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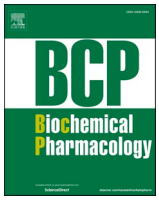

Review

Renal sympathetic activity: A key modulator of pressure natriuresis in hypertension

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A B S T R A C T

Hypertension is a complex disorder ensuing necessarily from alterations in the pressure-natriuresis relationship, the main determinant of long-term control of blood pressure. This mechanism sets natriuresis to the level of blood pressure, so that increasing pressure translates into higher osmotically driven diuresis to reduce volemia and control blood pressure. External factors affecting the renal handling of sodium regulate the pressure-natriuresis relationship so that more or less natriuresis is attained for each level of blood pressure. Hypertension can thus only develop following primary alterations in the pressure to natriuresis balance, or by abnormal activity of the regulation network. On the other hand, increased sympathetic tone is a very frequent finding in most forms of hypertension, long regarded as a key element in the pathophysiological scenario. In this article, we critically analyze the interplay of the renal component of the sympathetic nervous system and the pressure-natriuresis mechanism in the development of hypertension. A special focus is placed on discussing recent findings supporting a role of baroreceptors as a component, along with the afference of reno-renal reflex, of the input to the nucleus tractus solitarius, the central structure governing the long-term regulation of renal sympathetic efferent tone.

1. Introduction

1.1. Necessary involvement of the kidneys in hypertension

Hypertension, a persistent elevation in blood pressure (BP), is a complex disorder [1] with over 30 % prevalence in the adult population globally [2]. Hypertension is the main modifiable risk factor for cardiovascular disease and is associated with premature death worldwide [3,4]. Recognizing the mechanisms involved in the physiological regulation of BP is essential for understanding the alterations underpinning hypertension. In most cases, the precise and ultimate causes are yet undetermined, despite multiple genetic, hormonal, nervous and environmental factors and lifestyle have been linked to hypertension [1]. However, the work of Guyton [5,6] unveiled that the pressure-sensitive natriuretic function of the kidneys (i.e., the pressure-natriuresis mechanism, PN) was the main and the sole mechanism responsible for the long-term control of blood pressure. Pressure-natriuresis thus sets the basal BP level on which transitory variations constantly occur because of the action of environmental stimuli or of other BP regulating mechanisms with more time-limited action range, such as immediate baroreflex-mediated cardiovascular adaptation. A corollary follows that, for hypertension to ensue, regardless of the form or cause, a distortion of the pressure-natriuresis relationship must occur [7].

Abbreviations: Ang II, angiotensin II; ANP, atrial natriuretic peptide; ATR1, type 1 angiotensin II receptors; BP, blood pressure; CBF, cortical blood flow; CVLM, caudal ventrolateral medulla; DRX, dorsal rhizotomy; GFR, glomerular filtration rate; 20-HETE, 20-hydroxyeicosatetraenoic acid; MBF, medullary blood flow; NO, nitric oxide; NTS, nucleus tractus solitarius; PCT, proximal convoluted tubule; PN, pressure-natriuresis mechanism; RBF, renal blood flow; RIHP, renal interstitial hydrostatic pressure; RPP, renal perfusion pressure; RSNA, renal sympathetic nerve activity; RVLM, rostral ventrolateral medulla; SAD, sinoaortic denervation; SNS, sympathetic nervous system; TPR, total peripheral resistance.

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Hypertension may thus ensue from primary alterations in the pressure-natriuresis relationship, or from secondary alterations in this mechanism caused by extrarenal stimuli. Among the extrarenal causes, increased sympathetic activity is a well-known determinant of BP [8–11]. In this article, we analyze in an integrative manner the current knowledge on the mechanism of pressure-natriuresis as a basis to shed light on the pathophysiological links of the nervous system with hypertension, and also the potential cause of the increased sympathetic activity, with a special focus on the long-term role of baroreceptors.

The kidneys govern long-term BP by regulating extracellular fluid volume (Fig. 1). Under normal conditions, the relationship between PN and sodium excretion (i.e., represented by the PN curve) balances the intake and output of sodium and, secondary to it, of water, driven by osmotic forces. Upon a systemic increase in BP, the kidneys rise sodium and water excretion restoring BP to normal and *vice versa* [6]. This mechanism is also observed in isolated kidneys [12–14], although the PN curve's shape differs due to the action of nervous and endocrine effectors disengaging the amount of sodium excreted at each BP level [6].

Importantly, PN is a non-adaptive mechanism that works with infinite gain to completely compensate BP fluctuations. Therefore, a chronic elevation of blood pressure (i.e., such as in hypertension) requires an alteration in the normal PN relationship so that sodium balance can only be achieved at a higher BP level [6]. In fact, if renal perfusion pressure (RPP) is servo-controlled to prevent increases in systemic BP reaching the kidneys, a higher pressure does not translate into a higher sodium excretion [15]. Under servo-controlled RPP, chronic infusion of angiotensin II (Ang II) [16], aldosterone [17], or vasopressin [18], prevents sodium balance and thus markedly enhances the hypertensive effect of these hormones. Moreover, if RPP is unilaterally servo-controlled below control levels, a reduction in sodium excretion is only observed in the servo-controlled kidney alongside an increase in natriuresis in the contralateral kidney when animals are subject to enhanced neurohumoral tone equally affecting both kidneys. These observations support the critical importance of perfusion pressure in the control of sodium excretion [19].

