Renal electrolyte handling

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Outline

- Sodium balance
- Potassium balance
- Phosphate balance
- Calcium balance
- Magnesium balance

Sodium handling

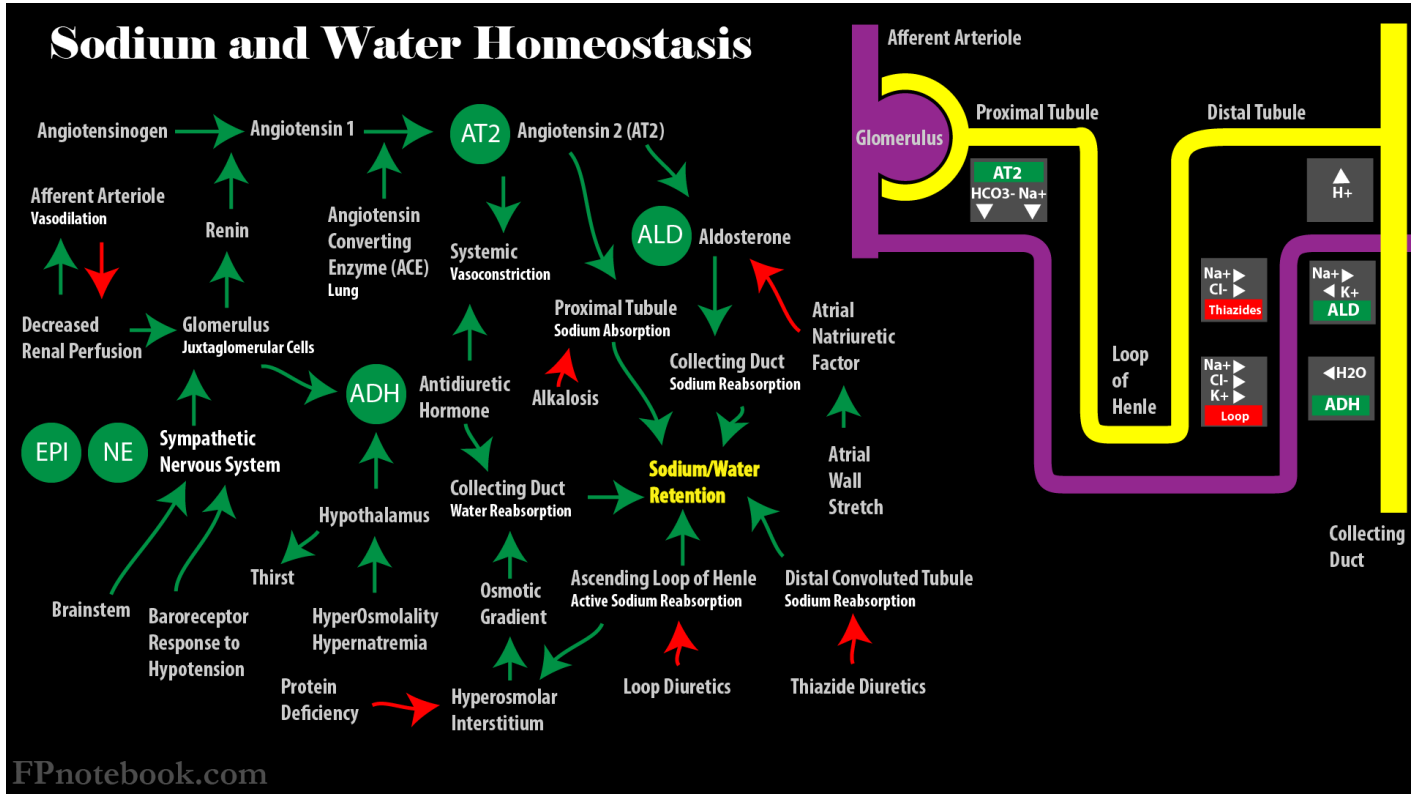
Sodium handling

Sodium homeostasis

Major intracellular ion

Serum levels tightly regulated

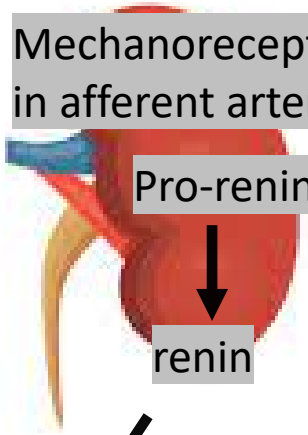
- Aldosterone
- ADH
- Angiotensin II
- PTH
- Catecholamines
- ANP



Sodium handling

↓BP → ↓ renal perfusion

Mechanoreceptors in afferent arteriole

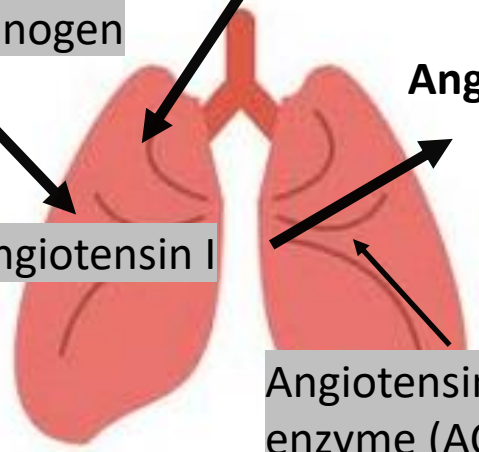


Pro-renin

↓

renin

Angiotensinogen



Angiotensin I

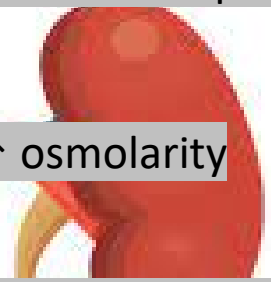
Angiotensin-converting enzyme (ACE)

Angiotensin II

AT_1 receptors

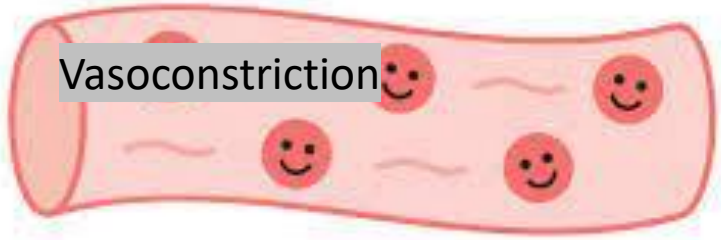
Adrenal cortex: **aldosterone** → ↑ ENaCs on principal cells of kidney

Na^+-H^+ pump in PCT → ↑ osmolarity



Increases thirst and stimulates ADH → ↑ aquaporins in CD (V2) and vasoconstriction (V1)

Arterioles → Vasoconstriction



(MAP = CO x SVR)

Sodium handling

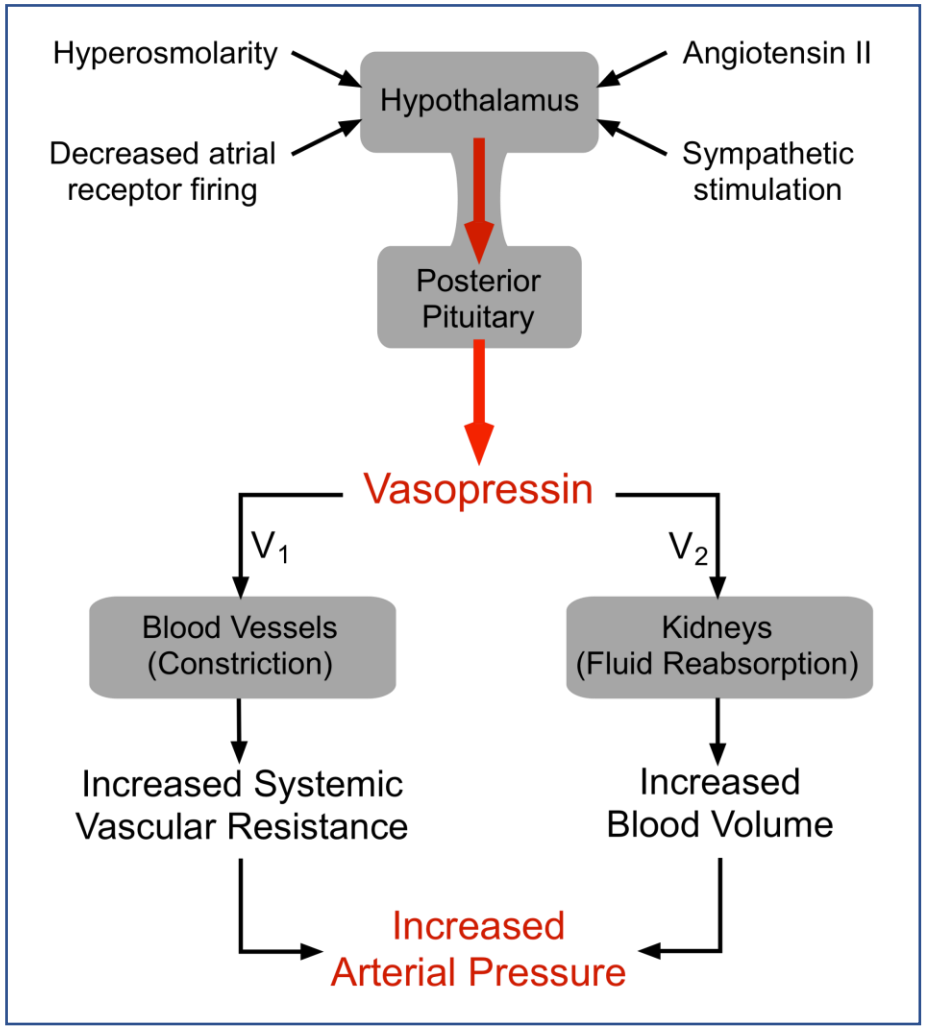
ADH

In response to 2 stimuli:

- ↑ serum osmolarity
- ↓ in blood volume and BP

2 receptors:

