Chapter

Pressure Natriuresis in Blood Pressure Control

Vedran Đambić and Aleksandar Kibel

Abstract

The kidneys play an important role in controlling arterial blood pressure by regulating extracellular fluid volume, through excretion of sodium and water, which is called pressure natriuresis, or diuresis. Sodium and water homeostasis is controlled by the integrated physiological functions of organ systems, including renal mechanisms, but also with an influence of the renal and non-renal sympathetic nervous system and the endocrine system (renin-angiotensin-aldosterone system, cardiac natriuretic peptides, antidiuretic hormone, and oxytocin). Pressure natriuresis represents the basal level for arterial blood pressure dysregulation. The imbalance of complex renal and non-renal hemodynamic and neurohumoral mechanisms leads to the disruption of antidiuretic mechanisms, which results in the development of arterial hypertension. Knowledge of all mechanisms enables an integrated understanding of the regulation of arterial blood pressure, which is a key step in the targeted and individual treatment of one of the most common diseases today.

Keywords: pressure natriuresis, diuresis, arterial blood pressure, kidneys, sodium, renin-angiotensin-aldosterone system, sympathetic nervous system, cardiac natriuretic peptides, hypertension

1. Introduction

The kidneys manage blood pressure by regulating the volume of extracellular fluid through the primary excretion of sodium and the secondary excretion of water through osmosis [1].

After a systemic increase in blood pressure, there is an increase in renal perfusion pressure, which results in the inhibition of renal tubular reabsorptive mechanisms and increased excretion of sodium and water to return blood pressure to normal, which is called pressure natriuresis, that is, diuresis [1, 2].

Pressure natriuresis is the main, non-adaptive mechanism with infinite gain responsible for long-term control of blood pressure with the goal of daily full compensation of blood pressure fluctuations [1].

2. Insight into the mechanism of pressure natriuresis

Sodium homeostasis is controlled by the integrated physiological functions of organ systems including the hemodynamic (peripheral and renal arteries) and neurohumoral systems (renal sympathetic nerves, renal autacoids, renin-angiotensin-aldosterone system, cardiac natriuretic peptides, antidiuretic hormone, and oxytocin) [3, 4].

The blood pressure value in the body is the point at which pressure natriuresis and the volume of extracellular fluid are in balance [2]. An increase in blood pressure leads to an increase in renal perfusion pressure (RPP). An increase in shear stress in the preglomerular vasculature due to autoregulatory vasoconstriction in response to rise in RPP activates endothelial nitric oxide synthase and NO production, increased release of prostaglandin E2 and renal kinins, and a decrease in intrarenal angiotensin II in the outer medulla, resulting in an increase in medullary blood flow (MBF) as a result of reduced vascular resistance of renal medulla arteries mediated by guanosine 3′,5′-cyclic monophosphate (cGMP) and protein kinase G [1, 2]. An increase in medullary blood flow (MBF) due to renal encapsulation leads to an increase in renal interstitial hydrostatic pressure (RIHP, 40% contribution to the mechanism of pressure natriuresis) around the vasa recta, which disturbs the balance of Starling forces. Thus, changes in pressure natriuresis do not significantly affect glomerular filtration rate (GFR) because the afferent myogenic response and the tubuloglomerular feedback mechanism effectively keep GFR constant over a wide range of systolic blood pressure levels [2].

