
General Physiology and Pathophysiology of the Renin–Angiotensin System

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Abstract The renin–angiotensin system (RAS), one of the oldest hormone systems, is a complex regulatory system with many identifiable actions. However, it may primarily be viewed as a powerful regulatory system for the conservation of salt and blood volume, and the preservation of an adequate blood pressure (BP). To circumvent the major threats of low blood volume and low BP, animals and our ancestors, with a diet relatively poor in sodium, needed powerful mechanisms for salt and water conservation, and their organisms relied heavily on the RAS. Many of the diverse actions of angiotensin II, the major end product of the RAS, can be viewed in a single conceptual framework, as serving to prevent life-threatening shrinkage of intravascular volume (rapid actions of angiotensin, in combination with the sympathetic nervous system), to help maintain volume homeostasis by minimizing the changes in arterial pressure and fluid volumes required to achieve sodium balance (prevention of salt-sensitivity), and to increase the efficiency of cardiovascular dynamics by promoting the growth of the heart and vessels, and sensitizing blood vessels to vasoconstrictor agents (slowest actions of angiotensin). Activation of the RAS is therefore a useful response in many demanding situations. However, an increased activity of the RAS, especially in combination with other cardiovascular risks factors, may lead to a cascade of deleterious effects. Many of these pathophysiological actions of angiotensin II may still be viewed as being homeostatic in principle, but harmful if carried to excess.

Keywords Renin release · Blood volume · Blood pressure · Sodium balance · Salt-sensitivity · Pressure natriuresis · Hypertension · Cardiovascular hypertrophy

Abbreviations

ACE	Angiotensin-converting enzyme
AGT	Angiotensinogen
Ang II	Angiotensin II
AT ₁ -R	AT ₁ -receptor
BP	Blood pressure
GFR	Glomerular filtration rate
NO	Nitric oxide
PNC	pressure-natriuresis curve
RAS	Renin–angiotensin system
TGF	Tubuloglomerular feedbacks

The renin–angiotensin system (RAS), one of the oldest hormone systems, is a strong control system for salt conservation, blood volume and blood pressure (BP) preservation. To circumvent the major threats of low blood volume and low BP, animals and our ancestors, with a diet relatively poor in sodium, needed powerful mechanisms for salt and water conservation, and their organisms relied heavily on the RAS. The purpose of this chapter is to give a general overview of the RAS, to stress its usefulness in daily homeostasis, but also to show how its effectiveness can be detrimental in certain circumstances.

1 The Major Players of the Renin–Angiotensin System

1.1 History of the Discovery of the RAS

The story of the discovery of the RAS began more than 100 years ago, on 8 November 1896, when the Finnish physiologist Robert A. Tigerstedt (1853–1923), who was at that time Professor of Physiology at the Karolinska Institute in Stockholm, and Per Gustav Bergman, a medical student, set up to do a crucial experiment. Inspired by the French physiologist Charles-Édouard Brown-Séquard, who started a trend for discovering “inner secretions” in organs by injecting extracts from donor organs into animals, Tigerstedt and Bergman injected cold extracts of donor rabbit kidneys into the jugular vein of recipient rabbits and showed that those extracts consistently increased BP. They concluded that the kidney contained a pressor substance they named renin. In further experiments, they showed that this pressor substance was located in the renal cortex and that the pressure response did not require an intact nervous system (Tigerstedt and Bergman 1898). Intriguingly, these observations were forgotten for many years.

The possibility that the kidney may release a pressor substance was revived by Harry Goldblatt, who could induce experimental hypertension in dogs by clipping one or both renal arteries (Goldblatt et al. 1934). These observations led to a renewed interest in a renal pressor substance, and in 1939 two independent laboratories, Page, Helmer and Kohlstaedt in Indianapolis, and Braun-Menendez, Fasciola and Leloir in Argentina, showed that renin was not itself a pressor substance, but an enzyme acting upon a protein to release a peptide vasoconstrictor that became known as angiotensin (Braun-Menendez and Page 1958).

1.2 The Renin–Angiotensin Cascade

Slowly over the years, the RAS was elucidated, as illustrated in Fig. 1. In response to certain stimuli, renin, a proteolytic enzyme produced by the kidney, is released into the circulation and acts on angiotensinogen (AGT), a circulating

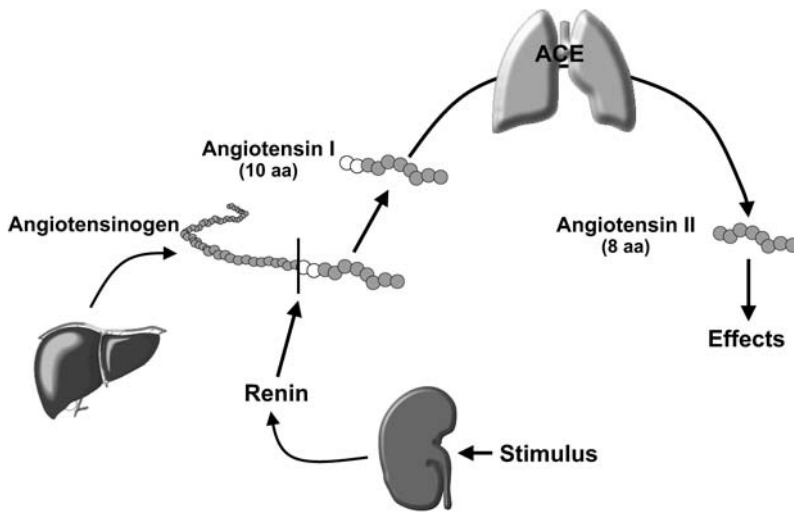


Fig. 1 Simple diagram of the RAS pathway

protein (α_2 -globulin) produced by the liver. Renin cleaves AGT to produce angiotensin I (Ang I) a small fragment of only 10 amino acids. Ang I has no biological action in itself, but is converted to angiotensin II (Ang II), an active octapeptide, by angiotensin-converting enzyme (ACE), an enzyme present on the cell surface of many cells and particularly on vascular endothelial cells. As all blood leaving the kidneys and liver eventually flows through the lung, the pulmonary vascular endothelium plays a major role in the rapid conversion of Ang I into Ang II. Finally, Ang II will bind to specific cell surface angiotensin-receptors to elicit multiple actions.

At this stage, for the sake of completeness, four important remarks should be made:

1. Ang I and Ang II can be generated by alternate enzymatic pathways (Fig. 2). Enzymes other than renin, such as tonin and cathepsin D, can promote the formation of Ang I. Similarly, enzymes other than ACE, such as trypsin, cathepsin G or heart chymase, can facilitate the conversion of Ang I into Ang II. However, the contribution of these alternative pathways in Ang II production in humans is still unclear.
2. ACE can act on substrates other than Ang I. Particularly, ACE can promote the degradation of bradykinin, substance P and other small peptides. Although the physiological role of this enzymatic conversion is unclear, pharmacological blockade of ACE with specific inhibitors leads to an accumulation of bradykinin and substance P, which may be responsible for some of the beneficial effects (antihypertensive), but also some of the adverse effects (angioedema, cough) of ACE inhibitors.