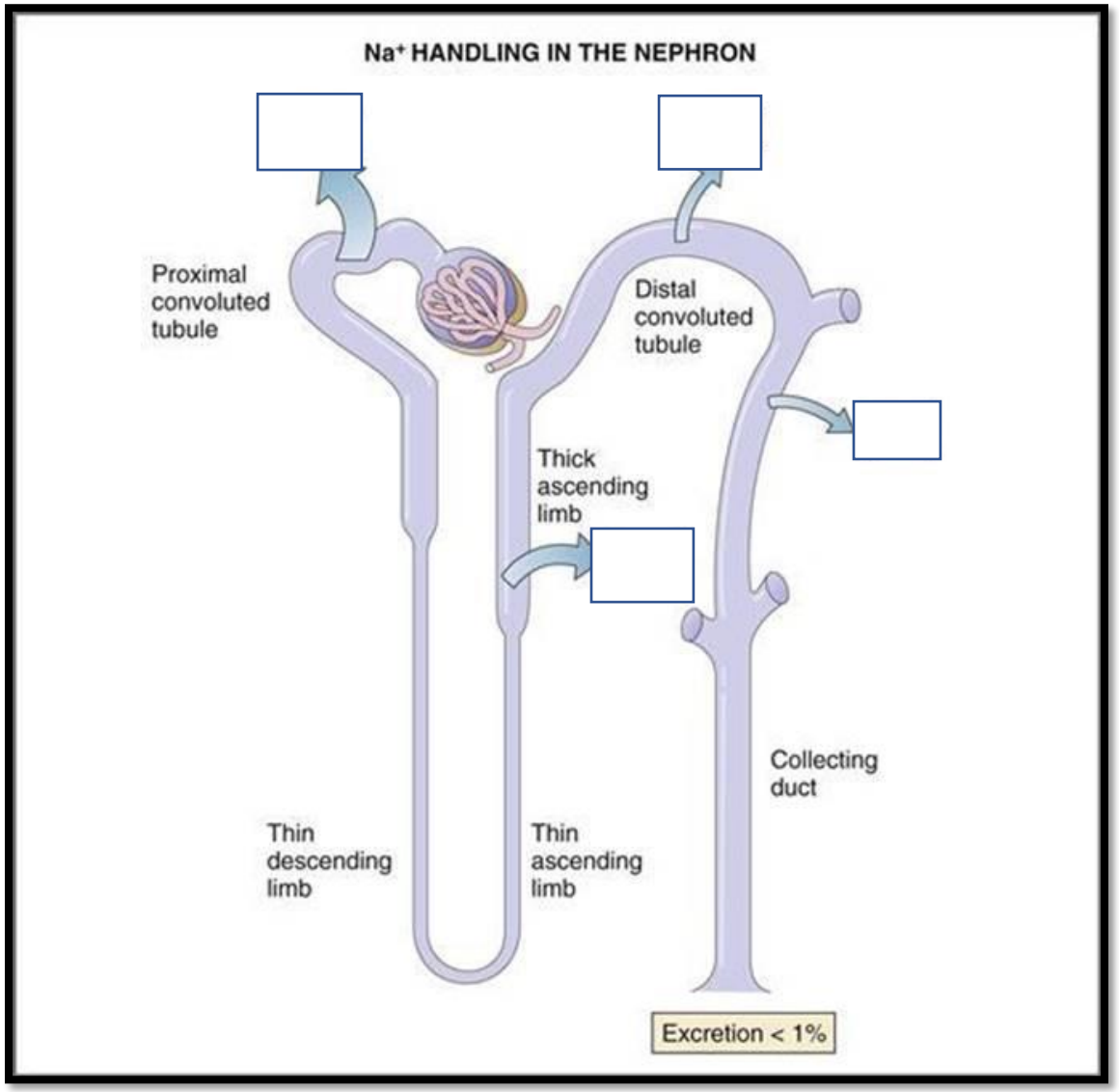
- V_1 – present in smooth muscle → vasoconstriction → ↑ TPR
- V_2 – principal cells in CD → ↑ AQ1 → H2O reabsorption



Sodium handling

Renal handling of sodium

Fill in the blanks



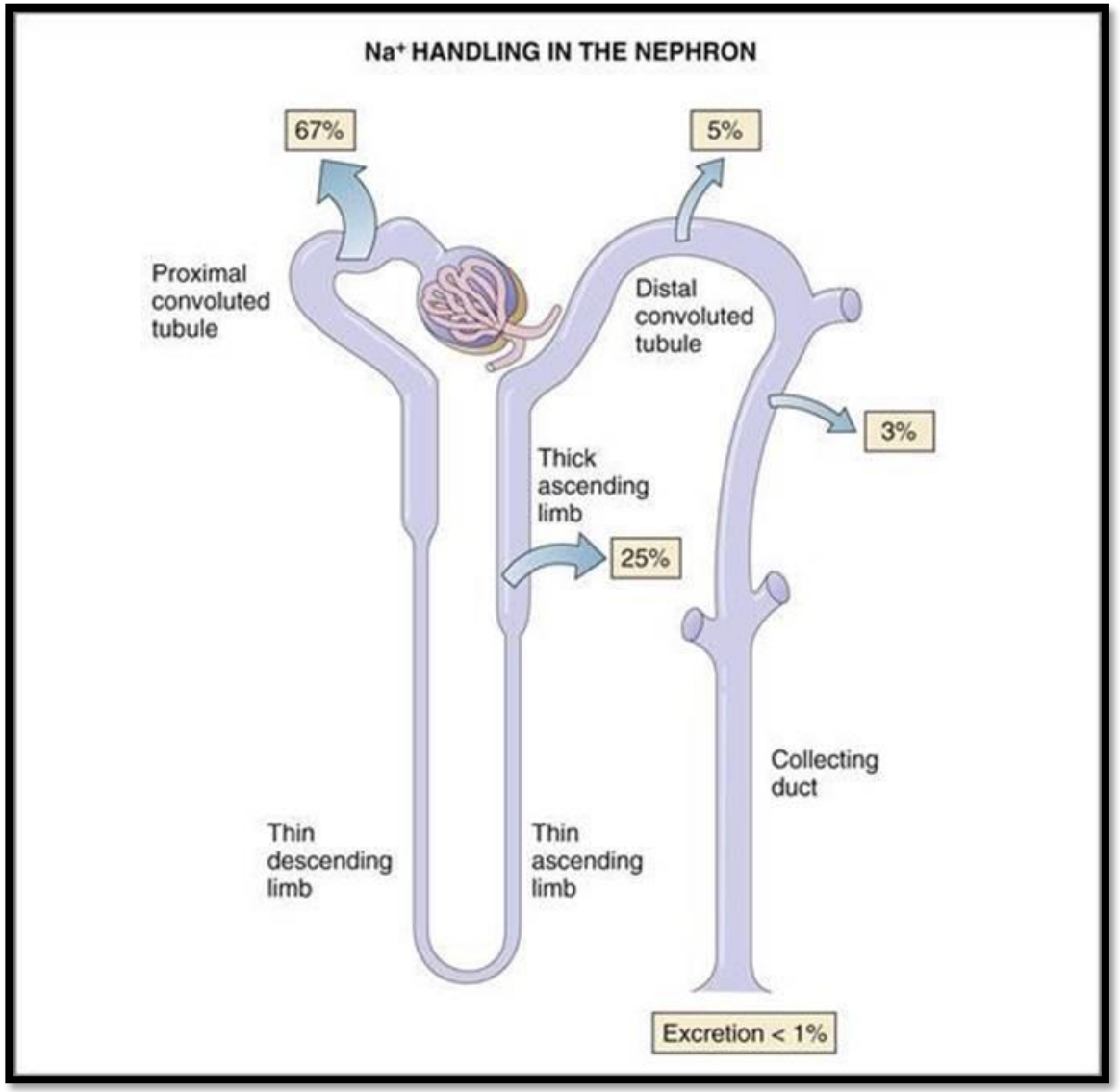
Sodium handling

Renal handling of sodium

Na^+ is freely filtered

Net reabsorption 99%

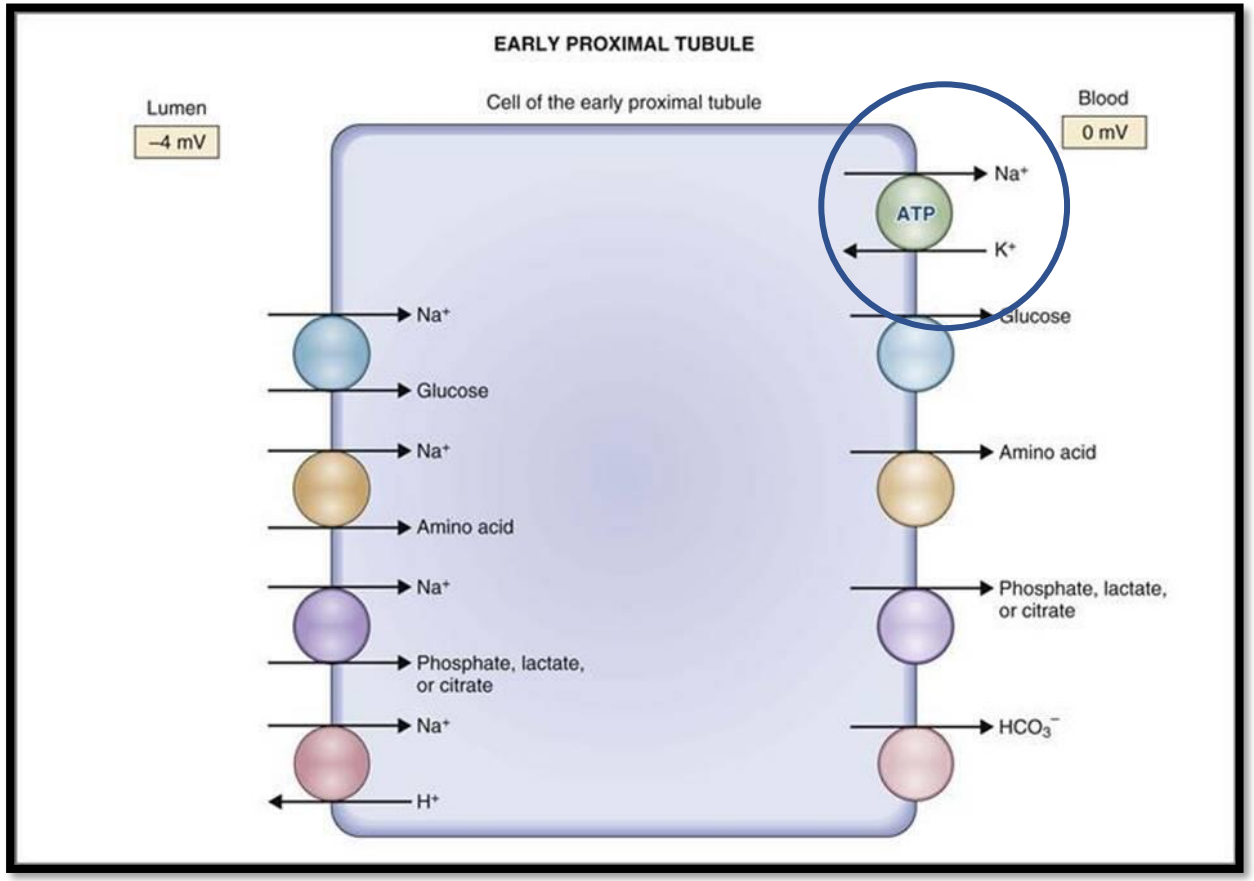
- PCT – 67%
- Thick ascending LOH – 25%
- Early DCT – 5%
- Late DCT and CD – fine tuning - 3%