The key driver of pressure natriuresis is increased RIHP leading to antagonism of paracellular passive osmotic reabsorption of sodium and water in the proximal tubule and loop of Henle and causing rapid redistribution of sodium/hydrogen transporter isoform 3 (NHE3) out of the apical brush border along with inhibition of basolateral Na^+K^+-ATPase (NKA) in the proximal tubule [2, 5]. NHE3 in the proximal tubule reabsorbs ~65% of filtered Na^+ [2]. It is expressed in all segments of the nephron, except for the macula-dense and intercalated cells of the distal nephron [6]. The sodium/chloride cotransporter (NCC) in the apical membrane of the distal convoluted tubule (DCT) participates in salt reabsorption [7]. The epithelial Na + channel (ENaC) plays a key role in the absorption of Na^+ in the collecting duct of the kidney, the expression of which is significantly increased by aldosterone and vasopressin [8]. Sodium-dependent Pi cotransporters (2 Na-Pi), especially the type 2 Na-Pi cotransporter, include three cotransporter isoforms that are expressed on the brush membrane of the renal proximal tubules and enhance the excretion of not only phosphate but also sodium, as demonstrated by immunoblotting of NHE3 knockout mice [9]. In the basolateral membrane of renal epithelial cells, there is Na^+K^+-ATPase, which is not only well known as an ion pump but also a new class of receptors associated with the Src family kinase signaling pathway. Increased renal perfusion pressure resulting in increased endogenous cGMP activates the Src pathway, resulting in internalization and inactivation of NKA and decreased expression and activity of (NHE-3), thereby reducing Na^+ reabsorption [10]. $Na^+K^+2Cl^-$ cotransporter class 2 (NKCC2) is localized on the apical membrane of the epithelial cells of the thick ascending limb of the loop of Henle and the macula densa and is responsible for ~20–25% of NaCl reabsorption and modulates the preglomerular resistance of the afferent arteriole and the secretion of renin from granule cells of the juxtaglomerular apparatus (JGA) [11]. Na^+ glucose transporters (SGLT1 and SGLT2) are located in the proximal tubule of the nephron, which also contributes to sodium reabsorption (SGLT2 transports Na^+ and glucose in a 2:1 ratio, while SGLT2 transports in a 1:1 ratio) [6].

As mentioned, during the increase in renal perfusion pressure, there is also the release of paracrine factors (renal autocoids) that lead to the activation or inhibition of pro-natriuretic and antinatriuretic mediators. The main paracrine modulators of pressure natriuresis are angiotensin II (Ang II), 20-hydroxyeicosatetraenoic acid (20-HETE, metabolite of arachidonic acid produced by cytochrome P450), nitric oxide (NO), prostaglandin E2, renal kinins, adenosine triphosphate (ATP), endothelin 1, medullary O_2^- and H_2O_2. Paracrine factors significantly contribute to the redistribution of the NHE3 transporter, the internalization of the distal tubule sodium/chloride cotransporter, and the internalization of the type 2 Na-Pi cotransporter into cytoplasmic vesicles in microvilli [4].

The main antinatriuretic mediators are Ang II, aldosterone, HETE and Antidiuretic hormone (ADH) [4]. The main indirect effect of Ang II is a decrease in peritubular capillary pressure and an increase in Na transport. The direct action is realized through the angiotensin receptor (AT1 receptor) in the kidney, increasing the activity of NHE3 (but not Na-Pi cotransporter type 2) in the microvilli, the Na^+Cl^- cotransporter in the distal tubule and ENaC in the collecting duct [12, 13]. Angiotensin III (Ang III) mediated activation of angiotensin II receptor type 2 (AT 2 R) *via* protein phosphatase 2A (PP2A), bradykinin, nitric oxide, and cGMP signaling cascade results in increased natriuresis [14]. Aldosterone acts on mineralocorticoid receptors located in the distal tubule and collecting duct of the nephron, increasing Na reabsorption and potassium excretion through Na/ENaCs and potassium channels by NKA [4]. HETEs prevent NHE3 redistribution, Na-Pi cotransporter type 2 internalization, and inhibition of the basolateral NKA. Medullary O_2^- and H_2O_2 reduce the natriuretic response to increased RPP by a currently unknown mechanism [2]. ADH is extremely sensitive to the increase in Na concentration in the plasma and achieves its antinatriuretic (antidiuretic) effect *via* the V2 receptor in the kidney by increasing the reabsorption of water in the collecting duct of the nephron through the formation of aqueous aquaporin 2 (AQP2) and by increasing the number of ENaCs in the thick ascending limb that reabsorbs Na^+ [4]. The V1a receptor mediates the pro-natriuretic effect by inhibiting the renal reabsorption of Na in the connecting tubules and collecting ducts [4]. Oxytocin achieves its natriuretic effects directly by increasing the rate of glomerular filtration and decreasing tubular reabsorption of Na, and indirectly by cardiac excretion of Atrial natriuretic peptide (ANP), as well as by reducing the polydipsia response by acting on the tuberomammillary nucleus [4, 15].

