Renal

Renal blood flow regulation mechanisms

- **Autoregulation**
  - The myogenic mechanism: where an increase in intravascular pressure stimulates stretch receptors in the vessel wall causing a reflex smooth muscle contraction and hence vessel vasoconstriction and reduced flow.
  - The tubuloglomerular feedback mechanism: where an increase in tubular flow rate (with a resultant increase in tubular NaCl concentration detected by the macula densa) causes the juxtaglomerular apparatus to release adenosine which produces afferent arteriolar vasoconstriction and reduces GFR.
- **Renin-Angiotensin II system**
  - The juxtaglomerular apparatus releases renin in response to a drop in afferent arteriolar pressure, a fall in tubular flow rate, or a fall in tubular NaCl concentration at the macula densa.
  - Other stimuli include sympathetic nerve stimulation of beta1-adrenergic receptors on granular cells and a fall in angiotensin II levels.
  - Renin promotes the production of angiotensin II which acts to vasoconstrict afferent and efferent arterioles (the dominant effect is on efferent arteriolar constriction so the GFR is increased).
- **Prostaglandins**
  - Many peripheral vasoconstrictors stimulate the renal production of vasodilating prostaglandins such as PGE2 and PGI2 (prostacyclin) which protect the kidney from severe vasoconstriction.
- **Vasoactive peptides**
  - Bradykinin, released in the distal tubule and glomerulus, promotes prostaglandin synthesis and vasodilation.
  - Natriuretic peptides, released from cardiac cells, produce systemic vasodilation.
  - Endothelin, produced in renal vascular endothelial cells and tubules, is a potent vasoconstrictor.
  - Vasopressin (ADH) promotes vasoconstriction and antidiuretic action.
  - Adrenomedullin promotes renal vasodilation and is produced in the kidney.
- **Other regulatory pathways**
  - Renal nerves contain sympathetic neurons which release noradrenaline which causes constriction of both afferent and efferent arterioles and promotes renin release.
  - Dopamine at low doses has a vasodilatory effect. At higher concentrations dopamine causes renal vasoconstriction and promotes renin release.
  - Nitric oxide is a potent vasodilator that is synthesised in the macula densa, endothelium and mesangial cells and upregulated in response to mechanical shear stress.

↑ **Sympathetic input** - e.g. from baroreceptors

1. ↑ renal and peripheral vasoconstriction
2. ↑ ADH
3. ↑ stimulation granular cells to release renin

Angiotensin II

- ↑ renal and peripheral vasoconstriction
- ↑ Na reabsorption PCT
- Stimulate ADH

- Stimulate aldosterone
- Stimulate thirst
- Reduce renin

Anion gap = [Na+] + [K+] – [Cl-] – [HCO_3-]

A high anion gap metabolic acidosis usually occurs as a consequence of the accumulation of organic acid or the impaired excretion of H+ ions. The mnemonic **CAT MUDPILES** is a useful way of remembering the causes of a high anion gap metabolic acidosis:

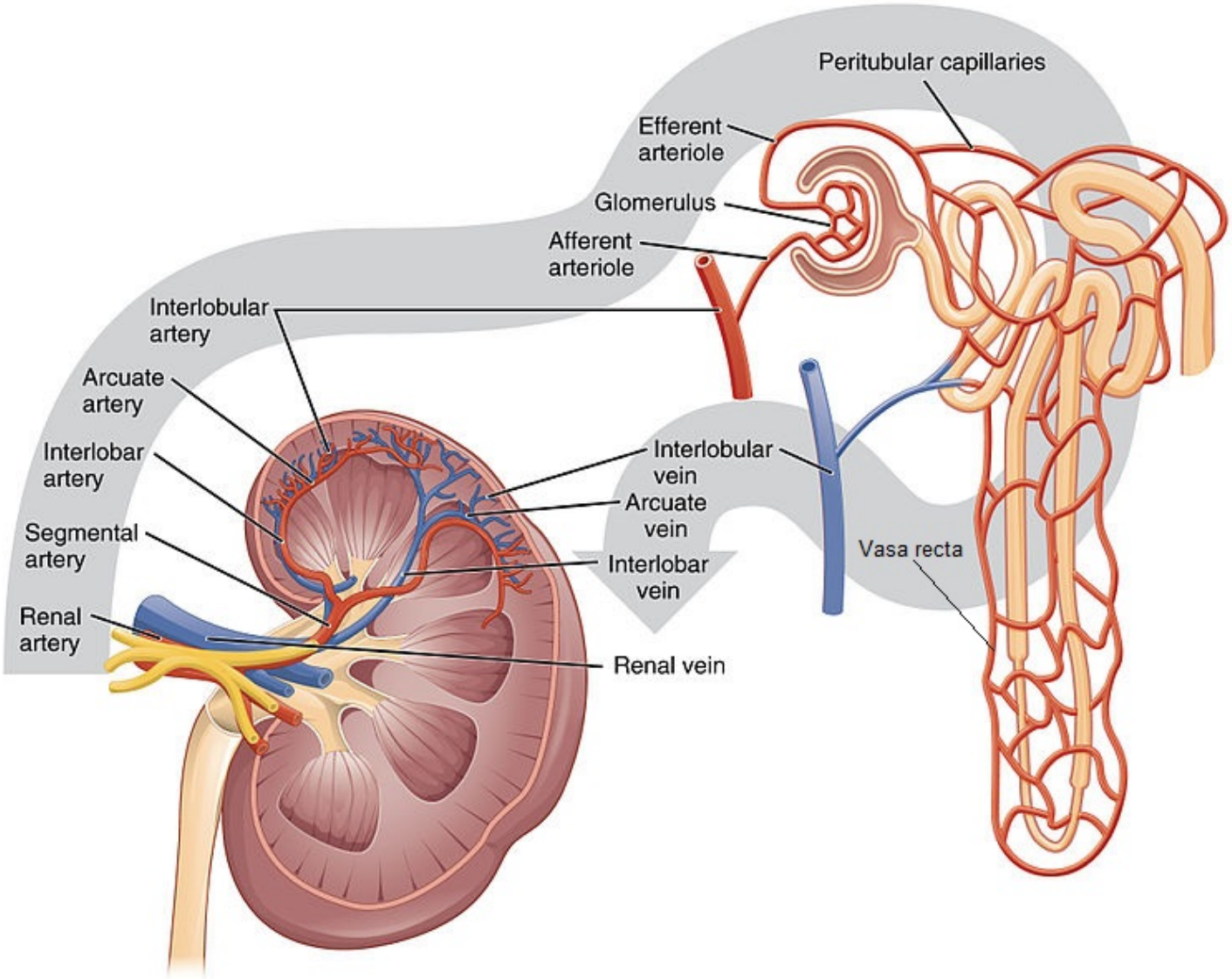
- **C**arbon monoxide
- **A**lcoholic ketoacidosis
- **T**oluene
- **M**etformin, **M**ethanol
- **U**raemia
- **D**iabetic ketoacidosis
- **P**ropylene glycol
- **I**ron, **I**soniazid
- **L**actic acidosis
- **E**thylene glycol
- **S**alicylates

