Regulation of arterial blood pressure

U Ackermann

Each beat of the heart causes the arterial blood pressure to rise from its diastolic value (about 80 mmHg) to its systolic value (about 120 mmHg). The difference between systolic and diastolic arterial pressure is called the pulse pressure. Although systolic and diastolic blood pressures are usually measured, clinical information about cardiovascular function is more readily understood if systolic pressure is thought of as the sum of diastolic and pulse pressures. This is because these pressures are mainly determined by a few important parameters:

- The chief determinants of pulse pressure are cardiac performance and aortic stiffness (I am avoiding the term elasticity because its mechanical meaning is opposite to its vernacular meaning). An increase in either of these variables will increase pulse pressure.
- The main determinants of diastolic blood pressure are the mean circulatory filling pressure, total peripheral vascular resistance and the interval between successive heart beats. Diastolic arterial blood pressure will increase if there is an increase in any one of mean or total peripheral vascular resistance or heart rate (decreased R-R interval).
- Mean circulatory filling pressure is the value to which arterial blood pressure would fall if the heart stopped beating. Mean circulatory filling pressure is directly related to blood volume and the overall stiffness of the vascular system.

Mean arterial blood pressure is the average pressure prevailing over a few heart beats. It is a mathematical concept and its calculation from diastolic and pulse pressure values depends on the shape of the arterial pressure pulse. This shape varies at different locations in the body, but is approximately a triangle with a broad time-base if the arterial blood pressure is measured directly by central catheter. For such a shape the mean value can be approximated by the formula:

$$\text{Mean arterial blood pressure} = \text{diastolic pressure} + 1/3 \text{ pulse pressure}$$

Mean arterial blood pressure represents the average force (driving pressure) propelling blood flow and of the different pressures listed above, it appears to be the one whose magnitude is physiologically controlled. Thus, in health, mean arterial blood pressure is closely regulated to be about 100 mmHg. Small deviations from this value occur regularly in the course of daily life, but compensatory mechanisms will regulate the pressure back towards 100 mmHg. For any individual and any level of physical activity, an optimal mean arterial blood pressure exists. This optimum is called the 'setpoint' (see below). The setpoint differs between the sexes and increases with age in any one individual but, over the course of 24 hours, there are comparatively narrow fluctuations about the setpoint.

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Why is the regulation of blood pressure necessary?

Each tissue must continuously receive the blood flow it needs in order to perform the metabolic activity that is demanded of it. Such blood flow is inversely proportional to the vascular resistance of the tissue. This resistance is related to the radius of blood vessels by Poiseuille's Law, which states that the resistance of a single, uniformly circular tube is related to the radius of the tube by the formula:

$$\text{Resistance} \propto \frac{1}{\text{Radius}^4}$$

If the metabolic activity of a tissue increases, the tissue requires more blood flow and the vascular resistance of the tissue is lowered by dilation of its blood vessels. Figure 1 shows that such local vasodilation has to decrease total peripheral vascular resistance. The formula relating mean arterial blood pressure to cardiac output and total peripheral vascular resistance (Figure 1) shows that if cardiac output remained unchanged, a fall in total peripheral vascular resistance would lower mean arterial blood pressure. Such a fall in central driving pressure would decrease the perfusion pressure of individual organs and lead to decreased perfusion of all other vascular beds, including those of the vital organs: brain and heart. Regulation of blood pressure is necessary in order to maintain, at all times and in spite of the vascular architecture, an adequate blood supply to the heart and the brain. Examples of the lethal consequences of massive local vasodilation that are beyond the compensatory capabilities of the regulatory system are seen in septic and anaphylactic shock.

What are the control points for the regulation of blood pressure?

The regulation of blood pressure involves the manipulation of three cardiovascular parameters: heart rate, stroke volume and total peripheral vascular resistance.

