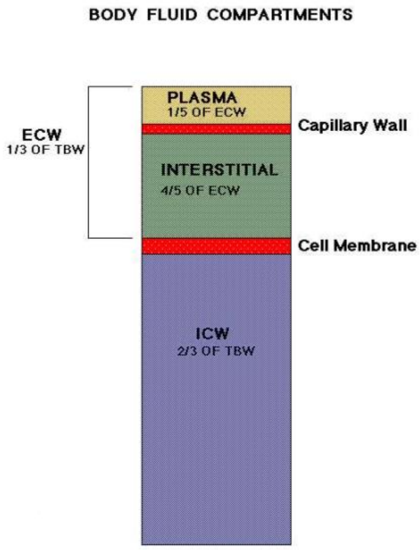
Renal physiology

The kidneys

Allow us to live on dry land.

- Body fluid volume is **small** (~5L (blood + serum))
- Composition can **change rapidly** e.g. due to increase in metabolic rate



Kidneys maintain composition of the ECF within the narrow limits compatible with life

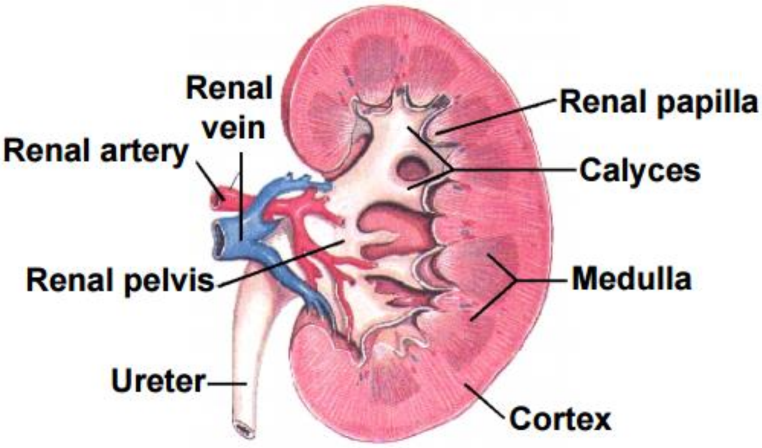
Body fluid compartments

- Body is **45 – 75%** water
- % of body weight that is water depends on **amount of fat** – fat people have less water
- Average male = 60% water
- Average female = 50% water (extra fat layer)

TBW – Total Body Water (1/3 ECW + 2/3 ECW)
EBW – Extracellular Water (20% plasma + 80% interstitial fluid)
ICW – Intra Cellular Water

Urinary system

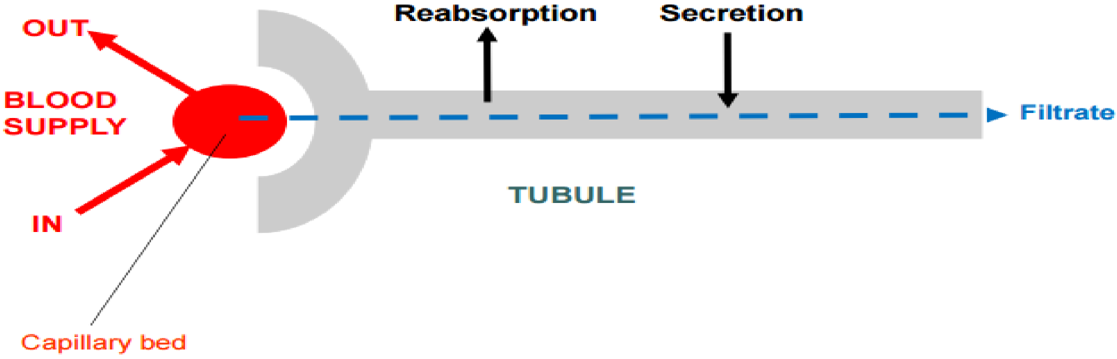
- Kidneys
  - Renal artery
  - Renal vein
- Ureters
- Bladder
- Urethra



Specific functions of the kidneys

- Maintain H_2O balance in body
- Regulate volume of ECF and concentration of ECF ions (K^+, Na^+, Cl^-, HCO_3^-, Ca^{2+}, Mg^{2+}, SO_4^{2-}, PO_4^{3-}, and H^+)
- Maintain plasma volume & osmolarity
- Control acid-base balance (help w/ alkylosis)
- Excretion of waste & foreign products e.g. drug metabolites, toxins
- Secreting **hormones** e.g. **erythropoietin** & **renin**