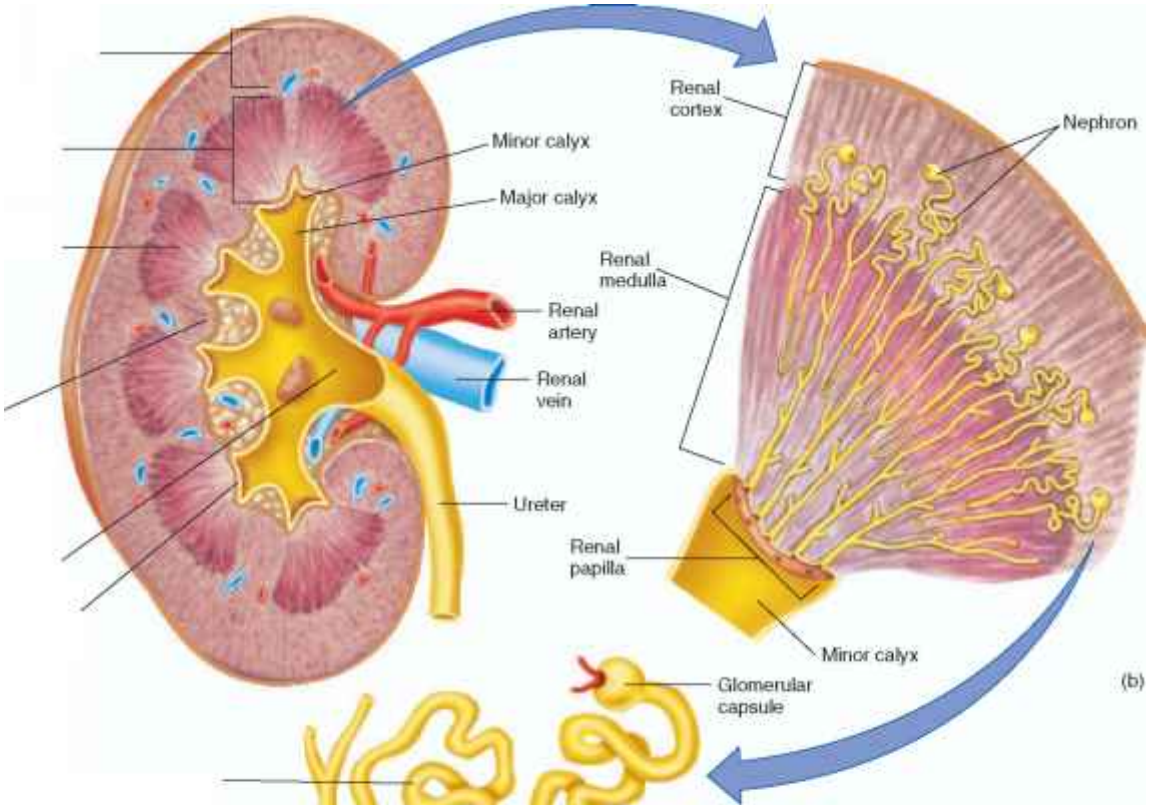
A normal anion gap metabolic acidosis usually results from the loss of HCO_3- ions from the extracellular fluid. The mnemonic **CAGE** is a useful way of remembering the causes of a low anion gap metabolic acidosis:

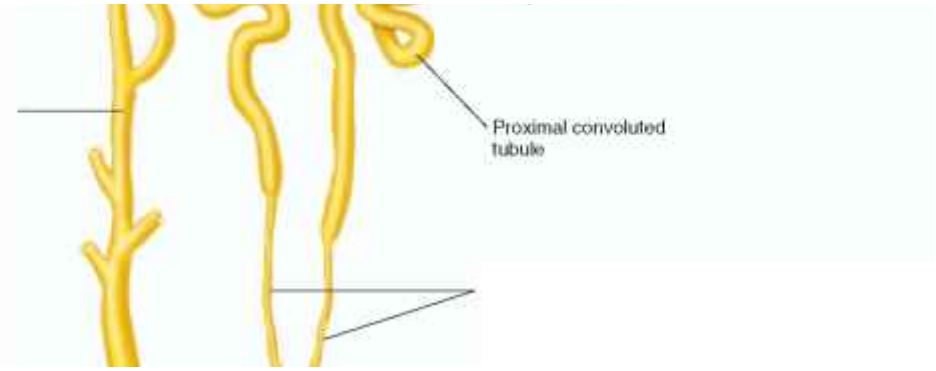
- **C**hloride excess
- **A**cetazolamide, **A**ddison's disease
- **G**astrointestinal causes (diarrhoea, vomiting, fistulae)
- **E**xtra (Renal tubular acidosis)

Anion gap:

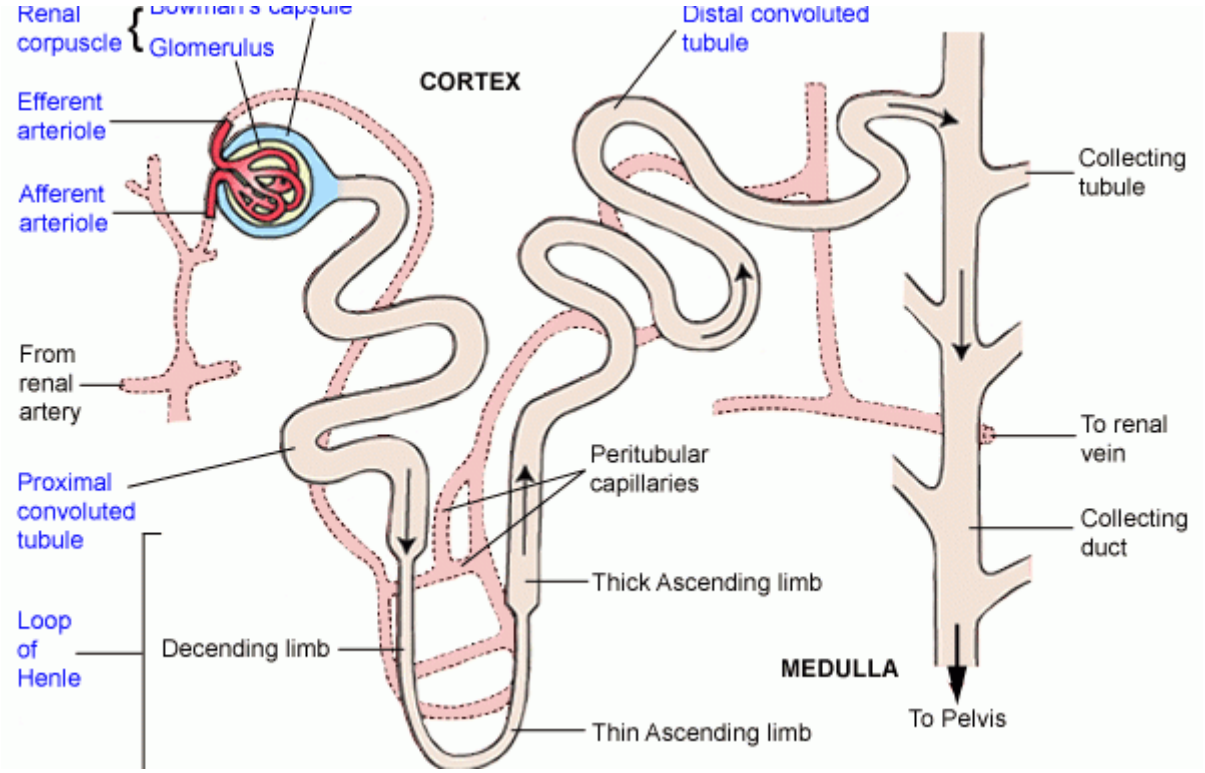
- High anion gap = presence of other causes of acidosis
- Is the difference between the measured anions and cations
- **Equation =** (Na + K) - (Cl- + HCO3-)
  - Normal anion gap = 6-16 mmol/l
- <u>Causes of ↑ anion gap</u>
  - DKA
  - Lactic acidosis
  - Salicylate poisoning
  - Ureamia (renal failure)
  - Infection
  - Iron overdose
- <u>Causes of normal anion gap</u>
  - Spironolactone
  - Renal tubular acidosis
  - Hyperparathyroidism
  - Diarrhoea

