The Endocrine Regulation of Blood Pressure 23

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Abstract

Blood pressure is a vital parameter controlled by very complex mechanisms mainly involving neuronal and endocrine effectors. The sympathetic-adrenal system (SAS) and the renin-angiotensin-aldosterone system (RAAS), besides paracrine mechanisms in the vessel wall, are the main players of these complex networks that permit the maintenance of blood pressure, sufficient for the perfusion of organs and tissues. These systems regulate the cardiac pump, the circulating volume, and the peripheral resistances. They are the targets of almost all the drugs prescribed to hypertensive patients.

In addition to these major neurohormonal systems, many other factors can modulate blood pressure participating in the control of the blood volume or the peripheral resistances. These factors include, among the others, natriuretic peptides, dopamine, nitric oxide, endothelin-1, vasopressin, and cortisol.

Keywords

Blood pressure • Sympathetic-adrenal system • Renin • Angiotensins • Aldosterone • Vasopressin • Nitric oxide • Endothelin-1 • Dopamine • Natriuretic peptides • Cortisol

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Contents

Introduction

Cells, tissue, and organs need blood supply to survive and function. Blood circulates in a closed system constituted by arteries and veins, because of pressure gradients generated by the contractile activity of the heart. The blood pressure (BP) warrants the perfusion of the tissues and is the results of cardiac output, blood volume, and peripheral resistances. It is continuously monitored and controlled by a complex network of integrated systems regulating these three main factors. Among these, the sympathetic-adrenal system (SAS) and the renin-angiotensin-aldosterone system (RAAS) play a major role in BP control although many other factors participate in this extremely complex regulation acting at the central (aortic) as well as the peripheral (tissue) levels. As a consequence, almost all the most widely used antihypertensive drugs are aimed at lowering the blood volume and the activity of the SAS and the RAAS.

In this paper we will review the physiology of these two systems and we will briefly mention the many other "minor" factors influencing BP.

The Sympathetic-Adrenal System (SAS)

The SAS is part of the autonomic nervous system that also includes the parasympathetic nervous system. It is involved in the homeostasis of many vital functions such as the cardiovascular (Goldstein 1995).

The anatomical and chemical characteristics of the SAS allow very rapid responses to the internal and external stimuli, and therefore the SAS is the quickest system devoted to the maintenance of cardiovascular homeostasis.

The SAS is functionally integrated with other homeostatic systems such as the endocrine system, whose responses, which are slow-onset but more persistent, may, in turn, modulate the SAS function (Goldstein et al. 1998).

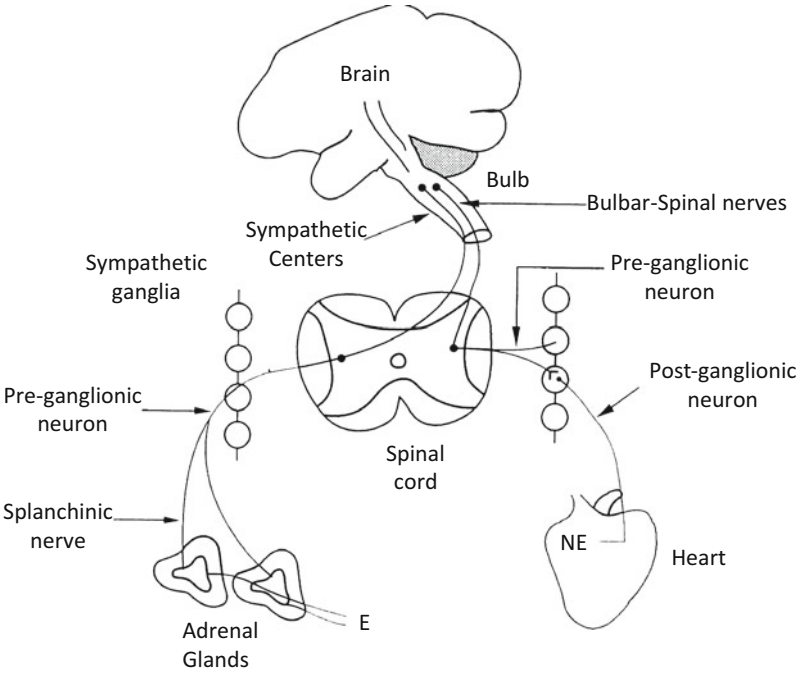

Fig. 1 Schematic representation of the anatomical organization of the sympathetic-adrenal system

The SAS has two effector branches constituted by a neuronal and an endocrine one: the first is represented by the sympathetic nerves releasing the neurotransmitter norepinephrine (NE) in the synaptic cleft; the second is represented by the chromaffin cells of the adrenal medulla secreting the hormone epinephrine (E) in the blood stream (Fig. 1).