The **nephron**: functional unit of the kidney



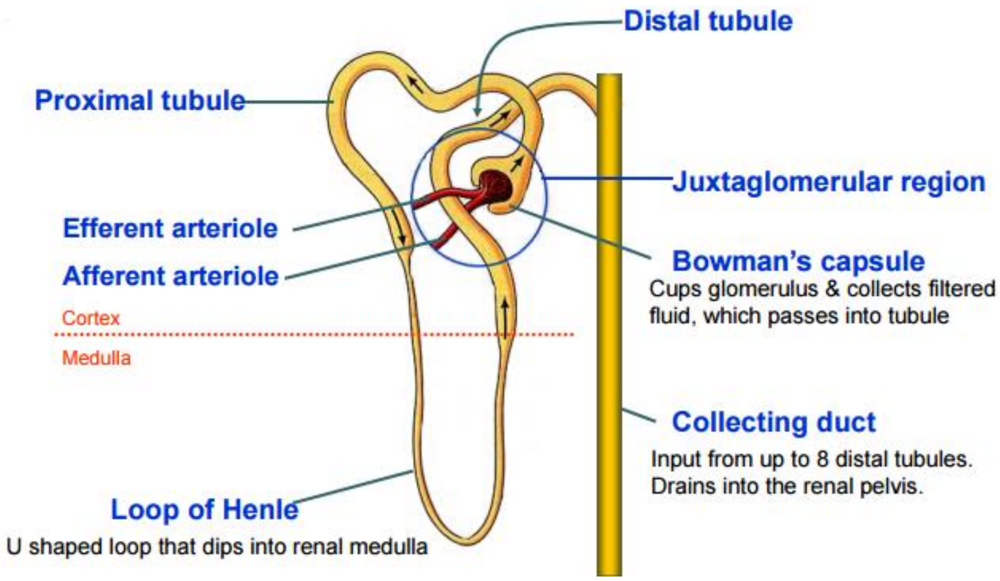
Design: **blood supply → filter → tubular system**

- Blood comes in via **capillary bed**, filtered out into the nephron through **Bowman's capsule**
- Reabsorption occurs in **Proximal Convoluted Tubule**
- **Secretion** removes foreign agents

Arrangement of the nephrons gives two **distinct regions** of the kidney: **Renal cortex** (**granular**), and **renal medulla** (with **renal pyramids**)

Each nephron contains:

1. Vascular component
    - **Glomerulus** – ball-like tuft of capillaries where blood plasma is filtered
    - Comes from **renal artery**:
        - Supplied by **afferent arteriole**
        - Drained by **efferent arteriole**
            - Subdivides into **peritubular capillaries** which later re-joins to form venules and **renal vein**
2. Tubular component



Two types of nephron

- **Juxtamedullary nephrons**
    - **15—20%** of total (humans)
    - Glomeruli in **inner cortex**
    - Loop of Henle **descends fully into medulla**
    - **Peritubular capillaries** near loop form **straight vessels known as vasa recta**
    - Concentrates urine
- **Cortical nephrons**
    - **~80%** of total human nephrons
    - Glomeruli in **outer cortex**
    - Loop of Henle dips only **slightly** into medulla

Summary of renal processes

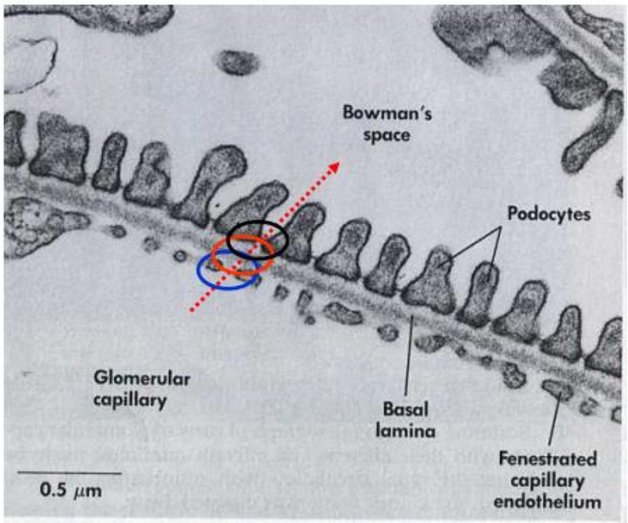
- Glomerular filtration of protein free plasma

- Tubular reabsorption – valued substances reabsorbed from tubular lumen, transferred back to blood
- Tubular secretion – waste removed from blood to **tubular lumen** via the **tubular cells**

Plasma constituents **not reabsorbed** pass into **renal pelvis** and are transferred as urine to the bladder for excretion.