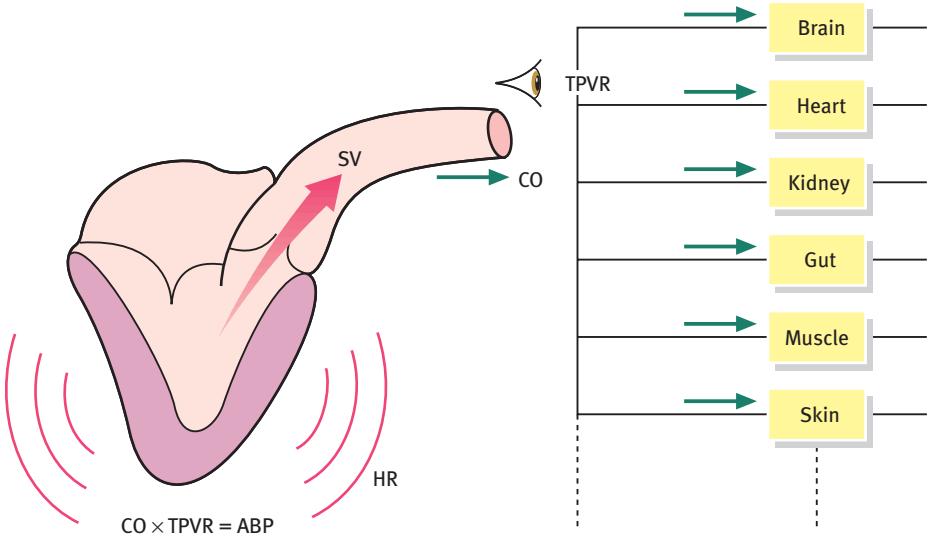
Regulation of heart rate

Heart rate is set by the rate of generation of action potential in the dominant cardiac pacemaker cells. It is increased by agents that are positively chronotropic (e.g. cardiac sympathetic nervous activity) and it is decreased by agents that are negatively chronotropic (e.g. cardiac parasympathetic nervous activity).

Regulation of stroke volume

The major determinant of left ventricular stroke volume is cardiac performance. Four factors determine cardiac performance: preload, afterload, heart rate and contractility.

Vascular architecture



Most vascular beds are arranged in parallel so that they receive blood flow from a common source: the left ventricle. Total flow per minute from the left ventricle is the cardiac output (CO), which is the product of heart rate (HR) and the ventricular volume ejected with each beat (stroke volume, SV). Each tissue offers resistance to the flow of blood and the total peripheral vascular resistance (TPVR) is the resistance that would be seen by an imaginary viewer looking down the aorta from the aortic valve. The product of CO and TPVR is approximately the mean arterial blood pressure (ABP), which can be regarded as the net force driving flow into all tissues.

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- In the normal heart and up to an optimum preload, an increase in preload will lead to increased ventricular performance. This is also known as Starling's Law of the heart.
- An increase in afterload will decrease ventricular performance. However, the healthy heart is capable of increasing ventricular contractility in response to increased afterload. This compensatory mechanism is called the Anrep effect. It is believed to be caused by metabolically induced subendocardial diastolic hyperaemia in reaction to greater systolic compression of the coronary vasculature.
- The effect of heart rate on ventricular performance is called the Bowditch effect or the Treppe phenomenon. Its outcome depends on the initial heart rate. If the initial rate is not already abnormally high, an increase in rate will cause an increase in performance.
- Short-term changes in contractility arise predominantly from neurohumorally initiated changes in the conductivity of calcium channels. Long-term changes arise from changes in the isoform properties of the contractile proteins, actin and myosin.

Regulation of total peripheral vascular resistance

Peripheral vascular resistance is chiefly determined by the luminal diameter of arterioles (which depends on the degree of constriction of vascular smooth muscle surrounding the arterioles). In any one tissue and at any time, vascular smooth muscle is subjected to the simultaneous influence of vasodilator factors (mostly byproducts of tissue metabolism) and vasoconstrictor factors (mostly sympathetic nervous activity and vasoconstrictor chemicals such as adrenaline, angiotensin II or vasopressin). Regulation of total peripheral vascular resistance is achieved by sympathetically mediated vasoconstriction of any tissue that is not producing vasodilating metabolic byproducts.

What are the mechanisms for the regulation of blood pressure?

Generally, the regulatory system functions to correct deviations of arterial blood pressure from the setpoint value. Such a system requires three components:

- Sensors that respond to a pressure-related variable and convey an appropriately coded signal to an evaluator.
- Evaluators translate the incoming code from the sensors, compare the existing blood pressure with the setpoint and issue the appropriate commands for compensatory actions.
- Effector mechanisms bring about changes in heart rate, cardiac performance and total peripheral vascular resistance so as to reduce the difference between existing blood pressure and setpoint.