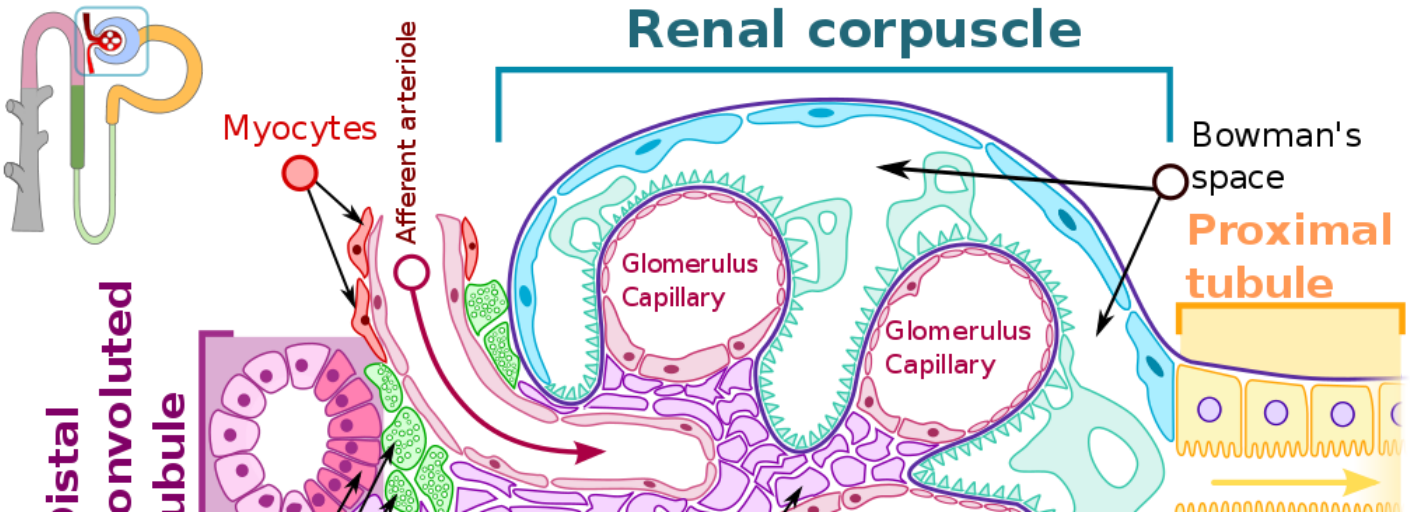

Peritubular capillaries
Efferent arteriole
Glomerulus
Afferent arteriole
Interlobular artery
Arcuate artery
Interlobar artery
Segmental artery
Renal artery
Interlobular vein
Arcuate vein
Interlobar vein
Renal vein
Vasa recta

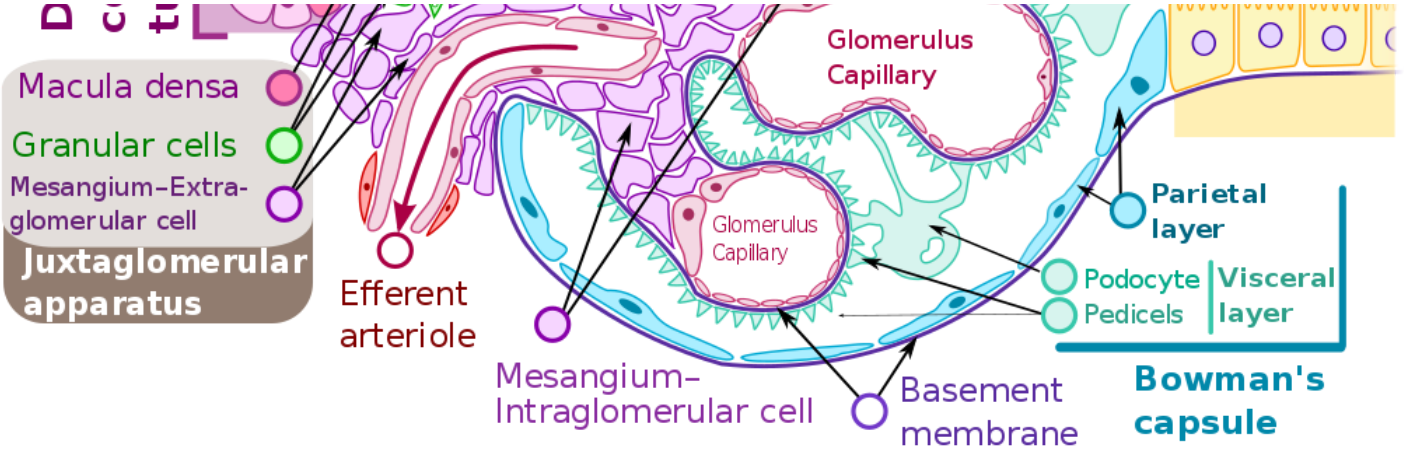

Renal cortex
Nephron
Minor calyx
Major calyx
Renal medulla
Renal artery
Renal vein
Ureter
Renal papilla
Minor calyx
Glomerular capsule
(b)



NEPHRON DRAINS INTO MINOR CALYX







Juxtaglomerular apparatus

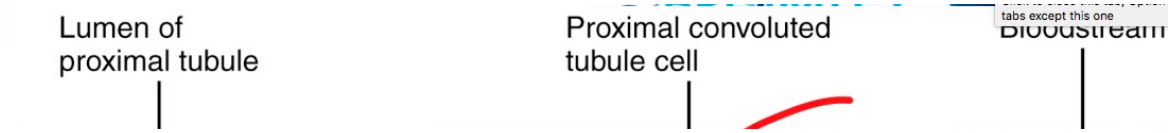
1. Juxtaglomerular cells (granular cells)
    - Secrete RENIN, in response to:
        - Beta 1 adrenergic receptor stimulation
        - ↓ NaCl in macula densa
        - ↓ renal perfusion pressure (directly detected by JG/granular cells)
            - (Detects tubular flow rate and renal perfusion pressure)
2. Macula densa
    - Respond to NaCl levels
    - ↑ NaCl = ↑ afferent arteriole constriction
    - ↓ NaCl = ↑ NO and prostaglandin secretion —> ↑ afferent arteriole dilation
3. Extra-glomerular mesangial cells
    - Between afferent and efferent arterioles - help to control vascular tone and GFR