Glomerular filtration

- **Extracellular** phenomenon – goes **between** cells but NOT through them
- **Wall of capillary** is the filter
- Filtered fluid passes through **3 layers** that surround the glomerular capillaries (glomerular membrane):
    1. **Fenestrated capillary endothelium –** via pores between endothelial cells
        - Filters molecules by **size**
    2. **Basal lamina/basal membrane**
        - Mix of **collagen** (structural) & glycoproteins (**repel plasma proteins**)
        - **Negatively** charged
        - Filters out **proteins**
    3. **Podocytes**
        - **Filtration slits** between cellular foot processes
        - Distance between slits is **variable**
            - Alters rate of filtration
            - Don't change much in healthy people
        - Again filters molecules by **size**



Forces affecting glomerular filtration

1. **<u>Glomerular capillary blood pressure → +ve (~55mmHg)</u>**
    - <u>Increases in response to</u>:
        - Increase in systolic BP
        - **Increases afferent** arteriole diameter
            - Increases flow
        - **Decrease efferent** arteriole diameter
            - Induces **blood damming** in glomerulus

Osmosis: diffusion of water from area of higher concentration to area of lower concentration.

Measuring:

- Particles/Litre (regardless of what specific particle)
- Normal osmolarity = 300mosmol/L
- **Hyperosmotic** = higher osmolarity than cell or another solution
- **Hypoosmotic** = lower osmolarity than cell or another solution

2. **<u>Plasma-colloid osmotic pressure → -ve</u>**
    - Retention of blood proteins in the glomerulus **increases the osmolarity of the glomerular blood** compared to Bowman's capsule
    - Draws H_2O **back to the glomerulus**, opposing filtration

3. **Bowman's capsule hydrostatic pressure → -ve**
    - Fluid damming in Bowman's capsule (bottleneck) causes a **backwards pressure**
    - Opposes filtration

Glomerular filtration rate (GFR)

- GFR = rate of flow of filtrate (L/min)
- Depends on:
    1. Net filtration pressure (**NFP**)
        - NFP depends on:
            - Glomerular capillary blood pressure = **55 mmHg +ve**
            - Plasma-colloid osmotic pressure = **30 mmHg –ve**
            - Bowman's capsule hydrostatic pressure = **15 mm Hg –ve**
            - **NFP = 55 – (30 + 15) = 10 mmHg**
    2. **Permeability** and **surface area** of the glomerulus (K_f – filtration coefficient)
        - Usually **12.5mL/min**
- **GFR = NFP * K_f = 10 * 12.5 = 125 mL/min**
- Usually ~**180L/day**

Why filter at such a high rate?

- Regular & rapid waste and chemical removal
- High filtration rate allows entire plasma volume (~3L) to be filtered and processed by tubules many times per day – **precise and rapid control of fluid volume & composition**

Control of GFR – Autoregulation

- GFR usually remains **very stable** despite regular changes in systemic blood pressure throughout the day
- If there was **no autoregulation**
    - Mild exercise → increased blood pressure → increased GFR → increased urine production
    - At normal MAP (100 mmHg), GFR = 125 mL/min or 180 L/day which results in 1.5 L/day urine production.
    - Increasing MAP from 100 to 125 mmHg would increase GFR to 225 L/day and urine flow to **46.5 L/day** → **extreme fluid and salt loss**
        - **Counterproductive to survival!**