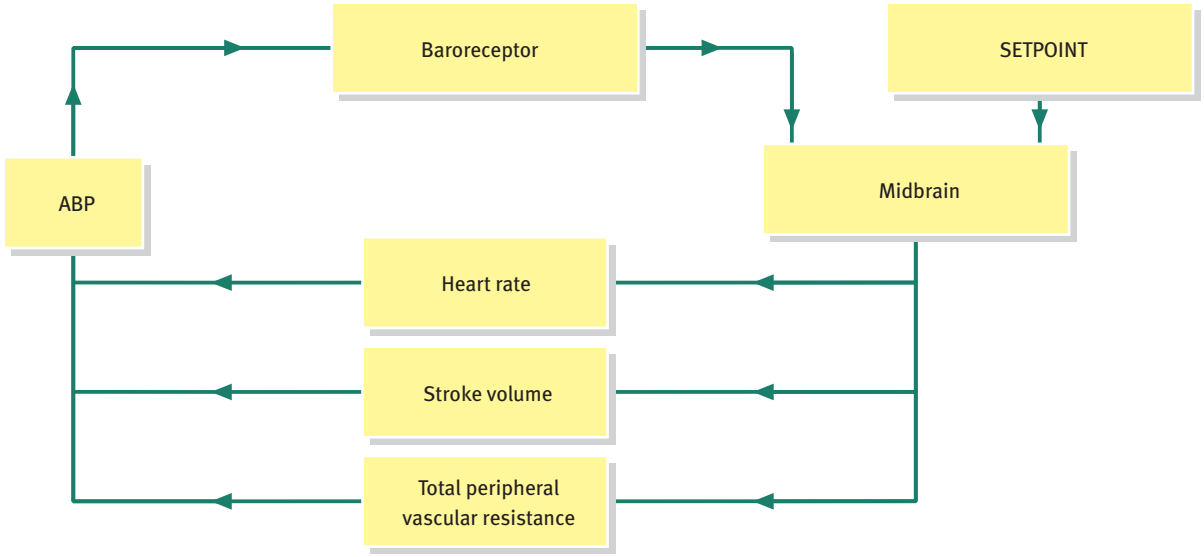
Short-term mechanisms of regulation of the blood pressure

The dominant short-term regulator of arterial blood pressure is the baroreceptor mechanism (Figure 2). The sensors are unencapsulated nerve endings in the wall of the carotid sinus and the aortic arch. Participating in this regulation are stretch sensors in the cardiac atria and the stretch-sensitivity of a few cells in the juxtaglomerular apparatus of renal afferent arterioles.

Figure 3 shows the evaluators for signals from these sensors and also the effector mechanisms.

The evaluators are located mostly in the pons/medulla region

The baroreceptor mechanism of blood pressure control



Arterial blood pressure (ABP) is sensed by baroreceptors, which are located primarily in the walls of the carotid sinuses and arch of the aorta. They translate wall stretch into action potentials that are conveyed to the midbrain region by fibres in the glossopharyngeal (IX) and vagus (X) nerves. Neurons in the pons and medulla regions of the midbrain compare existing blood pressure against the setpoint, which represents the desirable blood pressure under the circumstances. If there is a deviation of ABP from the setpoint then neurohumoral signals are generated and conveyed to the periphery so as to bring about appropriately corrective changes in heart rate, cardiac stroke volume and total peripheral vascular resistance.

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of the midbrain, particularly in the neurons of the nucleus tractus solitarius.

The effector mechanisms are:

- Increased production of angiotensin II by way of the renin–angiotensin cascade.
- Cardiac parasympathetic outflow from the neurons of the nucleus ambiguus and conveyed to the heart by way of the vagus nerve.
- Sympathetic nervous outflow from the neurons of the rostral ventrolateral medulla.
- Vasopressin, which is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus, transported along axons towards the posterior pituitary, and released by exocytosis into the circulation.

The setpoint for arterial blood pressure is that pressure which is appropriate and desirable for the prevailing conditions. Conditions include degree of physical activity, body temperature, degree of wakefulness, emotional state, and awareness of pain. Setpoint is believed to be refined postnatally as the body learns to respond appropriately to increasingly complex cardiovascular challenges.

