Redin-Angiotensin System: I
(The Juxtaglomerular Apparatus)

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 adrenal Na+ retaining and K+-secretion mineralocorticoid, aldosterone, which is produced by cells of the zona glomerulosa (Ch. 15). Aldosterone deficiency, whether it occurs in an animal or in a patient, results in hyperkalemia, metabolic acidosis, hypernatremia, peripheral circulatory failure, renal failure, and inexcusable 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 Na+ filtered; functional nephron segments have to reabsorb Na+ (i.e., antidiuretic 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 steroidal hormone 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+ concentration 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 the afferent and efferent arterioles come into contact (Fig. 3). The JG apparatus has two components: (1) It appears to contain 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, 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 tubule, and therefore the filtrate in the distal tubule will have a reduced NaCl concentration. Other factors that promote and inhibit renin release are elaborated in Part D. 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 of 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 ACE, 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 arteries, efferent arterioles of the kidney, and to a lesser extent, veins. Primary stimuli of angiotensin generation are a decrease in blood volume and/or pressure (e.g., hemorrhage), and a decrease in the glomerular filtration rate (GFR).

Angiotensin II receptors

These are two major classes of angiotensin II receptors (AT1 and AT2) on plasma membranes of target cells, with the AT1 class being further subdivided into AT1A and AT1B receptors. The AT1 receptors are coupled to a G-stimulatory (Gs) protein, which activates phospholipase C (PLC) and catalyzes hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) from the plasma membrane to produce diacylglycerol (DG) and inositol triphosphate (IP3). The IP3, in turn, promotes Ca2+ release into the cytoplasm. The AT2 receptors also act via a G protein, however they activate various phospholipases within cells, which in turn antagonize growth effects and open K+ channels. Additionally, AT1 receptor activation increases nitric oxide (NO) production, which in turn acts through cGMP.

The AT1 receptors are more plentiful in the fetus and neonate, where they may be assisting in maintaining a rather low vascular resistance. However, they apparently persis in the brain and other organs of adult animals. The AT2 subtypes are 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 AT1 receptors, while AT2 receptors are up-regulated. The AT2 receptors are found primarily in the pituitary and adrenal cortex, where high circulating levels of angiotensin II can help to reduce adrenocortical ACTH, and adrenal cortex output.

Independent Renin-Angiotensin Systems

In addition to the classic multigorgan 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 subcommissural 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.