The effector branch unit of the sympathetic system is composed by two neurons: a preganglionic neuron whose cell body is in the mediolateral area of the spinal cord and a postganglionic neuron, innervated by the previous one in the sympathetic ganglion. The cell bodies of the preganglionic neurons are located in the spinal cord at the level of the first thoracic vertebra down to the second lumbar one. The sympathetic ganglia are localized at the same levels on both sides of the column. The postganglionic neurons innervate peripheral vessels, tissues, and organs diffusely. The neurotransmitter released by the preganglionic nerve is acetylcholine, while the postganglionic nerve releases NE.

The activity of the sympathetic nerves is strictly controlled by neurons of the sympathetic centers located in the medulla oblongata. The activity of these sympathetic centers is, in turn, regulated by nervous pathways coming from the periphery of the body, as well as from higher centers of the brain. As a whole, the activity of the SAS is the final result of the integration of all the stimuli impinging on the medullary sympathetic centers (Goldstein 1995).

Among the most important factors modulating the activity of these centers are the afferent inputs from sites of the peripheral circulation, such as the arterial high-pressure and cardiac baroreceptors that are stretch receptors located in the walls of the arteries (especially important is the carotid sinus at the bifurcation of the common carotid artery) and cardiac/venous low-pressure receptors located in the walls of the cardiac atria.

The arterial high-pressure baroreceptors monitor the stretching of the arterial walls and elicit reflex responses that control arterial BP. The low-pressure baroreceptors monitor the stretch of the cardiac and pulmonary arterial walls and elicit reflex responses that maintain central blood volume (Goldstein 1995).

The SAS is differently activated by stressors: standing up elicits the response of the neuronal branch of the SAS characterized by NE release from the sympathetic nerve terminals, whereas hypoglycemia preferentially causes E release from the adrenal medulla. Both the branches are highly activated in case of a profound hypotension.

Sympathetic nerve stimulation causes a rapid constriction of arterioles, increasing regional resistance to blood flow and shifting the blood to other regions with lower resistance.

The arteriole vasoconstriction is mediated by the adrenergic α-receptors. At the cardiac level, the sympathetic discharge-induced NE release activates the β-receptors, thus increasing heart rate and contractility. Therefore, a diffuse sympathetic stimulation causes a BP increase due to increased cardiac output and peripheral resistances.

At the kidney level, sympathetic activation leads to a decrease in sodium excretion and, through β-receptor activation, to an increase in renin release by the juxtaglomerular cells (see below).

The hormonal branch of the SAS includes preganglionic neurons, which innervate the chromaffin cells of the adrenal medulla that may be considered a modified sympathetic ganglion. Chromaffin cells do not possess neuritis but secrete catecholamines, mainly E, in the circulation. An increase in E plasma levels causes a rapid increase in the heart rate and contractility, an increase in renin release, and a redistribution of blood volume toward the heart, brain, and skeletal muscles and away from the kidneys, skin, and gut.

A pathological catecholamine release in the blood circulation, as well as an abrupt neuronal sympathetic discharge, causes a rise in BP, sometimes to very high levels. Such conditions are exemplified by the catecholamine release by pheochromocytoma/paraganglioma (Lenders et al. 2005) and also by the sympathetic activation in panic disorders. Increased sympatho-neuronal outflow associated to hypertension is present also in various neurologic syndromes such as autonomic epilepsy, baroreceptor deafferentation, Guillain-Barre syndrome, generalized seizures, and bladder stimulation in tetraplegic patients (Goldstein 1995).

Conversely, a pathological decrease in sympathetic outflow induces a decrease in BP that, when profound, causes a vasodepressor syncope with fainting. Neurogenic orthostatic hypotension is present in diseases such as pure autonomic failure, multiple system atrophy, and dopamine-β-hydroxylase deficiency.

