REVISE NEPHROLOGY

Disorders of Sodium

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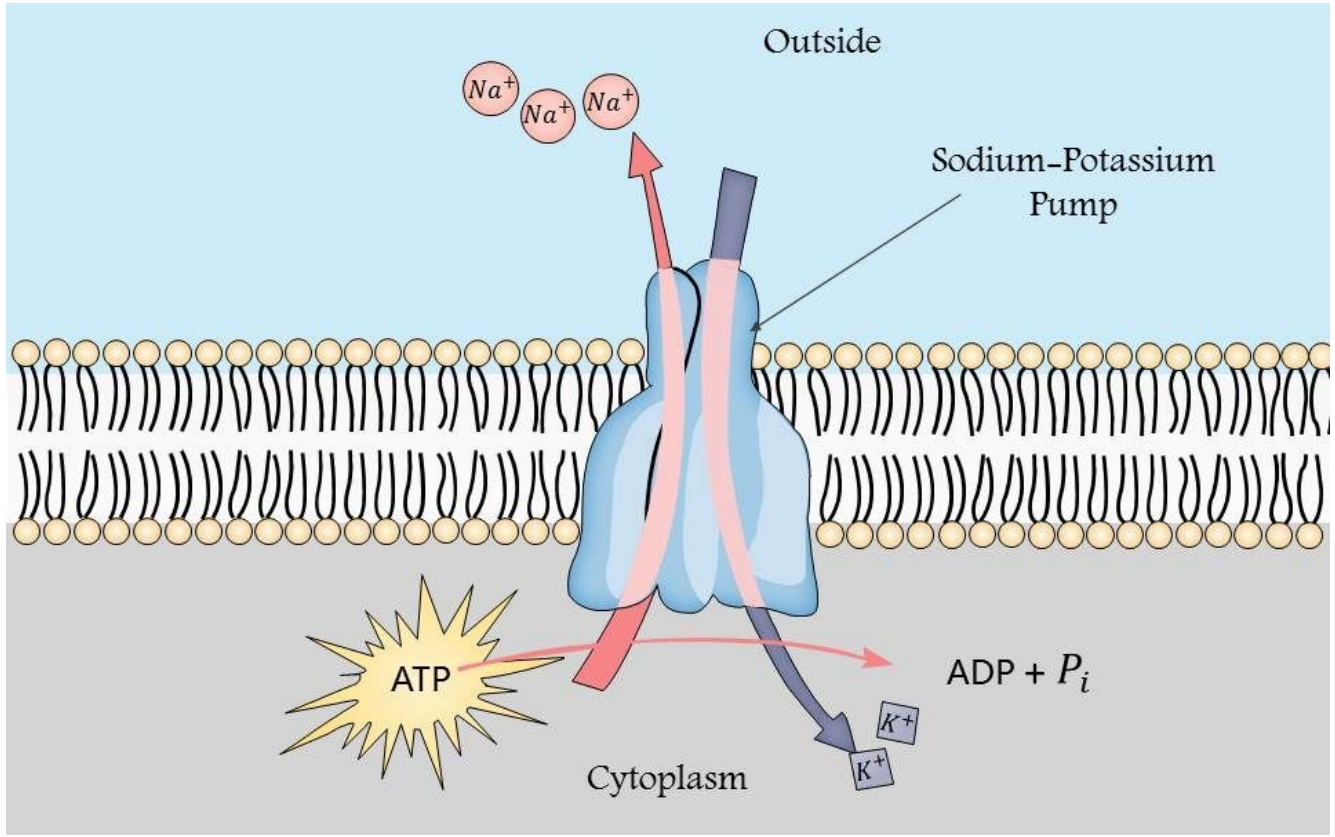
Key Concepts

- Action of aldosterone and ADH
- Counter-current mechanism
- Water distribution in the body
- Estimation of total body water
- What happens to plasma ADH levels in hypovolemic/ hypervolemic hyponatremia
- Pseudohyponatremia
- Hypo and hypernatremia

What does the kidney do?