Mechanism of autoregulation

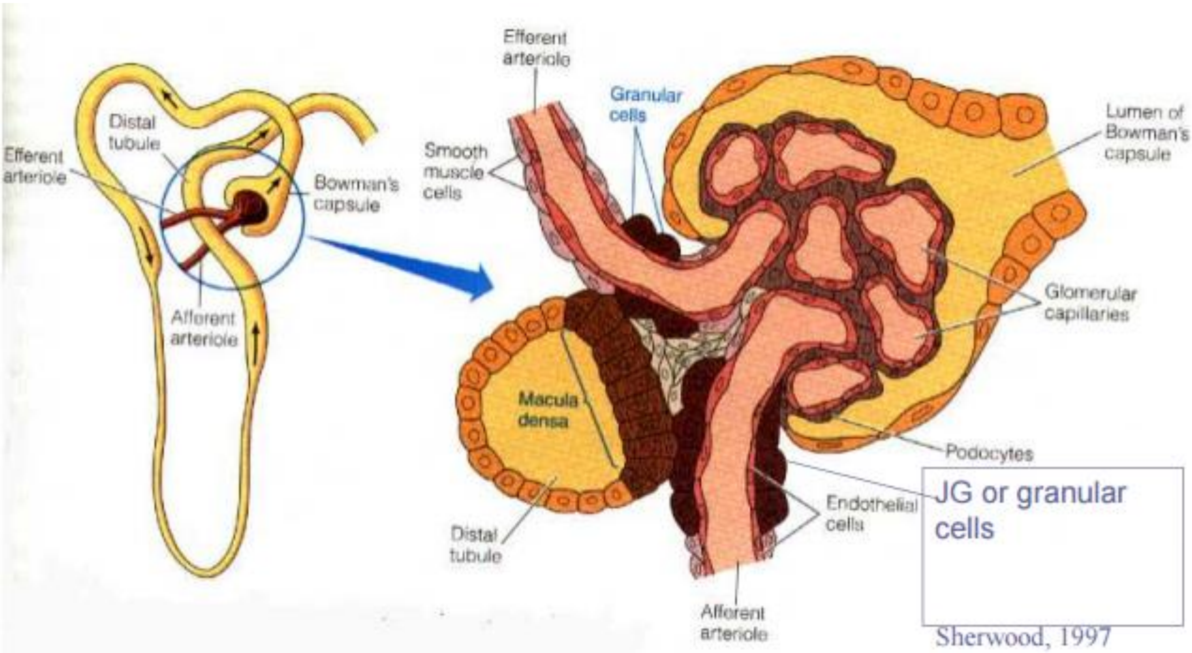
- Renal blood flow is automatically regulated in response to modest changes in blood pressure
    - Controlled at the **local** level (e.g. smooth muscle cells)
- Increased MAP triggers **vasoconstriction of afferent arteriole**, decreasing flow and reducing GFR
- If MAP drops **below normal**, GFR will become too low, so the afferent arterioles **vasodilate**, increasing flow and GFR, bringing GFR back to normal levels (e.g. when **sleeping**)
- Therefore within a certain range of MAP, GFR is maintained (~80 – 170 mmHg)

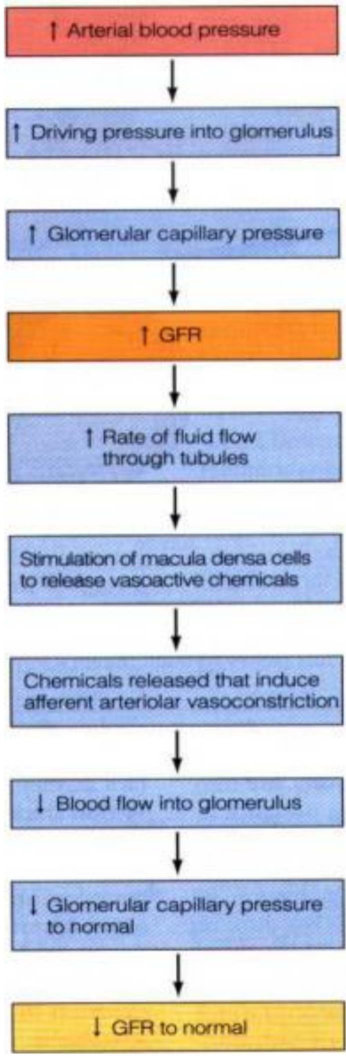
Mechanism:

1. **Myogenic mechanism**
    - Smooth muscle in afferent arteriole wall
        - **Automatically** constricts when **stretched** (i.e. increased BP)