The Renin-Angiotensin-Aldosterone System

Over a century after the identification of a "renin-like" activity in the canine kidney by Tigerstedt and Bergman (Tigerstedt and Bergman 1898), and more than 50 years after the purification of the vasoactive peptide angiotensin II (Ang II), carried out independently by Page and Braun-Menendez (Braun-Menendez and Page 1958), the characterization of the renin-angiotensin-aldosterone system (RAAS) continues relentless, thus broadening our understanding of the function of this key hormonal system, which has paramount clinical and therapeutic implications. The RAAS is currently regarded as both an endocrine and a paracrine system (Rocha and Stier 2001). The circulating RAAS entails a coordinated hormonal cascade, which begins with the biosynthesis of prohormone (prorenin) that undergoes proteolytic cleavage of the prosegment N-terminus peptide to give the bioactive renin. The latter is a secretory glycoprotein mainly made by the juxtaglomerular cells (JG) that line the afferent arteriole of the renal glomerulus. Renin is stored in granules of the JG cells and released first into the renal circulation and then, systemically, through a highly regulated exocytic process. Besides and in parallel to this, the kidney constitutively releases prorenin, which can be activated at the level of the pro(renin) receptor (Rocha and Stier 2001). Compelling evidence now indicates that the RAAS also acts as a paracrine system, which is directly involved in regulating the function of many organs, such as the adrenal gland, the reproductive system, the visceral adipose tissue, the vascular tissue, the eyes, the heart, and the brain.

Control of renin secretion is a key determinant of the RAAS activity, because renin regulates the initial and rate-limiting step of the RAAS by cleaving the N-terminal portion of the renin substrate (angiotensinogen) to form the biologically inert decapeptide angiotensin I (Ang I). Although mainly produced in the liver, angiotensinogen is also synthesized locally in tissues, such as the vessel wall and adipocytes. These sites might attain importance in disease conditions, as shown by the observation that adipocyte angiotensinogen deficiency, while not affecting plasma angiotensinogen levels under normal conditions, greatly reduced circulating Ang II under high-fat diets.

Ang I, the inactive decapeptide formed by renin, is hydrolyzed by the angiotensin-converting enzyme type 1 (ACE 1), which removes the C-terminal His-Leu dipeptide to form the octapeptide Ang II (Ang 1–8), which, alongside aldosterone, is the major mediator of the RAAS. Ang II was initially held to act via two different receptors, angiotensin II type 1 receptor (AT1R) and type 2 receptor (AT2R), which belong to the G-protein-coupled receptor (GPCR) family and share 34% of sequence homology. Upon stimulation these receptors induce effects that are altogether different and, most of the times, opposite: AT1R mediates the most known effects of Ang II, including vasoconstriction, cell growth, oxidative stress generation, inflammation, and vascular and cardiac hypertrophy. Moreover, in the adrenal cortex zona glomerulosa, AT1R activation increases inositol triphosphate formation, thus leading to release of Ca^{2+} from the endoplasmic reticulum, transcription of the aldosterone synthase (*CYP11B2*) gene, and aldosterone biosynthesis.

The AT2R is expressed in fetus, where it plays a major role in organ development, but also in adults, mainly in the adrenals, kidneys, uterus, ovary, heart, and specialized nuclei in the brain. Notwithstanding this, its role in adult animals and humans remained uncertain for decades, owing to the fact that specific agonists for AT2R were not available. Therefore, concomitant stimulation of the AT1R could not be avoided when using the AT2R natural ligand Ang II, which binds to AT1R and AT2R with almost equal affinity. Hence, given the higher abundance of the AT1R receptors in many organs, Ang II usually induces predominant AT1R effects. Moreover, the synthetic peptide CGP42112A, which was used to identify the AT2R, was thereafter found to have AT2R agonistic and antagonistic effects depending on its concentration. With the use of the first non-peptide AT2R agonist, compound 21 (C21), more information on the role of AT2R has been recently obtained. Thus, activation of the AT2R was found to result in vasodilatation, inhibition of cell proliferation, induction of apoptosis, extracellular matrix remodeling, and axonal regeneration. Moreover, this receptor was found to be upregulated in various pathological conditions, suggesting that it can serve a counter-regulatory role when overactivation of the AT1R occurs. Thus, the RAAS has a dual action in cardiovascular disease, playing both a detrimental and a protective role (Foulquier et al. 2012; Padia and Carey 2013). Accordingly, AT2R agonists are being tested for preventing hypertension-induced vascular and other end-organ damage.

