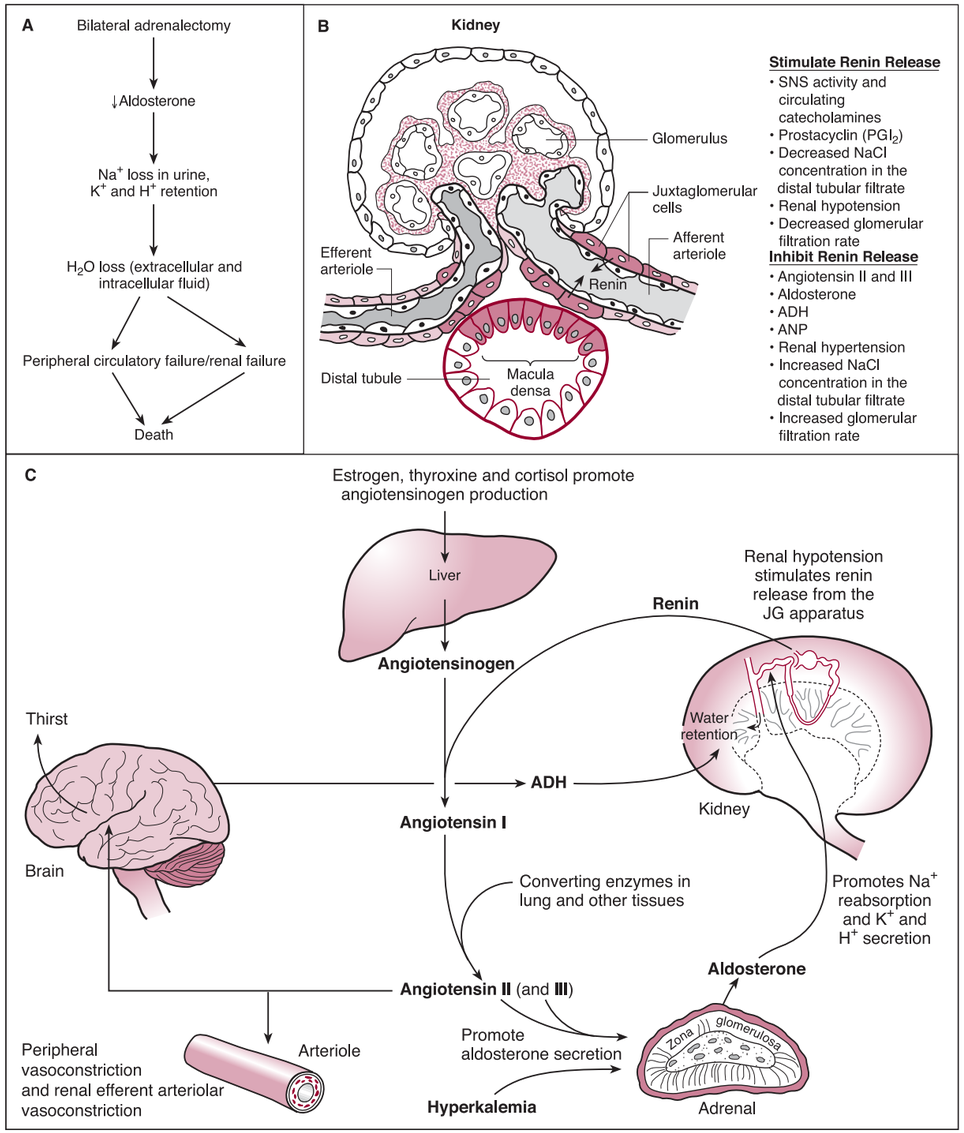
Ch27 Renin-Angiotensin System: I

(The Juxtaglomerular Apparatus)



Source: **Part B** modified from Ham AW. Histology. 7th ed. Philadelphia: JB Lippincott, 1974:753, and Ganong WF: The renin-angiotensin system and the central nervous system. Fed Proc 1977;36:1771.

Although hypophysectomy is not life-threatening, **bilateral adrenalectomy** is (**Part A**). The life-maintaining principles supplied by the adrenal cortices are cortisol, a glucocorticoid, and perhaps more importantly the renal Na^+-retaining and K^+-secreting mineralocorticoid, **aldosterone**, which is produced by cells of the **zona glomerulosa** (Ch. 26). Aldosterone deficiency, whether it occurs in an experimental animal or in a patient, results in hyperkalemia, metabolic acidosis, hyponatremia, peripheral circulatory failure, renal failure, and inexorably, **death**. Aldosterone secretion is only one of many factors affecting **urinary Na^+ excretion**. Other factors include the **glomerular filtration rate** (**GFR**), which directly affects the amount of time functional nephrons have to reabsorb Na^+; the **natriuretic peptides** (i.e., ANP, BNP, CNP and urodilatin; Ch. 31); the presence or absence of **osmotic diuresis**; and changes in **tubular Na^+ reabsorption** independent of aldosterone, for this steroid controls only **3%** of renal Na^+ reabsorption. It should also be noted that although aldosterone is an important hormone in the control of Na^+ balance, an acute reduction in plasma Na^+ of about 20 mEq/L is needed to stimulate aldosterone release, and changes of this magnitude are rare. However, the plasma K^+ concentration need increase only 1 mEq/L to stimulate aldosterone release, and transient increases of this magnitude may be expected following a K^+-rich meal.