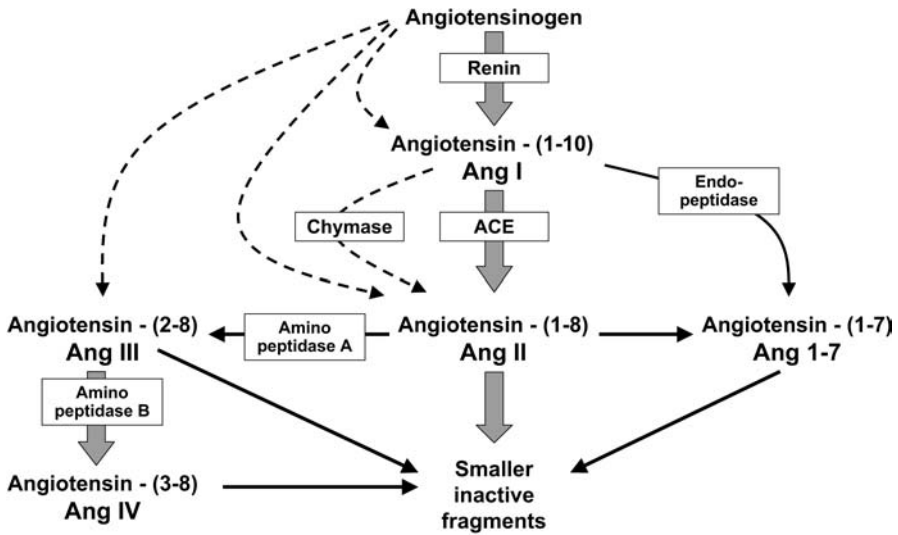


Fig. 2 Alternate pathways of angiotensin II formation and other angiotensin peptides

- There are several angiotensin peptides with biological effects (Fig. 2). Although Ang II [angiotensin-(1-8)] is the major end-product of the system, the action of other enzymes on Ang II may cleave a further one or two amino acids from the amino end, to yield Ang III [angiotensin-(2-8)] and Ang IV [angiotensin-(3-8)], respectively. Cleavage from the carboxyl end yields angiotensin-(1-7). Ang III and IV may play an important role in the brain, whereas angiotensin-(1-7) has vasodepressor properties and may contribute to the antihypertensive actions of ACE inhibitors; angiotensin-(1-7) may be formed directly from Ang I. These angiotensin peptides will not be discussed further in this Chapter, as they are the major focus of final two chapters of this volume.
- Components of the RAS reside within many tissues. Although most of the circulating renin comes from the kidney and most of the circulating AGT comes from the liver, components of the RAS (renin, AGT, ACE) may also be expressed locally within tissues. Circulating renin and AGT constitute the systemic RAS, and local components of the RAS constitute the tissue RAS. Local RAS have been described in many organs, such as the brain, heart, vascular wall, kidneys (interstitium), fat tissues, gut, pancreas, reproductive organs and the adrenals, and may play an important local role. For example: brain and intrarenal RAS are thought to contribute to salt balance and BP control; heart and vascular RAS are involved in cardiovascular pathology. The various tissue RAS will be discussed in detail in Part 4 of this book. In this chapter, we will focus on the physiological role of the systemic RAS.

1.3 Angiotensin II Acts on Specific Receptors

Two main cell surface receptors to Ang II have been identified: AT₁ and AT₂. In rodents, there are two isoforms of the AT₁ receptor, designated AT_{1a} and AT_{1b}. This distinction is, however, not relevant to humans, in which a single AT₁ receptor type is found. Other AT receptors have been described: AT₄R and AT₁₋₇R that mediate the effects of other angiotensin peptides and intracellular receptors.

Both the AT₁ and the AT₂ receptors have been cloned and belong to the superfamily of G protein-coupled receptors that contain seven transmembrane regions. They share about 34% homology and have distinct signal transduction pathways. The AT₁ receptor mediates all of the classical actions of Ang II (vasoconstriction, sodium retention, cell growth and proliferation), and can be selectively blocked with pharmacological agents known as sartans. AT₂ receptors are mainly expressed in fetal tissues and their number decreases in the postnatal period; however, their number increases again in tissue injury. AT₂ receptors promote vasodilatation, cell differentiation, inhibition of cell growth and apoptosis, and may play a counterbalancing role to the effects of Ang II on AT₁ receptors.

2 Regulation of Angiotensin II Formation

2.1 Synthesis of Circulating Renin

The human genome contains only one renin gene (Ren-1^c), whereas certain strains of mice, such as 129, have two distinct renin genes (Ren-1^d and Ren-2). Ren-1^c renin gene expression varies in different tissues, but the kidneys are the only organs that can contain substantial amounts of readily releasable active renin. Indeed, bilateral nephrectomy leads to practically undetectable levels of renin in the plasma. Renin is produced by the juxtaglomerular (JG) cells, specialized cells derived from vascular smooth muscle cells located at the end of the afferent arteriole. During sustained stimulation (such as with a low-salt diet), there is not only an increased expression in those cells, but also an expansion in expression to vascular cells situated upstream.

The initial step in renin synthesis is the formation of preprorenin by renin messenger RNA, which is transported into the rough endoplasmic reticulum. The “pre” sequence is then cleaved, leaving prorenin, a likely inactive form of renin. Subsequently, prorenin is transported through the Golgi apparatus, glycosylated with mannose-6-phosphate residues, and deposited in granules where the “pro” sequence is cleaved to form renin the active 40,000-Da single-chain polypeptide enzyme. Renin can then be released luminally into the circulation (or abluminally into the renal interstitium) by exocytosis in a regulated response to specific mediators.

2.2 Regulation of Renin Release

The juxtaglomerular apparatus plays a central role in the regulation of renin release. It comprises the afferent arteriole, the glomerular mesangium and the macula densa cells of the distal tubule of the same nephron. Three classical stimuli, all elicited by a decrease in BP or blood volume, are known to increase renin synthesis and release:

1. Decreased stretch of the afferent arteriole. The smooth muscle cells of the afferent arteriole are very sensitive to stretch. An increase in intravascular pressure raises intracellular calcium, leading to both a contraction of vascular smooth muscle cells (myogenic vasoconstriction) and an inhibition of renin release. Conversely, a low intravascular pressure in the afferent arteriole stimulates renin release. This is a local effect, which does not require any neural input.
2. Decreased delivery of salt (sodium chloride) to the macula densa. Macula densa cells are modified tubular cells at the end of the loop of Henle that ensure a steady input of salt to the distal tubular cells by controlling both the tone of the afferent arteriole (tubuloglomerular feedback, TGF) and the release of renin. Such a mechanism helps maintain glomerular filtration rate (GFR) at a relatively constant level. Decreases in distal tubular salt delivery are sensed by macula densa cells (probably via the amount of salt which is transported through the luminal Na-K-2Cl cotransporter). This leads to a decreased release of some chemical mediators (ATP, adenosine, NO) by macula densa cells and to an increased release of other mediators (prostaglandin PGE₂). In turn, this chemical modulation of JG cells dilates the afferent arteriole and stimulates renin release.
3. Adrenergic stimulation. The JG cells are directly innervated by sympathetic nerve endings, which act on β_1 -adrenergic receptors expressed on cell surface. This results in an increased formation of cyclic adenosine monophosphate (cAMP) that stimulates renin release. Renal sympathetic nerves have a very potent effect on renin release, occurring at levels of sympathetic activity much lower than those required for acute sodium retention or renal vasoconstriction (DiBona and Kopp 1997).