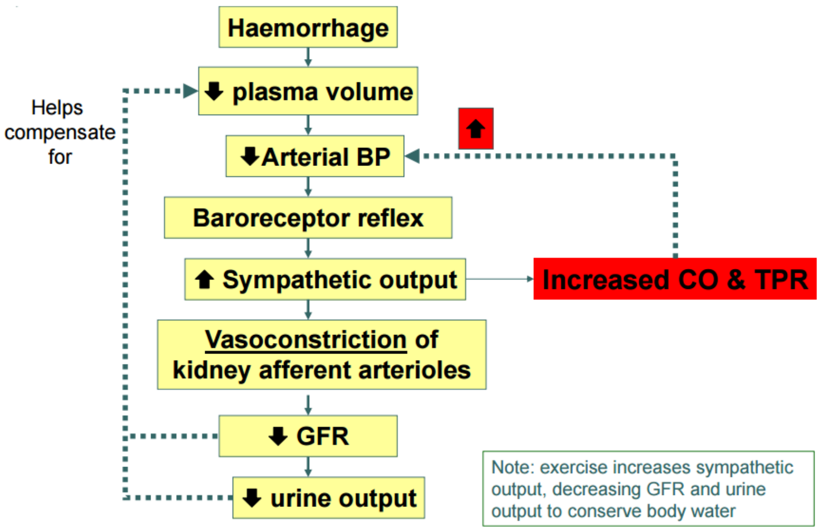
- **Automatically** relaxes when **destretched** (i.e. decrease BP)

2. Juxtaglomerular feedback

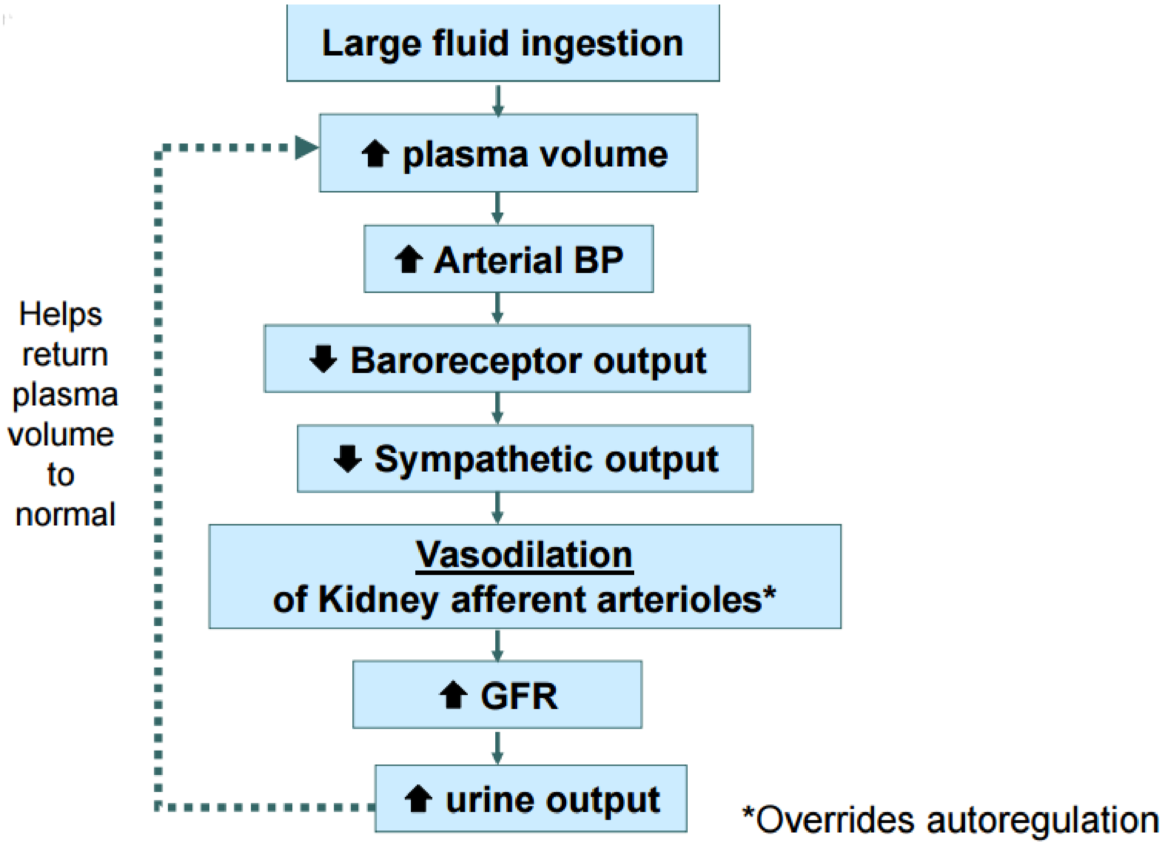




- Juxtaglomerular apparatus refers to:
  - Bowman's capsule + distal tubules
  - **Macula densa cells** (DCT)
    - Sensitive to **salt delivery** – signal to **release ATP** and **adenosine**
    - Causes **contraction** of **granular cells**
  - **Granular cells**
    - Modified smooth muscle cells
    - If you blocked the effects of ATP and adenosine release by macula densa cells on granular cells, **autoregulation would not cease due to the myogenic response!**
- If **MAP drops below 80mmHg**, autoregulation no longer works!
  - Due to the **baroreceptor reflex** turning off urine production
  - E.g. Haemorrhage



