o All filtered organic solutes

o \( \frac{2}{3} \) of NaCl and water isotonically – it appears to absorb isotonically because the water permeability is so high such that very small undetectable gradients can drive a large amount of water thus it appears isotonic as the gradients and the osmotic differences are so small

- Active Na transport underlies transport with most of it being coupled to the absorption of most solutes, organic and water. A key fundamental event that underlies other events.

Mechanism by which reabsorption occurs:

- Can be divided into two phases:

1. First half of tubule = sodium uptake coupled with
   a. Organic solutes, amino acids and glucose uptake
   b. Phosphate transport
   c. \( \text{HCO}_3 \) transport

2. Second half = sodium uptake coupled with
   a. \( \text{Cl}^- \) transport

**Glucose reabsorption mechanism:**

1. Sodium gradient established with \( \text{Na ATPase} \) present of BL membrane
2. Glucose secondary transport coupled with sodium gradient from lumen to sodin-glucose transporter in apical membrane
3. GLUT Glucose transporter present on BL membrane thus setting glucose down gradient into blood
4. There are two isoforms of the sodium-glucose transporter which are sterospecific for D glucose:
   a. \( \text{SGLT} \) in S1 and S2 which transports 1Na: 1 glucose
   b. \( \text{SGLT} \) in S3 which transports 2Na: 1 glucose – acts as a booster
5. There are different transporters on different parts of the tubule because the stoichiometry is doubled in S3 therefore the energy extracted from the gradient is SQUARED so last few glucose molecules can be scavenged from the proximal tubule
6. Reabsorption rate plateaus when all the transporters are saturated
7. The rate at which glucose is filtered and reabsorbed is what determines if glucose is excreted: if glucose filtration exceeds reabsorption excretion occurs

**Amino acid reabsorption mechanism:**

1. Similar manner to glucose reabsorption
2. stereospecific to L amino acids and have to be distinct transporters for different types of amino acids
   a. Basic cationic amino acids
   b. Anionic acidic amino acids
   c. Neutral amino acids
   d. Glycine and imino acids
3. It is known that specific transporters are required because inherited defects in them have been identified with the predisposition to forming kidney stones, cystinuria, being caused by a defect in the cationic amino acid absorption pathway
1. NH₃ is lipid soluble so crosses the membrane into the lumen and is converted to charged NH₄⁺ with the H⁺ secreted
2. PKₐ of NH₃ = 9 therefore H⁺ + NH₃ → NH₄⁺ is strongly to the right at physiological pH and as lumen pH decreases more NH₄⁺ is trapped in the lumen.
3. OTHER WAYS NH₄⁺ CAN BE GENERATED:
   a. NH₄⁺ MADE IN TUBULE CELLS FROM NH₃ AND H⁺ AND EXCRETED VIA Na/H exchanger
   b. NH₄⁺ REABSORBED IN Thin ascending loop of henele which pumps out K⁺ making the interstitial tissue more alkaline thus causing NH₄⁺ to dissociate to NH₃ and H⁺ again. These two then diffuse back into the collecting duct where they form NH₄⁺ and it is finally trapped.

7. This means that there can be a net gain and regeneration of HCO₃⁻ and net loss of H⁺
8. The CO₂ used is equivalent to the amount originally produced by the metabolising tissues therefore the HCO₃⁻ being produced is the same as the HCO₃⁻ that was depleted as a result of buffering the H⁺ before it was secreted into the lumen and buffered.

**THE DISTINCTION BETWEEN THE REGENERATION AND REABSORPTION OF HCO₃ IS DETERMINED BY WHAT HAPPENS TO H⁺:**

REABSORB = COMBINE WITH HCO₃
REGENERATION = COMBINE WITH BUFFER

**Secretion of HCO₃⁻ by Type B intercalated cells:**

- Ussing model shows simply by reversing the 2 proteins on the apical and BL membranes can the whole function of the cell change
  1. **Aninon exchanger** on apical membrane
  2. **H⁺ ATPase** on basolateral membrane
- They are few in number but increase in number when we are in an alkolic state such as vomiting so:
  - Down regulation of H⁺ secretion
  - Secretion of HCO₃⁻
- Type A intercalated cells can be converted to type B by either
  - Internal transfer of proteins
  - Turnover of cells results in more committing to be type B rather than type A

**K⁺ balance:**

- Reciprocal control between H⁺ and K⁺
- Hyperkalemia = acidosis
When there are changes in the GFR and therefore Na load presented to the nephron the proximal tubule reabsorbs a constant fraction of the load ~ 2/3rds which corresponds to a smaller absolute amount.