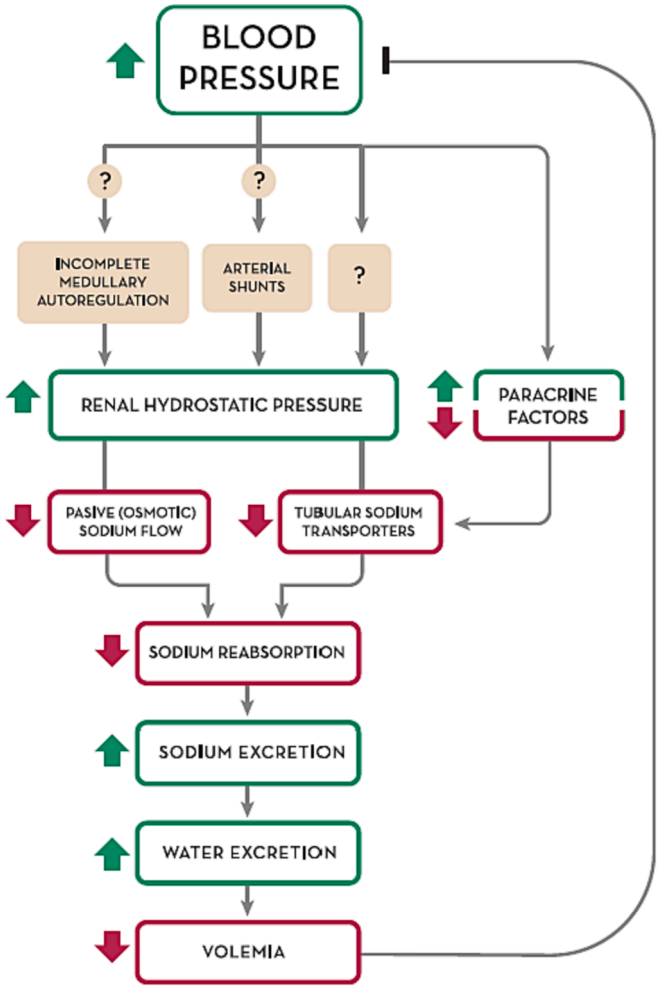

Fig. 1. Schematic representation of the pressure-natriuresis mechanism showing how changes in blood pressure translate into adaptive natriuretic responses that modify volemia to restore blood pressure. Arrow-headed, black lines represent a positive effect or activation. Blunted black lines represent a negative effect or inhibition. Green arrows show an increment, and red arrows a decrease. Question marks indicate that the associated mechanism has not been completely proved, or that it is ignored (i.e., that additional, yet unknown mechanisms might account for or mediate the effect).

Further support to the role of the kidneys in long-term BP regulation came from cross-transplant studies showing that hypertension follows the kidney. Transplantation of one kidney from a normotensive animal into a bilaterally nephrectomized hypertensive animal turns the recipient normotensive. Vice versa, bilaterally nephrectomized normotensive animals are rendered hypertensive by a solitary kidney donated by a hypertensive donor [20]. Identical conclusions are provided by the analysis of BP after kidney transplantation between normotensive and hypertensive patients with genetic or essential hypertension [21–23].

1.2. An insight into the mechanism of pressure natriuresis

Under normal conditions, the sodium/hydrogen exchanger isoform 3 (NHE3) in the proximal convoluted tubule (PCT) reabsorbs ~ 65 % of the filtered Na^+ [24]. In response to acute increases in BP, NHE3 transporters are redistributed out of the apical brush-border along with an inhibition of basolateral Na-K-ATPases [25]. This redistribution is rapidly reversed when BP is restored to basal levels [26]. Selective deletion of NHE3 transporter in mice increases the PN response and decreases BP [27]. Moreover, a higher NHE3 activity is associated with hypertension in spontaneously hypertensive rats [28] and with Ang II-induced hypertension [29]. Internalization of the Na-Pi cotransporter type 2 into cytoplasmic vesicles has also been observed following acute increases in BP [26]. Although the PCT hoards the bulk of tubular sodium reabsorption, the loop of Henle, the distal tubule and the collecting duct also contribute to the PN mechanism [30,31]. For example, an acute increase in BP leads to internalization of the distal tubule sodium/chloride cotransporter [32], and BP is well known to be increased in hyperaldosteronism by an elevation in water reabsorption in the collecting duct.

A critical issue regarding PN is how the kidneys sense changes in BP and then duly adapt sodium handling along the tubules, given that renal blood flow (RBF) and glomerular filtration rate (GFR) are efficiently preserved constant over a wide range of BP levels (80–180 mmHg) by the action of the afferent myogenic response and by the tubuloglomerular feedback mechanism [30]. Indeed, PN does not involve modifications in GFR or RBF [33,34], implicating that the increase in natriuresis must be mediated by a decrease in sodium reabsorption [35], mainly in the PCT [27,36,37]. A first hypothesis contends that PN is mediated by an increase in renal interstitial hydrostatic pressure (RIHP). A second hypothesis explains the natriuretic effects of BP by the release of paracrine factors impinging on the tubular handling of sodium [30,31].

Elevations in RPP produce concomitants increments in RIHP, even if GFR and RBF remain unaltered [38], which are transmitted through the whole renal interstitium due to encapsulation. Indeed, renal decapsulation prevents the increase in RIHP and curtails the natriuretic response [38–40]. In volume-expanded rats, however, renal decapsulation decreases sodium excretion only by 40 %, which suggests that additional mechanisms must be involved in the PN response [40]. In agreement, administration of isooncotic solutions directly into the renal

interstice increase RIHP and enhances natriuresis in a similar manner as increments in RPP [36,38]. An increased RIHP favors natriuresis by two mechanisms. On the one hand, by physically opposing paracellular passive, osmotic reabsorption of sodium and water and promoting the opposite flux in the PCT and descending limb of Henle. On the other hand, RIHP might also be implicated in the redistribution of NHE3 out the luminal membrane of PCT epithelial cells that impairs sodium reabsorption [31]. This effect is significantly mediated by paracrine factors such as 20-hydroxyeicosatetraenoic acid (20-HETE) [41].