Sodium handling

Na^+-K^+ pump

- Basolateral membrane
- Na^+ out of the cell
- Keeps intracellular Na^+ lower than lumen
- Maintains **lumen positive potential**
- Key provider of energy for other transport mechanisms



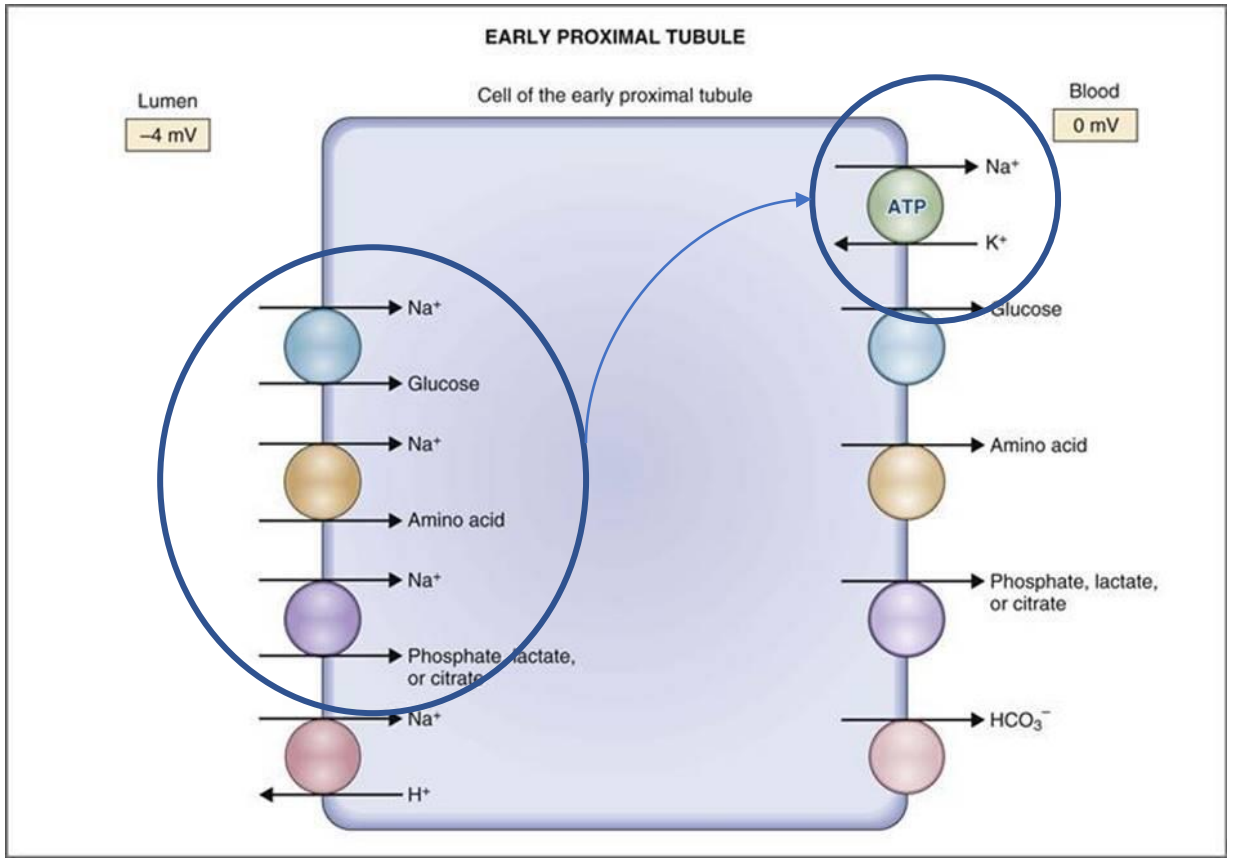
Sodium handling

Proximal convoluted tubule

- 67% of Na^+
- Water always follows – isosmotic reabsorption

Early PCT

- Cotransport with glucose, Amino acids, P^+, lactate and citrate
- Na^+ into the cell down electrochemical gradient
- Then extruded into bloodstream via Na^+-K^+ ATPase



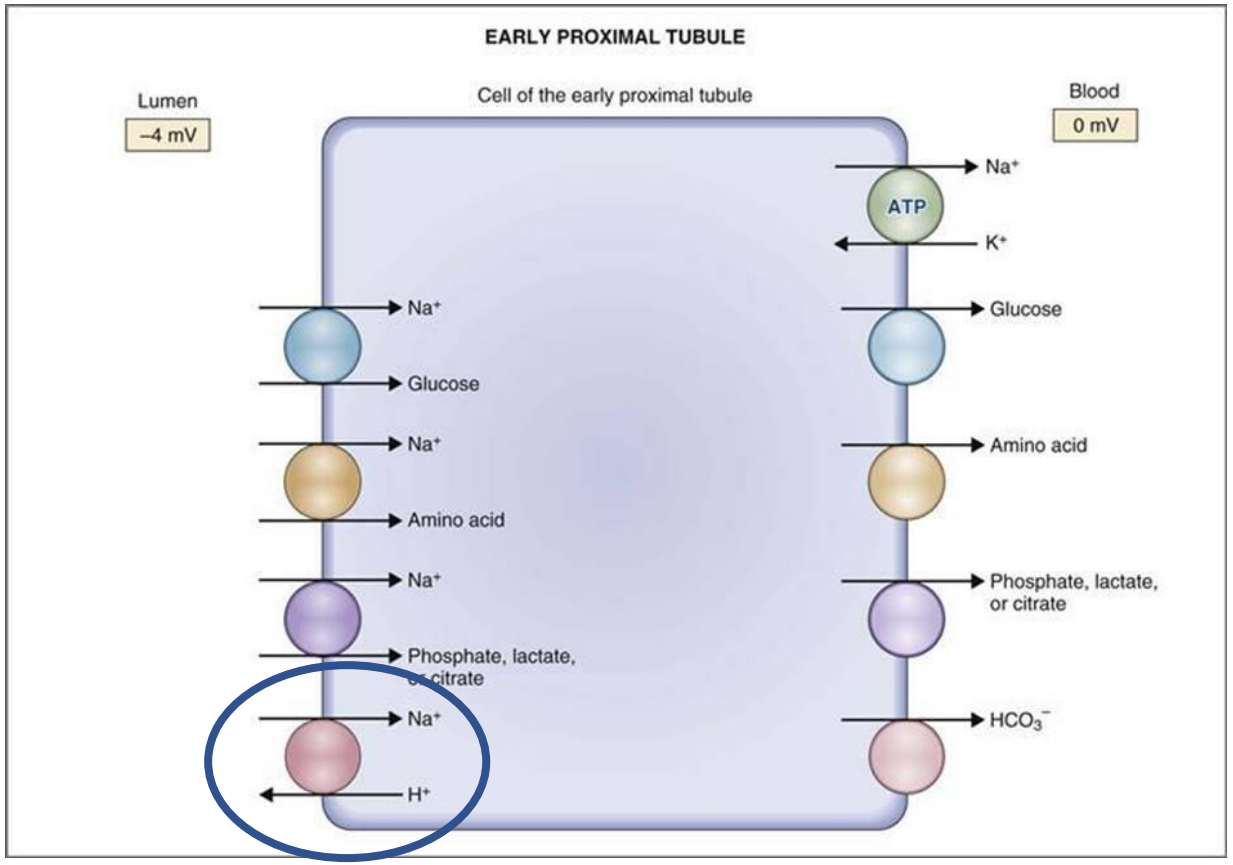
Sodium handling

Na^+- H^+ pump

- H^+ into lumen and combines with $HCO3^-$ → CO2 and H2O → back into cell → converts into H^+ and HCO3
- HCO3 reabsorbed, H^+ is pumped back out by Na^+- H^+
    - Result - Reabsorption of filtered $HCO3^-$

Result of these transport mechanisms:

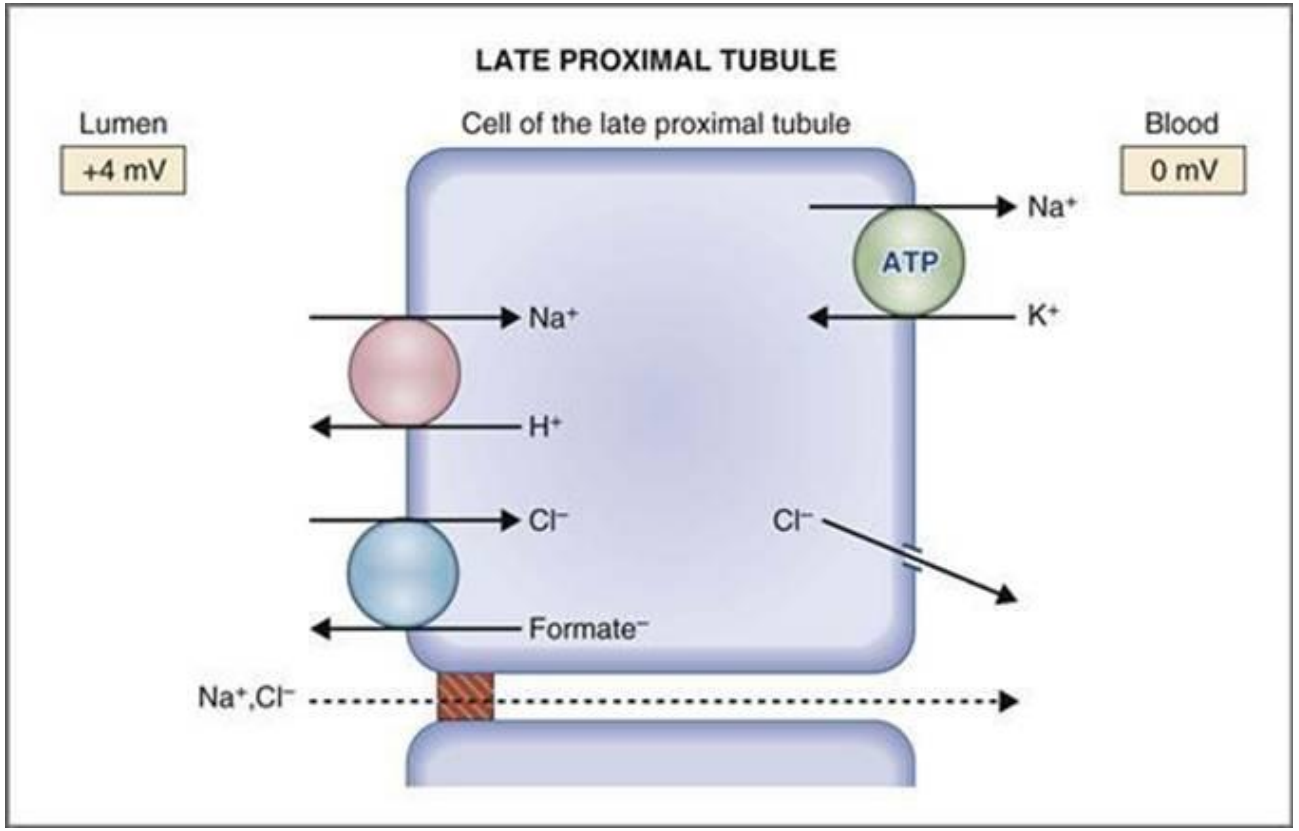
- 100% glucose and amino-acids reabsorbed
- 85% $HCO3^-$ is reabsorbed
- Most P^+, Lac and citrate reabsorbed
- **Lumen-positive potential difference** across the cells created by Na^+



