

## Q6 Describe the physiology of the Renin and Angiotensin system (Sept 2011)

**Renin** is a proteolytic enzyme produced and stored by the granular cells of the juxtaglomerular apparatus, which lies close to the glomerulus and distal tubule. Secretion is stimulated by:

- Pressure changes in the afferent arteriole
- Stimulation of the macula densa when changes occur in tubular NaCl concentration
- Renal sympathetic nerve activity (a direct  $\beta_1$  effect)
- Baroreceptor reflexes
- Negative feedback from ATII

Renin splits off the peptide angiotensin 1 from hepatic angiotensinogen (note renin is the rate-limiting step for activation of the RAAS). Angiotensin Converting Enzyme (ACE), found mainly in the pulmonary vascular endothelial cells, converts angiotensin 1 to **angiotensin II**. ATII acts on cell AT1 and AT2 receptors. Its effects include a general reduction in sodium and water excretion, and maintenance of circulating blood volume, GFR and blood pressure. Specifically:

### RENAL EFFECTS:

- Increases aldosterone production to stimulate sodium resorption in the collecting ducts
- Directly stimulates the Na/H exchanger in the proximal tubule, as well as the Na/K ATPase along the length of the tubule and the Na/Cl symporter in the distal tubule
- Constricts the efferent arteriole more than the afferent, due to the presence of local vasodilators. Constriction of the afferent arteriole reduces GFR. Constriction of the efferent more reduces peritubular capillary hydrostatic pressure, which increases net tubular resorption, especially from the proximal tubules. Secondly, by reducing renal blood flow, efferent arteriolar constriction raises the filtration fraction in the glomerulus and increases the concentration of proteins and the colloid osmotic pressure in the peritubular capillaries – this raises tubular resorption of sodium and water.

### SYSTEMIC EFFECTS:

- A potent general vasoconstrictor, ATII also increases sympathetic nervous system activity (by stimulating release of Nad from sympathetic nerve terminals), increasing TPR, BP and cardiac output
- Inactivates bradykinin (a vasodilator)
- Direct hypothalamic effect to increase thirst and water intake
- Stimulates ADH secretion to increase renal water retention

Angiotensin II is rapidly removed from the circulation, presumably by tissue peptidases.

**Aldosterone** is secreted from the zona glomerulosa of the adrenal cortex in response to ATII, increased plasma K<sup>+</sup> concentration and ACTH. It acts in the renal CCD to enhance the activity of ENaC and K<sup>+</sup> secretion by principal cells. It also induces the production of many proteins including Na/K ATPase in the basolateral membrane, and Na and K channels in the luminal membrane.