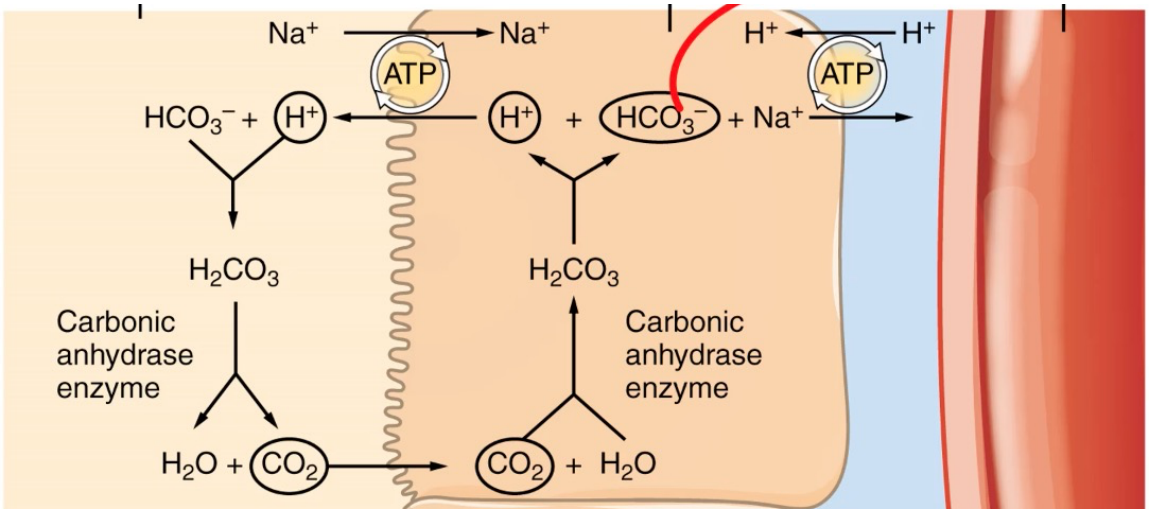
Filtration is at high pressure - around 60% of MAP = around 40mmHg

GFR autoregulation

- Maintained at approx 75-160 mmHg - hard to compensate and maintain GFR at extremes of BP
- 75% of fluid is reabsorbed

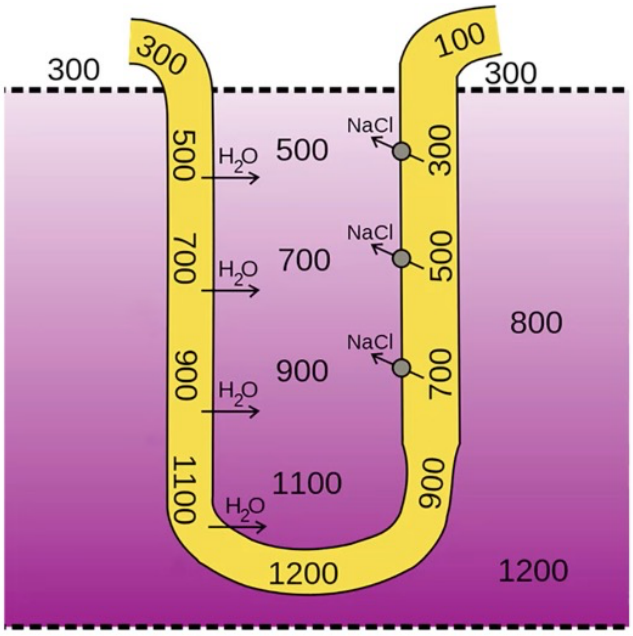
PCT

1. Secretion/absorption of substances
    1. Na+ transport - active ATP transport, around 70% of filtered Na is reabsorbed
    2. Glucose reabsorption - normally is totally reabsorbed, but saturable system, max around 11mmol/L. After that = osmotic diuresis
    3. Tubules also secrete exogenous substance - e.g. penicillin, salicylates other drugs etc
2. Acid base balance
    - 



- PCT helps with **<u>acid base balance</u>**
  - Na+ reabsorbed in exchange for H+ secretion
    - Secretion of H+ is equivalent to the resorption of HCO3-
  - All H+ created from metabolism are buffered by bicarbonate —> water and CO2
  - CO2 reabsorbed to make more bicarb for body and to excrete more H+
    - Bicarb —> into blood stream for buffering acid
  - *Tubules can ALSO create MORE bicarb if need be*

Loop of Henle

- Role is to dilute the fluid in tubules
- Active transport processes to resorb water and solutes into the medulla
- Fluid leaving into DCT is hypotonic
  1. Water *leaves* in descending limb
  2. Urea *enters* in ascending limb
  3. Na *leaves* in ascending limb
- 

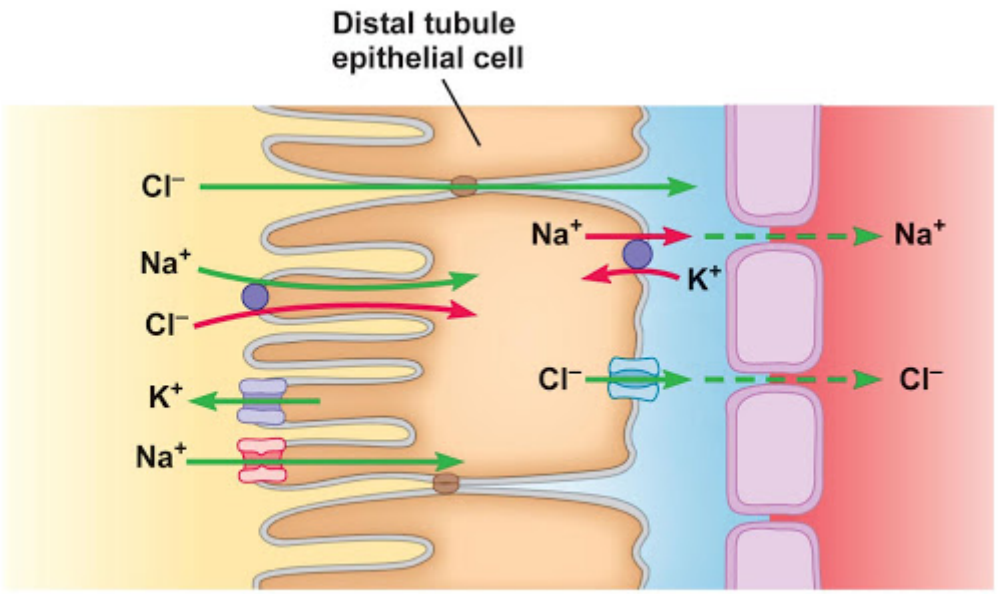
DCT

PRINCIPLE CELLS = involved in:

PRINCIPLE CELLS - involved in:

1. H2O reabsorption (via ADH and aquaporins)
2. Na+ reabsorption and K+ excretion

Fluid in DCT starts as hypotonic

- Sodium
  - 

    (b) Sodium reabsorption in the distal tubule

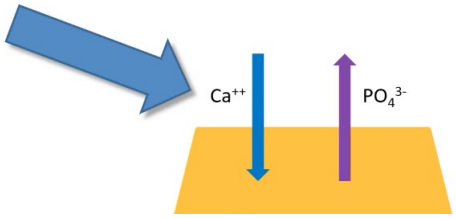
  - Sodium resorption accompanies Cl- on Na/Cl symporter
  - Fluid in lumen is also negative (because so much HCO3- resorption) so some Cl- diffuses into blood across lumen
    - *Aldosterone —>* ***acts on principal cells in DCT***
      - Na and K control happens here via aldosterone
      - Na / K exchange via aldosterone
      - Stimulated by:
        - Angiotensin II
        - ↑ K
        - ACTH
    - *Atrial natriuretic peptide*
      - Works to get rid of too much Na
      - Increased na —> increased H2O —> increased stretch of vessels and **atria** —> increased release of ANP from atria —> promotes excrete of Na and loss into urine
      - ANP acts to:
        - Inhibit Na+ reabsorption in the distal nephron (through inhibition of ENaC in principal cells)
        - Suppress the production of renin
        - Suppress the production of aldosterone
        - Suppress the production of ADH
        - Cause renal vasodilation, increasing the glomerular filtration rate

        The net result is increased excretion of water and Na^+ and hence reduced blood volume.

- Calcium
  - If low Ca —> increased PTH release —> increased reabsorption of Ca in DCT into bloodstream (and excites phosphate)

excites phosphate)

- **PTH**



Collecting duct

- Receives hypotonic filtrate from DCT
- **ADH/vasopressin acts here - on principle cells**
  - Aquaporin insertion
  - Gradient in medulla created by loop of Henle —> powerful osmotic gradient (1200 osmolality mmol/L) can resorb H2O back into body and concentrate the urine even further
  - Clinical
    - Excess ADH = SIADH
    - Low ADH = diabetes insipidus

Loop diuretics

- Na/K ATPase in ascending limb

Thiazides

- Na reabsorption in distal tubule

Amiloride

- Na/K exchange in distal tubule

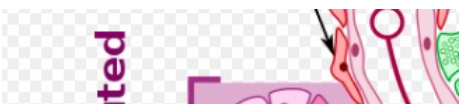
Spironolactone

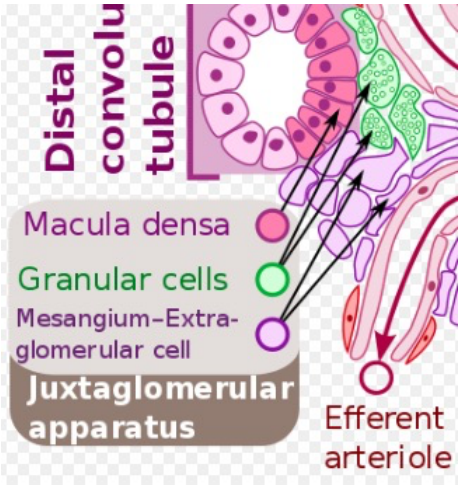
- aldosterone antagonist

H2O control

- Hypothalamus osmoreceptors detect osmolality
- If ≥280 mmol/L —>
  1. Stimulates thirst to take in water
  2. Hypothalamus makes ADH —> stored and secreted from posterior pituitary
     1. ADH increases water resorption from collecting ducts

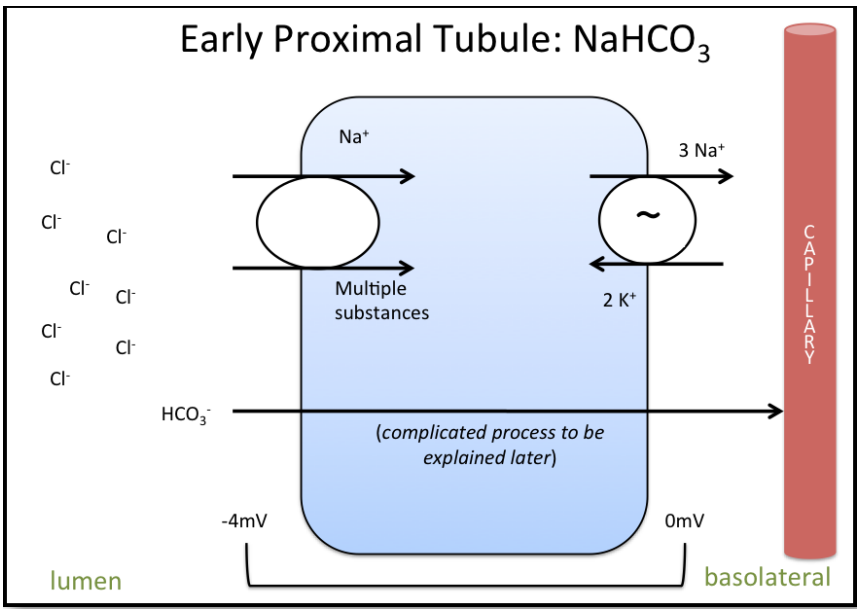
Na control



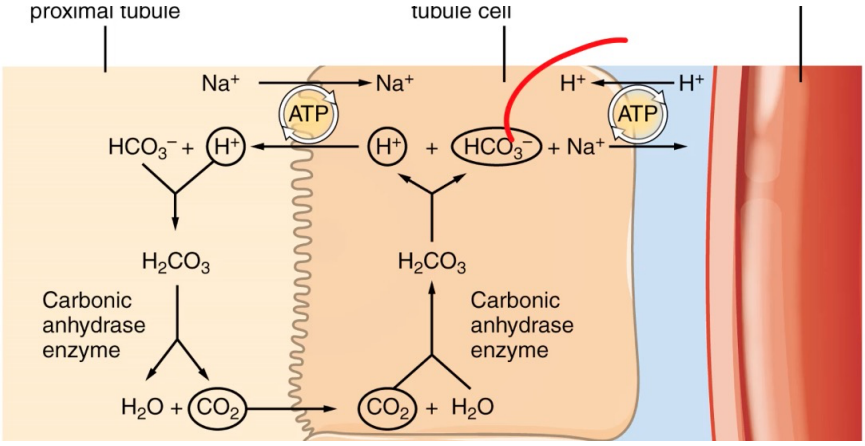


- Sodium too LOW
  - Macula densa in DCT detects low na in the DCT / low pressure in afferent arteriole —> stimulates:
    1. Afferent arteriorle dilatation to increase GFR flow
    2. Renin secretion from JGA
       1. —> renin angiotensin system is triggered —> aldosterone and sympathetic effects on GFR
- Sodium too HIGH
  - —> leads to increased blood volume —> increased atrial stretch —> increased ANP release
    - —> increased excretion of Na into urine
    - —> inhibits renin secretion