All three stimuli operate simultaneously and are usually stimulated by the same conditions: a decrease in blood pressure (BP). When BP falls, there is decreased stretch of JG cells and salt delivery to the macula densa (due to a decrease in GFR and an increase in proximal tubular reabsorption). In addition, the low arterial pressure unloads carotid and aortic baroreceptors, leading to renal sympathetic nerve activation and thus to β_1 -receptor stimulation.

In addition to these three classical stimuli, some circulating hormones or substances can directly stimulate or inhibit renin release by the juxtaglomerular apparatus. For the purpose of this chapter, two substances that inhibit renin re-

lease are particularly worth mentioning: atrial natriuretic peptide (ANP), a hormone released by the atria in response to an increased blood volume, and Ang II. The inhibitory effect of ANP contributes to renin suppression at high salt intake. The inhibitory effect of Ang II constitutes a “short-loop” negative feedback that allows a rapid suppression of renin release, in contrast to a “long-loop” negative feedback (suppression of renin release by hypertension and hypervolemia), which would require many hours or days.

2.3

Modulation of Angiotensin II Production

Under normal circumstances, renin is the rate-limiting step in the formation of Ang II. However, modulation of Ang II formation by other components of the RAS may come into consideration in certain situations.

Modulation by Angiotensinogen. AGT is the only known precursor protein to the family of angiotensin peptides. Systemic AGT originates primarily from hepatocytes where it is constitutively secreted, and is present in the plasma in stable concentrations (half-life of 16 h, in contrast to 20 min for renin). AGT secretion can be modulated by various compounds, such as glucocorticoids, estrogens, thyroid hormones, insulin, selected cytokines, and Ang II itself (Brasier and Li 1996).

Because the normal concentration of AGT is near the K_m for its reaction with renin (Gould and Green 1971), one would expect any change in AGT levels to be accompanied by parallel changes in the formation and actions of Ang II. On the other hand, an AGT-mediated increase in Ang II levels (and action) should lead to a suppression of renin release via both the short and long negative feedback loops, and thereby a return to normal levels of plasma Ang II concentration. Yet there is indirect evidence that AGT may play a role in human hypertension (Jeunemaitre et al. 1992).

To understand this paradox, two explanations can be presented: (1) A hypertensive effect of AGT is expected in situations when renin release is poorly modulated, such as during renal damage or in 129 mice which have two distinct renin genes, one of which is submaxillary and is not subject to the usual negative feedback control (Wang et al. 2002). Indeed, 129 mice engineered to carry one to four copies of the AGT gene have AGT concentrations and BP levels that correlate to the number of AGT gene copies (Kim et al. 1995). (2) High levels of systemic AGT may also promote hypertension by increasing local formation of Ang II in various tissues, where it is not subjected to systemic feedback control.

Modulation by ACE. Various substances, such as NO and Ang II itself, have been shown to downregulate the activity of ACE in endothelium. However, the physiological role of these modulations remains unclear. Experimental data from animals and computer simulations have indicated that modest changes in ACE activity in either direction have little effect on the production of Ang II itself

(Smithies et al. 2000). As a matter of fact, mice engineered to carry one to three copies of the ACE gene do not show any variation in blood pressure (Krege et al. 1997).

On the other hand, ACE is present not only on vascular endothelial cells, but also on the cell membranes of many different cells. High levels of ACE in the microvilli of proximal tubular cells may produce high local levels of Ang II, promoting sodium reabsorption. The presence of ACE in inflammatory cells could also contribute to vascular disease (Dzau 2001). Furthermore, high levels of ACE may decrease bradykinin levels and thus contribute to the diabetic proteinuria observed in diabetic mice with genetically higher ACE levels (Huang et al. 2001), or in humans with the insertion/deletion ACE polymorphism.

In addition to the various factors that regulate or modulate Ang II formation, there are also a number of mechanisms by which Ang II action may be regulated: e.g. variations in AT receptor density, interactions between AT₁ and AT₂ receptors, or post-receptor modulation. Those complex interactions will be dealt in subsequent chapters of this book.

3 The RAS Is an Important Physiological Control System

The RAS is a complex regulatory system with many identifiable actions. However, it may primarily be viewed as a powerful regulatory system for salt conservation, blood volume and BP. A minimal intake of salt is required to compensate for obligatory salt losses by urine, sweat, faeces and epithelial desquamation. When animals are put on an extremely poor sodium diet, they exhibit hypovolaemia with possibly impaired exercise performance, thus becoming easier prey for predators. Salt depletion also endangers species survival due to poor reproductive functions such as decreased fertility, decreased number of pups in the litter and decreased pup size (McBurnie et al. 1999).

In the case of man, our ancestors routinely consumed a poor sodium diet (10–30 mmol/day) (Eaton and Konner 1985; MacGregor and de Wardener 1998). Stringent mechanisms for salt conservation were thus required to regulate the amount of fluid in our bodies. Without an efficient RAS, our ancestors would have never survived the additional stresses associated with starvation or haemorrhage, and would not have the required hemodynamic reserve for fight-or-flight reactions.

The RAS is a complex system, with more than 60 Ang II actions. In this chapter, we will show how many of these diverse actions of Ang II can be viewed in a single conceptual framework, as serving to prevent life-threatening shrinkage of intravascular volume (rapid actions of angiotensin), to help achieve sodium balance without large alterations in BP (slower actions of angiotensin) and to increase the efficiency of cardiovascular dynamics by promoting the growth of the heart and vessels, and sensitizing blood vessels to vasoconstrictor agents (slowest actions of angiotensin).

3.1 The Rapid Actions of Angiotensin Prevent Life-Threatening Hypovolaemia and Hypotension

Most of the rapid actions of Ang II can be viewed as a concerted response that supports the circulation when it is threatened by intravascular volume shrinkage and/or hypotension. Indeed, the main physiological stimuli for RAS activation are low salt intake, blood volume and BP. In turn, Ang II acts to help raise blood volume and BP via combined actions illustrated in Fig. 3: all are exerted via the AT₁ receptor.

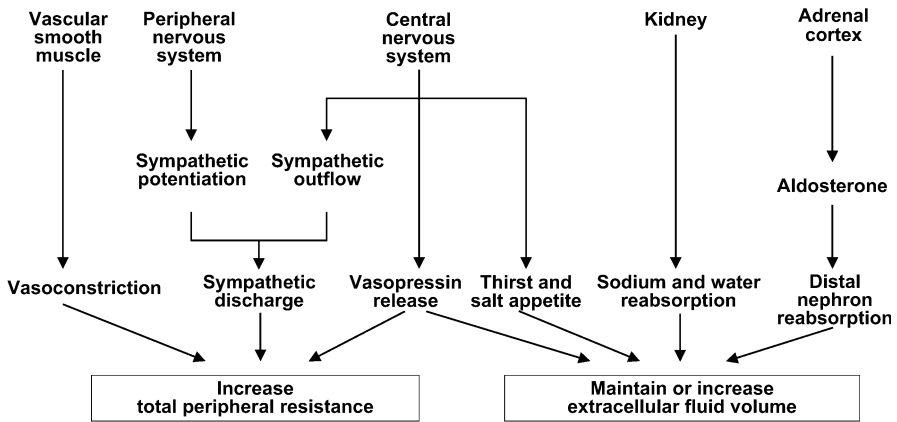


Fig. 3 Schematic diagram, showing the major effects of Ang II on total peripheral resistance and extracellular fluid volume preservation

3.1.1 Angiotensin Increases Total Peripheral Resistance

Ang II is a potent vasoconstrictor agent that elevates vascular tone by both direct and indirect mechanisms. Binding of Ang II to AT₁ receptors located on the surface of vascular smooth muscle cells leads to an immediate contraction. It is interesting to note that Ang II does not exert identical vasoconstrictor effects on all vessels. For example, renal post-glomerular (efferent) arterioles are exquisitely sensitive to Ang II, whereas pre-glomerular (afferent) arterioles show very little direct sensitivity to Ang II (Edwards 1983).