Along the same line, accumulating evidence exists that other metabolites of Ang I and II may have significant biological activity, particularly in tissues. Ang III (Ang-(2–8)) and Ang IV (Ang-(3–8)) are formed by the sequential removal of amino acids from the N-terminus of Ang II by the action of aminopeptidases. Moreover, Ang-(1–7) is formed from Ang II by the action of carboxypeptidases including the angiotensin-converting enzyme type 2 (ACE 2) as shown in Fig. 2.

Unlike ACE 1, this enzyme does not convert Ang I to Ang II; moreover, its activity is not blunted by ACE inhibitors. Ang-(1–7), which is detectable in the kidney of various species at levels comparable to those of Ang II, has a low affinity for AT1R and AT2R but a very high affinity for an additional Ang receptor defined as Mas receptor (MasR), whose role remains poorly known.

Nowadays, it is well established that in pathological conditions some of these new players such as ACE2, the peptides made by this enzyme – Ang-(1–7) and Ang-(1–9) – and MasR can counteract Ang II. For instance, the acute infusion of Ang-(1–7) increases glomerular filtration rate (GFR) and renal blood flow. Moreover, Ang-(1–7) induces vasodilation, acutely stimulates the formation of NO, and reduces oxidative stress by blunting components of the NAD(P)H oxidase complex in the afferent vessels that was associated with lower cortical oxygenated radical (ROS) and 8-isoprostane excretion. This new regulatory system is named the protective RAAS (McKinney et al. 2014; Passos-Silva et al. 2013).

Pathological activation of the RAAS, such as in renal artery stenosis or the very rare occurrence of a reninoma (tumor of the juxtaglomerular cells), causes arterial hypertension. Moreover, the RAAS plays a detrimental role in cardiovascular

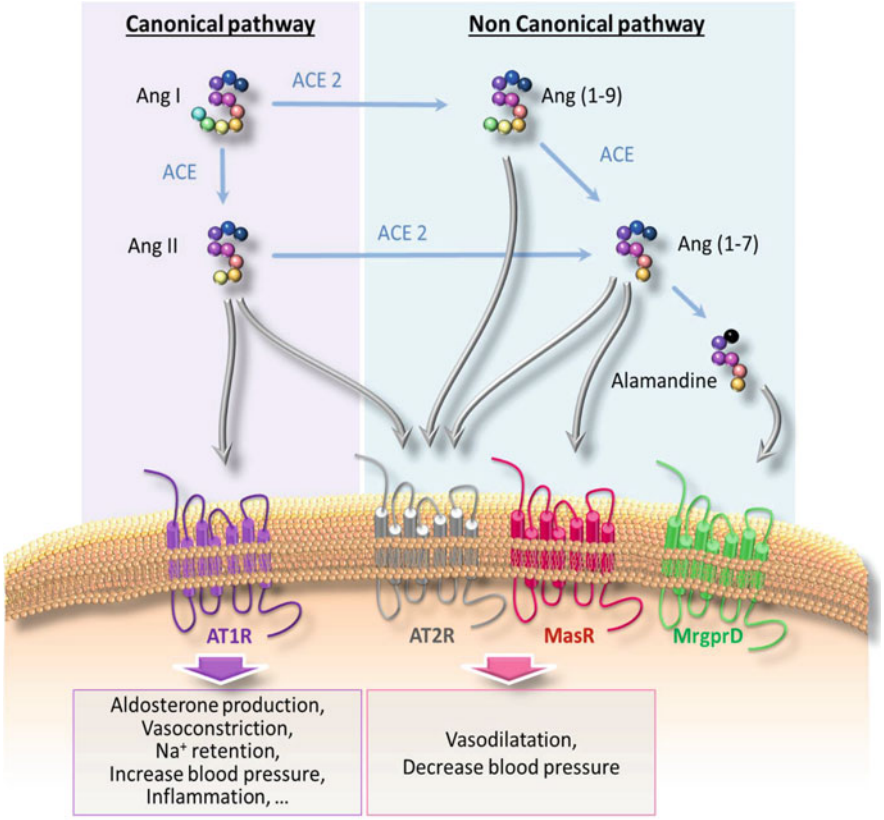

Fig. 2 Canonical and noncanonical pathways of the RAAS. The peptides are shown in *black* and the enzymes in *light blue*