Sodium handling

Late PCT

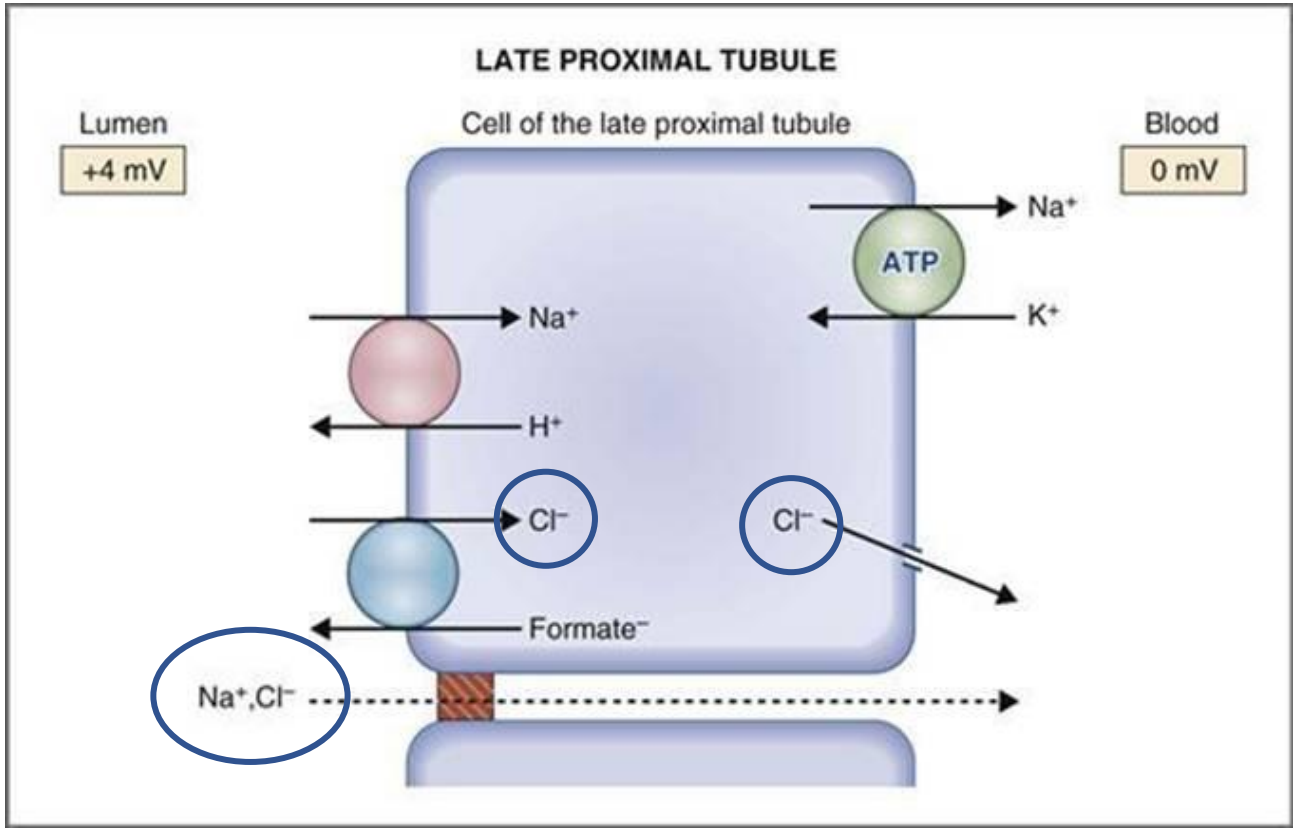
- High Cl^- concentration since $HCO3^-$ and H2O have been preferentially absorbed
- This segments absorbs primarily NaCl by 2 mechanisms:
  - Na^+-H^+ exchanger
  - Cl^--formate anion exchanger
- Both transport NaCl in
  - Na^+ extruded into blood via Na^+-K^+ ATPase and Cl^- by diffusion



Sodium handling

Paracellular route

- High Cl^- in lumen creates a gradient that stimulates diffusion
- This creates a Cl^- diffusion potential making the lumen more positive
- Na^+ follows driven by the lumen positive potential difference



Sodium handling

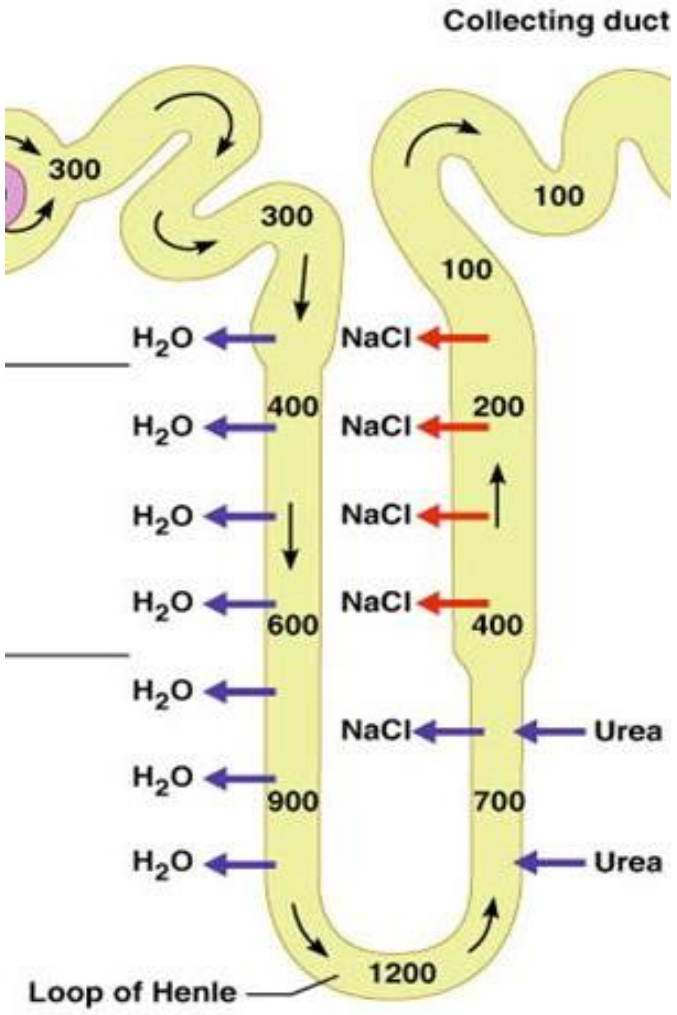
Loop of Henle

Thin descending limb

- High permeability to Na^+, urea and H2O
  - Na^+ and Cl^- are passively reabsorbed
  - Concentrating segment

Thin ascending limb

- Impermeable to H2O



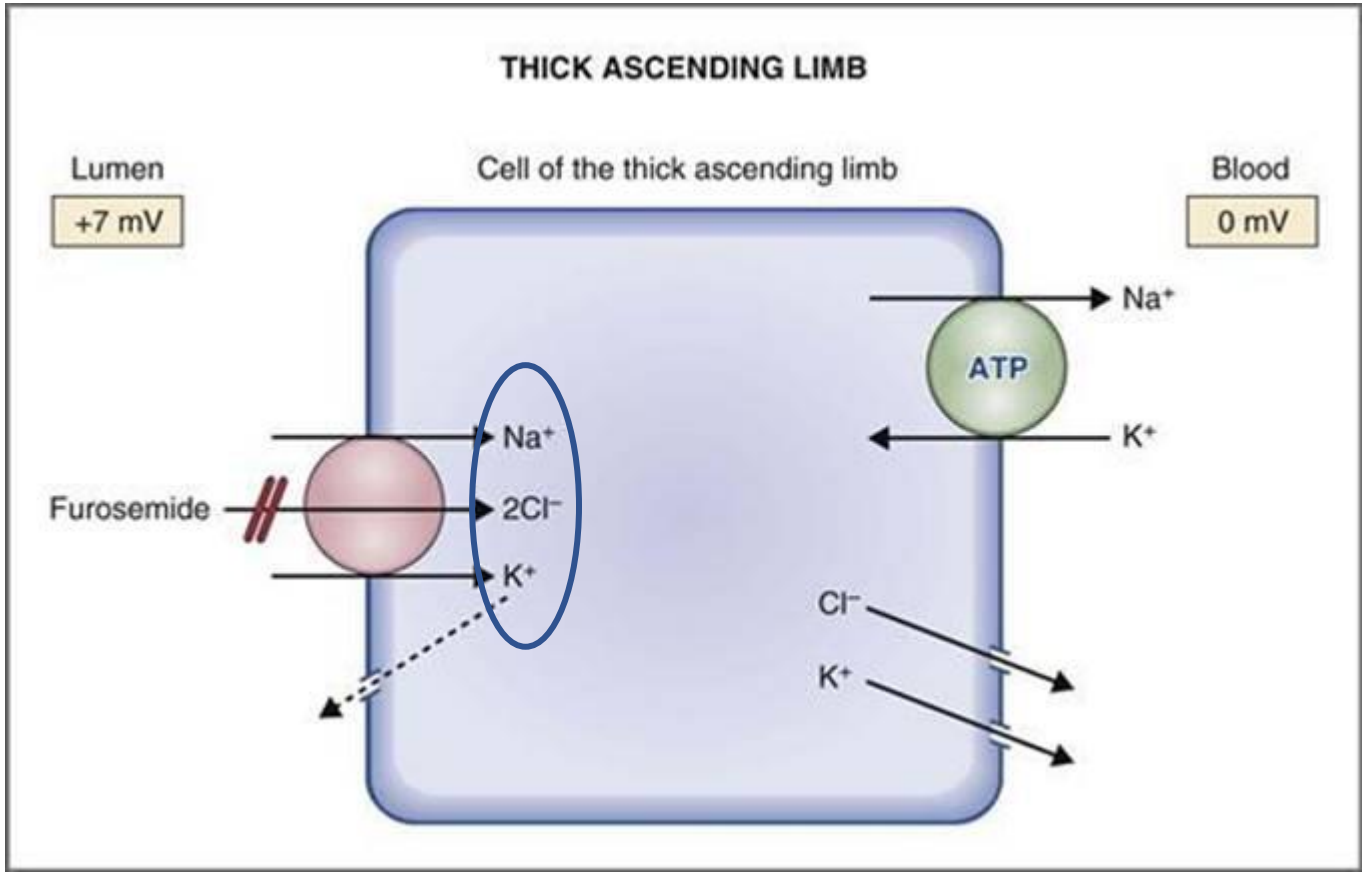
Sodium handling

Thick ascending limb

- Reabsorbs 25% of Na^+
- Load dependent mechanism

Na-K-2Cl^- pump

- Secondary active pump
- All 3 ions into the cell
  - Na^+ out via Na^+-K^+ ATPase
  - Cl^- and K^+ diffuse via basolateral channels following gradients
  - Some K^+ diffuses back into the lumen
- Net effect: slightly more positive charge into the cell
- Maintains lumen positive potential
  - Driving force for Ca^+ and Mg^+