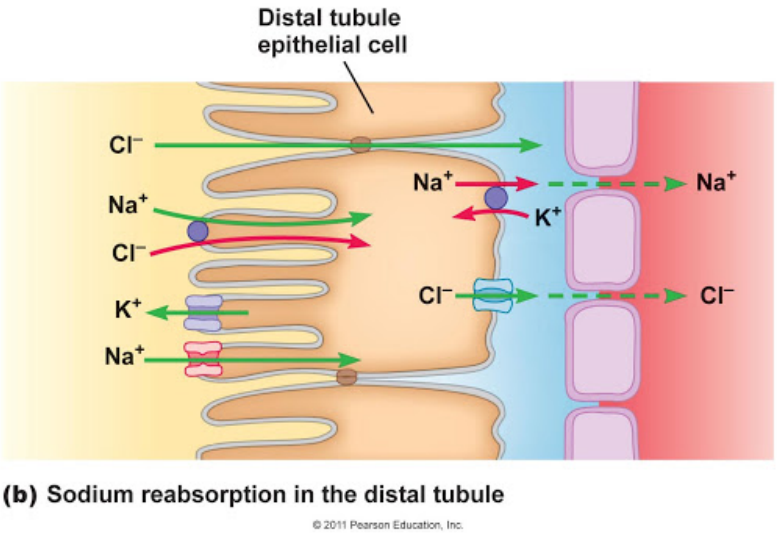
SODIUM along the nephron

- **PCT**
  - 70% resorbed here
  - Na and other substances:
    - Sodium gradient created by basal Na/K ATPase
    - Gradient drives co-transport of sodium with glucose, HCO3-, amino acids etc
    - Leaves lumen with high negative charge (from all the Cl-)
    - 

  - Na and HCO3
    - Exchange of H+ into lumen and Na+ into blood
    - Lumen of Proximal convoluted Bloodstream



- **Loop of Henle**
  - Thick ascending limb (impermeable to water)
    - Na gradient set up by Na/K ATPase on basolateral side of cell
    - Luminal side —> co transport down gradient of K, Cl, and Na
- **DCT**
  -



(b) Sodium reabsorption in the distal tubule

  - Na/K ATPase on basolateral side sets up Na gradient
  - Na/Cl symporter on luminal side —> Na and Cl both move across cell into blood

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ACID-BASE BALANCE

Acid-base regulated precisely by lungs (respiration) and kidneys

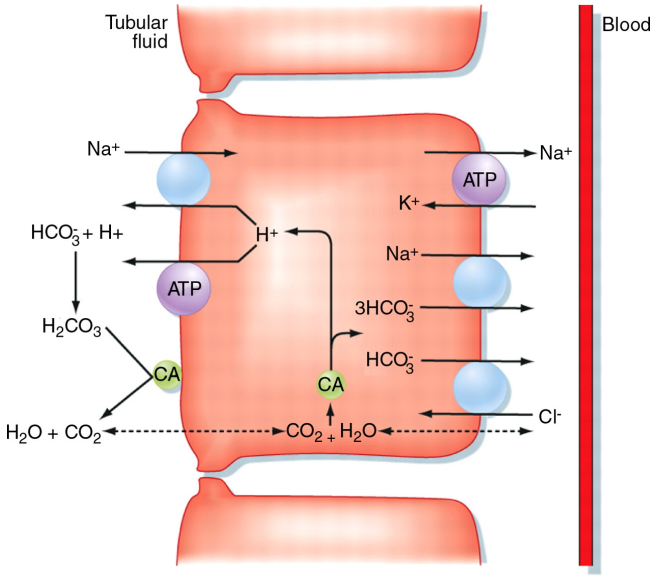
- CO2 controlled by lungs
- HCO3 controlled by kidneys