Ang II may also increase vascular tone by indirect mechanisms. Ang II increases sympathetic discharge via direct action at various brain structures that lack a blood-brain barrier, and can also potentiate the release of norepinephrine from adrenergic varicosities within peripheral tissues. This sympathetic effect is normally blunted or even suppressed *in vivo* by the vasoconstriction-induced rise in arterial pressure, which loads baroreceptors and results in a reflex de-

crease in sympathetic nerve activity (Lohmeier et al. 2000b). Situations associated with baroreflex impairment (such as heart failure or vasculopathies with aortic and carotid stiffness) may thus unmask the sympathoexcitatory actions of Ang II.

Another central action of Ang II is the stimulation of vasopressin release by the posterior pituitary gland. The quantitative contribution of this effect is not well established. However, very low levels of circulating vasopressin not only causes antidiuresis (via the V_2 -receptor), but can also increase total peripheral resistance (Montani et al. 1980) and favour a more efficient renal countercurrent system by vasoconstriction of renal vasa recta (Cowley 2000), thus facilitating renal retention of sodium and water.

3.1.2 Angiotensin Preserves Extracellular Fluid Volume

Ang II also acts to maintain or increase extracellular fluid volume (ECFV), both by promoting water and sodium intakes, and by decreasing water and sodium excretions. Intracerebral infusions of Ang II in experimental animals increase both thirst and salt appetite, leading to increased water drinking, and preferential drinking of a saline solution when the animal is offered both saline and water solutions. This effect is also seen in response to moderate elevation of circulating Ang II levels, due to its actions on various regions of the brain involved in thirst and salt appetite (Fitzsimons 1998).

Ang II acts on many other tissues with the same general goal of sodium and ECFV preservation. It enhances epithelial sodium transport in the gut. In the kidney, it promotes Na^+/H^+ exchange in the apical membrane of proximal tubular cells, augmenting sodium reabsorption. Renal vasoconstriction with predominantly post-glomerular constriction leads to a decrease in peritubular capillary hydrostatic pressure, and to an increase in filtration fraction that concentrates post-glomerular plasma protein concentration, further boosting sodium reabsorption (Hall 1986a). Constriction of efferent arterioles of juxtamedullary nephrons and/or a direct action on vasa recta lowers renal papillary blood flow, enhancing urine-concentrating capability. Finally, Ang II acts on the adrenal glands to promote secretion of aldosterone, a sodium-retaining hormone acting on the distal parts of the nephron.

3.1.3 Other Physiological Actions of Angiotensin Contribute to Corporal Integrity

Other actions of Ang II that may seem unusual or even harmful at first glance, do fit well in the general scheme of homeostatic functions. Some of these actions include:

- a. Preservation of glomerular filtration rate at low perfusion pressures. When arterial pressure increases suddenly, myogenic and TGF-induced vasocon-

strictions of the afferent arteriole protect the glomerulus, thereby preventing large increases in GFR. When arterial pressure decreases, these mechanisms are reversed; i.e. decreases afferent arteriolar tone. However, they are not very effective in maintaining GFR in situations of low perfusion pressures, and thus constriction of efferent arteriole by angiotensin then becomes crucial to preserve GFR. In situations when the RAS is activated (low salt intake, volume depletion), blockade of the RAS does indeed impair autoregulation of GFR at low perfusion pressures (Hall et al. 1977). This situation is well known to clinicians prescribing inhibitors of the RAS in hypertensive patients with renal artery stenosis (Hricik et al. 1983). Mechanisms for preservation of GFR during low salt intake and volume depletion are important as they allow the kidney to continue its filtrating and detoxifying functions.

- b. Haematopoiesis. ACE inhibitors often lead to a reduction in haematocrit, and RAS activation leads to erythropoiesis. Ang II stimulates the renal production of erythropoietin via an AT_1 receptor-dependent pathway (Gossmann et al. 2001) by decreasing oxygen concentration around peritubular fibroblasts. This action is due to the combined action of Ang II in decreasing renal blood flow and thus oxygen delivery, and in increasing tubular sodium reabsorption and thus oxygen consumption. Ang II may also act directly on AT_1 receptors present on erythroid precursor cells of the bone marrow (Rodgers et al. 2000). In situations of chronic volume depletion (e.g. during extreme salt deprivation or following haemorrhage), an increased haematocrit would compensate for the hypovolaemia-induced decrease in cardiac output.
- c. Procoagulatory effects. The mild stimulatory effects of Ang II on the coagulation cascade and on platelet activation (Larsson et al. 2000) can be viewed as a volume-conserving reaction during haemorrhage.
- d. Stimulation of liver glycogenolysis. Ang II infusion leads to an elevation in blood glucose levels (Machado et al. 1998) as a consequence of an AT_1 -receptor dependent action on hepatic glycogen phosphorylase (Keppens et al. 1993). Hyperglycaemia becomes useful in fight-or-flight situations, as this condition provides energetic fuel to the skeletal muscles.
- e. Inotropic actions. Ang II increases cardiac contractility (Mattiuzzi 1997). The exact mechanism of this action remains poorly understood, but it may be related both to a potentiation of norepinephrine release at adrenergic endings, and to a direct effect of Ang II on the myocardium. In any case, this represents a useful response during situations such as acute hypovolaemia (e.g. following haemorrhage).

3.1.4

Activation of the RAS Is a Useful Response in Many Demanding Situations

- a. An effective RAS attenuates orthostatic hypotension. Standing upright leads to an accumulation of blood in the legs, a decrease in venous return and thereby a decrease in cardiac output. In turn, arterial pressure decreases, which stimulates renin release in a matter of minutes, helping to restore BP.

Complementary systems (sympathetic nervous system and vasopressin) work concurrently to oppose acute drops in BP, and thus compensate for a poorly reactive RAS. Blockade of the RAS may lead to severe orthostatic hypotension if autonomic function or vasopressin release is impaired, or in situations of pre-existing hypovolaemia. Hypertensive patients with restricted sodium intake (10 mmol/day for 5 days) suffered from circulatory collapse during an orthostatic tilt, when renin release was prevented from rising by pretreatment with propranolol (Morganti et al. 1979).

- b. An effective RAS prevents hypotension during low salt intake or during dehydration. A poor sodium diet or a state of dehydration leads to a decrease in circulatory filling pressures and blood volume. However, activation of the RAS in these circumstances leads to a restoration of filling pressures and blood volume to near normal values, raising BP back to normal. The importance of RAS activation during low salt intake is illustrated by the fact that blockade of the RAS in dogs maintained on sodium intake of 5 mmol/day for 1 week lowered mean arterial pressure to about 68 mmHg (Hall et al. 1980)—a low value perhaps tolerated at rest, but probably not very well during exercise or orthostasis. Marked hypotension has also been described in patients treated with ACE inhibitors who experience gastrointestinal fluid loss or other types of volume depletion (McMurray and Matthews 1987).