Another factor controlling aldosterone release is the **renin–angiotensin system**, a multifactorial physiologic control system working to control blood pressure and volume. A major component of the renin–angiotensin system is the **juxtaglomerular (JG) apparatus** of the kidney. The JG apparatus is a combination of specialized vascular and tubular cells located near the glomerulus, where afferent and efferent arterioles come into close contact with the distal tubule (**Part B**). The JG cells are specialized myoepithelial cells of the afferent arteriole that synthesize, store, and secrete into blood a proteolytic enzyme called **renin** (not to be confused with **rennin**, a milk clotting enzyme secreted by the stomach's of young animals). **Macula densa** cells are specialized distal renal tubular epithelial cells that sense the low NaCl concentration of the filtrate, and directly signal **JG cells** to secrete renin into blood. When glomerular filtration is reduced (e.g., following blood loss), there is more time for NaCl reabsorption in the proximal nephron, and therefore the filtrate in the distal tubule will have a reduced NaCl concentration. Other factors that promote and inhibit renin release are listed in **Part B.** The circulating half-life of this polypeptide in plasma is about **15 minutes**.

Part C depicts the processes involved in the renin–angiotensin system. Circulating renin splits the end off a liver-derived plasma protein called **angiotensinogen** (or **renin substrate**), thus generating the decapeptide **angiotensin I.** Within a few seconds, two additional amino acids are split off angiotensin I to form **angiotensin II.** This conversion occurs mainly in pulmonary capillary endothelial cells through the activity of dipeptidyl carboxypeptidase, otherwise known as **angiotensin-converting enzyme** (**ACE**). This enzyme is found to a lesser degree in blood plasma and renal tissue. **Angiotensin II** persists in blood for approximately **1 minute**, but it is rapidly inactivated by a number of different blood and tissue enzymes collectively called **angiotensinase** (**Part D**, Ch. 28). While active in blood, angiotensin II stimulates aldosterone synthesis and release from the adrenal cortex, among other actions.

The Angiotensins

Angiotensin II is one of the most potent known **vasoconstrictors**. It promotes norepinephrine release from sympathetic nerve endings (Ch. 33), as well as epinephrine and norepinephrine release from the adrenal medulla. It also vasoconstricts peripheral arterioles, efferent arterioles of the kidney, and to a lesser extent, veins. Primary stimuli for angiotensin generation are a **decrease in blood volume and/or pressure** (e.g., hemorrhage), and a **decrease in the glomerular filtration rate** (**GFR**).

Arteriolar constriction increases peripheral resistance, thereby raising arterial pressure back toward normal. Also, mild constriction of veins increases mean circulatory filling pressure, sometimes by as much as 20%, which promotes an increased tendency for venous return of blood to the heart (i.e., "preload"), helping it to pump against the extra pressure load.

Other effects of angiotensin II are primarily related to more long-term body fluid volume restoration: **1**) it has a direct effect on proximal tubules of the kidneys to enhance NaCl reabsorption; **2**) it stimulates aldosterone secretion; **3**) it stimulates thirst; and **4**) it promotes ADH and ACTH secretion. Angiotensin II also decreases sensitivity of the baroreceptor reflex, thus potentiating its pressor effects.

A metabolic product of angiotensin II, des-Asp-angiotensin II or **angiotensin III,** is as potent as angiotensin II in releasing aldosterone but is a less effective pressor agent. It is important in rats, where it accounts for almost 60% of angiotensin activity. In humans and dogs, only about 10% of angiotensin activity is attributable to angiotensin III. Further catabolism of angiotensin III produces a hexapeptide known as **angiotensin IV**, which is thought to have little biologic activity.

Angiotensin II Receptors

There appears to be two major classes of **angiotensin II receptors** (**AT_1** and **AT_2**) on plasma membranes of target cells, with the AT_1 class being further subdivided into **AT_{1A}** and **AT_{1B}** receptors. The AT_1 receptors are coupled to a G-stimulatory (G_s) protein, which activates phospholipase C (PLC) and catalyzes hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) from the plasma membrane to produce diacylglycerol (DG) and inositol triphosphate (IP_3; Ch. 5). The IP_3, in turn, promotes Ca^{2+} release into the cytoplasm. The AT_2 receptors also act via a G_s protein, however they activate various phosphatases within cells, which in turn antagonize growth effects and open K^+ channels. Additionally, AT_2 receptor activation increases nitric oxide (NO) production, which in turn acts through cGMP.

The **AT_2** receptors are more plentiful in the fetus and neonate, where they may be assisting in maintaining a rather **low** vascular resistance. However, they apparently persist in the brain and other organs of adult animals. The AT_{1A} subtype is found in blood vessel walls, in the brain, and in several other organs, and appears to help mediate many of the known effects of angiotensin II. High levels of angiotensin II down-regulate AT_{1A} receptors, while AT_{1B} receptors are up-regulated. The AT_{1B} receptors are found primarily in the pituitary and adrenal cortex, where high circulating levels of angiotensin II can help to assure adequate ADH, ACTH, and aldosterone output.

Independent Renin-Angiotensin Systems

In addition to the classic multiorgan system described above that generates circulating angiotensin II, several different tissues of the body appear to contain independent renin–angiotensin systems that can generate this polypeptide, apparently for **local use**. Components of this system, for example, are found in walls of blood vessels, in the uterus and placenta, and in fetal membranes, and prorenin is found in amniotic fluid. In addition, components of this system have also been identified in the eyes, exocrine pancreas, heart, adrenal cortex, testes, ovaries, anterior pituitary, pineal, and brain.

Although these local systems do not appear to contribute significantly to circulating renin or angiotensin levels under normal conditions, they may do so with malignancy. For example, certain renin-secreting ovarian tumors have been known to cause hypertension.

Angiotensin II does not cross the BBB, but it affects circumventricular organs of the CNS (i.e., the subfornical organ, organum vasculosum of the lamina terminalis, and area postrema that lack a classical BBB). Through these organs it can produce neurally-mediated increases in blood pressure, and increase water intake.