1. Myogenic response
   a. Important in protecting glomerular capillaries against rapid changes in pressure
   b. Intrinsic property of vascular smooth muscle where elevations in transmural pressure induce the contraction of preglomerular arterioles mostly at the level of the afferent arteriole
   c. Via stretch activated calcium channels mechanism

2. Glomerulartubular balance:
   - Achieved by pertiubular and lumial apical membrane mechanism
     a. Peritubular capillary mechanism
        i. Reabsorption from interstitial space to peritubular capillaries is due to the starling forces
        ii. These starling forces which favour reabsorption are:
            1. High Osmotic/ontonic pressure gradients
            2. Low Hydrostatic pressure gradients
        iii. This mechanism reduces the backflux from the interstitial space into the lumen

\[
\begin{align*}
\text{↑ in GFR} & \quad \text{↑ in efferent arteriole resistance} \\
\text{↑ in efferent arteriole ontonic pressure} & \quad \text{↓ in efferent arteriole hydrostatic pressure} \\
\text{↑ in peritubular ontonic pressure} & \quad \text{↓ in peritubular hydrostatic pressure} \\
\text{↑ in absorption of water and solutes} & \quad \text{↑ in solute concentration in efferent arteriole}
\end{align*}
\]
Sympathetic nervous system control

↓ in extracellular circulating fluid **volume**

↓ in **blood pressure** which is detected by **baroreceptors**

↑ in renal sympathetic nervous activity

↑ in renin release

↑ in angiotensin II release

↑ in renal vascular **resistance** due to constriction of the afferent arteriole

↓ in peritubular **hydrostatic pressure**

increased resorption of Na so less Na excretion

**ATRIAL NATRIURETIC PEPTIDE** – released when there is an **OVERLOAD OF ECF VOLUME**: causes decrease in water and Na retention by control of the renin – aldosterone II axis

- ANP is a 28 AA peptide which is released from the atria in response to stretch and causes vascular smooth muscle relaxation thus antagonising the renin-angiotensin II axis.

1. Increase in volume causes the stretch of the atria which releases ANP
2. ANP causes the **vasodilation** of afferent and efferent glomerular arterioles
3. This increases the GFR therefore increasing **sodium load**
4. This decreases renin secretion
5. Decrease in aldosterone secretion
6. **Antagonism** of ADH in the collecting duct
7. Na absorption blocked in **medullary collecting duct** via the blockage of Na **channels by cGMP**

**C). NATRIURETIC HUMORAL FACTORS:**
Effect of ADH on water permeability:

1. ADH binds to V2 receptor on principle cells membrane
2. This activates adenyl cyclase via a G protein which increases cAMP concentration
3. This activates PKA which phosphorylates the CREB protein in the nucleus and this binds to the CREB gene
4. This stimulates the vesicles contained AQP2 under the apical membrane to fuse with it increasing number of AQP2 in membrane

Experimental evidence for aquaporin protein being added in CLUSTERS:

This was carried out before it was known it was aquaporins however there was a suspicion of ADH causing protein movement

1. Animal model, brattlebro rats which lack ADH due to having diabetes insipidus
2. Freeze fracture of apical membrane of Collecting duct of animals taken
3. Without ADH there are still indentation in the membrane showing the animal retains all the machinery just lacks the trigger that is ADH
4. With ADH greater number of dimples seen in freeze fracture showing evidence for fusion of vesicles in cluster

Other actions of ADH:

1. Activates UT urea transporters in collecting duct allowing urea to be reabsorbed so it can act as an osmotic pull
2. Stimulates NKCC in thin ascending loop of Henele – so sodium can drain out water
3. Vasoconstriction – slows down medullary blood flow and blood flow in vasa recta thus increasing absorption of water and solutes as maximises time for equilibrium to occur

Effective circulating volume:

1. Volume sensors
   Cardiovasular – change in sympathetic discharge
   a. Baroreceptors – carotid arch
   b. Atrial stretch receptors
   c. Pulmonary stretch receptors
   d. Pressure receptors in renal afferent arterioles

Renal:
   a. Macula densa – senses Na load which is representative of GFR and therefore pressure which represents effective circulating volume