3.2

The Slower Actions of Angiotensin Contribute to Sodium Balance

All the aforementioned renal actions of Ang II, not only help maintain ECFV and BP during prolonged periods of low salt intake, but play also an important role in defending ECFV and BP in the face of high salt intake. The beauty of the RAS is that it works in both directions. In one direction, the system is stimulated by low BP and blood volume induced by a low salt intake, and acts to oppose these perturbations by way of a classical negative feedback system. In the other direction, the system is suppressed in situations of increased BP and blood volume such as may be induced by high salt intake. One of the major roles of a normal RAS regulation is to prevent volume-dependent salt sensitivity. To illustrate this concept, a few words on the role of the kidney on long-term BP control are needed.

3.2.1

The Cardiovascular System Is More Than a Simple Closed Circuit

The cardiovascular system is often viewed as a simple closed circuit consisting of a pump (the heart) and a series of tubes with varying resistance (the vasculature). In this model, all that counts for BP control is the strength of the heart and the resistance of the peripheral vasculature. A more complete representation of circulatory function and BP control would be a cardiovascular system with an input from the outside (fluid and salt intakes) and an output to the out-

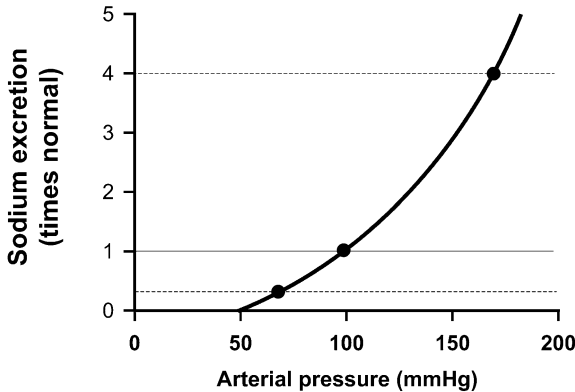


Fig. 4 The basic concept of pressure natriuresis to achieve sodium balance. Three levels of salt intake are depicted (normal, 0.2×normal and 4×normal). Equilibrium is reached at the intersection between the pressure natriuresis curve and the corresponding level of salt intake

side (urinary excretion). Any change in the input would alter blood volume and thereby BP, which in turn leads to changes in the output via pressure-natriuresis. In fact, changes in renal perfusion pressure, regardless of whether the kidney is studied *in vivo* or *in vitro*, lead to profound changes in sodium excretion, as illustrated by the solid curve in Fig. 4. The intrarenal mechanisms for this phenomenon have been detailed elsewhere (Granger et al. 2002).

3.2.2

Fluid Volume Equilibrium Is Reached When Salt Excretion Is Equal to Salt Intake

The pressure-natriuresis curve (PNC) in Fig. 4 is at the centre of blood volume and BP control. If the body gains too much fluid (e.g. acute volume load), BP increases. This leads to increased excretion of salt and water via the pressure-natriuresis mechanism, bringing blood volume and BP back towards normal. Conversely, if one loses fluids (e.g. haemorrhage), BP decreases and the kidneys retain salt and water, which helps return blood volume and BP to normal. Equilibrium is thus reached at the intersection point of the PNC with the corresponding salt intake level, as shown on Fig. 4.

Based on this concept, one can understand the general renal body fluid feedback mechanism (Hall et al. 1986b). Any imbalance between salt intake and output will lead to a cascade of events that oppose the initial disturbance; i.e. a classical negative feedback loop. For example, if salt intake is greater than output, ECFV increases, thereby increasing blood volume and thus the mean filling pressure of the circulation; this then increases cardiac output, and thus BP. In turn, the higher BP increases salt output, which opposes the effects of the initial increase in salt intake by way of the pressure-natriuresis mechanism. The system acts very slowly (hours or days), but it has an infinite gain and corrects completely any error in salt balance.

This simplified feedback loop may not explain the whole story. According to this analysis, a fourfold increase in salt intake would lead to volume retention until BP increases to well over 150 mmHg (Fig. 4). Sodium balance would be reached, but at the expense of profound volume retention and tremendous hypertension. Similarly, a poor sodium diet (for example, 1/5 of normal) would require a drop in BP by 30 or 40 mmHg to achieve a state of sodium balance. Yet, this sensitivity to salt does not fit with the small variations in BP that are normally observed when animals (Hall et al. 1980) and humans (Luft et al. 1979) are subjected to large variations of salt intake. Clearly, additional mechanisms must come into play.

3.2.3

The Pressure Natriuresis Curve Is Modulated by Changes in Salt Intake

The PNC depicted in Fig. 4 is not immovable. In fact, it becomes steeper and is shifted to the left during high salt intake. This allows the body to achieve sodium balance with minimal increases in blood pressure. Conversely, during low salt intake, the PNC becomes flatter and is shifted to the right. Joining the equilibrium points at the various salt intakes reveals a very steep “chronic” relationship with little changes in BP (Fig. 5). That is, the chronic relationship between salt intake and blood pressure has become relatively salt-insensitive.

Various neurohormonal mechanisms contribute to the adjustment of the PNC. RAS modulation, above all, plays a crucial role in the adaptation to changes in salt intake. RAS suppression at high salt intake facilitates sodium excretion, and RAS stimulation at low salt intake contributes to sodium conservation. The importance of this modulation is illustrated by the dramatic salt-induced changes in BP that occur when the RAS is blocked with an ACE inhibitor, or when circulating Ang II levels are fixed with an intravenous infusion of angio-

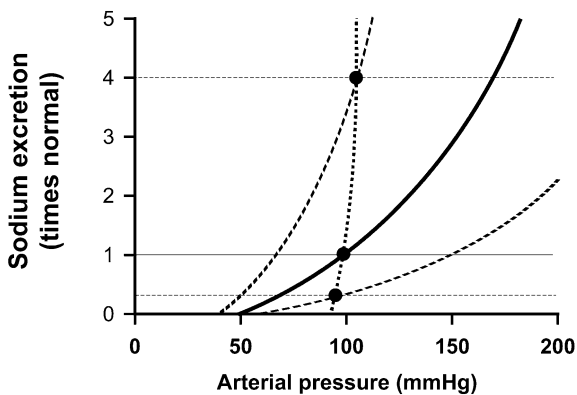


Fig. 5 The modulation of the pressure natriuresis curve during alterations in salt intake allows the body to achieve sodium balance with minimal changes in arterial pressure (*steep dotted line*)

