REGULATION OF BODY Na and ECFV

Because the **major osmotically effective** solutes in the ECF are **Na+** salts the amount of water present in the ECF compartment depends on the Na+ content of the body.

1. Sensors of changes in ECFV.

Atrial receptors. Small (10%) decreases in ECFV, due to corresponding changes in dietary Na+ or simply redistribution of ECFV between central (heart and lungs) and peripheral (legs) blood reservoirs, are sensed by stretch receptors at the low pressure side of the circulation, such as the atrial stretch receptors. These receptors, when less stretched send fewer neural inhibitory impulses to the central sympathetic nervous system..

Macula densa. Moderately large decreases in ECFV capable of reducing GFR or of increasing PT Na+ reabsorption will decrease the NaCl load reaching the macula densa. Decreased transport of NaCl by macula densa cells results in decreases in cytosolic [Ca2+]i, which through not well defined messengers (possibly less release of arachidonic acid metabolites or adenosine), leads to decreases in cytosolic [Ca2+]i in the granular cells of the afferent arteriole, which in turn increases renin release while decreasing the afferent arteriole vascular tone.

Renal vascular baroreceptor. Decreased stretch at the renal afferent arterioles due to large changes in ECFV resulting in low mean renal arterial pressure or increased preglomerular resistance, reduces Ca2+ influx into granular cells of these arterioles and promotes renin release.

Systemic arterial baroreceptors. Large decreases in ECFV, CO or systemic peripheral vascular resistance resulting in reduced MAP are sensed by the arterial (carotid and aortic) baroreceptors, which reduce the inhibitory neural afferent input to the central sympathetic centers.

2. Neural mediators

Inhibitory neural afferent input to the central sympathetic centers in the hypothalamus originates in stretch receptors present on the low pressure side of the circulation such as in the left atria and reach the hypothalamus via the vagal (Xth) nerve. Inhibitory neural afferents also reach the sympathetic centers from the arterial baroreceptors through the IX and X nerves.

Sympathetic efferents reach the kidneys, specifically the granular cells of the juxtaglomerular apparatus, via the renal nerves and through ß-2 receptors mediate renin release in response to increases in sympathetic output.

Sympathetic efferent effects are also mediated through release of catecholamines which bind to a-1 receptors, leading to constriction of renal and extrarenal arterioles and mesangial cells, and stimulation of proximal tubule Na-K-ATPase.

3. Humoral mediators

AII (angiotensin II). Release of renin, stimulated by the sympathetics, by low MAP, or by low NaCl delivery to the macula densa, promotes conversion of plasma angiotensinogen to AI; conversion of AI to AII occurs spontaneously under the influence of ACE (angiotensin converting enzyme).

AII is an potent vasoconstrictor which reduces RPF, but because its dominant effect is on the efferent arteriole, it maintains glomerular Pc and reduces Pc at the peritubular capillaries. These effects maintain GFR, increase filtration fraction (GFR/RPF) and peritubular capillary osmotic pressure, and increase proximal tubule reabsorption of Na and water.

In addition, AII stimulates proximal tubule Na-H exchange and Na-bicarbonate reabsorption by reducing intracellular cAMP through a Gi protein linked to the AII receptor. This effect of AII accounts for the alkalosis often seen in volume depletion. In the adrenal cortex AII is a potent stimulus for the release of aldosterone.

Aldosterone produced at the zona glomerulosa of the adrenal cortex is a potent mineralocorticoid that promotes active sodium reabsorption along DT and CD. Aldosterone is released in response to AII, high plasma K and very large decreases in plasma Na.

Aldosterone competes with cortisol for binding to its receptor in principal cells. The enzyme 11-ß hydroxysteroid dehydrogenase converts cortisol to non-binding cortisone, allowing aldosterone to bind to the mineralocorticoid receptor preferentially. Inhibition of this enzyme (by licorice) results in a syndrome similar to excessive production of aldosterone, due to cortisol binding.

Receptor-bound aldosterone enters the nucleus of principal cells, where it increases transcription of luminal Na channel proteins, of Na-K-ATPase and of enzymes of energy metabolism, resulting in increased luminal entry into and increased basolateral extrusion of Na from the cells. Aldosterone also accelerates K secretion by principal cells and H-secretion by a -intercated cells of the CD.

ANP (atrial natriuretic peptide). Increases in volume at the low pressure side of the circulation stretch the atria, which release ANP to the circulation. ANP is a potent vasodilator that increases RPF, GFR, and peritubular Pc, and thus increases filtration and reduces proximal tubule reabsorption of Na and water. In addition, ANP inhibits Na reabsorption at the CD. Peptides analogous to ANP are produced in the brain (BNP) and in the kidneys (urodilatin). An endogenous ouabain-like inhibitor of Na transport is produced in the adrenals.

4. Effectors of change in renal Na excretion

The principal cells of the CD are major targets for aldosterone stimulated distal Na reabsorption and for ANP.

Changes in osmotic pressure and hydrostatic pressure in the peritubular capillaries alter proximal Na reabsorption. These forces reduce or increase the interstitial fluid pressure and promote or inhibit fluid and Na reabsorption, respectively. Proximal Na reabsorption is stimulated by AII, which increase Na-H exchange, and by noradrenaline, that stimulates the Na-K ATPase.

Small changes in renal hemodynamics (RPF and GFR) can have large effects on renal Na excretion.

Increased MAP decreases Na reabsorption in deep but not in surface nephrons. Redistribution of filtration between nephrons affects Na excretion.

Na reabsorption in the loop of Henle is increased when medullary blood flow decreases (ADH) and diminishes when medullary blood flow washes out the osmotic gradient.