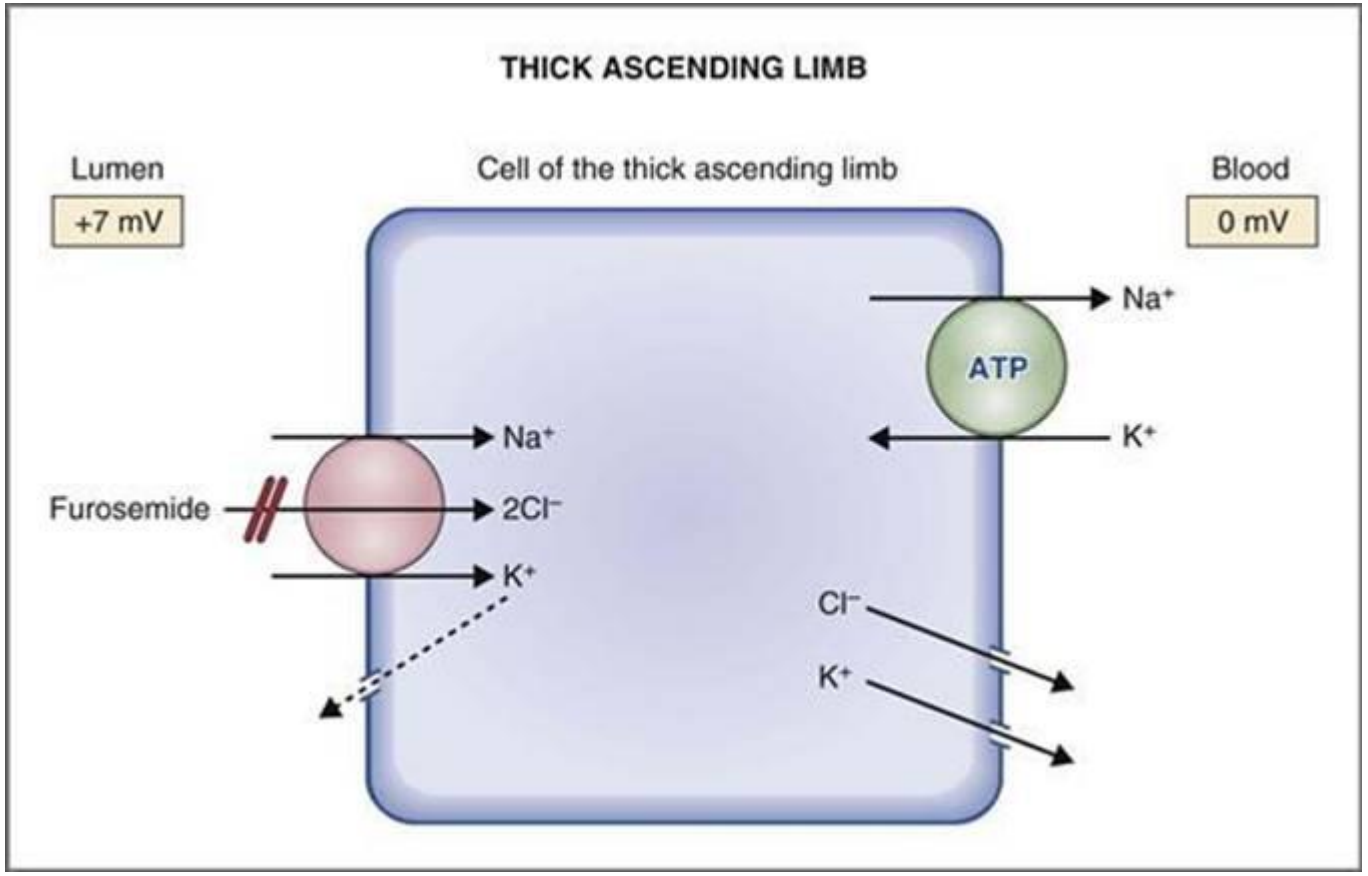


Sodium handling

Na^+-K^+-$2Cl^-$ pump

Loop diuretics and Na^+-K^+-$2Cl^-$ pump

- Attach to Cl^- binding site – all 3 cotransporters stop working
- Maximal dosages – all reabsorption stops



Sodium handling

State-of-the-Art Review

Journal of Veterinary Emergency and Critical Care **18**(1) 2008, pp 26–39
doi: 10.1111/j.1476-4431.2007.00267.x

The pharmacologic spectrum of furosemide

Lisa M. Abbott, DVM, MRCVS and Jan Kovacic, DVM, DACVECC

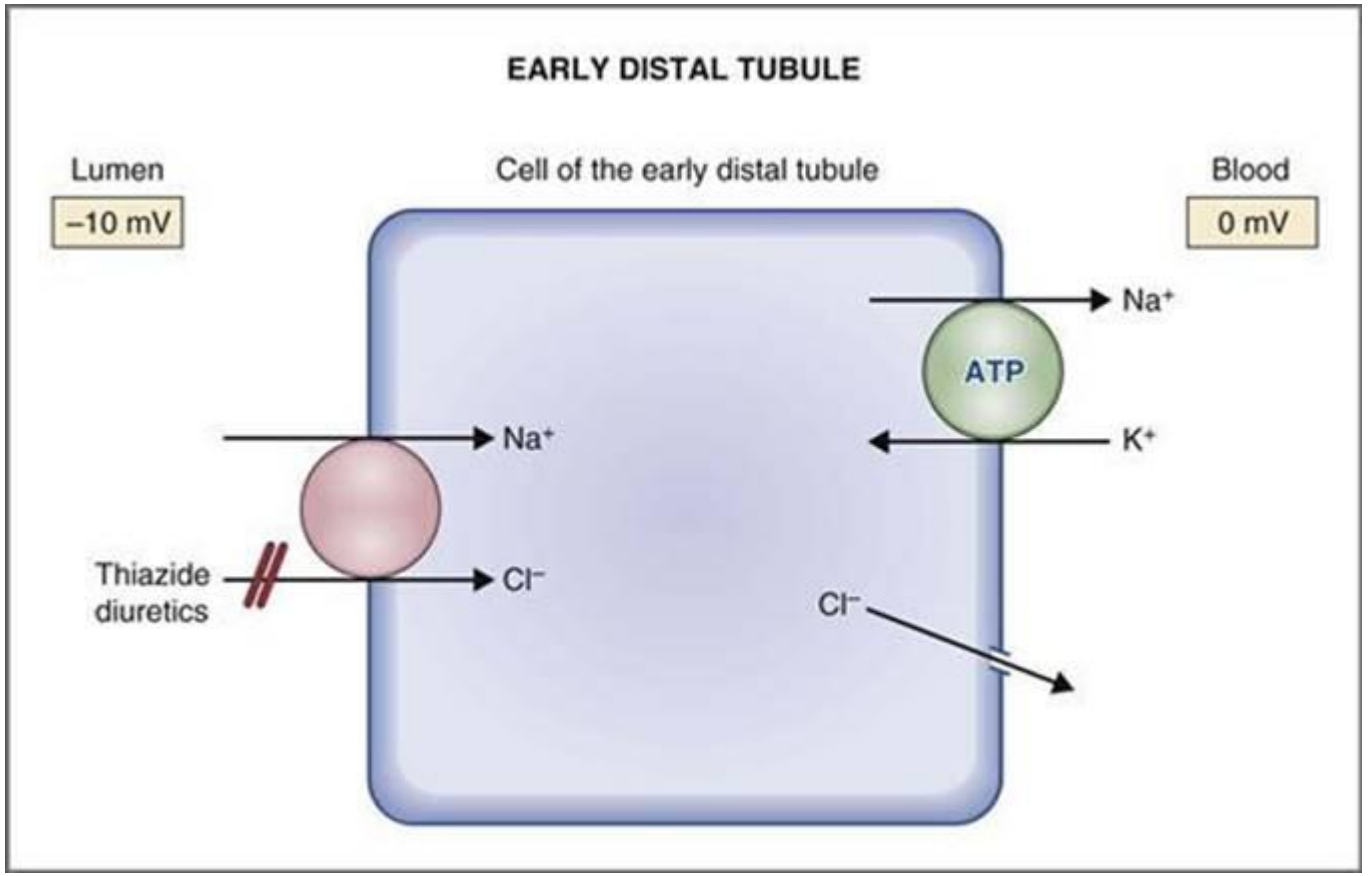
Sodium handling

DCT and collecting duct

- Reabsorbs 8%
- Reabsorption load dependent

Early DCT

- Impermeable to H_2O
- Reabsorbs 5% of Na^+ via NaCl cotransporter
- The energy derives from the Na^+ gradient
- Both ions enter the cell
- Na^+ into blood via Na^+-K^+ ATPase
- Cl^- diffuses via basolateral channel
- Electroneutral pump
- Inhibited by thiazide diuretics (Cl^- site)