damage in hypertension, including left ventricular hypertrophy (Dahlof et al. 2002), in renal damage (Keane et al. 2003), and also in heart failure as shown by randomized clinical trials with both ACE inhibitors (Swedberg et al. 1990) and mineralocorticoid receptor antagonists (the RALES investigators 1996).

Finally, as mentioned above, a fundamental component of the RAAS is aldosterone, which plays a key role for controlling sodium, potassium, and water balance, and ultimately blood pressure. Its major physiological targets are the epithelial cells, particularly those located in the distal nephron, colon, and salivary gland. At these sites aldosterone increases Na^+ reabsorption, in exchange for K^+ and H^+ excretion. Besides the actions on Na^+ balance, body fluid volumes, and blood pressure, aldosterone influences the function of the cardiovascular system by acting on the heart, vessels, and central nervous system. Accordingly, the key enzyme for aldosterone synthesis – aldosterone synthase – is regulated (besides Ang II) by several factors, including serum K^+, endothelin-1, dopamine, atrial natriuretic peptide

Table 1 Role of RAAS in cardiovascular diseases

RAAS component	Biochemical effects	Functional/pathological effects	Clinical manifestations
Angiotensin II	Increased intracellular Ca^{2+}	Vasoconstriction	Renovascular HBP, renin essential HBP
	Endothelin synthesis	Increased oxidative stress, vasoconstriction	Ischemia, infarction
	Decreased nitric oxide (NO) production	Inflammation, plaque growth and rupture	HBP, ischemia, infarction
	Release of pro-inflammatory mediators	Arterial hypertrophy, fibrosis, stiffening	HBP, ischemia, infarction
	Vascular smooth muscle cell migration and proliferation	Vascular fibrosis	Thrombosis, atherosclerosis
	Increased extracellular matrix formation	Plaque growth and rupture, cardiac remodeling	HBP, HF, and congestion
	Thromboxane A2 release	Clotting, platelet aggregation	Isolated systolic HBP
	Enhanced matrix metalloproteinase (MMP) production	Platelet aggregation	Atherosclerosis
	Increased synthesis of plasminogen inhibitor-1 (PAI-1)	Inflammation (via stimulation of production of monocyte chemoattractant protein (MCP)-1), increased activity of MMP-1 and MMP-3	Atherothrombosis
	Renovascular HBP, high renin essential HBP	Sodium retention	Atherosclerosis, HF
	Low-density lipoprotein (LDL) oxidation		Thrombosis,
	Stimulation of aldosterone production		Atherosclerosis
	Excess autonomous production		Atherosclerosis
			Thrombosis
			HBP, HF, congestion
Aldosterone	Excess autonomous production	Bilateral adrenal hyperplasia, aldosterone-producing adenoma	Primary aldosteronism
	Increased endothelial Na channel (ENAC)	Sodium and water retention	HBP, HF, congestion
	Hypokalemia and hypomagnesemia	Reentry mechanisms	Arrhythmias

(*continued*)

Table 1 (continued)

RAAS component	Biochemical effects	Functional/pathological effects	Clinical manifestations
	Increased oxidative stress and activation of inflammatory pathways	Inflammation, oxidative damage to DNA	Vascular and myocardial tissue damage Atherosclerosis
	Increased synthesis of collagen I and III and fibronectin	NO release	Atrial fibrillation, HF, and congestion HBP, HF
	Vascular smooth muscle cell migration and proliferation	Fibrosis, LVH	Vascular damage
		Vascular remodeling, hypertrophy, artery stiffness	Atherosclerosis

Foulquier et al. 2012; Gaddam et al. 2009; McKinney et al. 2014; Padia and Carey 2013; Passos-Silva et al. 2013; Rocha and Stier 2001; Willerson and Ridker 2004
HBP high blood pressure, *HF* heart failure, *LVH* left ventricular hypertrophy

(ANP), brain natriuretic peptide (BNP), urotensin II, and serotonin. When produced in excess and under conditions of high-to-normal Na^+ intake, aldosterone causes oxidative stress, inflammation, fibrosis, and oxidative damage to DNA. Hence, its production must be tightly controlled to maintain ion and fluid homeostasis and avoid hyperaldosteronism. Table 1 summarizes the fundamental role played by the RAAS in many cardiovascular diseases.