It remains unexplained how increments in RPP translate into higher RIHP in the presence of intact autoregulation (i.e., maintenance of RBF constant over a wide range of BP levels, provided by contraction or dilation of the afferent glomerular arterioles) (Fig. 1). A role for an increased medullary blood flow (MBF) began to gain importance in the study of the PN mechanism and long-term BP control when it was observed that sustained medullar interstitial administration of vasoconstrictor agents lead to hypertension [42,43], while the infusion of vasodilators in spontaneously hypertensive rats can decrease BP [44]. Based on observations that MBF was increased in volume-expanded rats [45–47], it was hypothesized that an increase in BP (and thus in RPP) would entail an elevation in MBF and an increase in hydrostatic pressure around the *vasa recta* that would disrupt the balance of Starling forces and increase RIHP in the medulla. Moreover, it was also suggested that an increase in MBF could also alter the osmotic gradient -washout- in the medulla and reduce tubular reabsorption in the loop of Henle [48,49], a hypothesis that has not received experimental backup [31].

It was then proposed that the increase in MBF might be facilitated by arterial shunts bypassing the glomeruli and connecting the afferent arteriole to the vasa recta [50] found in about 10 % of rat juxtamedullary glomeruli [51]. The increase in MBF secondary to a rise in RPP with no impact on whole kidney or cortical blood flow (CBF) [49] was explained by a redistribution of flow within the kidney [52]. Juxtamedullary nephrons, which canalize MBF, contribute only a small part of the total number of glomeruli, so that a 10 % increase in MBF would be compensated by a 1 % decrease in CBF, an alteration easily undetected by the regional flow measurement techniques available [52]. Based on computational modelling, Moss and Layton further argued that these shunts might open or close depending on the hydration status [50], although this hypothesis still lacks experimental support.

The increment in MBF might also result from poor medullary blood flow autoregulation, as occurs in volume-expanded rats [45–47]. However, the implication of poor medullary blood flow autoregulation in the PN mechanism has been also disputed when other authors observed, under different experimental conditions, that MBF is efficiently autoregulated in dogs [53], rabbits [54], rats with reduced diuresis [46,47], and even in other experiments with volume-expanded rats [34,55]. Because PN occurs in a variety of experimental and pathophysiological conditions, impaired juxtamedullary autoregulation cannot thus explain the increase in MBF [50,52].

Furthermore, recent studies have found that increasing MBF by 50 % does not decrease BP in three rat models of hypertension (spontaneously hypertensive rats, chronic infusion of Ang II and unilateral nephrectomy followed by high salt diet) within 30–75 min [56], and that exaggerated natriuresis in patients with essential hypertension following extracellular volume expansion happens without measurable elevations in CBF or MBF [57]. Therefore, it is unlikely that MBF constitutes an essential mechanism in the PN mechanism, although it may participate partially in specific circumstances [52].

1.3. Modulation of the pressure-natriuresis relationship: The basis of hypertension

A number of mediators and conditions modulate the pressure-natriuresis relationship so that more or less sodium is excreted for each level of BP, than that excreted by the sole action of pressure. Therefore, the PN relationship, and thus the PN curve, is shifted to the left or to the right, respectively. The position of the PN curve thus depends on the composite effect of the actual combination of effectors. Sustained intervention in this equilibrium, as by activating or inhibiting pro-natriuretic and anti-natriuretic mediators, moves the PN relationship accordingly. For example, chronic administration of an anti-natriuretic factor such as Ang II, or chronic inhibition of a pro-natriuretic mediator such as NO, renders experimental animals hypertensive. As a core characteristic of all forms of human and experimental hypertension, the PN curve is shifted rightwards with respect to the PN curve under normotensive conditions [7]. In hypertensive individuals natriuresis is less efficient than in normotensives through the whole range of BP and thus higher BP is necessary to attain sodium balance. Hypertension may only thus occur as a consequence of a primary offset of the intrinsic mechanisms linking BP with natriuresis, or by interfering with the modulators of this relationship (described next).

1.4. Paracrine regulation

Paracrine factors released in response to increases in RPP including Ang II, 20-HETE, nitric oxide (NO) and prostaglandins [30,31,37,58] modulate natriuresis and thus shift the PN curve to the right [31,59].

Prevention of the decrease in intrarenal Ang II following an acute increase in BP, reduces the natriuretic and diuretic response by 40–50 %, and interferes with NHE3 (but not Na-Pi cotransporter type 2) redistribution in the microvilli [60], and inhibits sodium/chloride cotransporter internalization in the distal tubule [32]. Moreover, Crowley *et al.* demonstrated the importance of renal type 1 Ang II receptors (ATR1) in BP control and in the development of hypertension by means of kidney cross transplantation studies among ATR1 knock-out mice and wild types. Lack of renal ATR1 was associated with lower basal BP and reduced Ang II-induced hypertension, while the opposite raised BP [61,62]. Subsequent studies observed that selective deletion of ATR1 in the PCT affects the basal control of BP [63–65], increasing the PN response and GFR [65], and reduces Ang II-induced hypertension [64,65]. Furthermore, ATR1 deletion is also associated with a reduced abundance of sodium transporters in the PCT and downstream [66].

Blockade of 80–90 % of 20-HETE formation decrease PN response by 40–50 % [41]. 20-HETE is a metabolite of arachidonic acid produced by cytochrome P450, its administration is associated with dose-dependent diuresis and natriuresis without GFR and RBF modifications [67]. The diuretic and natriuretic response to acute increases in BP is significantly decreased when cytochrome P450 inhibitors are present, because they prevent NHE3 redistribution and the inhibition of basolateral Na + pumps [68].

NO increases in the outer medulla in response to elevations in RPP. It has been hypothesized that the increase in shear stress in the preglomerular vasculature due to the autoregulatory vasoconstriction in response to an increase in RPP activates endothelial nitric oxide synthase and NO production, which increases MBF and RIHP [31] through cGMP and protein kinase G signaling [69,70]. NO also potentiates natriuresis by inhibiting sodium reabsorption in the PCT and the thick ascending limb of Henle and in the collecting duct [71], by acting on the Na + K + 2Cl-cotransporter [72] and the Na +/H + exchanger [73]. Interestingly, RIHP and natriuresis/diuresis, but not MBF, are reduced following decapsulation, which suggest the participation of NO in shaping PN [74]. Inhibitors of medullary NO synthase reduce sodium excretion and MBF [75–77], while their chronic administration results in increased BP [43]. Congruent, lower levels of medullar NO have been observed in Dahl salt-sensitive rats than in normotensive rats [78].