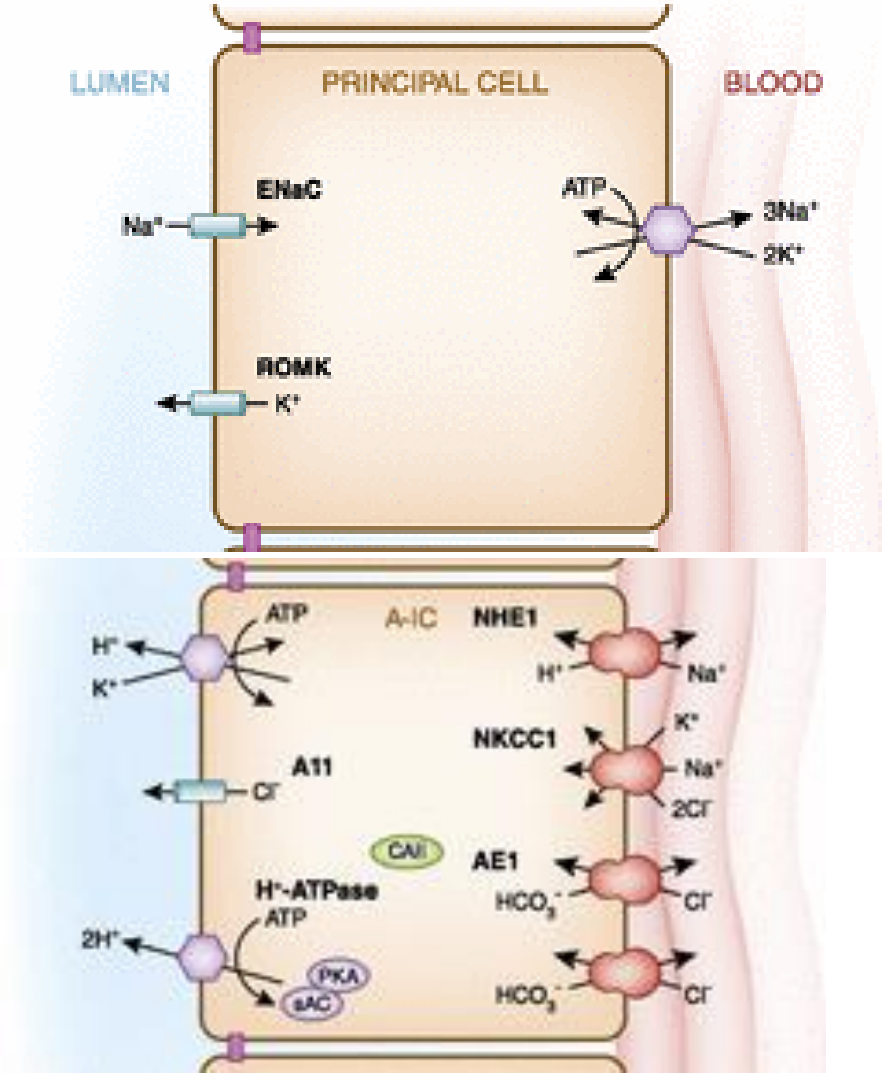
Sodium handling

Late DCT and collecting duct

- Reabsorb 3% of Na^+
- Fine tuning of Na^+ in urine

2 types of cells:

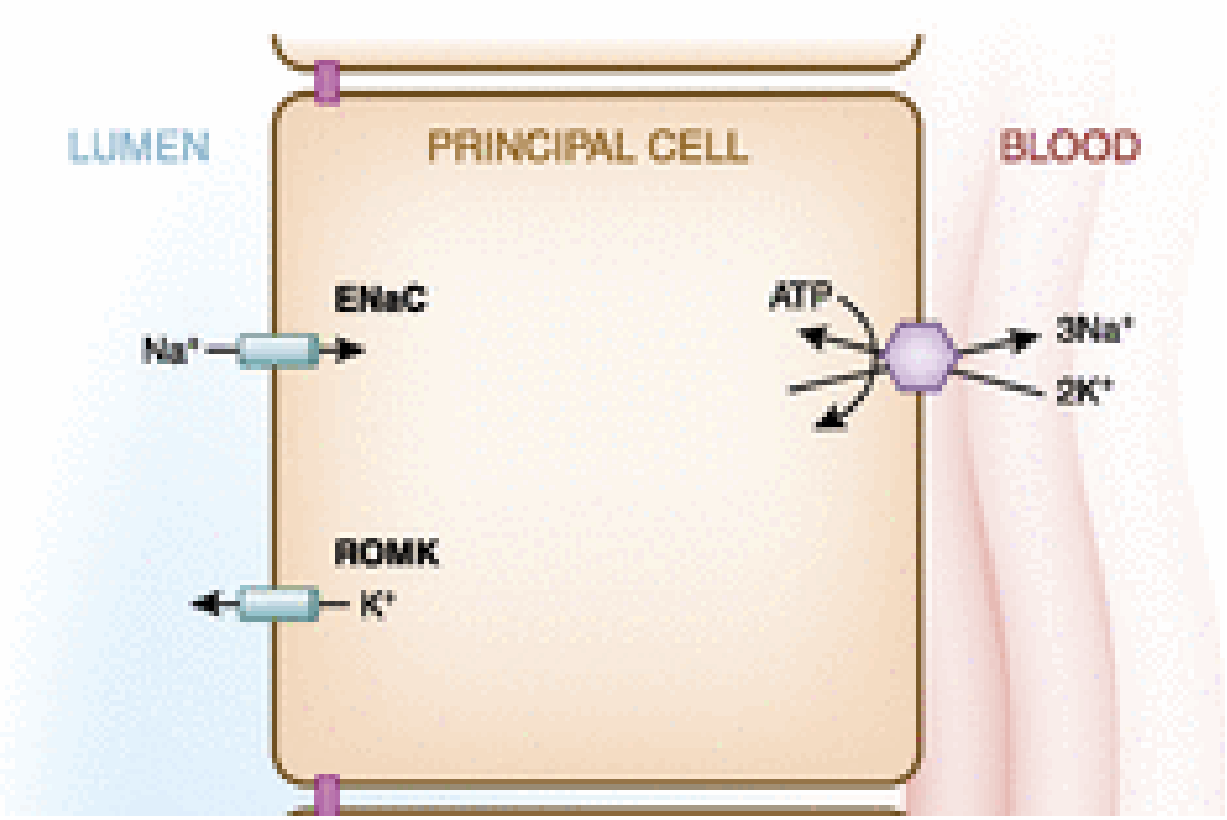
1) Principal cells
2) α-intercalated cells



Sodium handling

1) Principal cells
   - Na^+ reabsorption, K^+ excretion and H_2O reabsorption
   - Aldosterone-responsive
   - ADH-responsive

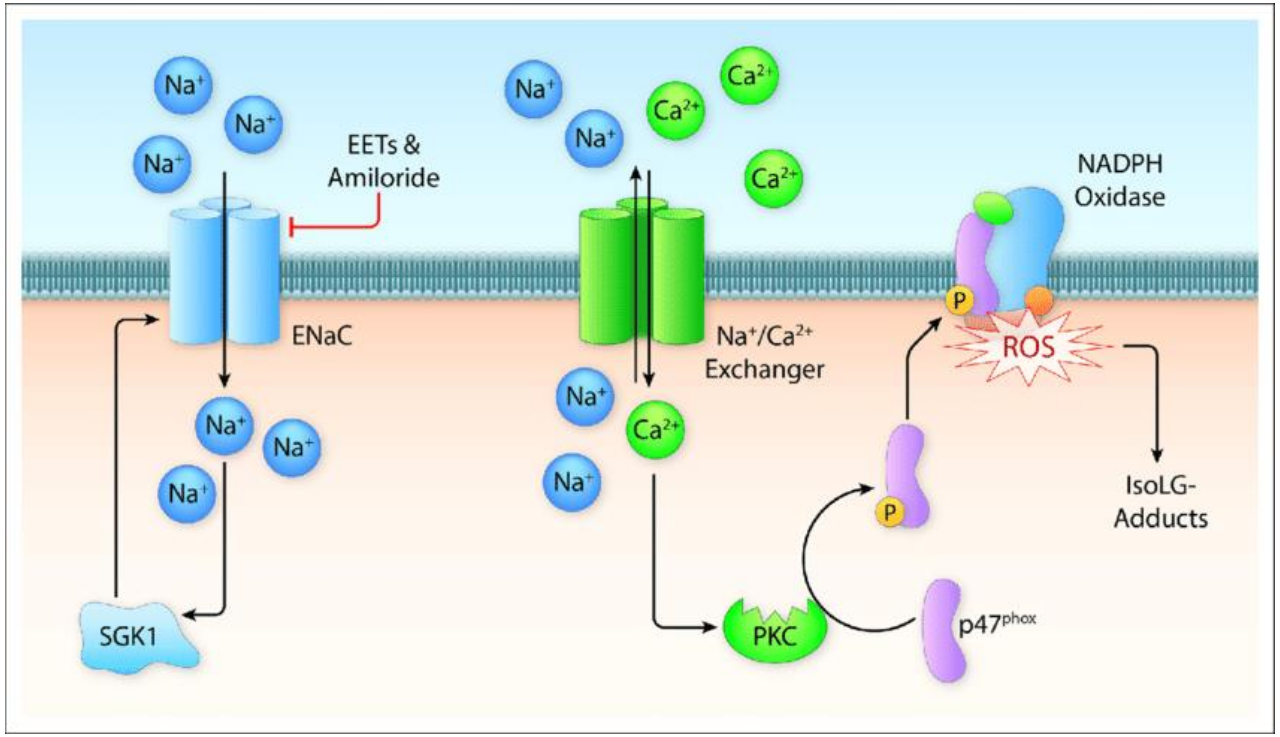
   - ENaCs and ROMK Channels



Sodium handling

Epithelial Na^+ channels (ENaC)

- Also present in colon, skin and lungs
- Action is regulated by aldosterone, steroids and ADH
  - Downregulation of ENaC – Liddle Syndrome
- Na^+ diffuses into cell down its gradient
- Pumped out Na^+-K^+ ATPase
- Cl^- might accompany Na^+ in these segments



Sodium handling

Am J Physiol Renal Physiol. 2009 Nov; 297(5): F1411–F1418.
Published online 2009 Aug 19. doi: 10.1152/ajprenal.00371.2009
PMCID: PMC2781343
PMID: 19692483

Activation of the epithelial Na^+ channel in the collecting duct by vasopressin contributes to water reabsorption

