- All filtered organic solutes
- 2/3rds 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 abosorption of most solutes, organic and water. A key fundemental 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. **HCO3** transport

2. Second half = sodium uptake coupled with
    a. **Cl-** transport

**Glucose rebsorption mechanism:**

1. Sodium gradient established with **Na ATPase** present of BL membrane
2. Glucose secondary transport coupled with sodium gradient from lumen on **sodium-glucose transporter** in apical membrane
3. **GLUT Glucose transporter** present on BL membrane transporting glucose down gradient into blood
4. There are two isoforms of the sodium glucose transporter which are sterospecific for D glucose:
    a. **SGLT2** in S1, S2 which transports **1Na: 1 glucose**
    b. **SGLT1** in S3 which transports **2Na: 1 glucose –** acts as a booster
5. There are different transporters on different parts of the tubule because the stoicheomitry 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. stereopecific 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 aicds
    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. $NH_3$ is **lipid soluble** so crosses the membrane into the lumen and is converted to charged $NH_4^+$ with the H+ secreted
2. **PKa of NH3 = 9** therefore **H + NH3 → $NH_4^+$** 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. **$NH_4^+$ 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 $NH_4^+$ to dissociate to NH3 and H+ again. These two then diffuse back into the collecting duct where they form $NH_4^+$ 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 REABSORBTION OF HCO3 IS DETERMINED BY WHAT HAPPENS TO THE H+ ION:*

REABSORB = COMBINE WITH HCO3
REGENERATION = COMBIEN 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 alkolitic 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**

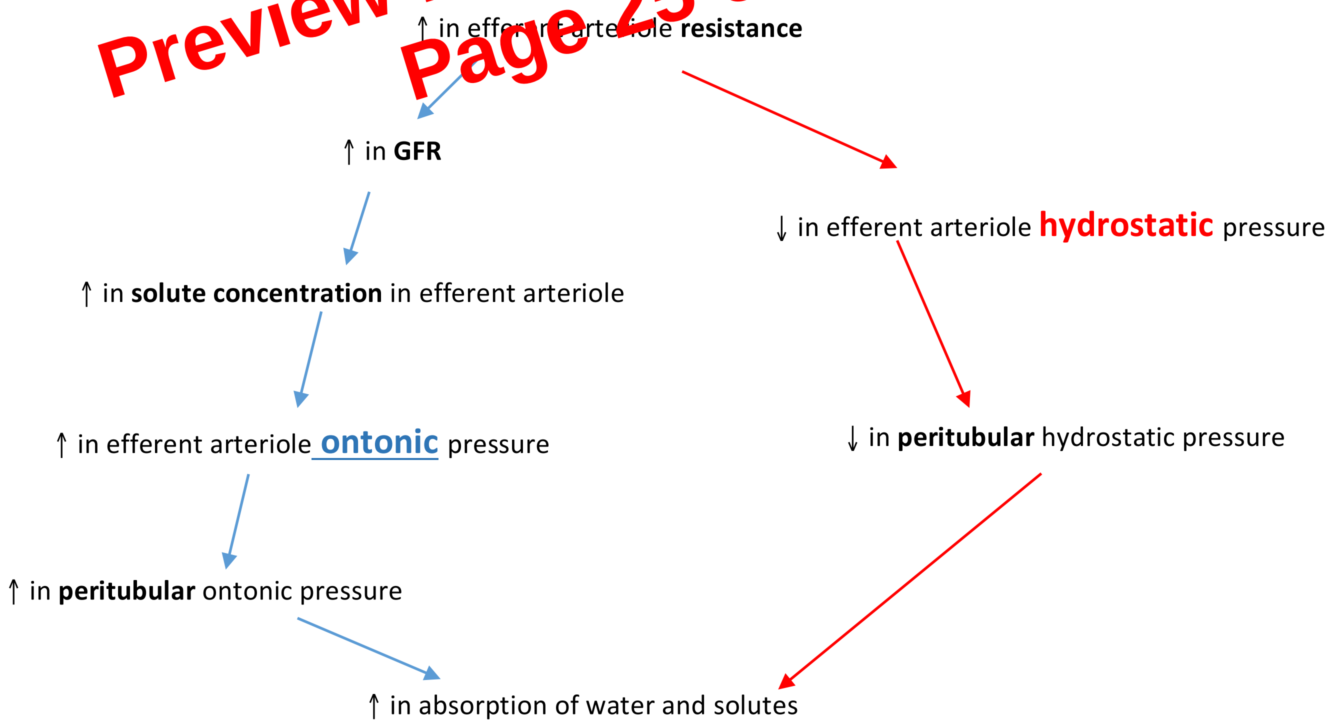
    a. Importanat in protecting **glomerular capillaries** against rapid changes in pressure
    b. Intrinsic property of vascular smooth muscle where elevations in transmural pressure induce the contraction of preglomeruluar arterioles mostly at the level of the afferent arteriole
    c. Via stretch activated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

2. **Glomerulartubular balance:**

- Achieved by pertiubular and lumial apical membrane mechanism

    a. **Peritubular capillary mechanism**
        i. Reabsorption from interstitial space to pertitubular 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 fro the interstitial space into the lumen





Sympathetic nervous system control

↓ in extracellular circulating fluid **volume**

↓

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

↓

↑ in renal sympathetic nervous activity → Decrease in medullary **blood flow** (vasa recta) → increased reabsorption of Na so less Na excretion

↓

↑ in **renin** release

↓

↑ in **angiotensin II** release

↓

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

↓

↓ in peritubular **hydrostatic pressure**

↓

increased reabsorption 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 s**odium 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 APQ2 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. **Vasocontriction –** 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. **Pulomary 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**