Prostaglandin E2 is involved in the regulation of sodium reabsorption in the PCT in response to increased RIHP [79] and also, in the inhibition of sodium reabsorption in the collecting duct [80]. Prostaglandin E2 is a potent vasodilator in the medulla and counteracts the vasoconstrictor effects of the intrarenal Ang II [81]. The use of cyclooxygenase 1 antagonist blunts the natriuretic response to increased RIHP [82,83].

Other paracrine factors interfering with the PN mechanism include ATP, which modulates sodium transport via epithelial sodium channels in the collecting duct [84], and endothelin-1 that via ET_B receptor in the medulla promotes diuresis and natriuresis through NO, cGMP, and protein kinase G signaling [85]. Also, medullary O_2^- and H_2O_2 reduce the natriuretic response to increased RPP [86].

1.5. Pathophysiological conditions affecting pressure natriuresis: Focus on salt sensitivity

Condition such as loss of nephrons, increased sympathetic activity, bilateral renal artery stenosis, and salt sensitivity are known to shift the normal pressure natriuresis curve to the right. Stenosis and increased sympathetic activity cause a parallel shift to the right and represent models of salt-resistant hypertension, whereas loss of renal mass and Ang II infusion represent salt-sensitive models with a decreased slope of the curve [87,88].

Salt-sensitivity defines an exacerbated increase in BP after a high salt intake compared to salt-resistance, in which BP is not (or only slightly) increased [89]. Salt sensitivity is present in normotensive and hypertensive individuals and is associated with increased cardiovascular risk and mortality [90]. BP response to high sodium intake varies in each individual [89]. Genetic, hormonal, nervous and environmental factors may influence interindividual variations in salt sensitivity [91], which is also favored by older age, obesity and black race [89,91].

The pathophysiologic mechanisms explaining salt-sensitive hypertension are not fully clarified. Guyton and colleges proposed that the involvement of a kidney dysfunction encompassing an inefficient sodium excretion during salt intake would be followed by a proportional water retention to preserve osmolarity and lead to an increase in extracellular volume and a rise in BP [6,92,93]. The slope of the PN curve in salt-sensitive hypertension is less steep and therefore is necessary more pressure to eliminate the same amount of salt [88,93].

An alternative hypothesis is supported by observations that salt-resistant patients show a greater reduction in total peripheral resistance (TPR) during salt intake than salt-sensitive patients. According to this hypothesis, salt sensitivity is explained by a defective decrease in TPR during high salt intake [94]. Nevertheless, other authors argue that TRP alterations are transient and its influence on long-term BP control is limited. Using HumMod, a complex mathematical model of interactive human physiology, Clemmer *et al* demonstrated that maintaining TPR constant during high salt intake produces only an acute (transient) BP change that was lost after one week. Moreover, these authors also demonstrated that increased tubular reabsorption of sodium and the renin-angiotensin-aldosterone system are important factors in salt-sensitive hypertension [88]. Consistent with this argument, several studies have shown differences in sodium reabsorption between salt-sensitive and salt-resistant hypertension. Salt-sensitive individuals show higher sodium reabsorption in the PCT than salt-resistant individuals [95,96]. In addition, Dahl salt-sensitive rats with high-salt diet showed an increase in epithelial sodium channels expression and activity (despite aldosterone decrease) compared with Dahl salt-resistant rats [97].

The case of salt-sensitivity exemplifies how conditions interfering with the renal handling (mostly reabsorption) of sodium impact the pressure natriuresis relationship by disengaging the stablished natriuresis obtained at each level of BP. Conditions chronically altering natriuresis may thus form part of the regulation network governing the basal level of BP and may thus contribute to conforming the BP status within the normotensive or the hypertensive range.

1.6. The sympathetic nervous system in hypertension: Effects of renal sympathetic activation on renal function

Although its multifactorial etiology, hypertension initiation and maintenance has long been related to increased activity of the sympathetic nervous system (SNS) [11]. The SNS exerts many BP-modulating effects that regulate cardiac output and TPR. None of these effects may though explain a role in the long-term regulation of BP. It is specifically the renal component of the SNS that, by modulating the PN relationship, may participate in the genesis and development of hypertension [98]. Consistent with this concept, rats with experimental and spontaneous hypertension undergo a significant reduction of BP after renal denervation [99] that provides strong evidence in favor of a role of the SNS in the long-term control of BP. In fact, renal denervation has become a therapeutic alternative within the antihypertensive arsenal [100] and, according to the European guidelines on hypertension management, the election treatment for drug-refractory hypertension [101].

Over-activity of renal sympathetic nerves alters renal hemodynamics, urinary sodium excretion and renin secretion, which in turn lead to a rightward shift of the pressure-natriuresis curve, as described in section 3. Sympathetic neural pathways innervating the kidneys originate at the intermediolateral column of the spinal cord, from the T6 to the L2 segments (although interspecies variability exists). Neural projections exit the spinal cord by the ventral horns and the sympathetic preganglionic fibers synapse on the cell bodies of postganglionic neurons in either paravertebral chain ganglia, or one of the prevertebral ganglia (aorticorenal, celiac, superior mesenteric). Interspecies variability is also significant at this level [102]. Renal sympathetic postganglionic nerves exit the ganglia and enter the hilus of the kidney along the renal arteries and veins. Fiber bundles branch around the vasculature penetrating throughout the renal cortex, the outer band of the medulla and, to a lesser extent, along the inner medulla [103].