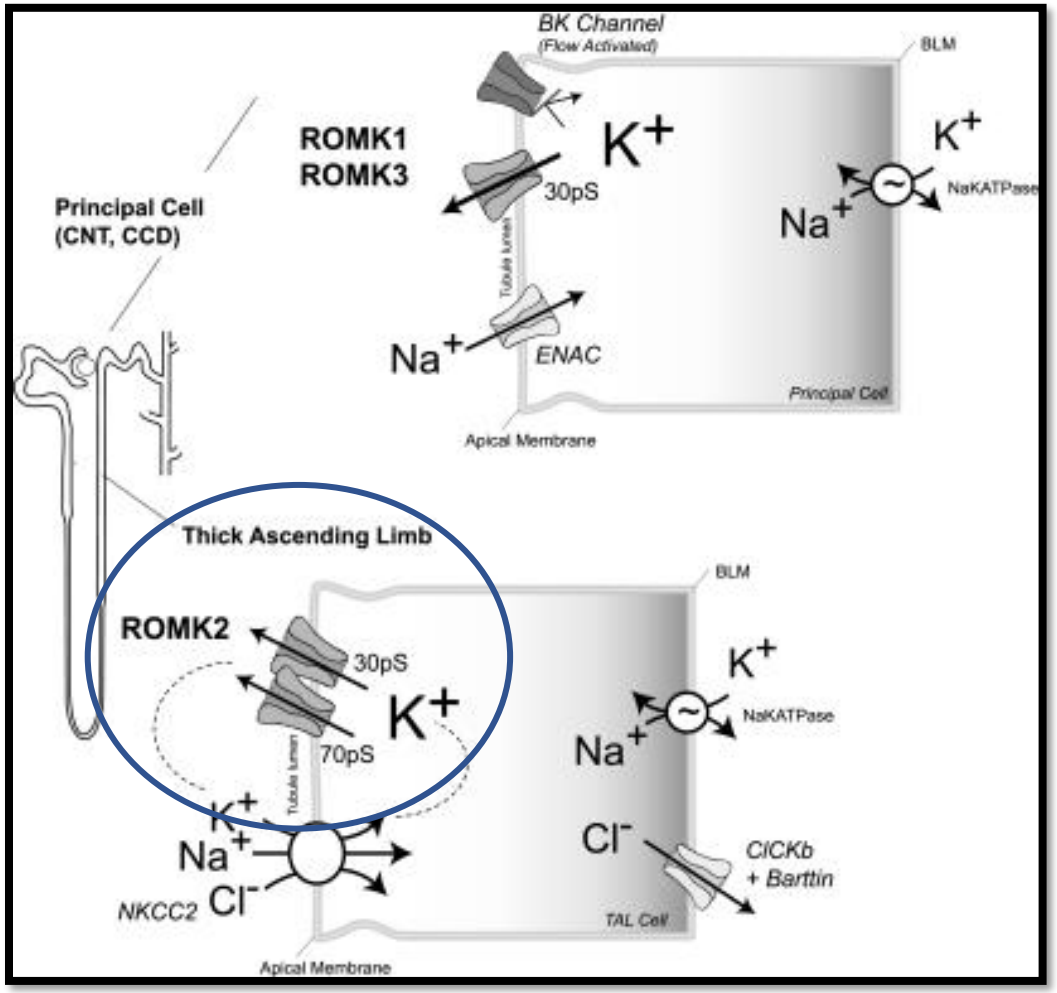
Vladislav Bugaj, Oleh Pochynyuk, and James D. Stockand

- Not only aldosterone, but ADH also stimulates Na^+ reabsorption

Sodium handling

Renal outer medullary K^+ channel (ROMK)

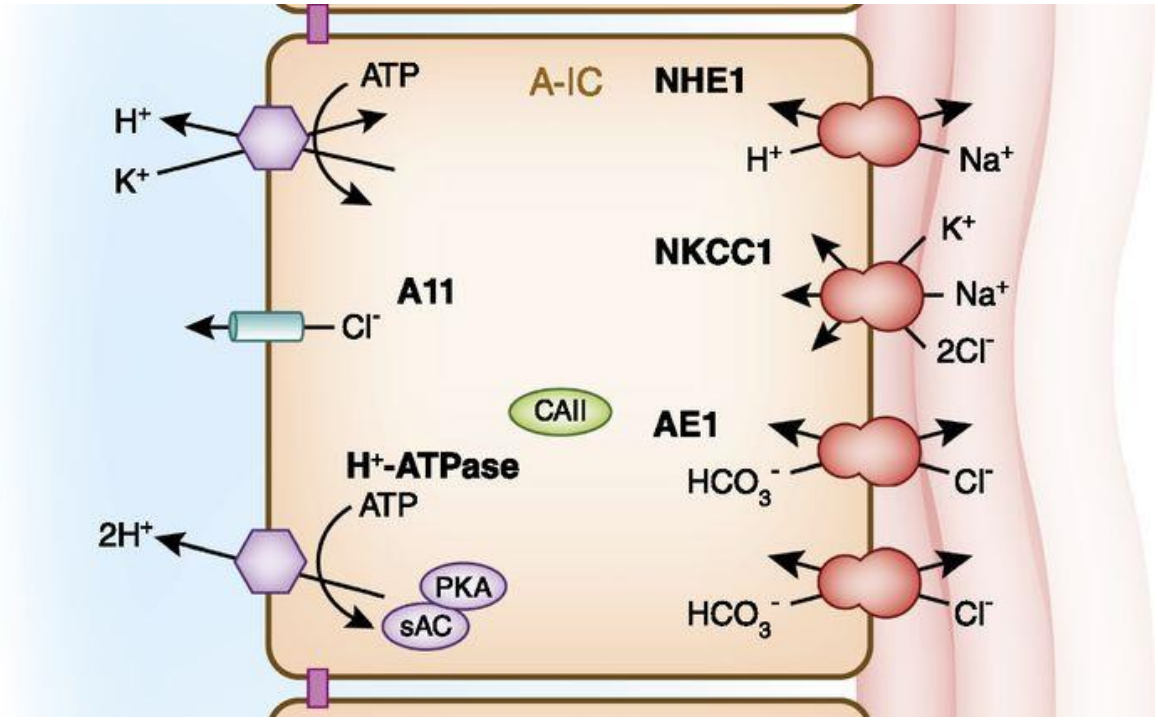
- Predominant and highly regulated K^+ secretory pathway
- Required to safeguard the efficient turnover of the Na^+-K^+-$2Cl^-$



Sodium handling

2) α-intercalated cells:

- K^+ reabsorption and H^+ secretion
- Acid secretion



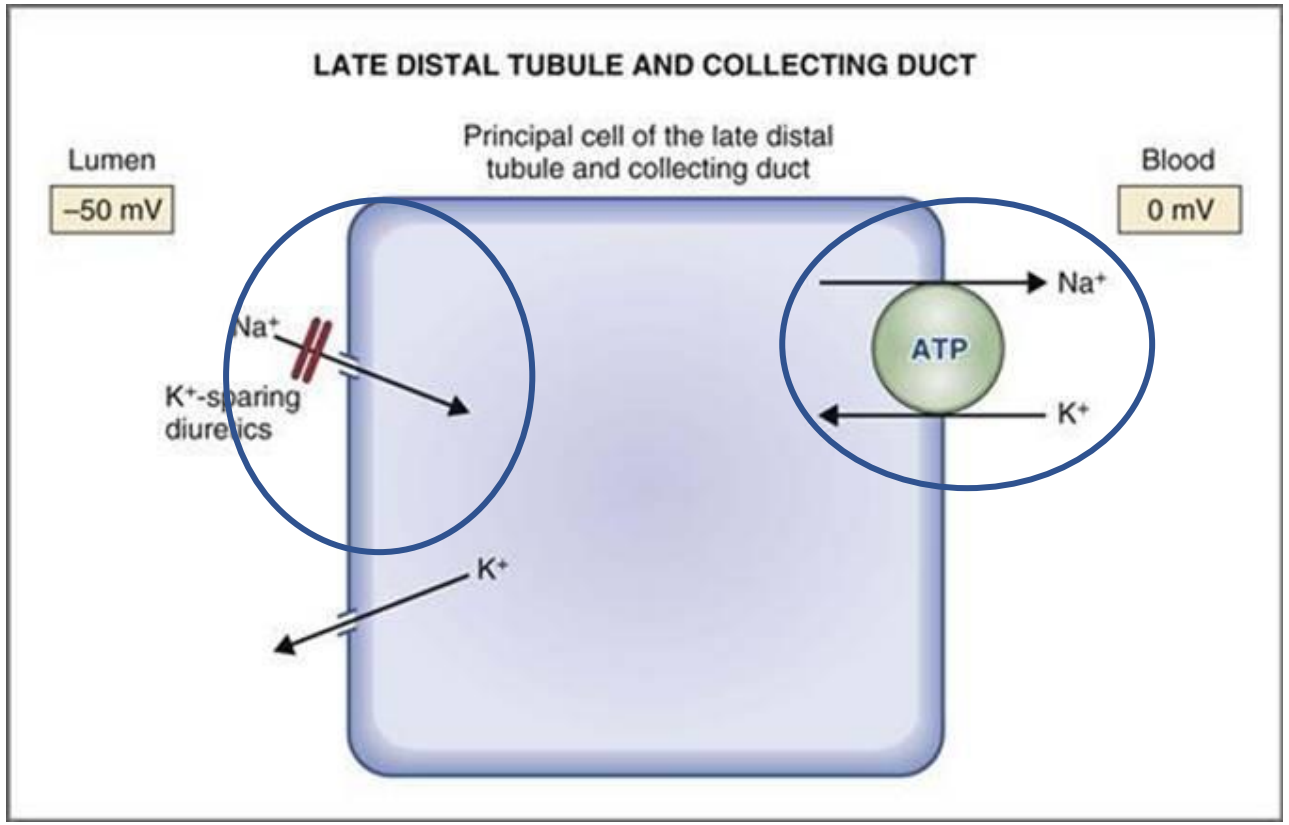
Sodium handling

Aldosterone

- Increases Na^+ reabsorption by inducing more ENaCs along with the Na^+-K^+ ATPase

K^+ sparring diuretics

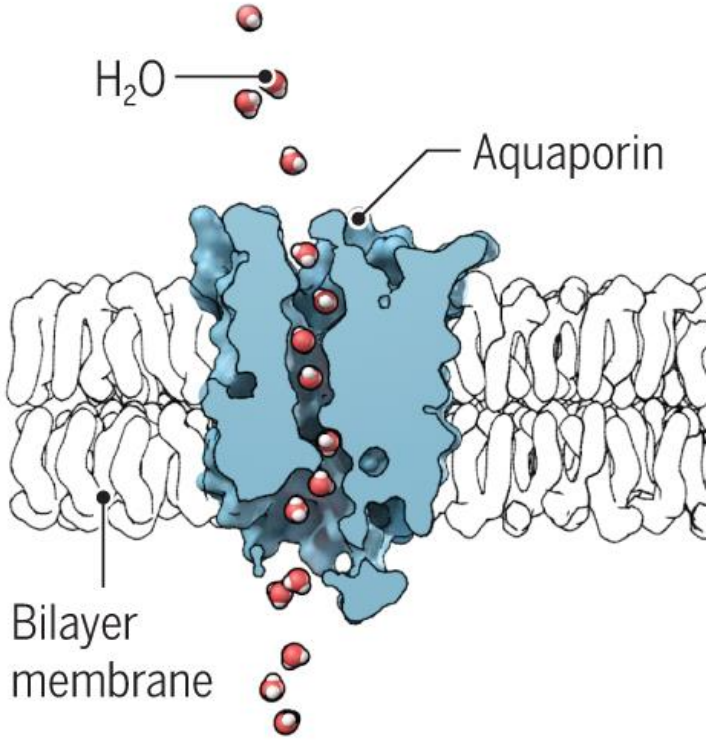
- Spironolactone – prevents aldosterone from entering the nucleus
- Amiloride and triamterene – Bind to the luminal membrane Na^+ channels and inhibit Na^+ reabsorption