- GFR of 125ml/minute…180 L fluid filtered at the glomeruli daily
- 98-99% of above reabsorbed in the tubules
- > 90% of the water reabsorbed is a passive process…as water ALWAYS follows Na
- Only in the collecting duct is water absorbed actively and independent of Na by Aquaporin 2 channel stimulated by ADH

Na-K-ATPase pumps 3 Na out and pulls 2 K into cells

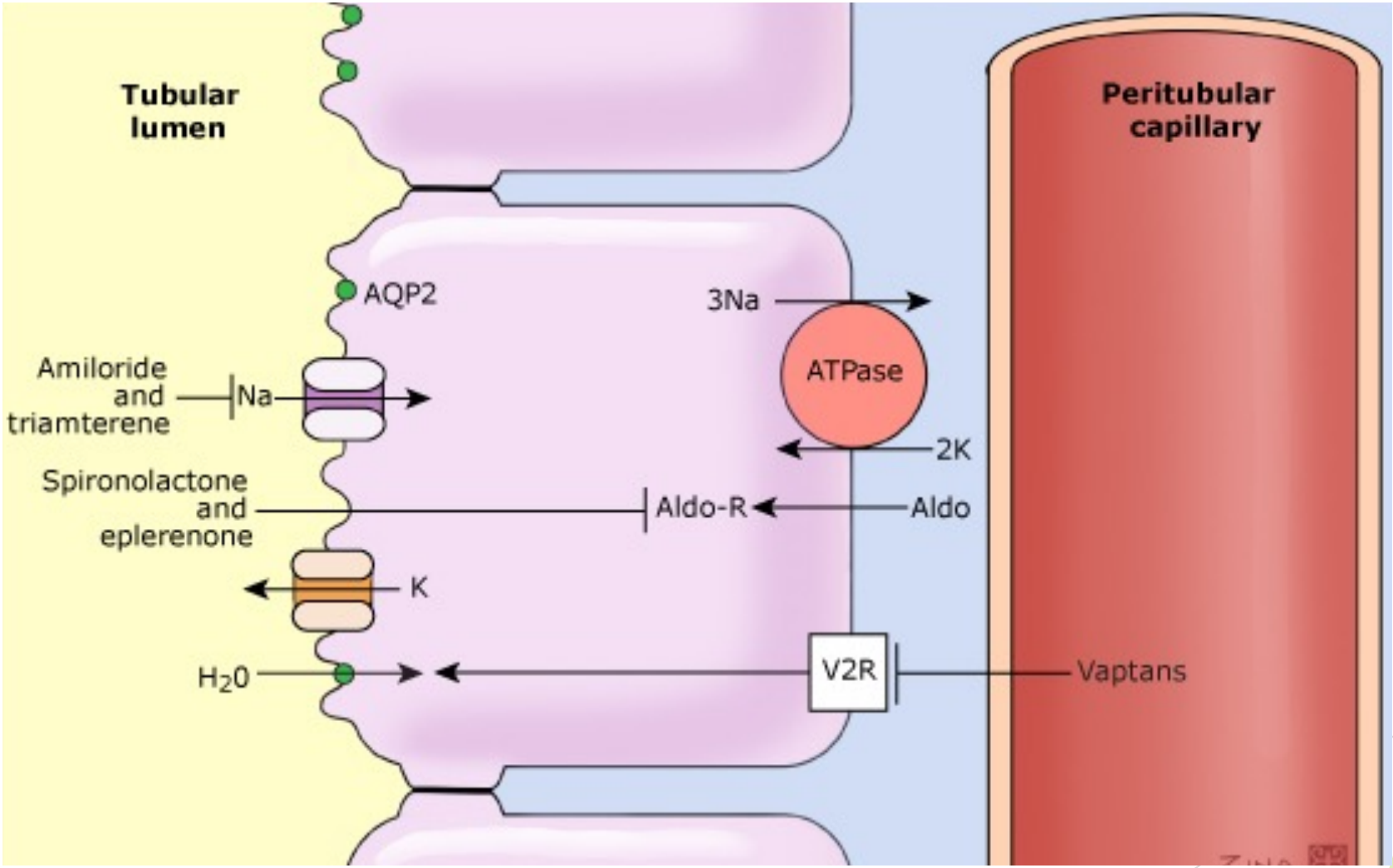


The Na ATP and Electrogenic Pump

Why is Na reabsorbed by the tubular cell so easily?