The pro-natriuretic effect of NO manifests through the inhibition of sodium reabsorption in the PCT and the thick ascending limb of Henle and in the collecting duct by acting on the $Na^+K^+2Cl^-$ cotransporter and the Na^+/H exchanger. Prostaglandin E2 inhibits sodium reabsorption in the PCT and in the collecting duct and, as a potent vasodilator in the medulla, suppresses the vasoconstrictor effects of intrarenal Ang II [4]. Endothelin-1 has natriuretic effects mediated through the dilation of renal blood vessels *via* the endothelin receptor (ETA) receptor, while endogenous stimulation of ETB in the kidney exerts antinatriuretic effects *via* renal tubular NO, cGMP, and protein kinase G signaling [16]. ANP and B-type natriuretic peptide (BNP) act on the natriuretic peptide receptor A (NPR-A) inducing vasodilation of the afferent glomerular arteriole and vasoconstriction of the efferent glomerular arteriole (increasing the glomerular filtration rate) and reducing the activity of the cation channel that mediates electrogenic Na absorption to exert its pro-natriuretic effect [4]. Purinergic signaling also contributes to the regulation of natriuresis *via* a metabotropic GPCR (P2Y 2 receptor) whose activation *via* ATP and uridine-5′-triphosphate (UTP) increases sodium excretion by blocking ENaC [17]. Also, intracellular calcium and

free oxygen radicals can significantly increase the expression of ENaC in oxidative stress [18]. The renal dopaminergic system inhibits sodium transport in all segments of the nephron and causes at least 50% of renal sodium excretion in conditions of moderate sodium excess [19]. Dopamine receptor-1 (D1R) activation inhibits luminal transport of sodium ions (NHE3, NaPi-Iic), while activation inhibits NKA activity and increases NHE3 degradation *via* USP-mediated ubiquitinylation [19].

Inhibitors of the sodium-glucose cotransporter 2 (SGLT2) of increased glucose excretion increase diuresis and natriuresis by reducing sodium reabsorption in the most proximal segments of the renal tubule and additionally inhibit the sodium-hydrogen exchanger 3, but due to strong counter-regulatory responses that are associated with the regulation of vasopressin, aldosterone, ketoglutarate, uromodulin, and carbonic anhydrase, any natriuretic or osmotic diuretic effect of SGLT2 inhibitors was canceled [6, 20, 21].

3. Influence of sympathetic nervous system activity on pressure natriuresis

The activity of the sympathetic nervous system contributes significantly to the long-term control of arterial blood pressure. Excessive activity of renal sympathetic nerves changes renal hemodynamics, urinary sodium excretion, and renin secretion. Afferent (sensory) information originates from arterial baroreceptors (in the carotid sinus and aortic arch) and peripheral organs (including the kidneys). Afferent fibers of the renal sympathetic nervous system are located within the wall of the renal pelvis in the interlobular and arcuate arteries and, to a lesser extent, around the interlobular arteries and afferent arterioles [1]. Afferent fibers travel to the nucleus tractus solitarius (NTS) and paraventricular nucleus of the hypothalamus, where they integrate and result in activation of the caudal ventrolateral medulla (CVLM) and rostral ventrolateral medulla (RVLM). RVLM efferent neurons project to sympathetic preganglionic neurons in the spinal cord [22]. Neural projections exit the spinal cord (intermediolateral column of the spinal cord, from T6 to L2 segments) *via* ventral horns and synapses of sympathetic preganglionic fibers (paravertebral chain or aorticorenal, celiac, superior mesenteric ganglia). Postganglionic nerves enter the renal hilus along the renal arteries and veins and branch around the vasculature of the cortex and medulla of the kidney (α1A-adrenoreceptor) to the granular cells of the juxtaglomerular apparatus (β1-adrenoreceptors) and the basal membrane of the tubular epithelial cells inside the nephron (α 1A - and α 1B -adrenoreceptors). The main neurotransmitters of afferent fibers are substance P and a peptide related to the calcitonin gene, while that of efferent fibers is noradrenaline [1]. Renal sympathetic nerves directly regulate natriuresis by regulating renal β1-adrenergic receptors, resulting in renin release, and stimulating renal α1-adrenergic receptors, resulting in sodium reabsorption [23]. By vasoconstricting the afferent and efferent arterioles, the sympathetic nervous system directly proportionally reduces renal blood flow (RBF) and glomerular filtration. It causes an increase in renin secretion by activating the JGA, which leads to the activation of the RAAS. In the proximal tubules, catecholamines activate the basolateral NKA and increase NHE3 activity, allowing the entry of Na^+ from the tubule lumen into the epithelial cells (increasing sodium and water reabsorption). Low-intensity stimulation of the sympathetic nervous system leads to only renin secretion, while the decrease in RBF and GFR was observed only at the highest levels of renal sympathetic nerve activity, which leads to a significant decrease in pressure natriuresis [1].

