic hypertension, it is conceivable that salt sensitivity is caused by a combination of genetic variants that code for tubular sodium transporters or proteins involved in regulatory pathways. Whereas a single nucleotide polymorphism has no significant effect on salt sensitivity, the interaction of multiple combined single nucleotide polymorphisms can lead to salt-sensitive hypertension. Manunta et al. evaluated the separate and combined impacts of the ADD1 (Gly460Trp), WNK1 (rs880054 A/G), and NEDD4L (rs4149601 G/A) polymorphisms on the renal and blood pressure responses to an acute salt load, the reduction in blood pressure after one month of treatment with 12.5 mg of hydrochlorothiazide, and ambulatory 24-h blood pressure. Individually, the variants exhibited modest effects on the specific phenotypes that were studied. However, they found that relatively common alleles in the ADD1, WNK1, and

NEDD4L genes, when present in combination, have significant effects on renal sodium handling, blood pressure, and antihypertensive response to thiazides [9].

2. Sodium and Potassium Intake

It is well known that a high sodium intake is associated with elevated blood pressure. In multiple populations, the rise in blood pressure with age is directly correlated with increasing levels of sodium intake. Multiple scattered groups who consume less than 50 mmol of sodium per day have little or no hypertension. When individuals consume excessive amounts of sodium, hypertension can develop. [10]. Sodium restriction to a level below 100 mmol per day will lower blood pressure in most individuals [11].

Sodium taken into the body is primarily localized in the extracellular space due to the activity of Na^+/K^+-ATPase, which is present in all cell membranes. To maintain the osmolality of extracellular fluid and cell volumes, sodium intake is typically accompanied by water retention. The resulting expansion of extracellular fluid and plasma volume can lead to hypertension if the mechanism of pressure-natriuresis fails to work. However, a certain portion of sodium is not confined to the extracellular space. After an increase in dietary salt, the excess sodium accumulates in the subcutaneous interstitium, binding to proteoglycans. This osmotically inactive Na^+ storage contributes to regulating body sodium balance and blood pressure, as it can be drained through the lymphatics [12]. The increased interstitial tonicity activates the tonicity-responsive enhancer binding protein (TonEBP) in macrophages that infiltrate the interstitium of the skin. TonEBP transactivates the vascular endothelial growth factor C (VEGF-C) gene and enhances VEGF-C secretion by macrophages. This increases lymphatic capillary density and attenuates the blood pressure response to high salt [13].

Epidemiological studies suggest an association between potassium intake and blood pressure. A previous meta-analysis of 22 randomized controlled trials and 11 cohort studies has shown that increased potassium intake reduces blood pressure in individuals with hypertension [14]. In a study involving 102,216 adults from 18 countries, researchers found an inverse relationship between urinary potassium excretion and systolic blood pressure. This relationship was more pronounced in individuals with hypertension compared to those without it, and it became steeper with increasing age [15]. The analysis of the Dietary Approaches to Stop Hypertension Sodium Trial (DASH-Sodium) dataset showed that systolic blood pressure increased when potassium intake was less than 1 g per day [16].

Potassium deficiency can be linked to the development of salt-sensitive hypertension because it reduces the secretion of K^+ while increasing the retention of Na^+ [17]. Low dietary K^+ intake activates NCC in the distal convoluted tubule, leading to an increase in NaCl reabsorption. The resulting low distal Na^+ delivery will reduce K^+ secretion through ROMK in the connecting tubule and cortical collecting duct. A high K^+ diet, on the contrary, may relieve hypertension by inducing natriuresis (NCC downregulation) and direct vascular effects for vasodilation and decalcification [18].

3. Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS is one of the major regulators of renal sodium reabsorption. Renin is secreted from the kidney and cleaves angiotensinogen, which is produced by the liver, into angiotensin I. Angiotensin I is converted to angiotensin II by the enzyme angiotensin-converting enzyme (ACE), which is found in the lungs and kidneys.

Angiotensin II induces hypertension by increasing renal sodium reabsorption and constricting arterioles. Hypertension is induced when angiotensin II is not suppressed despite increased salt intake. Rats with angiotensin II-induced hypertension exhibit a rightward shift in the pressure-natriuresis curve, primarily due to a significant impairment of sodium excretion. The reversal of these effects by losartan suggests that the AT1 receptor mediates the shift in the pressure-natriuresis curve in angiotensin II-induced hypertension [19][20].