- In tubular epithelial cells, the basolateral Na K-ATPase extrudes 3 Na and pulls in 2 K ions from blood
- Result: intracellular Na deficiency and K excess in tubular cells
- Na deficient tubular epithelial cells reclaim Na from tubular lumen
- Water follows the Na from the tubule into the tubular cells
- In the collecting duct aldosterone accounts for an extra Na reabsorption (1-2% of total Na reabsorbed)

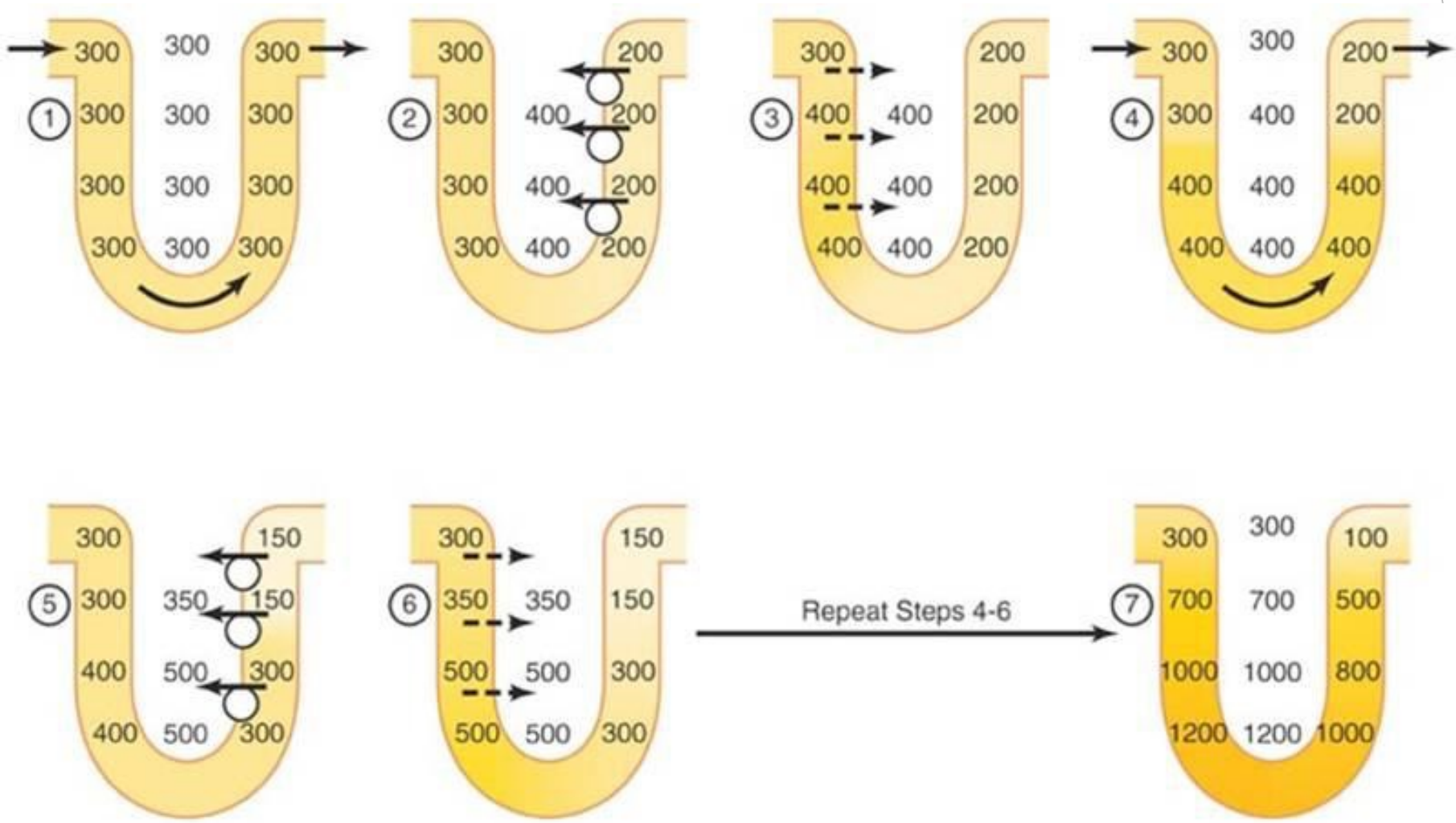
Aldosterone



Increased medullary osmolality- counter-current mechanism

- **Loop of Henle reabsorb up to 40% of total Na but only 25% of water**
- **The descending limb is highly permeable to water but the thick ascending limb is impermeable to water… basis for countercurrent mechanism**
- **Helps to maintain osmotic gradient from 290 mOsm/kg at cortex to 1200 mOsm/kg at tip of medulla**
- ***NOTE: ADH controlled reabsorption of water in the cortical duct is dependent on the above osmotic gradient***
- ***A question then- does frusemide cause hyponatremia in the euvolemic patient?***