- If MAP gets **too high**, e.g. large fluid ingestion
  - Increase in plasma volume leads to increase in MAP
  - Baroreceptor reflex is **reduced** (→ decrease in basal sympathetic output)
  - **Vasodilation** of afferent arterioles
  - Increase in GFR



Tubular reabsorption

- All plasma constituents **except proteins** filtered non-discriminately
- Many valuable substances need to be **reabsorbed**
  - Reabsorption takes place in **tubular part** of nephron
  - Tubular reabsorption is **highly selective** for required substances.
    - E.g. 100% of sugars and 99.5% of salts are reabsorbed
  - Only **excess amounts** of required substances are not absorbed (e.g. excess salt when you eat fish & chips)
  - **Wastes** are not reabsorbed and are eliminated as urine
  - **Most H_2O** (99%) is reabsorbed, but some (**1%**) leaves as it is required for keeping wastes **in solution** (unlike birds which have paste-like urine)

Tubular anatomy

- Single layer of **epithelial cells** connected with **tight junctions**
- Basolateral membrane = side of epithelial cell that **faces interstitial fluid (adjacent to capillary)**
- Lumenal membrane = side of epithelial cell on **inside of lumen**
- Solutes **diffuse** through the **epithelial cell** into the interstitial fluid where it may diffuse back into the capillary

- Water is dragged through with the solute due to the increase in osmolarity in the interstitial fluid

Na_+ reabsorption

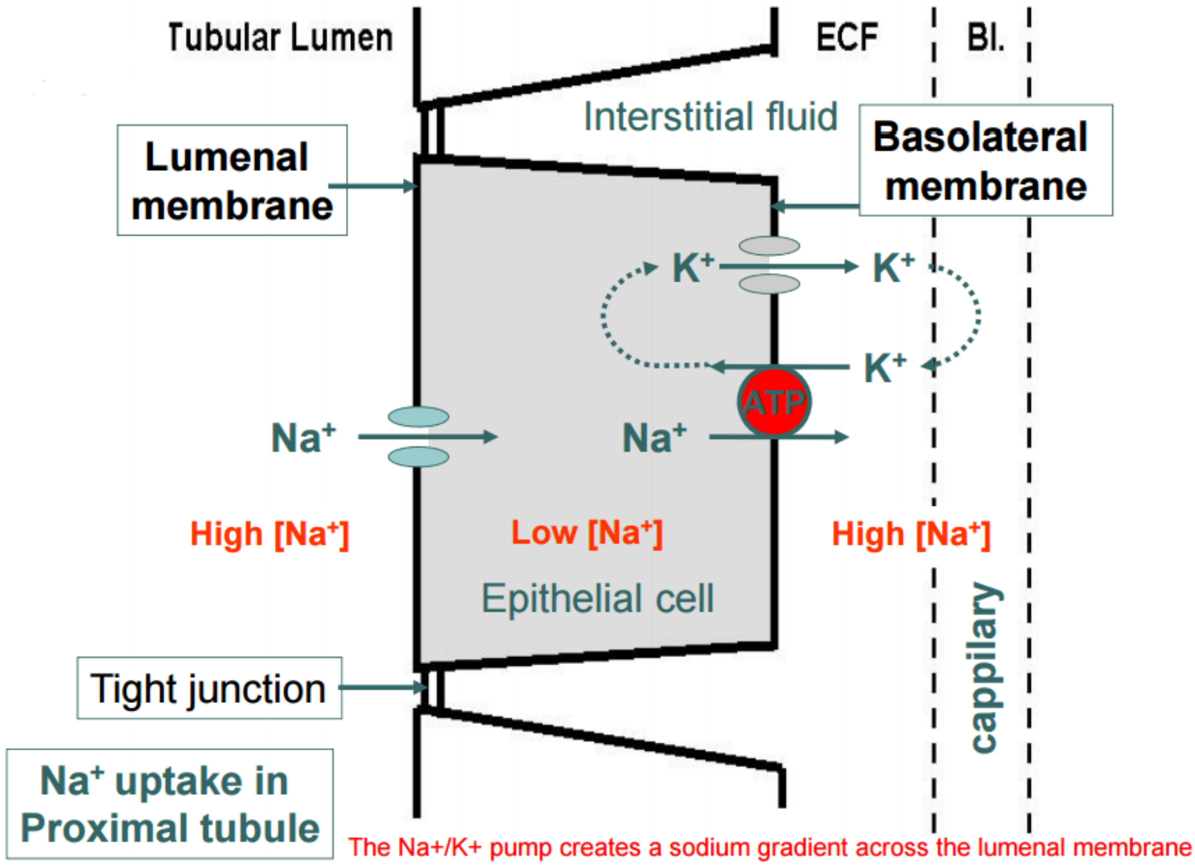
- Other ions follow same mechanism
- 67% of Na^+ reabsorption occurs in **proximal tubule**
  - **Obligatory** reabsorption – not under control
- 25% occurs in **Loop of Henle**
  - **Obligatory**
- 8% occurs in **distal tubule**
  - **Hormonal control**
    - With a salty diet, the 8% is lost in urine
    - If salt deficient, 8% reabsorbed
- All transport is through **cotransporters** and other transporters