Renal sympathetic efferent nerves are mostly adrenergic and thus involve norepinephrine as the primary neurotransmitter [104]. Sympathetic efferent neurons innervate all cortical and outer medullar segments of the intrarenal vasculature (being more abundant in afferent and efferent glomerular arterioles) [103], the granular cells of the juxtaglomerular apparatus [105], and the basement membrane of tubular epithelial cells within the nephron [106]. Vascular smooth muscle cells contain α_{1A}-adrenoceptors whose activation mediate vasoconstriction of afferent and efferent arterioles decreasing RBF and GFR. This is an effect whose magnitude is directly proportional to the level of sympathetic activation [104]. Juxtaglomerular cells have a high number of β_1-adrenoceptors that when stimulated cause renin secretion and, subsequently, activation of the (local and systemic) renin-angiotensin system leading to Ang II and aldosterone production. The more intense the efferent sympathetic nerve activity, the higher the renin secretion rate [107]. Within the nephron, adrenoceptors modulate different functions which eventually lead to decreased natriuresis. In the proximal tubules, catecholamines activate the basolateral Na^+/K^+-ATPase [108], stimulate α_{1A}- and α_{1B}-adrenoceptors, and increase NHE3 activity allowing Na^+ entry from the tubular lumen into the epithelial cells and contributing to an increase in sodium and water reabsorption [109].

The different effects caused by renal sympathetic nerve activation have been shown to follow a progressive recruitment pattern in which growing stimulation leads to the activation of one, two or three of these functions [102]. In anesthetized dogs [107,110,111], rats [112,113] and cats [114], when the renal sympathetic nerve is directly stimulated at low intensity, only renin secretion is enhanced, with no evidence of modifications in fluid/sodium reabsorption, RBF or GFR. As stimulation is increased, along with a higher secretion of renin, decreases in natriuresis and diuresis are observed, again with no changes in renal hemodynamics. Finally, RBF and GFR reductions are only observed at the highest renal sympathetic nerve activity (RSNA) levels, which also cause more extensive secretion of renin and a considerable decline of sodium and water excretion. This progressive sequence was also evidenced in human patients following increasing activation of the sympathetic nervous system [115]. Escalating functionality endows the SNS with physiological windows for the individual control of different renal functions. However, as these functions mutually interact, a balanced

status exists that may be disrupted by pathologically abnormal renal sympathetic hyperactivity. Accordingly, hypertension must be understood as one of the elements of a complex equilibrium of renal (and non-renal) functions among which increased RSNA may be a primary alteration or a secondary and necessary response to optimize homeostasis under reset circumstances. In this sense, knowledge of the mechanisms regulating RSNA and unveiling the origin of its alterations is of critical importance to address hypertension therapy.

1.7. Modulation of renal sympathetic nerve activity: Potential origins of its hyperactivation in hypertension

Central mechanisms in the brainstem and hypothalamus are able to modulate the level of renal sympathetic nerve activity. Sensory information originated in arterial baroreceptors and peripheral organs (including the kidneys) travels to the nucleus tractus solitarius (NTS) where is integrated and results in activation of the caudal ventrolateral medulla (CVLM) and the rostral ventrolateral medulla (RVLM). The paraventricular nucleus in the hypothalamus also provides direct inputs [116]. The RVLM is a key player in the regulation of efferent renal nerve activity and BP by its sympatho-excitatory function. Depressing RVLM activity leads to important reductions in BP and sympathetic nerve activity [117]. RVLM neurons project to sympathetic preganglionic neurons in the spinal cord that further project to the kidneys via postganglionic neurons that innervate different renal structures [118], as described in section 4.

Besides the efferent innervation, which transmits information from the central nervous system to the renal structures, kidneys are also innervated by sensory or afferent nerve fibers that project towards the RVLM via the NTS and paraventricular nucleus and modulate sympathetic efferences to peripheral organs (including the kidney itself) [119,120]. These sensory nerves are mainly located within the wall of the renal pelvis [121] and around the branches of the renal artery (i.e., in the interlobular and arcuate arteries, and to a lesser extent around interlobular arteries and afferent arterioles) [122]. The main neurotransmitters for these sensory nerves are substance P and calcitonin gene-related peptide [123]. Three classes of stimuli activate afferent renal nerves: mechanical deformation of nerve endings (such under increases in pelvic pressure, i.e., during urine flow), changes in the chemical environment, and renal pain [124,125]. On the other hand, chemosensitive nerves respond to renal ischemia or changes in the urine chemical composition [126]. The importance of the sympathetic afferent renal nerve activation is related to the role of the reno-renal reflex in BP regulation [127], as described in section 5.3.

1.8. Role of the baroreflex in the long-term control of renal sympathetic activity

Baroreceptors are specialized stretch receptors sensitive to changes in BP, which are located within specific areas of arterial blood vessel walls (specifically, in the carotid sinus and aortic arch) [128]. When activated by stretching (as it occurs when BP increases), baroreceptors globally inhibit sympathetic activity, and hence RSNA, thus achieving a rapid control of BP by lowering TPR and cardiac output. More specifically, when BP increases, aortic and carotid baroreceptors are activated and stimulate NTS neurons that project to and activate CVLM neurons. CVLM inhibitory GABAergic neurons suppress RVLM neuronal activity, leading to decreased activity of the sympathetic nerve and hence blood pressure reduction [118].

Baroreflex has long been well recognized as a key mechanism in the acute regulation of BP. Until two decades ago, it was thought that this mechanism had no role in the long-term control of BP. First, because during sustained changes of BP, baroreceptors rapidly adapt (within hours or few days) to the new level of BP and reset their basal activity to the new level of BP. In 1956, McCubbin *et al.* recorded baroreceptor nerve activity at different levels of endosinus pressure in control and hypertensive dogs. They demonstrated that whereas normotensive animals showed afferent nerve activity at 60, 120, and 240 mmHg, hypertensive animals only showed nerve activity at 240 mm Hg. Moreover, normotensive dogs showed continuous firing of baroreceptors at high pressure levels whereas baroreceptors in hypertensive dogs fired in an intermittent pattern following the same stimulus. The authors concluded that in hypertensive dogs, baroreceptors had been reset to buffer changes in BP at a higher level [129]. Subsequent studies in rats demonstrated that baroreceptor resetting reached its maximum 48 h after the increment in BP [130]. Many other authors have confirmed baroreceptor resetting after sustained changes of BP in several species, including rabbits [131,132], rats [133,134] and dogs [135,136].