Excessive aldosterone biosynthesis autonomous from these regulators occurs in primary aldosteronism (PA), the most common form of secondary hypertension with an estimated prevalence of about 11.2% in referred patients and about 2% in primary care and as high as 20% in patients with resistant hypertension (Douma et al. 2008). The two major causes of PA are unilateral aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH), accounting together for 95% of cases (Boulkroun et al. 2015).

Conversely, hypoaldosteronism, mainly due to Addison disease, in spite of increased renin and angiotensin release, causes hypotension. Hyporeninemic hypoaldosteronism due to nonsteroidal anti-inflammatory drugs usually manifests itself with hyperkalemia rather than hypotension.

In summary, with the discoveries of new pathways, including the protective ones, and novel actions of the RAAS component, several potential new targets for therapeutic interventions have been identified and are currently under testing with the final goal to develop new drugs to combat hypertension and cardiovascular disease. In fact, drugs currently in clinical trials include C21, encapsulated Ang-(1–7), novel mineralocorticoid receptor antagonists, and aldosterone synthase inhibitors. They might eventually provide additional weapons besides the well-established RAAS inhibitors as beta-blockers, ACE inhibitors, AT1R antagonists, and renin inhibitors.

Other Factors Influencing Blood Pressure Control

Natriuretic Peptides

Natriuretic peptides (NP) belong to a family of hormones all sharing a common 17 amino acid ring and differing for NH2 and COOH residues outside the ring (Nakao et al. 1992). All family members are characterized by a similar molecular structure and similar biological effects mainly exerted at the cardiovascular level (Levin et al. 1998).

Atrial natriuretic peptide (ANP) is released by the cardiac atria when their wall tension increases. B-type natriuretic peptide (BNP) derives from a precursor (Pro-BNP) mainly synthesized and released by the cardiac ventricles in response to an increase in ventricular wall tension.

Once released, Pro-BNP is cleaved in two fragments: the C-terminal (BNP) is constituted by 32 amino acids and is biologically active, while the N-terminal, constituted by 76 amino acids, is not but is measured as a biomarker of activation of BNP synthesis.

C-type natriuretic peptide (CNP) derives from a 122 amino acid precursor and is characterized by 22 amino acids. It is secreted in the central nervous system, the kidney, and the endothelial tissue in response to shear stress.

The main physiological actions of NP occur in the kidney, where they exert a potent vasodilatory effect and regulate blood volume through sodium and water excretion, thus contributing to BP homeostasis.

They also cause, by paracrine and autocrine actions, relaxation of the vascular muscle walls, thus inducing vasodilation and decrease in BP. Finally, NP inhibit the secretion of other vasoactive hormones such as renin, aldosterone, vasopressin, and endothelin-1.

In summary, NP participate in cardiovascular homeostasis counteracting acute and chronic volume overload and exerting opposite actions to those elicited by the SAS and the RAAS.

Dopamine

Dopamine (DA) is a catecholamine acting at different levels in the body. In the central and peripheral nervous system, DA acts as a neurotransmitter, whereas in the kidney it acts as a paracrine hormone at the tubular level where the high activity of the enzyme DOPA decarboxylase transforms circulating L-DOPA into DA. Urinary DA reflects tubular synthesis. Activation of dopaminergic receptors at the periphery increases natriuresis and diuresis by several mechanisms: acting on DA1 receptors on vascular smooth muscle cells, DA causes increase in renal blood flow, augmenting glomerular filtration of sodium; acting on DA2 presynaptic receptors, DA inhibits NE release from the sympathetic nerve terminals, thus reducing the sympathetic-mediated vasoconstriction, and aldosterone release from the adrenal cortex, thus preventing its pressor actions (Rossitto et al. 2016). Finally, in the kidney, DA acts as a paracrine hormone at DA1 receptors on proximal convoluted tubular cells,

inhibiting Na/K ATPase and reducing sodium reabsorption (Carey et al. 1990). Thus, on the whole, endogenous DA acts as a natriuretic and hypotensive hormone.