Peripheral actions of effector mechanisms

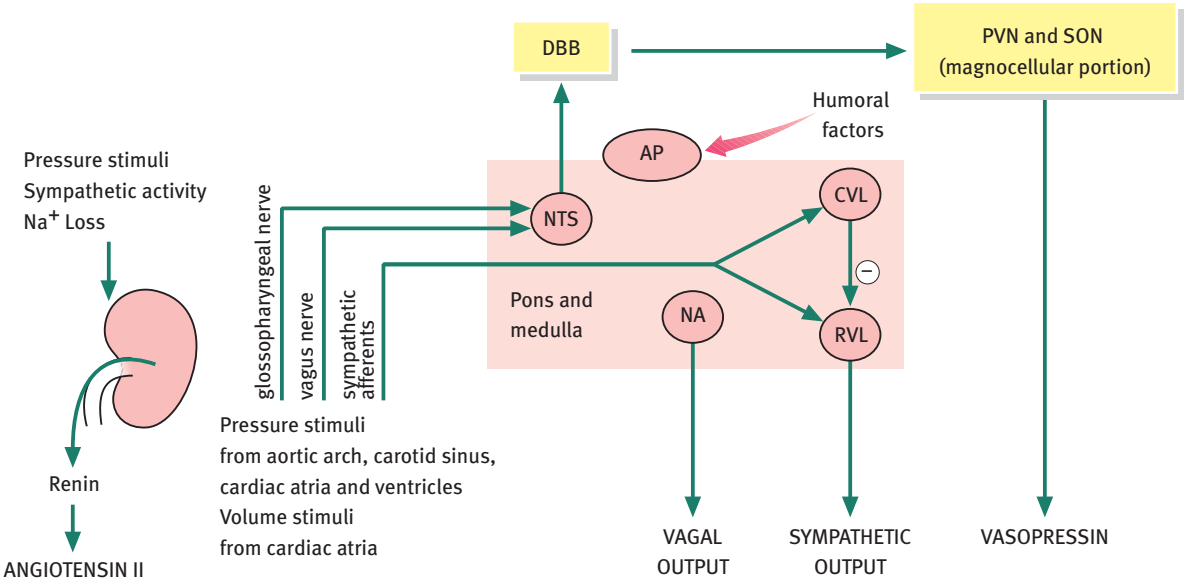
Angiotensin II – in the short term, the main cardiovascular effects of angiotensin II are mediated by the activation of AT_1 receptors in the membranes of vascular smooth muscle cells. Such activation elevates levels of intracellular calcium ions and leads to vasoconstriction. Angiotensin II also increases renal retention of sodium ions and water by:

- acting on receptors in the proximal and late distal convoluted tubule of the nephron
- promoting the synthesis and release of the salt-retaining hormone aldosterone, from adrenal cortical zona glomerulosa cells.

Activity of parasympathetic nerves – efferent fibres of the vagus nerves innervate the cardiac pacemaker cells and, to some extent, the atrial myocytes and conductive tissue of the cardiac ventricles. Action potentials result in the release of acetylcholine from the terminal butons and subsequent activation of M_2 muscarinic receptors, which leads mainly to a decrease in heart rate. Atrial performance is decreased but, in a healthy heart (where atrial contraction contributes only a small fraction of ventricular diastolic filling) atrial performance influences overall cardiac performance only at high pulse rates.

Activity of sympathetic nerves – action potential is translated into release of adrenaline from chromaffin cells in the adrenal medulla, renin release from renal juxtaglomerular cells, and noradrenaline release at peripheral synapses, which are found in cardiac myocytes and the vascular smooth muscle that surrounds blood vessels. Subsequent cardiovascular effects of adrenaline and noradrenaline are initiated when these catecholamines activate α

Interrelationships between pressure sensors and effector mechanisms of regulation of blood pressure



Juxtaglomerular cells of the renal afferent arteriole respond to decreased stretch with increased synthesis and release of renin. Renin initiates a cascade that leads to the production of angiotensin II.

Nerve endings in the cardiopulmonary region respond to increased or decreased stretch with corresponding changes in the frequency of action potentials. These are received and evaluated mostly in the neurons of the nucleus tractus solitarius (NTS). NTS neurons interact multilaterally with higher centres of the brain, as well as with more adjacent neurons in nuclei such as the nucleus ambiguus (NA), the caudal ventrolateral medulla (CVL) and rostral ventrolateral medulla (RVL). Blood-borne factors can reach midbrain nuclei by way of the area postrema (AP), which is a region that lacks the blood–brain barrier that prevents humoral factors from reaching most other central neurons. The NA generates vagal output to the heart and the RVL is the origin of sympathetic nervous activity. Neurons of the CVL exert tonic inhibitory influence on the RVL. Vasopressin has both vascular and renal actions and originates in neurons of the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus.

DBB: Diagonal band of Broca.

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and β adrenoreceptors that are found in cell membranes of the target tissues. The differential effects of adrenaline and noradrenaline on adrenergic receptors are beyond the scope of this overview. The final effects of increased sympathetic nervous activity are

- increased heart rate (β_1-activation)
- increased cardiac contractility (β_1-activation)
- increased vascular resistance (α_1-activation).