A second argument that discarded baroreceptors as long-term regulators of BP came from the observation that sinoaortic denervation (SAD, an often-used method to disrupt baroreceptor afferent signals to the brain) did not cause chronic increases in average BP. This was first demonstrated by Cowley in 1973, in an interesting study where BP was continuously monitored 24 h per day in control and SAD dogs. Their results showed very similar average 24-hour BP in SAD and control dogs. However, SAD dogs showed important fluctuations in arterial blood pressure throughout the day whereas control dogs showed much stable patterns, thus indicating that baroreflex minimizes changes in BP rather than sets the chronic level of blood pressure [137]. After this study, many others have confirmed in different species that SAD did not affect long-term values of mean BP [138–140].

In the early 2000 s, the dogma that baroreceptors completely and rapidly reset upon chronic changes in BP was questioned or suspected not to be entirely correct. Lohmeier et al. (2000) used a dog model with surgical split bladder and unilateral renal denervation, which allowed separate assessment of urinary sodium excretion from both kidneys while exposed to the same humoral influences and similar perfusion pressure. With this model, differences in excretion between both kidneys indirectly reflect RSNA level. Hypertension was then induced by continuous infusion of Ang II for 5 days, which elevated BP 30–35 mmHg. The results showed an increase in sodium excretion in the innervated kidney in comparison with the denervated kidney. This difference could only be attributed to the suppression of RSNA in the innervated kidney, and hence a lack of such inhibitory influence in the denervated kidney. Then, dogs were submitted to cardiopulmonary denervation and SAD, and Ang II infusion was administered again for 5 days, showing a decrease in sodium excretion in the innervated kidney, the opposite response to that observed when the cardiovascular afferents were intact. These data suggested that during Ang II-induced hypertension, RSNA is inhibited by activation of baroreceptors or cardiopulmonary afferents (or both). Moreover, when these reflexes are abolished, Ang II increases sympathetic activity [141]. As 5 days of Ang II infusion is not enough time to reach steady-state conditions, Lohmeier et al. decided to expand their analysis and performed the experiments during longer periods of Ang II induced hypertension (10 days of Ang II infusion), thus reaching stable hypertension and sodium balance. The increase in sodium excretion in the innervated kidney was sustained during the 10-day infusion, highlighting that baroreflex resetting is not complete as inhibition of RSNA is maintained during chronic Ang II hypertension [142].

At this point the increased sympathetic outflow regained prominence as a possible player in hypertension development, as well as the potential role of the baroreceptors in the long-term control of BP. Further research using telemetry-based devices to directly and continuously record the activity of renal sympathetic nerve was performed in rabbits before, during and after 7 days of Ang II-induced hypertension [143]. Electrical recordings revealed a sustained decrease in RSNA in response to Ang II infusion for at least 7 days. Baroreflex response was determined before and on days 2 and 7 of the Ang II infusion, showing no evidence of resetting of the mean arterial pressure-RSNA curve. This indicated that baroreflexes continue to influence RSNA during sustained changes in arterial pressure and support their role as mediators of the

sympathoinhibition during Ang II infusion [143]. Moreover, when rabbits were previously subject to SAD, RSNA was not inhibited 7 days after Ang II infusion [144]. These results confirmed incomplete baroreceptor resetting under Ang II hypertension (at least those involved in RSNA) and highlight the importance of baroreflex control of renal function in the BP regulation not only in acute but also in chronic phases of Ang II hypertension.

Despite the demonstration that baroreceptor resetting is not complete under certain conditions, the second argument against a role for baroreceptors in long-term regulation of blood pressure (SAD do not lead to hypertension) remained unexplained. However, demonstration of the enormous plasticity of the nervous system and neural remodeling might explain the development of central adaptations following SAD (i.e., any remaining fibers could compensate the effects of denervation) which are able to reduce the initial sympathetic activation and hence the associated increase in BP [145]. Consistent with the rapid increase of blood pressure after SAD that normalizes within 3 days in rats [138], SAD causes a severe but short-lasting increase of sympathetic nerve activity and activation of C1 presynaptic neurons [a subset of RVLM neurons], which returns to normal levels within a few days [146]. Hence, the hypothetical mechanism which leads to restoration of the sympathetic nerve activity and blood pressure to control levels after SAD should be upstream from the RVLM [147]. This mechanism might be related to neuron compensation or homeostatic plasticity [148], reinnervation of arterial baroreceptor afferences [149] or enhancement of RVLM neuronal activity resultant from cerebral blood flow-mediated regulation [150].

Interestingly, when baroreceptors were chronically stimulated with electrodes implanted around the carotid sinus, a reduction in sympathetic activity and BP ensued and persisted for 3 weeks with very little time-depending attenuation [151–153]. In contrast to the observations after SAD, these interesting studies demonstrate that chronic baroreceptor stimulation is not compensated or attenuated by decreases in the inhibition of sympathetic activity mediated by central neuroplasticity and suggest that resetting, instead of being centrally mediated, must be due to electrical adaptions that occur at the baroreceptors themselves. In fact, recent and ongoing studies are investigating the use of baroreflex stimulation to reduce blood pressure in different forms of drug-resistant hypertension [154]. Activation of baroreceptors with specially designed devices that deliver continuous stimulation signals to the carotid sinus, chronically suppresses sympathetic nerve activity with no evidence of resetting upon time, which leads to a decrease in blood pressure of 20 mmHg and a reduction of heart rate of 15 beats/min [152]. In summary, the theory of arterial baroreflexes contribution to long-term control of sympathetic activity and BP has been recently rescued and is becoming increasingly important in the study of new therapeutic strategies in the treatment of hypertension from different etiologies.