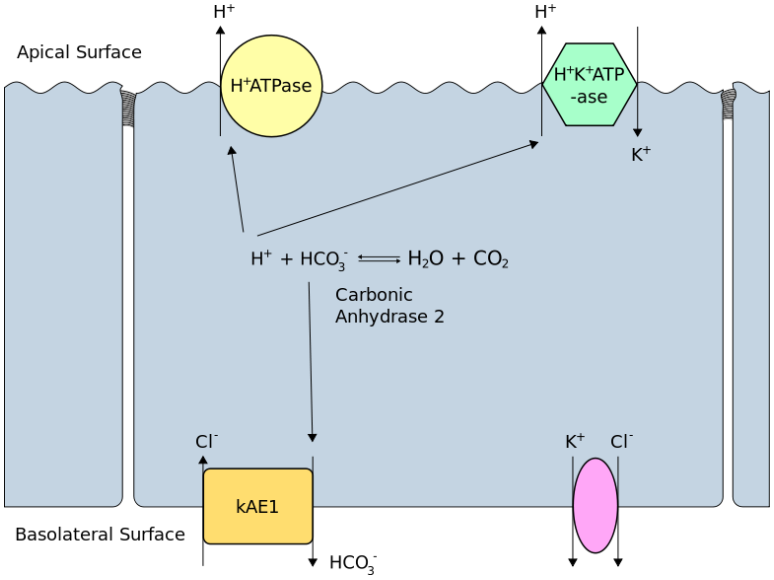
<u>Renal control</u>

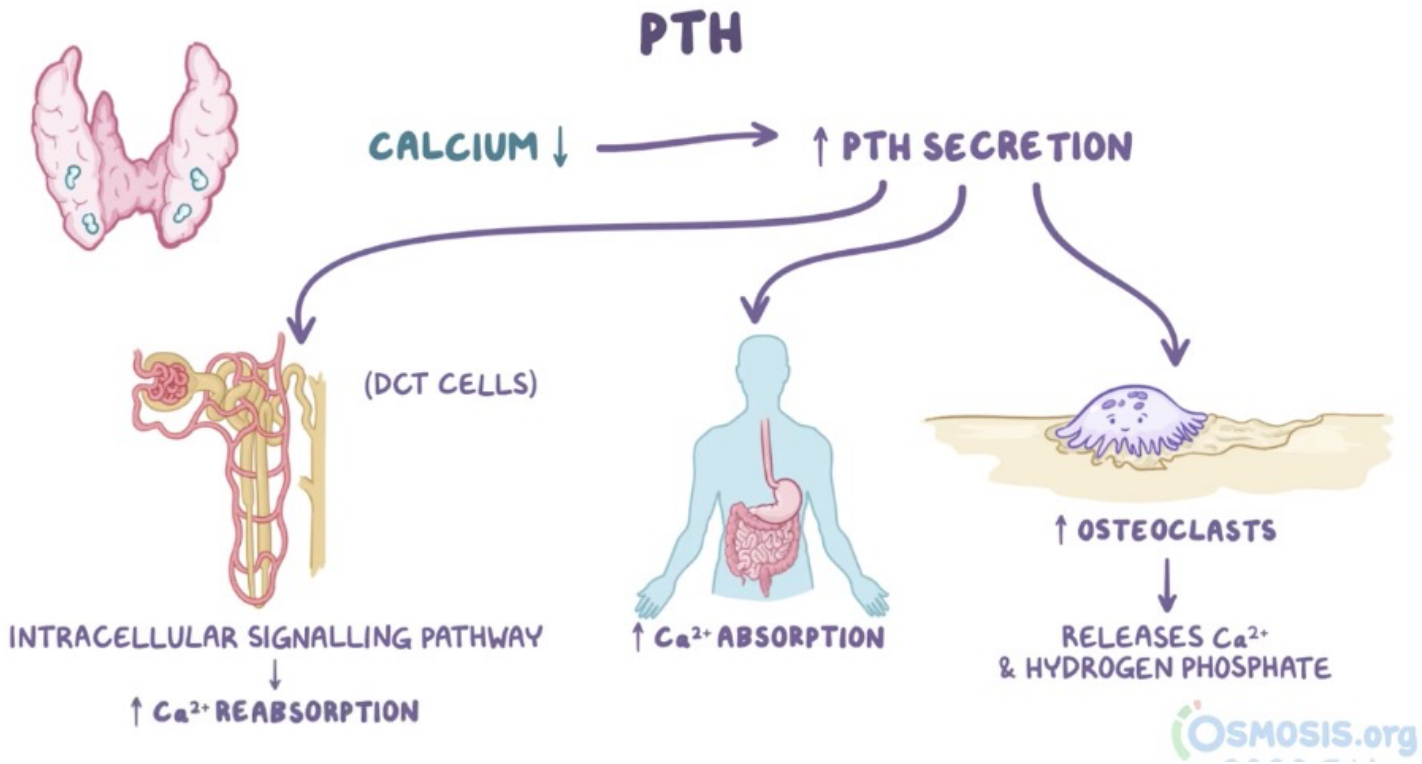
Bicarb freely filtered at nephron

Less than 0.1% of filtered bicarb is excreted in urine - vast majority reabsorbed

- **PCT**
  - 80% of bicarb reabsorbed in PCT:
    1. At luminal membrane in PCT = 2 transport mechanisms of H+ from cell into lumen

        - H+ ATPase
        - H+/Na+ antiporters (Na absorbed at PCT in exchange for H+ into lumen)
    2. HCO3 + H+ (by carbonic anhydrase) —> H2CO3 —> immediately dissociates to H2O and CO2
    3. H2O and CO2 —> freely filter into luminal cells —> recombine (via carbonic anhydrase) to form HCO3 and H+
        1. H+ —> recycled out into lumen (via the two transporters above)
        2. HCO3 —> absorbed into interstitium and systemic circulation
    - 

- **DCT**
    - Secretion of H+ from body into lumen stimulates reabsorption of any remaining HCO3
        - Directly proportional to pH. If more acidotic (lower pH) then more H+ secreted and more HCO3 reabsorbed
    - Beginning of DCT = mainly Na+ and H+ exchange
    - Later in DCT - Na gradient too low so becomes primary active transport
        1. K+/H+ ATPase
        2. H+ ATPase
    - 



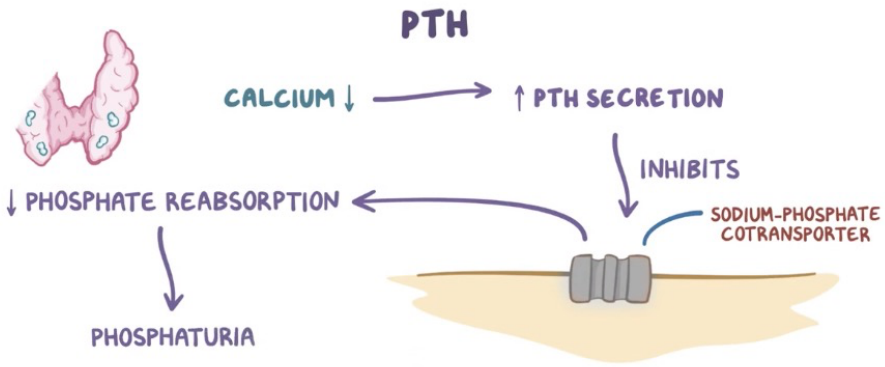
CALCIUM handling - 99% is in the bones

- Functions
  - Blood coagulation
  - Neurotransmission
  - Enzyme activity
- Normal value = 2.2-2.6 mmol/L (both free ionised and bound Ca2+)
  - 50% = free ionised
  - 45% = bound to albumin
  - 5% = bound to other ions
- Free, unbound Ca2+ is freely filtered at nephron
  - 70% reabsorbed PCT
  - 20% reabsorbed loop of Henle (Na-K-Cl cotransporter)
  - 5-10% reabsorbed in DCT
- **Hormonal** control on Ca in kidneys
  - Parathyroid hormone -
    - ↑ Ca reabsorption with ↑ Ca ATPase on basolateral membrane and activating Ca entry channels on apical side so flows from lumen —> cell —> systemic circulation
    - ↓ phosphate reabsorption
  - Vitamin D -
    - ↑ Ca reabs orption in DCT by ↑ activation of Ca ATPase basolateral membrane in DCT
    - ↑ gut absorption of Ca in gut
  - Calcitonin (from parafolicullar cells on thyroid gland) -

- ↓ plasma Ca levels
  1. inhibits resorption of Ca and phosphate from bone
  2. ↓ renal calcium and phosphate reabsorption