Nitric Oxide

Nitric oxide (NO) is a small molecule, composed by a nitrogen and oxygen atom, synthesized from its precursor L-arginine by the activity of NO synthase (NOS), an enzyme present in activated inflammatory cells (inducible NOS – iNOS) and in neuronal (nNOS) and endothelial (eNOS) cells where it is constitutively produced and secreted (Lowenstein et al. 1994).

NO has a very short half-life of about 30 s. Among the different NOS isoforms, the most important at the cardiovascular level is eNOS: by releasing NO it induces vasodilation, thus regulating local blood pressure, and inhibits platelet aggregation. Endothelial NO is the main factor mediating vasodilation in response to the shear stress caused by a local flow increase (Corretti et al. 2002). NO is also an important endothelial factor counteracting the vasoconstriction induced by angiotensin II and endothelin-1.

Endothelin-1

Endothelium has to be regarded as a paracrine organ regulating vascular tone as well as other functions such as platelet aggregation and vascular cell proliferation (Behrendt and Ganz 2002). It secretes not only vasodilating agent such as NO but also vasoconstrictor factors such as endothelin-1 (ET).

Endothelins are a group of peptides of 21 amino acids, which include three different isoforms (ET-1, ET-2, and ET-3) (Inoue et al. 1989). ET-1 is the most represented isoform at the vascular level, where it exerts a potent vasoconstriction, acting on type A receptors (ET_A) located in the vascular smooth muscle cells.

ET-1 exerts additional relevant cardiovascular effects acting at different organs. In the vascular bed, ET-1 also acts on ET_B receptors, located on the endothelial cells, where it causes vasodilation. In the heart, ET-1 exerts a chronotropic and inotropic effect in vitro, whereas in vivo it decreases cardiac output, due to baroreceptor-mediated decrease in heart rate and increased afterload. In the kidney, ET-1 causes constriction of both afferent and efferent arterioles and decrease in glomerular filtration rate and renal plasma flow, through ET_A receptors. At the tubular level, ET-1 decreases sodium and water reabsorption through ET_B receptors. Moreover, ET-1, by acting on ET_B receptors, mediates the epithelial mesenchymal transition induced by Ang II, a process whereby tubular epithelial cells transform into fibroblasts, which produce extracellular matrix proteins, ultimately leading to hypertensive nephroangiosclerosis (Seccia et al. 2016). Hence, ET-1 is held to play a key role in the progression of hypertensive renal disease to chronic kidney disease and ultimately end-stage kidney failure.

ET-1 affects also the RAAS, stimulating ACE activity and enhancing aldosterone release from the adrenal cortex. In fact, the adrenocortical zona glomerulosa

cells can produce ET-1 and express both ET_A and ET_B receptors (Rossi et al. 1994); the latter mediate a potent secretagogue effect of ET-1 on aldosterone (Belloni et al. 1996).

As a whole, ET causes increase in BP through regional and systemic vasoconstriction (Clarke et al. 1989) contributing to the occurrence of diseases such as essential hypertension, pulmonary hypertension, chronic renal failure, and chronic heart failure.