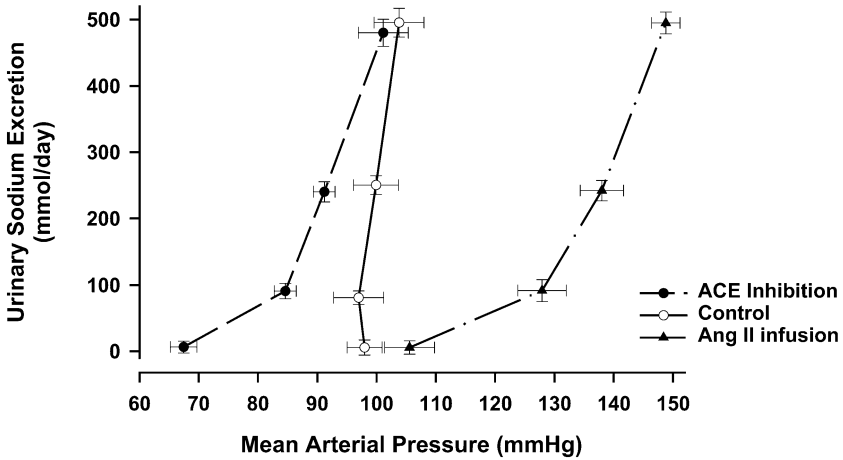


Fig. 6 Steady-state relationships between mean arterial pressure and urinary sodium excretion in dogs subjected to varying salt intakes from 5 mmol/day to 500 mmol/day, lasting 1 week at every level. The dogs were studied under three conditions: (1) with an intact RAS; (2) during chronic blockade of the RAS with captopril; (3) during fixed elevated circulating levels of Ang II via an intravenous infusion of Ang II at 5 ng/kg/min. (From Hall et al. 1980, by permission)

tensin (Hall et al. 1980) (Fig. 6). Lack of RAS activation during low salt intake leads to a dramatic decrease in mean arterial pressure to less than 70 mmHg.

But by which mechanisms do Ang II levels vary with changes in salt intake? The sequence of events is presented in Fig. 7. The initial increase in salt intake (salt with little water) leads to increased plasma osmolality, resulting in thirst

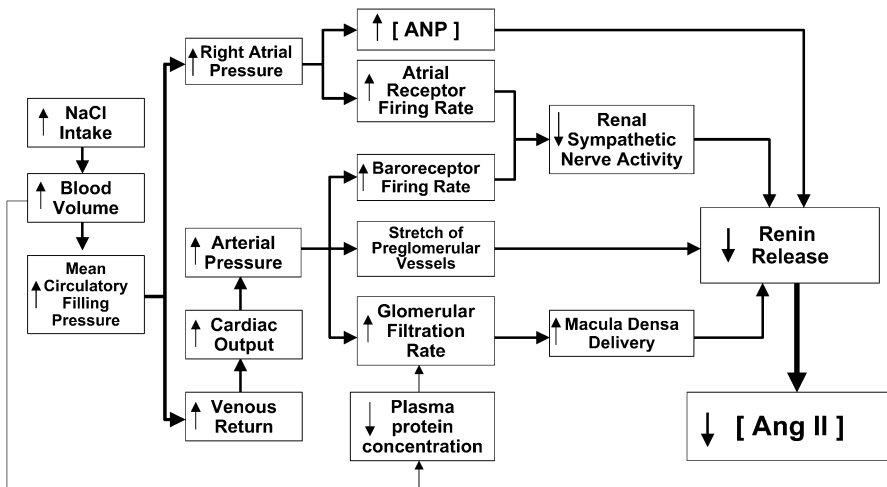


Fig. 7 Block diagram illustrating the mechanisms whereby an increased in salt intake leads to a decrease in Ang II formation

and drinking and thus an increase in extracellular fluid volume. This then increases blood volume and decreases, at least acutely, plasma protein concentration. Subsequently, a complex but logical sequence of events takes place. The decrease in plasma protein concentration favours an increased fluid filtration across the glomerular capillary membrane. The greater blood volume increases mean circulating filling pressure (greater content for the same container), resulting in both an increase in right atrial pressure and venous return.

The increased right atrial pressure stretches the right atrium, and loads low pressure receptors that reflexly decrease vasopressin secretion and renal nerve sympathetic activity. Atrial stretch leads also to a direct increased release of atrial natriuretic peptide (ANP), a hormone that has a direct inhibitory action on renin release (and aldosterone secretion). By its vasodilatory action on preglomerular vessels, ANP also promotes an increase in GFR.

The greater venous return increases cardiac output and thus arterial pressure, which in turn leads to three events: (1) loading of arterial carotid and aortic baroreceptors, and resulting in a decreased renal sympathetic nerve activity; (2) mechanical stretch of preglomerular vessels; (3) increase in delivery of fluid and salt to the macula densa, mediated by the small increase in GFR (favoured by physical forces and accentuated by the vasodilatory ability of ANP on the afferent arteriole). Altogether, these three events promote a decrease in renin release, and thus in Ang II levels.

A similar flowchart can be applied, but in the reverse direction, to explain the increased Ang II levels during low salt intake. Volume depletion leads to a decrease in filling pressures and arterial pressure. Unloading of atrial and arterial baroreceptors, decreased ANP concentration, decreased preglomerular stretch and decreased salt-delivery to the macula densa all contribute to the stimulation of renin release.

3.2.4

The Inability to Modulate the RAS Leads to Salt Sensitivity

As shown in Fig. 6, the ability to suppress renin release during high salt intake and to stimulate renin release during low salt intake is the cornerstone of having very little salt sensitivity. If the RAS is blocked with an ACE inhibitor or if Ang II levels are not allowed to fluctuate naturally in response to varying salt intakes, rapid, volume-dependent salt sensitivity ensues.

Thus one of the major roles of the RAS is to prevent a large drop in BP (and ECFV) during low salt intakes, and a large increase in BP (and ECFV) during high salt intakes. In other words, when the ability to suppress renin at high salt intakes is lost, volume-dependent salt sensitivity develops. This particularly may occur in the following two situations:

- a. Ageing. Circulating renin levels decrease steadily with age (Weidmann et al. 1975), possibly related to the observed decrease in glomerular number and size that occur with ageing (Nyengaard and Bendtsen 1992). The response

of renin in older individuals is also blunted when the RAS is either stimulated (volume contraction) or inhibited (volume expansion) (Luft et al. 1992). The lower basal levels of plasma renin activity and poor reactivity of the RAS may help explain the higher prevalence of salt sensitivity in older subjects.

- b. Low-renin essential hypertension. About one quarter of all essential hypertensive patients have low renin levels that are poorly stimulated by a low salt intake (Fisher et al. 2002). Because renin levels are low to start with, the incapacity to further suppress renin at high salt intake may explain the salt sensitivity frequently observed in low-renin essential hypertension.

On the other end of the PNC, the concept of RAS modulation is particularly useful to understand the increased effectiveness of ACE inhibitors or angiotensin-receptor blockers in lowering blood pressure, if treatment is combined with a reduction in salt intake or with the use of diuretics.

3.3

The Slowest Actions of Angiotensin Increase the Efficiency of the Cardiovascular System

3.3.1

Angiotensin Promotes Vascular Growth and Cardiac Hypertrophy

By way of its effect on the AT₁ receptor, Ang II is also a growth factor, acting on vascular smooth muscle cells and cardiac myocytes. The trophic response to Ang II leads to a slow structural remodelling that helps maintain a higher BP. With a greater vascular muscle mass that increases both the strength of vascular contraction and the sensitivity to chronic vasoconstrictors, the vascular system becomes more effective in maintaining a high vascular tone. With a larger myocardial mass that increases cardiac strength, the heart becomes more capable in maintaining a high blood pressure. In both cases, activation of the local tissue RAS may play an important role in this trophic response.