In addition to the baroreflex mediated by sympathetic nervous activity, there are additional mechanisms mediated by baroreceptor activation in the control of pressure natriuresis. Increased levels of circulating ANP contribute to increased sodium excretion and decreased blood pressure. Activation of baroreceptors leads to a decrease in cardiac output and an increase in cardiac pressure, which stretches the walls of the atria, resulting in the release of ANP. ANP provides a central link between the heart and kidney that mediates increased natriuresis during chronic baroreflex activation. ANP represents a compensatory mechanism for increasing natriuresis in the absence of renal sympathoinhibition, which speaks in favor of the cooperative redundancy of these two mechanisms [1].

The reno-renal reflex is formed by the activation of mechanosensory afferent nerves, which leads to reflex inhibition of the ipsi- and contralateral activity of the efferent sympathetic nerve of the kidney and consequent increased compensatory natriuresis with a significant contribution to the regulatory network of sodium and water homeostasis. An increase in the activity of the efferent renal sympathetic nerve enhances the activity of the afferent renal sympathetic nerve, while the increased afferent activity inhibits the efferent activity by negative feedback of the reno-renal reflex (prevents excessive activation of the renal sympathetic nerves and sodium retention). This mechanism is activated after sodium or fluid overload. However, there are pathological conditions (e.g., some forms of chronic kidney disease, renal artery stenosis, or phenol-induced kidney damage) in which this inhibitory reflex is impaired, resulting in a vicious cycle of increased sympathetic activity with a consequent increase in arterial blood pressure. It is important to emphasize that at the level of the nucleus tractus solitarius (NTS) and the paraventricular nucleus of the hypothalamus, input information triggered by baroreceptors is integrated with renal afferent signals, to obtain an integrated reference response of the renal sympathetic nerve. In the absence of an afferent innervation signal, baroreceptors cannot influence efferent sympathetic renal activity [1].

Mechanical deformation of nerve endings (increased pressure in the pelvis, i.e., during urine flow), changes in the chemical composition of urine, renal ischemia and renal pain are the main stimuli of afferent renal sympathetic nerve fibers [24].

Arterial hypertension must be understood as a complex balance of renal (and non-renal) mechanisms, among which is increased sympathetic nervous activity, which can be a primary change or a secondary one. Therefore, knowledge of the mechanisms of renal sympathetic nerve activity modulation is of key importance for the treatment of especially resistant hypertension [1].

4. Factors contributing to changes in pressure natriuresis

Chronically changing pressure natriuresis is a complex regulatory system at the kidney level that controls the basal level of blood pressure and contributes to the regulation of blood pressure within the normotensive or hypertensive range. Chronic hypertension can occur in case of a disorder of this long-term mechanism, which has the capacity for potentially boundless gain and non-adaptive performance. In hypertensive individuals, pressure natriuresis is less effective than in normotensive individuals across the entire blood pressure range, and therefore a higher blood pressure is required to achieve sodium balance. Hypertension can therefore only occur as a result of a primary shift in the intrinsic mechanisms linking blood pressure to natriuresis or disruption of modulators of this relationship. The relationship

between specific blood pressure levels and corresponding natriuresis (and diuresis) is defined by the PN curve, the position and shape of which are determined by all the components that participate in sodium reabsorption, whose function is impaired in different pathophysiological scenarios. Mechanisms that promote sodium reabsorption (i.e., decrease sodium excretion) shift the PN curve to the right (leading to arterial hypertension, since a higher BP is necessary for each level of natriuresis), while mechanisms that decrease sodium reabsorption (i.e., increase sodium excretion) shift the curve to the left [1].

In hypertension, the mechanism of pressure natriuresis is abnormal because sodium excretion is the same as in normotension despite elevated arterial pressure [2]. Combined effects of transient increase in blood pressure, oxidative stress, inflammation, local vasoconstriction, chronic kidney disease, nephron loss, bilateral renal artery stenosis, salt retention, high salt intake, increased renal sympathetic activity, lack of nitric oxide in the kidneys, adverse effects of drugs on the kidneys and inefficient use of diuretics can lead to disturbances of pressure natriuresis and shift the pressure curve to the right [1, 2].