1.9. Baroreceptor-mediated control of blood pressure beyond renal sympathetic activity

Further research showed that bilateral renal denervation does not prevent the long-term fall of BP caused by baroreceptor stimulation, which unveils additional baroreflex-mediated mechanisms independent of RSNA [155]. Interestingly, in these experiments a noticeable (two- to threefold) increase in plasma levels of atrial natriuretic peptide (ANP) was observed [155]. Activation of the baroreflexes causes a sustained reduction in heart rate due to the suppression of cardiac sympathetic tone and the increment of cardiac parasympathetic nerve activity [152,155–158]. This inhibition of cardiac output (mainly by decrease in heart rate) together with an increase in plasma volume was hypothesized to be responsible of an increase in cardiac pressure that might lead to atrial wall stretching and a subsequent release of ANP. In this way, increased levels of circulating ANP after baroreceptor stimulation would contribute to the increased sodium excretion and reduced BP [155].

In support to this hypothesis, in subjects with resistant hypertension who had been previously subjected to renal nerve ablation therapy with no successful results in lowering their BP, subsequent baroreceptor electrical stimulation with implantable devices produced a sustained reduction of BP [156,159]. Additionally, treatment of hypertensive patients with bisoprolol (a beta-adrenergic blocker) led to bradycardia, atrial distension and increased plasma levels of ANP which contributed the antihypertensive effects of the drug [160].

Mathematical models integrating pathophysiological processes have reveal additional support to the role of baroreceptor mediated ANP in BP regulation [161]. A recent study by Clemmer *et al.* (2018) using the HumMod model revealed that during chronic activation of the baroreflexes, ANP provides the pivotal link between the heart and the kidneys that mediates an increased natriuresis and contributes to the decrease in BP. According to this model, when renal sympathetic nerve activity is maintained at control level, baroreceptor activation leads to an exaggerated ANP secretion and subsequent natriuresis to attain BP control. Interestingly, if plasma ANP levels are also held constant at control levels together with clamped renal sympathetic nerve activity (to prevent the increase in ANP), baroreflex activation is unable to achieve sodium balance at decreased blood pressure levels. These experiments highlight the relevance of mediated ANP-mediated, compensatory mechanisms to increase natriuresis in the absence of renal sympathoinhibition [162].

More recently, another *in silico* study using HumMod assessed the contributions of renal sympathetic nerve activity and ANP levels to the regulation of BP during baroreceptor activation in a virtually simulated population with obesity-induced hypertension [163]. The results again suggested that during chronic baroreceptor activation, both inhibition of RSNA and enhanced levels of ANP contribute in an independent manner to reduce BP. These results also unveil some cooperative redundancy between these two mechanisms, as they individually reduce blood pressure in the absence of the other. In these simulations the rise of ANP levels was also accompanied by reduced sodium reabsorption [163]. Altogether, these studies introduce ANP and baroreceptor activation as potential antihypertensive strategies for conditions in which renal nerves are not intact.

1.10. The reno-renal reflex in the long-term control of renal sympathetic activity

Demonstration of a reno-renal reflex was obtained in rats in the mid-1980 s. Stretch activation of the mechanosensory afferent nerves elicited a reflex inhibition of the ipsi- and contra-lateral kidney efferent sympathetic nerve activity that leaded to compensatory natriuresis and diuresis [164–166]. This reflex was shown to operate in healthy normotensive animals under conditions involving a high urinary flow rate (i.e., high sodium diets or volume expansion), in which afferent nerves are tonically active. This result is supported by studies in which activation of afferent renal nerves is observed when the healthy animals are subject to a 3 mmHg increase in the renal pelvic pressure (a magnitude often observed during physiological conditions of high urine flow rate) [124,167,168]. Moreover, unilateral renal denervation (afferent and efferent nerve fibers) blocked the increased natriuresis previously observed after increasing afferent renal sympathetic nerve activity by pelvic wall stretching, thus further supporting the existence of an inhibitory reno-renal reflex mechanism [165].

Under physiological conditions, efferent renal sympathetic nerve activity is maintained at low levels by means of the negative feedback exerted by the reno-renal reflex, thus controlling natriuresis and BP. However, the interplay between sensory afferents and sympathetic efferent nerves is intricate, increases in efferent renal sympathetic nerve activity enhance afferent renal sympathetic nerve activity [169], and the increased afferent activity inhibits efferent activity by the negative feedback loop of the reno-renal reflex, as a regulation system preventing overactivation of renal sympathetic nerves. Activation of this reflex seems to significantly contribute to the regulation network involved in

the control of water and sodium homeostasis, and thus also of volemia and BP. This concept is supported by the low-activation threshold of the renal mechanosensory nerves and the natriuretic effect of the reno-renal reflex. Indeed, in healthy animals with intact nerves, this mechanism is activated following sodium or fluid overload as in, i.e., rats fed with a sodium enriched diet, which show an increased reno-renal reflex and an enhanced excretion of sodium when compared with rats fed with low sodium diet [167]. Furthermore, intact afferent renal innervation has been demonstrated to be essential to increase the sodium excretion while maintaining BP at basal levels when dietary sodium intake is high [170]. In fact, rats in which dorsal rhizotomy (DRX) is performed to specifically interrupt afferent renal innervation, display propensity to NaCl-sensitive hypertension [171,172].

The increase in BP observed in DRX rats fed with a high sodium diet raises the interesting question of why the arterial baroreflex does not buffer the increased BP or the enhanced efferent sympathetic nerve activity under these conditions, given that baroreflexes are activated after high-sodium intake [173]. In this regard, the extent of BP increment produced by feeding rats with a high sodium diet is similar in DRX and in SAD [174]. This observation may be explained by central interaction of the neural input driven by baroreceptors with the renal afference, to yield an integrated renal sympathetic nerve efferent response [175–178]. Furthermore, the control of the renal efferent sympathetic nerve activity by the arterial baroreflex was altered in DRX rats with a high-sodium diet whereas somatic and environmental stimulation of these rats did lead to an increased efferent renal sympathetic nerve activity, suggesting that the activation of renal afferent nerves which takes place under high-sodium diet conditions contributes to the inhibition of the renal efferences mediated by baroreceptors, in order to prevent sodium retention [171].