3.3.2

Angiotensin Stimulates Superoxide Anion Formation

The superoxide radical (O_2^-) is produced endogenously during normal mitochondrial respiration and by various oxidases, especially NADH ((nicotinamide adenine dinucleotide, reduced) and NADPH (nicotinamide adenine dinucleotide phosphate, reduced) oxidases. The superoxide anion may play a physiological role in various tissues as a signalling molecule and may contribute to the regulation of vascular tone (Touyz 2000), particularly in the renal microvasculature (Schnackenberg 2002). In normotensive anaesthetized rats, the administration of tempol, a mimetic of the enzyme superoxide dismutase that decreases superoxide levels, causes an increase in medullary blood flow, urine flow and sodium

excretion (Zou et al. 2001), but has no effect on basal afferent arterioles. This suggests that the superoxide anion may participate in maintaining the basal tone of the renal medullary microcirculation. In normal conditions, superoxide may also scavenge the NO formed in macula densa cells by neuronal NO synthase, thereby increasing the gain of the TGF (Ren et al. 2002). Both effects tend to increase the renal ability to retain salt.

Ang II can, via activation of the AT₁ receptor, stimulate NAD(P)H-oxidase and thereby the production of the superoxide anion. Some of the effects of Ang II on vasoconstriction and renal sodium retention may thus be mediated by oxygen radicals. For example, infusions of low doses of Ang II do not produce immediate hypertension, but a slow, progressive elevation of BP over hours or days. Furthermore, the administration of tempol attenuates or prevents Ang II-induced hypertension (Ortiz et al. 2001). The stimulation of oxygen radicals by Ang II may thus be viewed as a slow physiological response to enhance the long-term vasoconstrictor and sodium-retaining effects of Ang II.

4 Pathophysiology of the RAS

So far, we have reviewed the actions of the RAS from the general point of view of cardiovascular homeostasis. However, increased activity of the RAS, especially in combination with other cardiovascular risks factors, may lead to a cascade of deleterious effects such as hypertension, cardiovascular hypertrophy, oxidative stress with endothelial dysfunction, atherosclerosis and tissue inflammation. Many of these pathophysiological actions of Ang II will be reviewed in detail in other chapters of this book. At this stage, it is interesting to consider that many of these Ang II actions may still be viewed as being homeostatic in principle, but harmful if carried to excess.

4.1 The RAS May Contribute to the Higher Cardiovascular Risks of Males

Although being male is not exactly a pathological situation, men before the age of 50 show a higher prevalence of hypertension and a greater cardiovascular morbidity than premenopausal women. Blood pressure in a normotensive population is also higher in men than in women. Interestingly, men have higher plasma renin activities than women, and there is indirect evidence that increased levels of renin may contribute to increased cardiovascular risks. Indeed, hypertensive patients with high levels of plasma renin activity are at higher risk of developing stroke or myocardial infarction than those with low plasma renin activity (Brunner et al. 1972).

Plasma renin levels are higher in male spontaneous hypertensive rats (SHR) and their BP is 25–30 mmHg higher than in female SHR (Reckelhoff et al. 2000). On the other hand, castrated male SHR, female SHR and ovariectomized female SHR all show about the same level of BP. In contrast, female ovariectomized

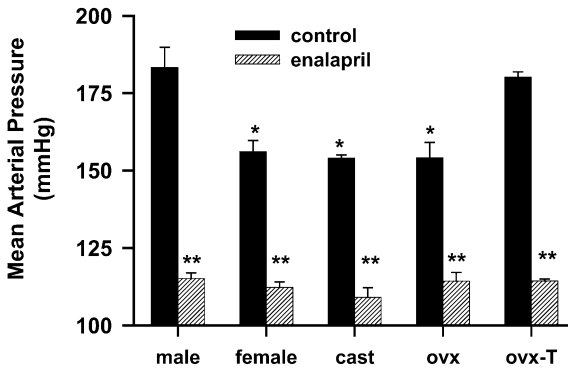


Fig. 8 Mean arterial pressure in five groups of SHR: male, female, castrated males (*cast*), ovariectomized females (*ovx*) and ovariectomized females receiving testosterone (*ovx-T*). Animals were studied with an intact RAS (*black bars*) or after chronic blockade of the RAS with enalapril (*shaded bars*). (From Reckelhoff et al. 2000, by permission)

SHR, given testosterone, show a degree of hypertension approaching the level observed in male SHR, pointing to the role of testosterone in the more severe hypertension of male SHR (Fig. 8). When the RAS is blocked with enalapril, all five groups of animals show remarkably similar BP levels, suggesting that the pressure difference between male and female SHR is due entirely to a more active RAS in male animals, and testosterone may contribute to the higher renin levels in males. This is consistent with the observation that normotensive castrated male Sprague Dawley rats, with undetectable serum testosterone levels, have low renin levels, and that implantation of testosterone pellets of increasing concentrations not only raise testosterone levels in blood, but also plasma renin activity with a significant linear correlation ($r=0.904$) between the two variables (Reckelhoff et al. 2001). Whether this animal observation can be extrapolated to humans remains to be further investigated.

4.2

The RAS Contributes to Many Forms of Hypertension

In humans, known causes of arterial hypertension account for less than 10% of all cases of hypertension (Kaplan 1998). Most often, a precise cause cannot be found and the hypertension is said to be “essential”. Since Ang II elevates BP, it is appealing to implicate an overreactivity of the RAS in the pathogenesis of certain forms of hypertension.

4.2.1

Role of the RAS in Renovascular Hypertension

Since the classical experiments of Goldblatt, many studies have appeared, inducing hypertension in animal models by clipping one or both renal arteries. How-

ever, the contribution of the RAS in renovascular hypertension depends on the type of stenosis.

- a. One kidney-one clip (1K1C) hypertension. Experimentally, a stenotic clip is placed on the renal artery of one kidney whereas the contralateral kidney is removed. The renal artery stenosis reduces renal perfusion pressure, which may explain many of the initial events, including sodium retention and stimulation of the RAS. However, as the animal retains volume over time and becomes hypertensive, the glomerular pressure tends to return towards normal and there is no longer a strong stimulus for renin release. At this stage, administration of an ACE inhibitor has little effect on BP. The hypertension is volume-dependent but no longer renin-dependent. The clinical equivalent of 1K1C is renal artery stenosis in a patient with a solitary kidney, or bilateral renal artery stenoses (2K2C) or stenosis of the aorta above the origin of the renal arteries. All three situations are characterized by a low renal perfusion pressure.
- b. Two kidney-one clip (2K1C) hypertension. The pathogenesis of hypertension in this model is more complex. The stenotic kidney is underperfused and thus secretes large amounts of renin. The resulting elevation in plasma Ang II acts on the intact contralateral kidney, both by a direct effect and via stimulation of aldosterone secretion to promote enhanced sodium reabsorption. Initially, both kidneys may retain salt, but the stenotic kidney with its lower distal renal artery pressure and its locally stimulated RAS retains much more salt than the contralateral kidney. As BP rises due to the volume expansion, systemic BP increases ultimately high enough to achieve sodium balance by the pressure natriuresis mechanism, sodium excretion being now slightly elevated in the intact kidney and slightly decreased in the stenotic kidney (Mizelle et al. 1993). Because there is a continuing stimulus for renin release from the stenotic kidney and possible accumulation of intrarenal Ang II in the nonstenotic kidney (Navar et al. 1998), this hypertension is highly angiotensin-dependent and responds well to blockers of the RAS.