Vasopressin – the cardiovascular effects of vasopressin result from activation of V_1 receptors in vascular smooth muscle and such activation causes vasoconstriction. Vasopressin also acts on V_2 receptors in the cortical collecting duct of the nephron. Such action results mostly in the insertion of aquaporins (water channels) into the luminal membrane and leads to increased reabsorption (decreased excretion) of water from the nephrons.

The overall system of short-term regulation of blood pressure

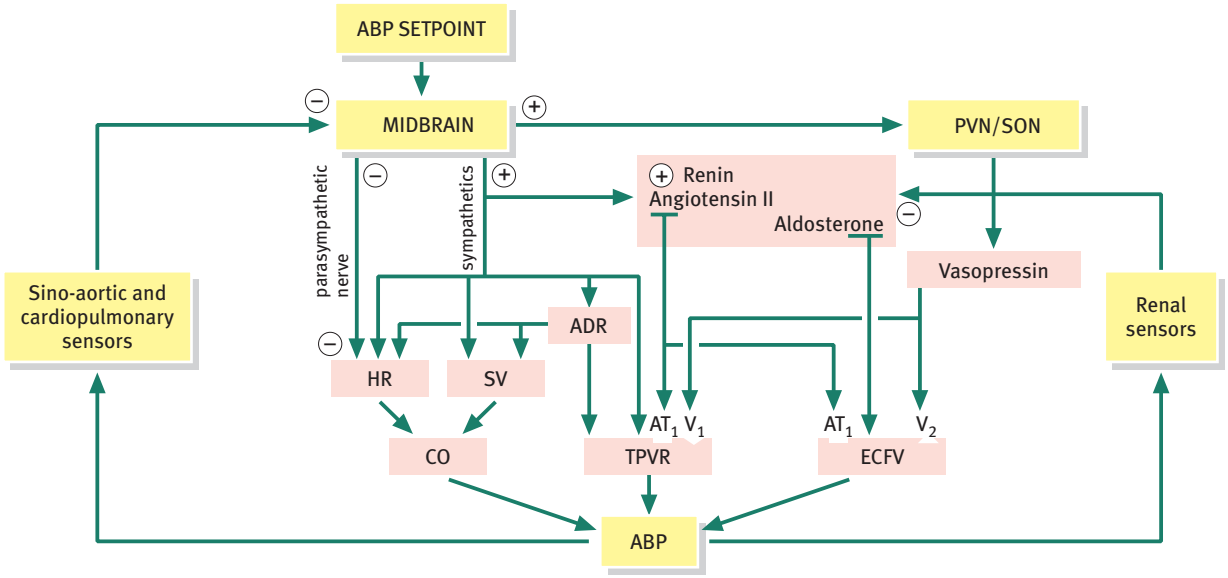
Figure 4 summarizes the sensors, evaluators and effectors that coordinate the regulation of blood pressure on a timescale from one minute to several days. The system exhibits the features of feedback regulation in that:

- peripheral sensors convey to central evaluators, the action potential-encoded information that describes current blood pressure
- the central evaluators compare existing blood pressure with the desirable setpoint
- the evaluators cause appropriate responses in parasympathetic nervous activity, sympathetic nervous activity, synthesis of angiotensin II and release of vasopressin in order to eliminate the error between setpoint and existing blood pressure.

Long-term mechanisms of regulation of blood pressure

Many aspects of regulation of blood pressure over a period of years to decades remain subjects of investigation and are controversial. However, epidemiological findings related to salt intake, renal cross-transplantation studies in genetically hypertensive rats, and clinical experience with angiotensin-converting enzyme inhibitors