There is local and independent control of angiotensin II within the kidney, which influences sodium excretion and regulates blood pressure. Angiotensin II is formed intrarenally from systemically delivered angiotensin I and intrarenally formed angiotensin I through ACE. Proximal tubule cells are believed to secrete angiotensin II into the tubular fluid in order to activate luminal angiotensin II receptors [21]. The AT1 receptors are located on the apical and basal membranes of the proximal tubule, as well as on the basal membrane of collecting duct cells. In the proximal tubule, angiotensin II binds to the AT1 receptor and upregulates the Na^+/H^+ exchanger 3 (NHE3). In animal models, NHE3 plays a critical role in the development of angiotensin II-induced hypertension [22]. Moreover, the genetic deletion of NHE3 specifically in the proximal tubules of the kidney reduces blood pressure by enhancing the pressure natriuretic response [23].

In the collecting duct's principal cells, angiotensin II binds to the AT1 receptor and upregulates the ENaC. In the collecting duct's type B intercalated cells, angiotensin II induces dephosphorylation of the mineralocorticoid receptor (MR) through the AT1 receptor. This renders the MR susceptible to aldosterone binding, which stimulates pendrin [24]. Pendrin is a Cl^-/HCO_3^- exchanger that regulates extracellular fluid volume and electrolyte balance downstream of aldosterone signaling [25].

Angiotensin II also acts on the adrenal glands to produce aldosterone, which promotes sodium reabsorption and induces hypertension. The NCC and ENaC are the major sodium transporters regulated by aldosterone in the distal convoluted tubule and collecting duct, respectively. Serum- and glucocorticoid-regulated kinase 1 (SGK1) is a crucial gene product induced by aldosterone in the distal nephron [26]. The SGK1-Nedd4-2 pathway affects the trafficking of ENaC and the abundance of NCC protein [27].

In addition to the kidney, MR is present in virtually all cells of the cardiovascular system, including endothelial cells, vascular smooth muscle cells (VSMCs), and cardiomyocytes. Increased signaling of endothelial cell MR can lead to the activation of endothelial sodium channels, reduced production of nitric oxide, oxidative stress, and inflammation [28]. MR activation in VSMCs directly contributes to vascular oxidative stress, vasoconstriction, and arterial hypertension [29]. MR signaling in innate and adaptive immune cells can also contribute to hypertension and hypertensive end-organ damage by upregulating the expression of proinflammatory genes [30].

4. Sympathetic Nervous System (SNS)

The SNS activity is another crucial factor in regulating blood pressure. Activation of renal sympathetic (efferent) nerves increases tubular sodium reabsorption, renin release, and renal vascular resistance. This, in turn, leads to a shift of the pressure-natriuresis curve to the right and contributes to the chronic elevation of blood pressure [31]. Consistent with this concept, rats with experimental and spontaneous hypertension undergo a significant reduction in blood pressure after renal denervation [32]. Renal denervation may be an adjunct treatment option in uncontrolled resistant hypertension. It may be considered as an alternative for patients who are unable to tolerate long-term medications at the required doses or cannot tolerate medications at all [33].

Central mechanisms in the brainstem and hypothalamus can modulate the level of renal sympathetic nerve activity. The rostral ventrolateral medulla (RVLM) is responsible for the basal and reflex control of sympathetic activity. RVLM neurons project to sympathetic preganglionic neurons in the spinal cord, which then project to the kidneys via postganglionic neurons. These postganglionic neurons innervate the three major neuroeffectors in the kidney [34].

The actions of the SNS on the kidney are dependent on both α- and β-adrenergic receptors. Increased renal sympathetic nerve activity stimulates the secretion of renin by activating β_1-adrenergic receptors in juxtaglomerular granular cells. It also results in an increase in renal tubular sodium reabsorption through the stimulation of α_{1B}-adrenergic receptors in renal tubular epithelial cells. Additionally, it causes a decrease in renal blood flow through the stimulation of α_{1A}-adrenergic receptors in the renal arterial resistance vessels [35].