4.2.2

Role of the RAS in Essential Hypertension

Low renin levels would be expected in essential hypertension because of the higher renal perfusion pressure. However, the observation that most hypertensive patients have either normal or high renin levels has led to the view that renin may play a critical role in the pathogenesis of many forms of essential hypertension (Laragh 1992). Several factors have been presented to explain these “inappropriate” high levels of renin, such as a state of high sympathetic drive found in many hypertensive patients (Julius 1988), nephron heterogeneity with a subpopulation of ischaemic nephrons responsible for increased tonic renin release (Sealey et al. 1988) or a defective feedback regulation with nonmodulation

of the RAS (Williams et al. 1992). As expected, patients with normal or high renin levels respond better to β -adrenergic blockers and ACE inhibitors, whereas low-renin hypertensive patients respond better to diuretic treatment.

4.3

Angiotensin-Induced Cardiac and Vascular Hypertrophies Are Risks Factors

As mentioned above, the growth-promoting actions of Ang II may be viewed as an appropriate response in conditions in which increased heart strength and prolonged vasoconstriction are required. A certain degree of vascular hypertrophy is also useful in volume-loading hypertension, as it minimizes the amount of volume retention needed within the vascular system to maintain an elevated blood pressure. Indeed, the various forms of volume-dependent hypertension (mineralocorticoid-induced hypertension, high salt intake with a reduced renal mass) are characterized experimentally by an initial increase in cardiac output followed by a secondary autoregulatory vasoconstriction that returns blood volume and cardiac output towards normal (Guyton 1980). Were it not for autoregulation and vascular hypertrophy, reestablishment of sodium balance would be accompanied by much larger changes in fluid volumes.

Although cardiac and vascular hypertrophies may be considered adaptive from the point of view of enhancing short-term survival, they are clearly detrimental when allowed to continue to progress over prolonged periods of time. The increased stiffness of the hypertrophied heart impairs ventricular relaxation and filling. In fact, left ventricular hypertrophy is considered an independent risk factor for cardiovascular events. Vascular hypertrophy makes arteries stiffer, leading to increased pulse pressure and increased pulse wave velocity. An increased pulse pressure for a given mean arterial pressure is in itself a cardiovascular risk factor: the higher systolic pressure constitutes an elevated left ventricular afterload while the lower diastolic pressure reduces the driving pressure for coronary blood flow. Increased pulse wave velocity results in a rapid return of reflection waves to the heart, increasing systolic pressure and decreasing diastolic pressure further. In this context, one can understand the beneficial health effects of blockers of the RAS in reversing cardiac and vascular hypertrophy.

4.4

Activation of the RAS Worsens Congestive Heart Failure

An activation of the RAS may be a natural response to the initial insult of heart failure. Various models of experimental heart failure (rapid ventricular pacing, pulmonary artery occlusion) in which the same animal could be studied before and after induction of heart failure, are characterized by a decrease in arterial pressure (Mizelle et al. 1989; Lohmeier et al. 1995, 2000a), which is expected to stimulate the RAS. Although there is only a modest activation of the RAS in the early compensated phase of heart failure (Lohmeier 2002), even small increments in Ang II concentration may favour fluid retention. The resulting increase

in fluid volumes could be beneficial, allowing cardiac output and arterial pressure to return towards normal.

However, excessive activation of the RAS in heart failure is clearly harmful. When exogenous Ang II was administered for 4 days to dogs in compensated heart failure, decompensation occurred with profound sodium retention and marked increases in plasma norepinephrine (Lohmeier et al. 2000a). Cardiopulmonary baroreflex suppression of sympathetic nerve activity, which is impaired in heart failure, could play a critical role in the transition from compensated to decompensated heart failure. Impaired sympathoinhibition would unmask the sympathoexcitatory actions of Ang II, resulting in a positive feedback. Ang II would increase sympathetic nerve activity, which stimulates renin secretion further. In turn, higher plasma levels of Ang II would further stimulate sympathetic activity. As a result, there would be a progressive fluid retention and progressive cardiac dysfunction. Consistent with this hypothesis is the observation that ACE inhibitors have been shown to delay the progression of heart failure and to improve symptoms and prolong survival in patients with ventricular dysfunction.

4.5

Systemic and Local Angiotensin May Initiate and Amplify Vascular Disease

Ang II has direct effect on endothelial and vascular smooth muscles cells, and may play a key role in initiating and amplifying vascular disease. In the normal state, there is a homeostatic balance between locally produced NO and oxygen radicals, such as the superoxide anion and hydrogen peroxide. Under these conditions, NO can exert all of its protective functions as vasodilator, inhibitor of platelet aggregation, inhibitor of vascular smooth muscle growth and migration, and inhibitor of the expression of proinflammatory molecules.

As aforementioned, Ang II by its action on AT₁ receptors can stimulate NAD(P)H oxidases, leading to the production of the oxygen radical superoxide. Quenching of NO by the superoxide anion not only reduces the bioavailability of NO (and thereby of all its protective functions), but also forms peroxynitrite (ONOO⁻), a powerful oxidant. The combined action of excess Ang II and oxidative stress may unleash a cascade of harmful effects, such as increased vasoconstriction, increased expression of chemoattractant proteins and leukocyte adhesion molecules, stimulation of thrombosis and vascular remodelling. The local inflammatory response promotes an accumulation of various inflammatory cells that can release enzymes that generate Ang II. For example, macrophages are rich in ACE, neutrophils in cathepsin G, mast cells in chymase. The increased local production of Ang II may further promote oxidative stress, leading to a vicious cycle of inflammation and subsequent increase in tissue Ang II (Dzau 2001).

If endothelial function is preserved, this positive feedback can easily be dampened by the actions of NO and antioxidants. However, in the presence of cardiovascular risk factors, the homeostatic balance between pro-oxidants and antioxidants is perturbed. Dyslipidaemia, diabetes and cigarette smoking can all

initiate endothelial dysfunction and promote oxidative stress. Excessive activity of the RAS potentiates the vicious cycle described above, inducing vascular remodelling, promoting atherosclerosis and upsetting the balance between the fibrinolytic and coagulation systems. The observations may explain why ACE inhibitors and angiotensin-receptor blockers have beneficial effects on cardiovascular events far beyond blood pressure reduction.

5 Conclusions

Without efficient mechanisms for conserving salt, our ancestors living on a diet relatively poor in sodium would have never survived, as they would not be able to respond to even moderate haemorrhage, and not have the required haemodynamic reserve for fight-or-flight reactions. Ang II, the major end-product of the RAS, has multiple actions that work in a concerted manner to maintain cardiovascular integrity and efficiency. Most of the rapid actions of Ang II can be viewed together, in combination with the sympathetic nervous system, to support the circulation when it is threatened by acute disturbances such as hypovolaemia and hypotension. Slower actions of Ang II help maintain volume homeostasis by minimizing the changes in arterial pressure and ECFV required to achieve sodium balance (prevention of salt sensitivity). Some of the very slow actions of Ang II, such as cardiac and vascular hypertrophy and oxidative stress, although potentially harmful, may be viewed as adaptive responses to improve the efficiency of fluid volume and BP preservation. However, such responses are clearly detrimental if carried to excess.

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