Summary of responses to a decrease in arterial blood pressure



As indicated by the minus signs, a fall in arterial blood pressure (ABP) reduces stretch-related input to the midbrain from central sensors and to renin-secreting juxtaglomerular cells in renal afferent arterioles. These changes lead the midbrain to respond with decreased parasympathetic outflow, increased sympathetic outflow and increased nerve traffic to the vasopressin-secreting nuclei of the hypothalamus (PVN/SON). Juxtaglomerular cells respond with increased renin secretion and subsequent increases in circulating angiotensin II and aldosterone. Cardiac parasympathetic nerve activity is inversely related to heart rate (HR). Therefore, withdrawal of cardiac parasympathetic tone will increase HR. Increased sympathetic activity increases juxtaglomerular renin secretion, HR, stroke volume (SV), total peripheral vascular resistance (TPVR) and adrenaline secretion (ADR) from the adrenal medulla. The effects of ADR on HR, SV and TPVR are generally added to those of increased sympathetic nerve activity. Angiotensin II acts through AT_1 receptors to constrict blood vessels (increase TPVR) and increase renal reabsorption of Na^+ and water. Its renal action, therefore, increases extracellular fluid volume (ECFV). Aldosterone increases ECFV by upregulation of Na^+/K^+ ATPase in the distal nephron. Vasopressin activates V_1 receptors in vascular smooth muscle to cause vasoconstriction and V_2 receptors in the distal nephron to increase renal water reabsorption. The net effects of increased HR, SV, TPVR and ECFV are to increase cardiac output (CO) and arterial blood pressure (ABP) towards the normal setpoint value.

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in humans have focused attention on the role of the kidney and the role of angiotensin II in long-term regulation.

The kidney in long-term regulation of blood pressure: while several organs excrete water and salt, only the kidney excretes them in a controlled manner and for the sole purpose of regulating the total body content of sodium ions and water. This regulation is exquisitely sensitive to renal perfusion pressure; even a small increase in renal arterial pressure can cause a large increase in the renal excretion of sodium ions. This relationship is called pressure natriuresis.

Early experiments suggested that hypertension develops when a small defect in kidney function causes renal retention of sodium ions and water, increases the volume of extracellular fluid and causes arterial blood pressure to rise to a level at which the pressure natriuresis mechanism can again maintain a balance between intake and output of sodium ions and water. It appears, therefore, that the long-term-controlled variable is not arterial blood pressure, but the balance between intake and output of fluid and electrolytes.

The concept that a defect in renal handling of salt and water will cause and maintain hypertension so that the higher renal perfusion pressure can once again balance renal output to oral intake is supported by experiments in humans and animals. The precise nature of the renal defect is more difficult to establish, but appears to be localized mainly to diminished reabsorption of sodium ions in the proximal convoluted tubule. Multiple dietary, metabolic, mechanical and genetic interactions may be involved.

Angiotensin II in the long-term regulation of blood pressure

Angiotensin II is produced in an enzymatic cascade that is started when the acid protease, renin, cleaves 4 amino acids from the terminal end of angiotensinogen, a 14-amino acid plasma globulin that is produced mainly in the liver. This step produces angiotensin I, which has little biological activity. Angiotensin-converting enzyme then cleaves two amino acids from angiotensin I, produc-

The actions of angiotensin II that have significant effects on the cardiovascular system

Domain of action	Site of action	Net cardiovascular effect
CNS	Median preoptic nucleus	↑ Drinking
	Nucleus tractus solitarius	↓ Baroreflex sensitivity
	Median preoptic nucleus and others → ↑ Vasopressin	Vasoconstriction and ↑ Renal water reabsorption
	Caudal + ventrolateral medulla → ↑ sympathetic tone	Vasoconstriction + ↑ Cardiac output +↑ RAAS
Kidney	Proximal and distal convoluted tubule	↑ Renal reabsorption of Na^+ and water → ↑ ECFV
Adrenal cortex	Zona glomerulosa cells → ↑ aldosterone	↑ Renal reabsorption of Na^+ and water → ↑ ECFV
Vascular smooth muscle	AT_1 receptors	Vasoconstriction
Blood vessels	Media and intima	↑ Ratio of wall:lumen
Heart	Myocytes	Cardiac hypertrophy and hyperplasia

ECFV: Extracellular fluid volume; RAAS: Renin–angiotensin–aldosterone system.

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ing angiotensin II. Angiotensin-converting enzyme is located on the plasma membrane of endothelial cells. The major source of renin is the juxtaglomerular cells of the renal afferent arteriole, but a variety of tissues produce small quantities of renin that can have large local significance. Small quantities of renin may be significant if the local action involves a tissue (e.g. kidney, rostral ventrolateral medulla) that has the capacity to influence systemic function.

The actions of angiotensin are initiated by its interaction with two kinds of membrane receptors, AT_1 and AT_2. The most overt actions of angiotensin II are due to activation of the AT_1 receptor.

Some of the many effects of angiotensin II are summarized in Figure 5. Angiotensin II promotes short-term and long-term increases in arterial blood pressure by a variety of mechanisms and it should, therefore, be no surprise that therapeutic interventions directed at inhibiting its effects have such pronounced clinical efficacy. ◆

FURTHER READING

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