Diffusion of a solute from one bath the other requires:

1. Concentration gradient
2. A pore or channel permeable to that solute

Pumps can transport solutes **<u>against</u>** the concentration gradient using **ATP** as an energy source.

Na^+-K^+-ATPase pump



- Maintains **low sodium concentration** in the **epithelial cell** by pumping out into the interstitial fluid
- Therefore the filtrate has a higher Na^+ concentration

- Na^+ ions diffuse through lumenal membrane into epithelial cell where they are again pumped out
- Pump works by exchanging K^+ from interstitial fluid with Na^+ from epithelial cell
  - Therefore, there is also a pore for K^+ ions to passively diffuse back across the basolateral membrane
  - Prevents K^+ build up as it passively travels down its own concentration gradient

Reabsorption of glucose, amino acids, and other nutrients in the nephron

- **All nutrients absorbed in the Proximal Tubule – obligatory**
  - Glucose:
    - Transported **using Na^+ gradient**
    - **Sodium-glucose co-transporter**
  - Amino acids:
    - **Amino acid-glucose co-transporter**
- Diffuse passively across basolateral membrane

Transport maximum (Tm) of solute uptake

- E.g. glucose
  - Normal is 125mg/min
  - Tm is 375mg/min
  - Only 375mg/min will be reabsorbed at any time
    - Amount of glucose excreted increases as renal absorption reaches Tm
      - Due to **saturation of Glucose-Na^+ co-transporters**