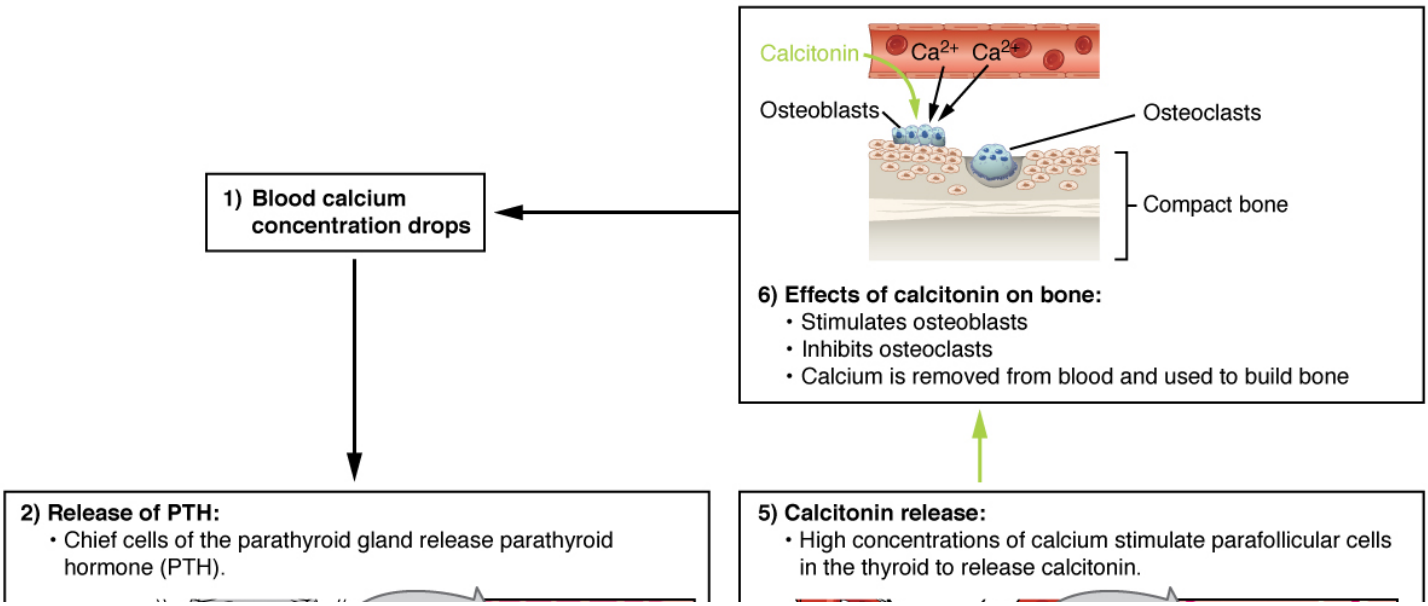
PHOSPHATE (PO4) handling

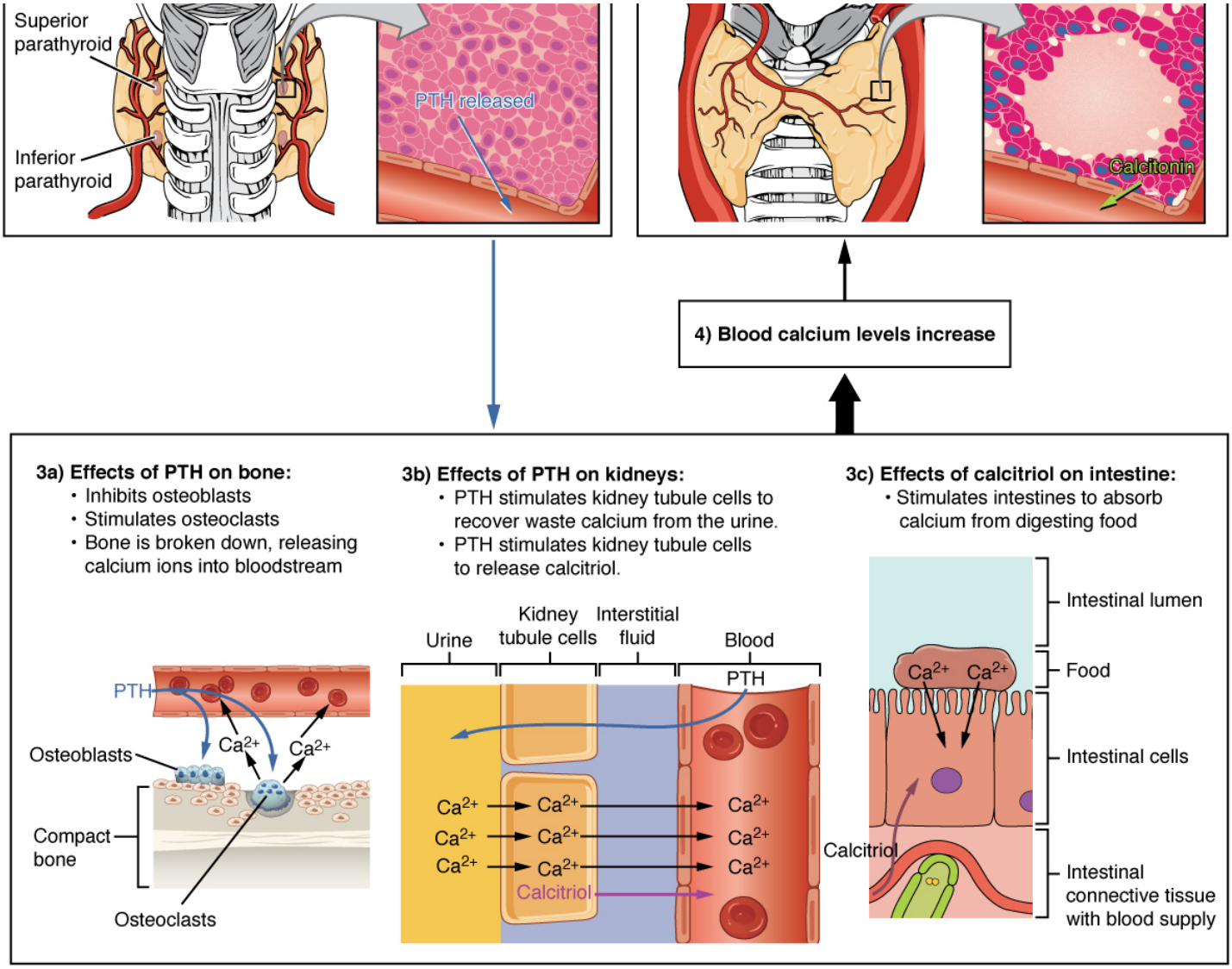
- Functions
  - ATP/ADP
  - Buffer for H+
  - Component of nucleotides
- In plasma - 90% free, 10% protein bond
  - Unbound phosphate freely filtered through glomerulus
  - 70% reabsorbed in PCT by Na/PO4 co-transporters
-



PO_4^{3-} renal excretion is regulated by:

- PTH (increases excretion by inhibiting reabsorption in the proximal tubule)
- activated vitamin D (decreases excretion by increasing reabsorption in the distal tubule)
- acidosis (increases excretion)
- glucocorticoids (increases excretion)
- calcitonin (increases excretion)

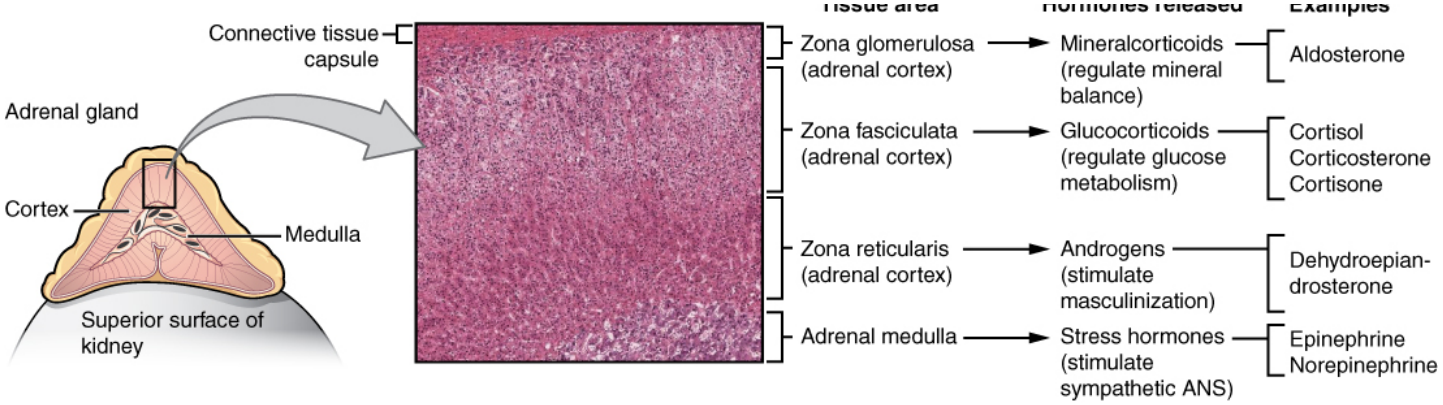




MUDPILES can be used to remember some of the causes of a raised anion gap acidosis:

- Methanol
- Uraemia (in renal failure)
- Diabetic ketoacidosis
- Propylene glycol overdose
- Infection/Iron overdose/Isoniazid/Inborn errors of metabolism
- Lactic acidosis
- Ethylene glycol overdose
- Salicylate overdose

Tissue area	Hormones released	Examples



- Medulla
  - Chromaffin cells in medulla secrete noradrenaline (20%) and adrenaline (80%)
  - Stimulated by SYMPATHETIC PREGANGLIONIC NEURONES
    - See below: preganglionic sympathetic neurone does not synapse —> goes straight to adrenal medulla
    -