Outline the determinants and regulation of extracellular fluid volume.

Background

Extracellular fluid (ECF) volume is the component of total body water (TBW) that is not contained within cells.

ECF is approximately 45% of TBW.

For a 70 kg male, TBW ≈ 42 L → ECF ≈ 19 L.

However, approximately 1/3 of ECF is contained within bone and connective tissue, which equilibrate slowly.

∴ functional (i.e. rapidly equilibrating) ECF volume ≈ 30% TBW ≈ 13 L.

Determinants of ECF Volume

The principle determinant of ECF volume is the total amount of osmotically active solute present in ECF.

The principle solutes in ECF are Na⁺ and Cl⁻ → account for 90% of ECF osmolality.

Cl⁻ concentration largely governed by Na⁺ concentration.

∴ main determinant of ECF volume is Na⁺.

Regulation of ECF Volume

The body regulates [Na⁺], and thus ECF volume, via the following mechanism:

- sensors: osmoreceptors, volume receptors, baroreceptors, intrarenal sensors
- controller: hypothalamus
- effectors: thirst, ADH, renin-angiotensin-aldosterone system (RAAS), ANP, intrarenal mechanisms

Sensors

(1) Osmoreceptors

- hypovolaemia is often associated with ↑osmolality
- [Na⁺] is a surrogate measure of osmolality → sensed by osmoreceptors located in the anterior hypothalamus (OVLT and SFO)
- Sensitive to ~ 1% change in ECF osmolality
- ↑osmolality → sensed → ↑thirst and ↑ADH

(2) Volume receptors

- ↑ECF volume → ↑stretching of vessel walls → sensed by volume receptors (low pressure baroreceptors) in atria, large veins and pulmonary vasculature
- volume receptors are less sensitive (only detects ~10% change in intravascular volume) but more potent than osmoreceptors (can override osmoreceptors)
- results in ↑ANP release and ↓ADH release

(3) High pressure baroreceptors

- ↓ECF volume → sensed by high pressure baroreceptors located in carotid sinus and aortic arch → ↓firing rate → ↑sympathetic outflow
- results in ↑RAAS and ↑ADH

(4) Intrarenal sensors
- sensors within the kidney (located in juxtaglomerular apparatus and macula densa) can detect ↓ECF via ↓filtered Na⁺ load and ↓arterial pressure
- respond via ↑RAAS

**Effectors (in response to ↓ECF)**

(1) ↑Thirst
- thirst → drinking → ↑ECF volume

(2) ↑RAAS
- ↑RAAS → ↑aldosterone → ↑Na + H₂O retention → ↑ECF volume
- ↑ATII → ↓RBF → ↓Na and H₂O filtration → ↑ECF volume
- ↑ATII → ↑ADH + ↑thirst

(3) ↑ADH
- ↑ADH → ↑thirst
- ↑ADH → ↑H₂O and urea reabsorption in collecting duct → ↑ECF volume

(4) ↓ANP
- ↓ANP → ↓GFR → ↓Na and H₂O filtration → ↑ECF volume

**Examiner’s comments**

The volume of ECF is primarily determined by the total amount of osmotically active solute present in this fluid compartment which is predominantly sodium and chloride. Changes in the amount of chloride are to a large extent secondary to changes in sodium. Hence the amount of sodium in the ECF is the most important determinant of ECF volume.

The factors that regulate ECF volume include angiotensin (which stimulates aldosterone and ADH secretion), aldosterone which causes renal sodium and chloride reabsorption, and ADH which promotes water retention by the kidneys. Changes in GFR alter the amount of sodium filtered. However, the fraction of sodium reabsorbed is held constant by glomerulotubular balance. This is different to tubuloglomerular feedback (the mechanism by which delivery of sodium and chloride to the macula densa feeds back to alter GFR). These two processes were often confused with each other.

Stimulation of osmoreceptors in the hypothalamus cause thirst and also increase ADH secretion. Atrial natriuretic peptide secreted by the atria in response to increased intravascular volume causes natriuresis. Sodium is also lost in sweat. Volume stimuli override the osmotic regulation of ADH secretion and hence water excretion.