The negative feedback of the reno-renal reflex contributes to sodium homeostasis by preventing sodium retention and overactivation of the renal sympathetic nerves and hence is an important mechanism in the control of BP. Nevertheless, there are pathological conditions (e.g., some forms of chronic renal disease) in which this inhibitory reflex is impaired. In these scenarios, renal afferent activation fails to inhibit renal efferent nerve activity resulting in a vicious cycle of increased sympathetic activity with the consequent increase in BP [179–181]. In agreement, hypertension induced by different renal insults (namely renal artery stenosis, or renal damage induced by phenol) is attenuated by ipsilateral removal of afferent inputs [182–184] but not by contralateral afferent denervation [184].

2. Integrative conclusions

As a chronic elevation of BP, hypertension can only ensue following distortion of the sole BP-regulating mechanism known to work in the long term with infinite gain and non-adaptive performance, namely pressure-induced natriuresis. Because of these characteristics, PN imposes the basal level of BP on which other regulation mechanisms induce or reverse transitory variations. PN is mediated by paracrine factors and changes in RIHP occurring even under effective renal autoregulation conditions. However, how changes in renal perfusion pressure (i.e., systemic BP) and paracrine influence modify RIHP is still undetermined. In turn, increases in RIHP (following BP elevation) oppose tubular sodium (and water) reabsorption and thus favor sodium (and water) excretion to reduce volemia and BP (Fig. 1). The relationship between specific levels of BP and the corresponding natriuresis (and diuresis) is defined by the PN curve that depicts a positive correlation of increasing BP levels translating into growing natriuresis and diuresis. The position and the shape of this curve is determined by the composite effect of all the determinants of sodium reabsorption, including BP (through RIHP) and endocrine and paracrine mediators modulating the activity of membrane transporters, whose activation tone is imposed by the pathophysiological scenario. Conditions or effectors promoting sodium reabsorption (i.e., reducing sodium excretion) shift the PN curve towards the right, as higher BP is necessary for each level of natriuresis (Fig. 2).

As a characteristic of all forms of human and experimental hypertension, the hypertensive PN curve is displaced to the right of the normotensive curve. The cause or causes of this shift are yet undetermined in most forms of hypertension. Cases with unknown cause are classified under the term *essential hypertension*. Given the multifactorial nature of hypertension, as revealed by epidemiological studies, it is likely that this syndrome fosters a variety of etiologically distinct types of hypertension unleashed by different factors decoupling the normal PN relationship. One of these factors, commonly found in most forms of hypertension, is the hyperactivity of the SNS and, more specifically, of the renal sympathetic nerves. Increased RSNA, which results from the altered equilibrium in the complex interplay of inputs from the baroreceptors and the reno-renal reflex at the central NTS, reduces natriuresis and reshapes the PN relationship rightward (Fig. 2).

However, because BP interacts with other important renal functions such as glomerular filtration and shares common regulation mechanisms, it is uncertain whether this increase in RSNA is a primary pro-hypertensive event or forms part of an adaptive response elicited to defend additional renal or extrarenal functions, such as peripheral tissue perfusion. Accordingly, an optimized and personalized approach to

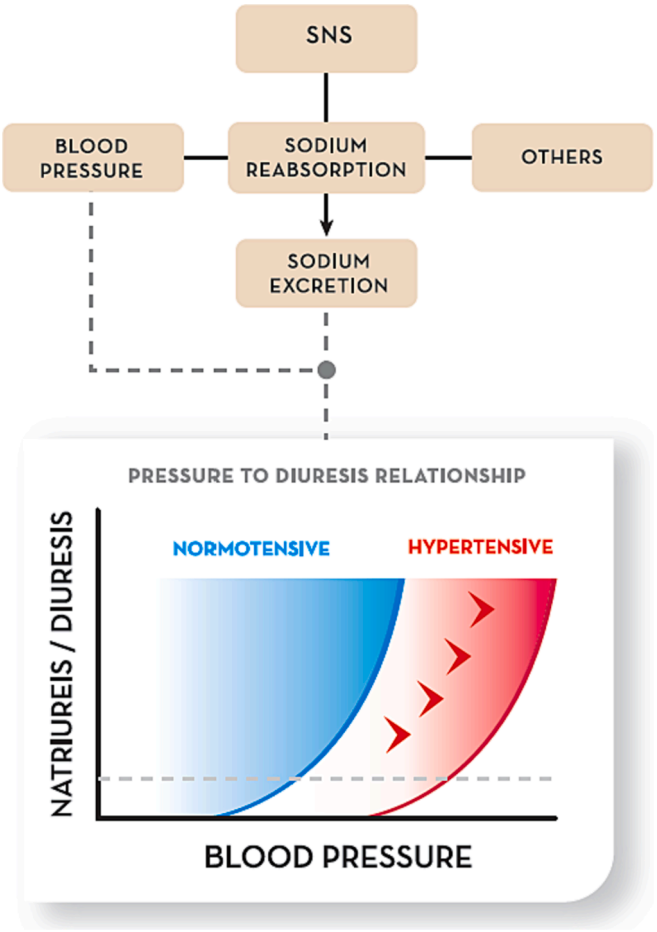

Fig. 2. Schematic representation of the action of factors external to the intrinsic pressure-to-natriuresis mechanism at modulating the pressure-natriuresis relationship. Among these factors, the action of the nervous system through the renal sympathetic activity is highlighted. External factors modulate the pressure-natriuresis relationship mainly by acting on tubular sodium reabsorption. A rightward displacement of the pressure-natriuresis curve (lower panel) and hypertension may thus result from a pathological alteration or physiological regulation of the intrinsic pressure natriuresis mechanism, or of the external factors.

hypertension must also integrate the whole equilibrium of functions to determine in each case the origin of the increased RSNA, and whether it becomes a suitable target for therapeutic intervention. In perspective, due to the complexity of these relationships, artificial intelligence driven computational modelling of these physiological functions might guide knowledge-based intervention.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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