Countercurrent Mechanism



Vasopressin - the key player

- Vasopressin (ADH) is the most important player in maintaining body water balance
- ADH increases the water permeability of the collecting duct cells allowing water to move from the tubule to the hypertonic interstitium
- Increase in plasma osmolality causes increased ADH secretion, and decreased plasma osmolality causes decreased secretion

ADH receptors

- **V1A**
  - Mediates vasoconstrictor effect
  - Cause glycogenolysis in the liver
  - Works as neurotransmitter in the brain and spinal cord
- **V1B**
  - Mediates ACTH secretion by the anterior pituitary
- **V2**
  - Causes rapid insertion of the aquaphorin-2 channels(water carrier) from the endosome to the luminal membranes
  - Water reabsorption by the ADH mediated aquaphorin-2 depends on the osmotic gradient in the medullary interstitium (not sure? Revise the counter current mechanism please)

Stimuli Effecting ADH Secretion

Increased secretion

- Increased plasma osmolality
- Decreased extracellular fluid volume
- Nausea and vomiting
- Pain, stress and exercise
- Angiotensin II
- Carbamazepine, chlorpropamide, cyclophosphamide and nicotine

Decreased secretion

- Decreased plasma osmolality
- Increased extracellular volume
- Alcohol

Total Body Water

- The average water content of adult human is approximately 60% of the body weight in males and 50% in females
  - 40 L water in a 72 kg body
- Intracellular fluid (2/3 of total body water): 25 L
- Extracellular fluid (1/3 of body water): 15 L which is split into
  - Plasma (1/5 of extracellular fluid): 3L
  - Interstitial fluid (4/5 of extracellular fluid): 12 L

Estimation of Body Water

- **REMEMBER THAT HYPONATREMIA IS WATER EXCESS WHILE HYPERNATREMIA IS WATER DEFICIT**
- **For hyponatremia**
  - **Water excess: 0.6W x (1- Na/140)**
- **For hypernatremia**
  - **Water deficit: 0.6W x ([Na/140]-1)**
- ***W is weight in kg; serum Na is in mmol/L and replace 0.6 by 0.5 in women to get the total body water (TBW)***
- **Let us use the above formula to calculate the excess body water in a 70 kg male with plasma Na of 130 mmol/L**
  - **Excess water: (0.6 x 70) x (1-130/140) = 42 x 0.0715 = 3.003 L**
- **Water deficit in a 70 kg male with plasma Na of 150 mmol/L**
  - **Water deficit: (0.6 x 70) x ([150/140]-1) = 42 x 0.0714 = 3 L**

Causes of Pseudohyponatremia (low plasma Na with normal osmolality)

Causes:

- Mannitol or hyperglycemia
- Disorders of lipids
  - Hypertriglyceridemia
  - Lipoprotein X accumulation (typically secondary to biliary obstruction or cholestasis such as PBC)
  - Familial hypercholesterolemia
- Abnormally high levels of protein, including native or exogenous immunoglobulins
  - Malignant monoclonal Gammopathies: multiple myeloma, and Waldenstrom macroglobulinemia
  - Chronic infectious disease states: hepatitis C or HIV
  - Malignant lymphoproliferative disorders
  - Myelodysplastic syndromes
  - Amyloidosis
  - Intravenous immunoglobulin therapy (IVIG)

Hyponatremia

- Usually caused by a failure to excrete water normally which in turn is due to inability to suppress ADH secretion
- *Exception: psychotic patients with primary polydipsia are hyponatremic despite appropriately suppressed ADH release*
- Classified as hypovolemic, euvolemic and hypervolemic hyponatremia