The proximal tubule is the primary target of SNS activity due to its abundant innervation by sympathetic nerve fibers [36]. The α_1-adrenergic receptors are mainly located on the basolateral membrane of the proximal tubule cell. It has been demonstrated that in primary cultures of proximal tubular cells, the abundance and activity of brush-border NHE3 are stimulated by norepinephrine and completely prevented by prior exposure to prazosin [37]. Therefore, the SNS upregulates NHE3 in the proximal tubule through an α_1-adrenoceptor-mediated mechanism. Intrarenal angiotensin II activity may also be stimulated by SNS hyperactivity in the proximal tubule [38].

The increased SNS activity in the kidney induces NCC activation, resulting in sodium retention and salt-sensitive hypertension [39]. Mouse distal convoluted tubule cells are enriched with β_1-adrenergic receptors, and norepinephrine rapidly increases the abundance of phosphorylated NCC, at least partially through oxidative stress-response kinase 1 (OSR1) [40]. In patients with essential hypertension, β-adrenergic receptor blockade increases plasma atrial natriuretic peptide levels, leading to improved pressure-natriuresis [41].

The kidney is also innervated by sensory (afferent) nerve fibers, which transmit information to the brain to modulate sympathetic outflow. Renal afferent neurons have small- to medium-sized cell bodies located in the lower thoracic and upper lumbar dorsal root ganglia and terminate in the spinal cord and the brainstem. Sensory nerve fibers are associated with all branches of the renal arteries in varying densities, and the renal pelvis has the highest density of sensory innervation compared to other structural components of the kidney. Renal sensory nerve fibers are typically categorized as mechanoreceptors and chemoreceptors. Mechanoreceptors in the renal pelvis detect changes in pelvic pressure

caused by the flow of urine. Type R1 chemoreceptors respond to renal ischemia, whereas R2 chemoreceptors sense changes in ionic composition [42].

The SNS mediates short-term increases in blood pressure, and heart rate may serve as a marker of sympathetic activity [43]. However, the evidence regarding whether psychosocial stress leads to chronic hypertension is mixed [44]. In a multicenter longitudinal study of 4762 young adults initially aged 18 to 30 years, the authors found that heart rate was an independent predictor of future diastolic hypertension [45]. Therefore, beta-blockers can be considered the first-line treatment for diastolic hypertension in young adults.

5. Loss of Kidney Function

With a decrease in glomerular filtration rate (GFR), the prevalence of salt sensitivity increases. A simultaneous decrease in sodium excretion will ultimately increase blood volume and cardiac output, thereby elevating blood pressure to the set point. Therefore, salt sensitivity reflects a failure of the kidneys to excrete sufficient salt in response to an increase in salt intake due to an underlying defect in the pressure-natriuresis response [46].

The fact that reducing the functioning renal mass induces salt-sensitive hypertension is known from the early animal experiments conducted by Guyton and his associates. In dogs with 70% of their total renal tissue removed, arterial pressure increased by 30% to 40% within 48 to 72 h after drinking isotonic saline. The elevated blood pressure was reduced to normal levels within 24 h by simply allowing the dogs to drink tap water again [47].

A subtle kidney injury without an overt decline in GFR may cause salt sensitivity [48]. Several factors were known to contribute to the high prevalence of salt-sensitive hypertension in patients with chronic kidney disease (CKD). First, CKD is associated with the inappropriate activation of the RAAS, leading to the accumulation of angiotensin II in the body. Second, renal injury increases sympathetic tone, even when the GFR remains unchanged. This results from stimulating afferent signals originating from the kidney [31]. Following renal injury, there are immediate increases in catecholamine turnover in the brain, accompanied by rises in blood pressure and renal sympathetic nerve activity [49]. Overactivity of the SNS in CKD stimulates renin production by the renal juxtaglomerular cells. Additionally, increased levels of angiotensin II in patients with CKD can directly stimulate SNS activity. Third, vascular endothelial dysfunction is associated with kidney dysfunction. CKD is a condition characterized by increased oxidative stress, impaired nitric oxide (NO) production, and elevated endothelin levels [50]. Moreover, renal sodium transporters may exhibit inadequate responses to salt intake in damaged kidneys.

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