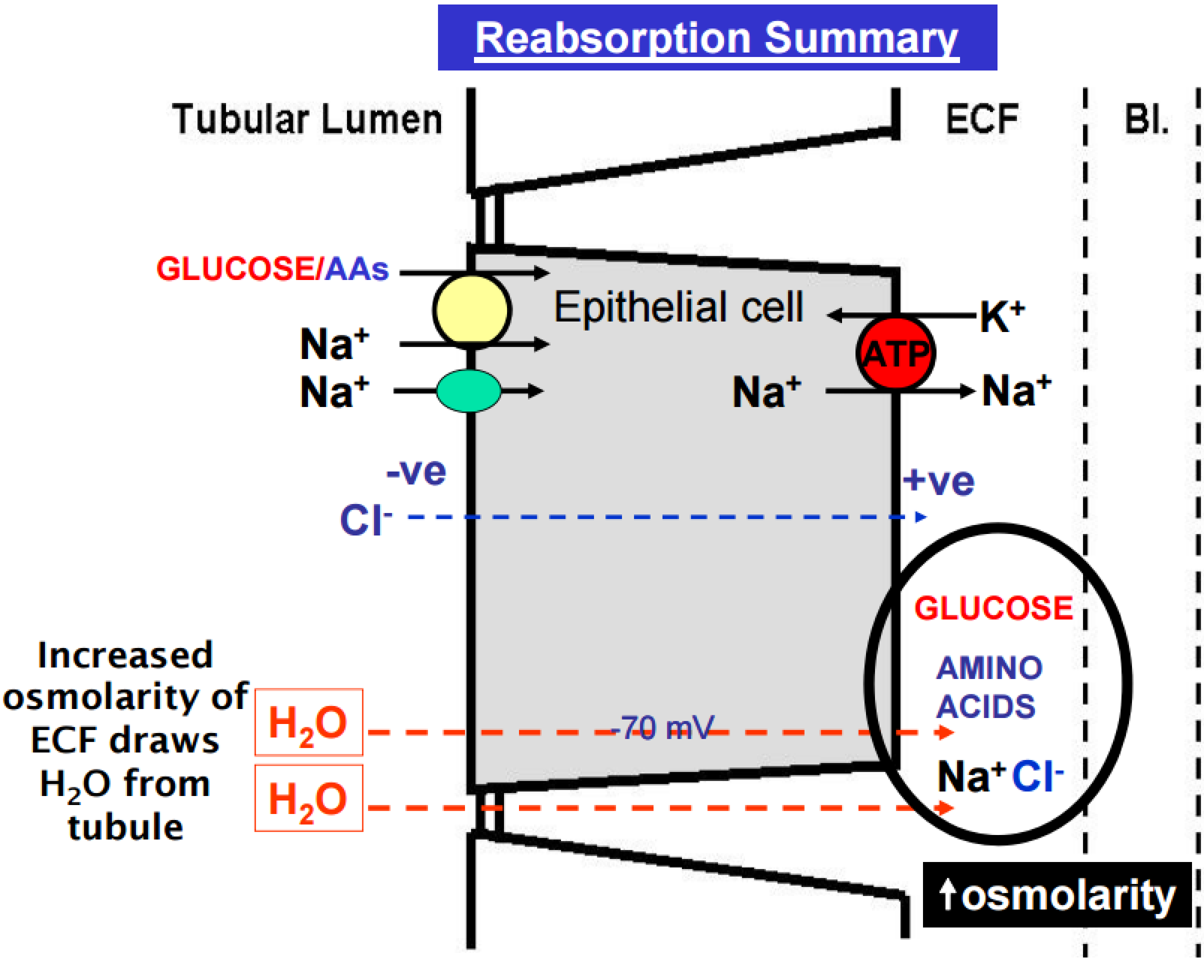
Chlorine ion uptake

- Increase in electronegativity because Na^+ is going out
- Creates an **electrical gradient**
- ECF is positive → **attracts Cl^- to the ECF**
- Cl^- transports both via **passive diffusion through cell AND tight junctions**

H_2O reabsorption

- 65% in **proximal tubule**
  - **Obligatory**
- 25% in **Loop of Henle**
  - **Obligatory**
- 20% in **distal tubule & collecting duct**
  - **Hormonal control**
- H2O reabsorption increases because of **osmotic gradient**
  - Created by the particles that have been moving to the ECF
  - Drags water through cells (**passive diffusion**) and **tight junctions**
- Funnelling effect → **creates a current**
  - Pushes water **into capillary**
- **Capillary colloid pressure** also aids in water uptake
  - Colloid pressure is **high** due to proteins in blood (cannot be filtered)

Reabsorption summary



- **Loss of the sodium-potassium-ATP pump would lead to loss of all reabsorption!**
  - Na^+ reabsorption would decrease
  - Cl^- reabsorption decrease
  - Amino acid/glucose reabsorption decrease as they depend on co-transport with Na+
  - Water reabsorption decrease

Definitions

<u>Osmosis:</u> **diffusion of H_2O from an area of higher H_2O** concentration to an area of lower H_2O concentration.

<u>Osmolarity</u>: Total solute concentration of a solution – relates to # of particles per litre (osM/L). 1 osM = 1 M particles per litre. Particles includes **any** ions such as Na^+, Cl^-, Ca^{2+} and **any molecule** such as glucose or amino acids. E.g. 1M glucose = 1 osM; 1M NaCl = 1 osM Na^+ & 1 osM Cl^- in solution = 2 osM.

<u>Hypoosmotic solution</u>: has **lower** osmolarity than another solution or cell cytoplasm.

<u>Hyperosmotic solution:</u> has **higher** osmolarity than another solution or cell cytoplasm.

<u>Isoosmotic solution</u>: has **same** osmolarity as another solution or cell cytoplasm.

<u>Tonicity:</u> relative term relating to a solution, and the **effects which the solution has on a cell**.

Hypertonic solution: causes cell to **swell**.

Hypertonic solution: causes cell to **shrink.**

Isotonic solution: does not affect cell.

Note: isosmotic solution is not necessarily isotonic!