Let's ask some questions…

- **Why is the hypovolemic patient hyponatremic when her albumin and Hb are high (being concentrated)?**
  - **Is she making more ADH than normal?**
  - **Is she making less ADH than normal?**
- **Why is the hypervolemic patient hyponatremic?**
  - **Is it dilutional?**
  - **Is she making more or less ADH than normal?**
- **If SIADH is '*inappropriate secretion of ADH*', then when do we see *appropriate* secretion of ADH in the context of hyponatremia?**

The answers

- ADH secretion in hyponatremia
  - Appropriately high in hypovolemic hyponatremia due to intravascular volume depletion
  - Appropriately high in hypervolemic hyponatremia due to intravascular volume depletion (in CCF/cirrhosis the extra water is in the extravascular space)
  - Inappropriately high in euvolemic hyponatremia- Syndrome of inappropriate ADH (SIADH)

Causes of hyponatremia

Hypovolemic hyponatremia	Hypervolemic hyponatremia	Euvolemic hyponatremia
Renal Na loss – Diuretic agents, – Osmotic diuretics (glucose, mannitol,) – Mineralocorticoid deficiency – Salt losing nephropathy – Cerebral salt wasting	CCF Cirrhosis Nephrotic syndrome	SIADH – Drugs: Carbamazepine, chlorpropamide, cyclophosphamide, SSRI and SNRI – CNS causes: encephalitis, meningitis, brain tumours, brain abscesses, stroke – Pulmonary causes: Pneumonia, TB, aspergillosis, lung abscess, lung Ca – Surgery – HIV
Extra renal Na loss – Diarrhoea – Vomiting – Excessive sweating – 3rd space fluid sequestration e.g. in bowel obstruction, peritonitis, severe burns etc.		Other causes – Thiazide diuretics – Hypothyroidism – Adrenal insufficiency

Diagnosis of SIADH:
The Schwartz and Bartter Clinical Criterion

- Serum sodium <135mEq/L
- Serum osmolality < 275 mOsm/kg
- Urine sodium >40 mEq/L
- Urine osmolality >100 mOsm/kg
- The absence of clinical evidence of volume depletion - normal skin turgor, blood pressure within the reference range
- The absence of other causes of hyponatremia - adrenal insufficiency, hypothyroidism, cardiac failure, pituitary insufficiency, renal disease with salt wastage, hepatic disease, drugs that impair renal water excretion.
- Correction of hyponatremia by fluid restriction

Treatment of SIADH

- Fluid restriction
- Hypertonic saline in symptomatic with severe hyponatremia
- Salt tablet plus loop diuretic
- Tolvaptan (vasopressin receptor antagonist): beware of the hepatotoxicity
- Urea
- Demeclocycline : beware of nephrotoxity, nausea, vomiting, photosensitivity and costs

Hypernatremia

- **Causes: Mostly due to decreased water intake**
    - **Impaired thirst due to hypothalamic disease**
    - **Sick and not drinking**
    - **Severe skin or GI loss**
  - **Administration of hypertonic saline**
  - **Ingestion sodium chloride**
  - **Diabetes insipidus usually does not cause hypernatremia unless:**
    - **Central lesion impairs both ADH release and thirst**
    - **Older patients with nephrogenic DI due to lithium**

Hypernatremia

- Even with large water losses, hypernatremia will not develop if thirst is intact, and water is available

- Diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state: As hyperglycaemia and hypovolemia are corrected, the serum sodium will rise because of an osmotic shift of water from extracellular fluid into cells and loss of extra water in the urine as excess glucose is excreted (osmotic diuresis)

Fluid replacement in hypernatremia with 5% dextrose

- Water deficit calculation: 0.6W x ([Na/140]-1)
- Hypernatremia is chronic if it has been present for longer than 48 hours and do not decrease serum Na by more than 12 mEq/L in 24 hours
  - Approx. 5% dextrose IV at 1.35 mL/kg/hour (maximum of 150 mL/hour)
- In acute hypernatremia (< 48 hours) more aggressive Na correction
  - 5% dextrose IV at 3-6 mL/kg/hour, up to a maximum of 666 mL/hour
- If struggling to get a line, give free water using NGT

It is not just about numbers. It's also about how the patient looks and feels.

Thank you