Arginine Vasopressin

Arginine vasopressin (AVP), also known as antidiuretic hormone, is a nonapeptide primarily secreted by the supraoptic and paraventricular nuclei of the hypothalamus. The regulation of AVP synthesis and secretion involves two processes, osmotic and pressure-volume. The first is very sensitive in that hypothalamic osmoreceptors may perceive even small changes in plasma osmolality, thus regulating AVP secretion. The pressure and volume regulation is mediated by specific receptors located in the carotid sinus/aortic arch and atria/pulmonary venous system, respectively; these pathways regulate AVP release through a tonic inhibitory action that decreases with significant fall in blood volume and pressure (about >10–20%). The most important physiologic action of AVP is to influence the rate of water excretion at the level of renal collecting tubules by promoting concentration of the urine. Other functions of AVP include contraction of smooth muscle in blood vessels, stimulation of ACTH secretion, and regulation of glycogenolysis in the liver. The effects of AVP are mediated through interaction with specific receptors, named V1a, V1b, and V2: the latter mediates the antidiuretic effect, while the remaining functions are mediated by the other receptors. In physiological conditions, AVP does not seem to play a significant role in the maintenance of BP (Gavras et al. 1982); moreover, disorders with excess or deficit of AVP secretion/action are characterized primarily by abnormalities of osmolality induced by abnormal excretion or retention of water, without significant effects on blood pressure. Thus, the pressure and volume regulation of AVP secretion probably plays a minor role in physiological conditions, but attains a major role in acute and large disturbance of hemodynamic states. In fact, in severe hypovolemic shock, when AVP release is very high, the hormone does contribute to the compensatory increase in systemic vascular resistance. In addition to activation of V1a receptors, AVP may induce vasoconstriction by other mechanisms such as modulation of ATP-sensitive K^+-channels, modulation of NO, and potentiation of adrenergic and other vasoconstrictor agents (den Ouden and Meinders 2005). Based on these concepts, vasopressin is commonly used as an adjunct to catecholamines to support blood pressure in refractory hypovolemic shock.

Cortisol

Cortisol, the major human glucocorticoid, is produced by the adrenocortical zona fasciculate; it is essential for the maintenance of body internal environment, the so-called homeostasis. Cortisol affects virtually all body organs influencing,

regulating, or modulating the changes that occur in the body in response to stress, including heart contraction and blood vessel tone. Cortisol participates in the maintenance of normal BP, as suggested by the observation that disorders of cortisol secretion, either in excess or deficit, are characterized by significant changes of BP levels, e.g., hypertension or hypotension, respectively. Cortisol may increase BP by several mechanisms: in vascular smooth muscle, it increases sensitivity to other pressor agents such as catecholamines and angiotensin II while interferes with NO-mediated endothelial dilatation (Grunfeld and Eloy 1987). In the kidney, cortisol shows high affinity for mineralocorticoid receptors and, depending on the activity of type 2 isoenzyme of 11-beta-hydroxysteroid-dehydrogenase, which converts cortisol to inactive cortisone, may exert a mineralocorticoid action with sodium retention, potassium loss, and volume expansion (Stewart 1999). At the heart level, cortisol increases cardiac output (Whitworth et al. 2005); moreover, it increases hepatic synthesis of the renin substrate angiotensinogen (Saruta et al. 1986).

Summary

BP is a vital physical parameter, which is essential to warrant blood supply to organs and tissues in any conditions, as different posture (supine or upright) or different behavior (rest or exercise). Therefore, not surprisingly, its regulation is extremely complex, depending on several strictly interconnected and finely regulated systems, which are able to control and adjust this parameter continuously on a beat-to-beat basis. BP, generated by heart action, depends on vascular peripheral resistances, generated by arterial contraction. However, it critically depends also on blood volume, mainly dependent on salt intake and kidney function. Blood volume, in turn, affects cardiac output. All these functions need a permanent control by sensors located in different sites of the cardiovascular tree (arteries, veins, heart). This continuous setting (and resetting) needs both rapid and long-lasting responses elicited by neuronal and hormonal mechanisms controlling heart activity, blood volume, and peripheral resistances. The two major systems responsible for BP control are the SAS and the RAAS. Their main role is to avoid a fall in BP and therefore their activation increases BP. When not regulated by the counteracting mechanisms, their activation is responsible for the occurrence of hypertension and, in the long run, cardiovascular damages.

Their activation is maximal in conditions of a profound hypotension, such as during large hemorrhage and dehydration: in these situations additional factors, such as vasopressin and cortisol release, may be recruited to maintain tissue perfusion.

Blood volume mostly depends on sodium and water reabsorption in the kidney. Both the SAS and the RAAS play a pivotal role at this level where other systems, such as natriuretic peptides and dopamine, counteract their sodium- and water-retaining action in an attempt to avoid excessive volume expansion.

Lastly, blood flow needs also a local, peripheral adjustment depending on tissue demands. This fine regulation is attained by means of local, mainly endothelial, vasodilating or vasoconstrictor factors, among which NO and endothelin-1 are the main players.

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