Cytokines can modulate salt and water balance by causing endothelial dysfunction, altering sympathetic tone, and/or increasing sodium transport along the nephron [25]. The main responsible cytokines affecting natriuresis are synthesized by pro-inflammatory T helper 1 and T helper 17 cells and M1 macrophages, namely tumor necrosis factor (TNF), interleukin 17A, interleukin 1 and interferon (IFN) [25].

Interestingly, therapeutic enlargement of renal lymphatic vessels (lymphangiogenesis) in mice increases natriuresis and lowers blood pressure under conditions of sodium retention [26].

5. Changes in pressure diuresis in salt-sensitive subjects

Salt sensitivity refers to a physiological characteristic in humans (and in animal models) in which blood pressure changes in parallel with changes in salt intake. Sodium homeostasis and salt sensitivity are not only associated with renal dysfunction but also with endothelial dysfunction, which may perhaps be connected to the accumulation of osmotically inactive sodium in the surface layer of the endothelium of skin blood vessels without accompanying water retention. The slope of the pressure-natriuretic relationship is less steep and shifts to the right in salt-sensitive individuals, and higher levels of blood pressure are required to increase sodium excretion and maintain sodium balance. Salt-sensitive individuals show sharp changes in blood pressure with acute or chronic salt deficiency or intake [2]. Also, the response of blood pressure to high sodium intake is individual due to the influence of genetic, hormonal, nervous and environmental factors, older age, obesity and black race. During salt sensitivity, there is an inadequate decrease in total peripheral resistance (TPR), which represents an acute (transient) change in blood pressure that disappears after a week. The long-term mechanism is greater sodium reabsorption in the PCT and an increase in the expression and activity of epithelial sodium channels (despite the reduction of aldosterone levels) [1]. Numerous factors have been proven that damage pressure natriuresis in the kidneys in the pathogenesis of salt-sensitive hypertension: autoimmune reactivity to the heat shock protein HSP70, SNPs in the sodium bicarbonate cotransporter gene SLC4A5 and SH2B adapter protein 3 genes, various inflammatory mediators such as gene-1 which activates recombination, interleukin (IL)-17A, interferon-gamma and IL-1β, low-potassium intake, dietary

fructose, and increased reactive oxygen species (ROS) production. A low-potassium diet is associated with hypertension because potassium affects sodium reabsorption by modulating the activity of the sodium chloride cotransporter and epithelial sodium channels in the distal nephron [2]. Increased dietary intake of potassium leads to increased excretion of sodium in the distal tubules (K^+-induced diuresis) as a result of dephosphorylation of NCC mediated by phosphatases [27]. Dietary fructose supplementation before and during increased dietary salt intake promotes the development of salt-sensitive hypertension by modulating the activity and expression of the renal sodium transporter [2].

6. Pressure and natriuresis responses decrease with age

With age, there is a decrease in natriuresis, which causes an increase in blood pressure in people without chronic kidney disease. The drop in natriuretic response is not caused by reduced eGFR but by increased sympathetic tone, changes in renal blood vessels, a drop in ANP levels, and changes in the expression and activity of certain receptors. Changes in the renal microvasculature (reduced number of glomerular and peritubular capillaries) are associated with reduced autoregulation of renal perfusion pressure and increased sodium reabsorption. Despite the decrease in the renin-angiotensin-aldosterone system concentration with age, increased intrarenal formation of Ang II and increased sensitivity to aldosterone have been shown. There was also increased expression of renal AT 1 R and increased activity of medullary NKA, which directly stimulates Ang II in the proximal renal tubules. In the distal tubules, NCCs were more expressed in aged rats, and a possible enhancement of sodium retention *via* NCCs was suggested in human studies of hypertensive subjects because the thiazide diuretic effect increased with age. That is why previously, some guidelines for the treatment of hypertension suggested that salt restriction and diuretics are the most effective antihypertensive treatment measures in elderly people [3].

7. Conclusion

Pressure natriuresis is one of the fundamental and most important mechanisms of normal blood pressure regulation. A complex set of mechanisms is responsible for the proper regulation of pressure antidiuresis, and consequently, various imbalances of this network may lead to elevated blood pressure and hypertension. A good understanding of these mechanisms is crucial for an integrated understanding of whole blood pressure regulation and is also key for the future development of personalized and targeted treatment approaches.

Conflict of interest

The authors have no conflict of interest to declare.

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