Sodium handling

Aquaporins:

- Inserted in the luminal membranes of the principal cells
- In the presence of ADH water is reabsorbed with NaCl



Sodium handling

Segment/Cell Type	Major Functions	Cellular Mechanisms	Hormone Actions	Diuretic Actions
Early Proximal Tubule	Isosmotic reabsorption of solute and water	Na^+-glucose, Na^+-amino acid, Na^+-phosphate cotransport	PTH inhibits Na^+-phosphate cotransport	Osmotic diuretics
		Na^+-H^+ exchange	Angiotensin II stimulates Na^+-H^+ exchange	Carbonic anhydrase inhibitors
Late Proximal Tubule	Isosmotic reabsorption of solute and water	NaCl reabsorption driven by Cl^- gradient	—	Osmotic diuretics
Thick Ascending Limb of the Loop of Henle	Reabsorption of NaCl without water Dilution of tubular fluid Single effect of countercurrent multiplication Reabsorption of Ca^{2+} and Mg^{2+} driven by lumen-positive potential	Na^+-K^+-$2Cl^-$ cotransport	ADH stimulates Na^+-K^+-$2Cl^-$ cotransport	Loop diuretics
Early Distal Tubule	Reabsorption of NaCl without water Dilution of tubular fluid	Na^+-Cl^- cotransport	PTH stimulates Ca^{2+} reabsorption	Thiazide diuretics
Late Distal Tubule and Collecting Ducts (principal cells)	Reabsorption of NaCl	Na^+ channels (ENaC)	Aldosterone stimulates Na^+ reabsorption	K^+-sparing diuretics
	K^+ secretion	K^+ channels	Aldosterone stimulates K^+ secretion	
	Variable water reabsorption	AQP2 water channels	ADH stimulates water reabsorption	
Late Distal Tubule and Collecting Ducts (α-intercalated cells)	Reabsorption of K^+ Secretion of H^+	H^+-K^+ ATPase H^+ ATPase	— Aldosterone simulates H^+ secretion	— K^+-sparing diuretics

Sodium handling

Diseases that affect Na^+ handling

Diabetes insipidus

- Lack of vasopressin
- Lack of renal receptor to the hormone
- Lack of response by the receptors

Final concentration of urine depends on ADH – hyposthenuria hallmark

2 types:

- Central
- Nephrogenic

Sodium handling

1) Central DI

- Complete or partial lack of secretion of ADH

Causes

- Neoplasia
- Trauma
- Inflammatory
- Congenital

2) Nephrogenic DI

- Failure of the kidney to respond to ADH
- Most common type in our patients
- Transient

Causes

- Pyometra – gram negative sepsis
- Hypercalcemia
- Hypokalemia
- Liver failure
- Congenital

Sodium handling

Diagnosis of DI

- PU/PD
- Hyposthenuric urine
- Full blood panel
- UA/Culture

Top 2 differentials

- Cushing's – Measure UPCs or LDDST
- Primary psychogenic polydipsia
  - Usually overhydrated
  - Low Na^+
  - Low osmolality

Sodium handling

Modified H2O deprivation test

- DI patients not be able to concentrate urine even under moderate dehydration
- USG raises over time – not DI

Desmopressin Acetate trial

- Measure baseline USG over a few days
- Begin desmopressin trail
- USG will steadily increase if CDI
- If no increase at all NDI or psychogenic polydipsia

Sodium handling

Syndrome of Inappropriate antidiuretic hormone

- Excess of ADH – free water excess
- Na^+ is lost to urine despite hyponatremia
  - Normovolemia inhibits aldosterone and renin secretion

Causes

- Head trauma
- Brain tumors
- Pulmonary tumors
- Aspergillosis
- Mechanical ventilation
- Drugs – opioids, chemo drugs

Sodium handling

Diagnosis

- Hyponatremia
- Hypoosmolality
- Urine osmolality > 150 mOsm/kg
- Urine Na^+ > 20 mEq/L (increased Na wasting)
- Plasma ADH unreliable

Treatment

- Hypertonic saline in emergencies vs slow correction of Na^+
- Demeclocycline inhibits action of ADH

Sodium handling

Renal response to Hypernatremia

Infusions of 5% NaCl solutions

- Tubular reabsorption of Na^+ per unit filtrate volume positively correlated with plasma Na^+ despite hypernatremia
- The proportions of Na^+ reabsorbed were inappropriate
  - Na^+ concentration in the reabsorbate was in excess of that in contemporary ultrafiltrate

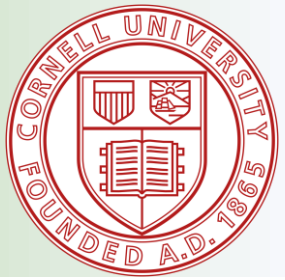
Glomerulotubular balance **holds** when the filtered load of Na^+ is increased by an increment in Na^+ as well as GFR

AMERICAN JOURNAL OF PHYSIOLOGY
Vol. 231, No. 2, August 1976. *Printed in U.S.A.*

Renal tubular reabsorptive response to hypernatremia

EMANUEL H. BRESLER, KRISTIN T. NIELSEN, M. CLINTON MILLER III,
AND MARTHA R. STROUD
Medical Research Division, Veterans Administration Hospital and Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana 70146; and Department of Biometry, Medical University of South Carolina, Charleston, South Carolina 29401

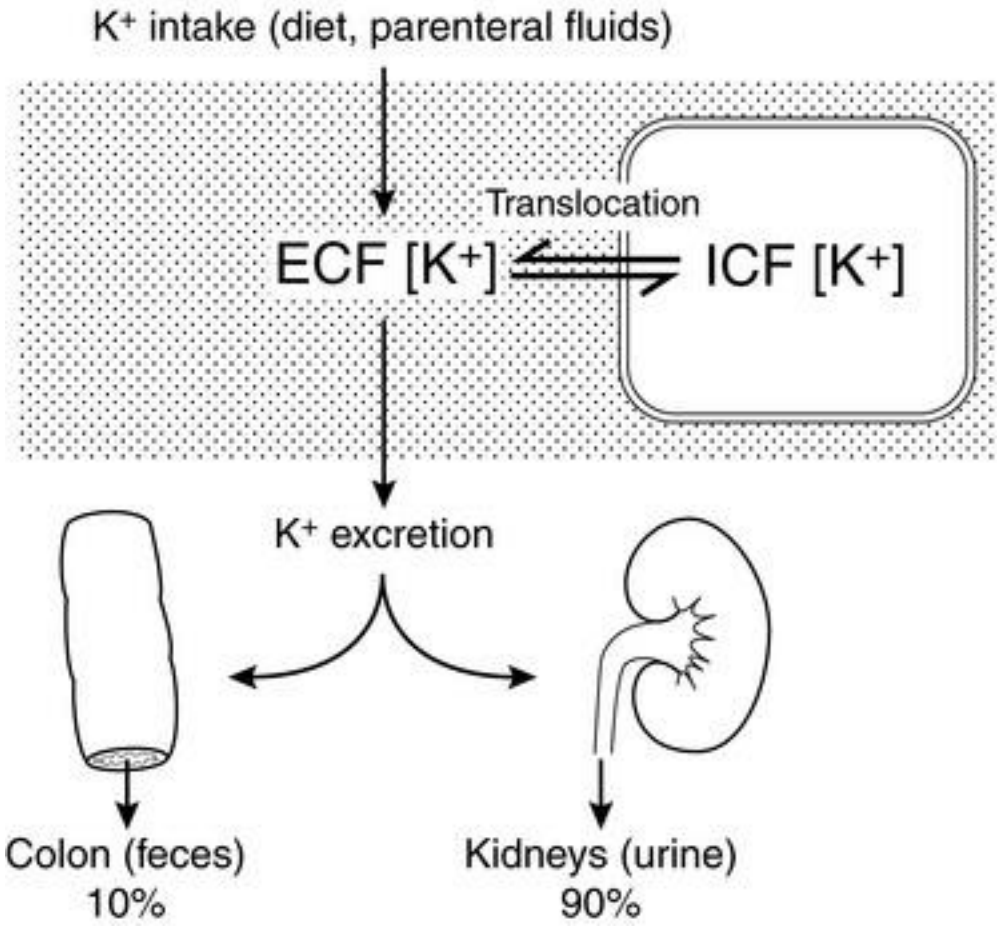
Potassium handling



Potassium handling

Potassium homeostasis

- Most of K^+ in intracellular fluid (98%)
- Intracell K^+ 150 mEq/L
  - Vs 4.5 mEq/L



Potassium handling

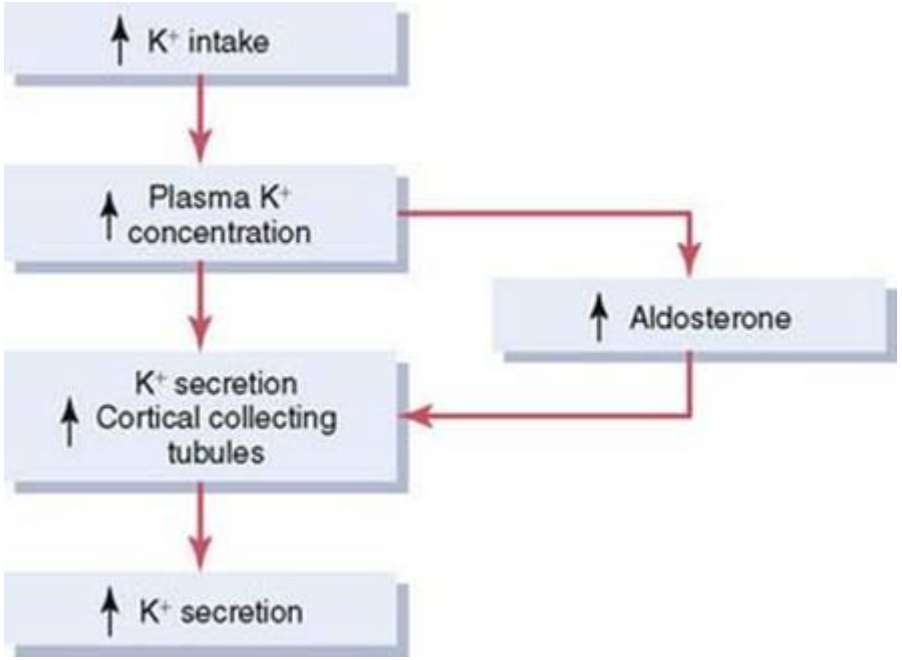
Regulation of kalemia

Aldosterone

- Increases Na^+ reabsorption, K^+ secretion, H^+ secretion

Regulation of aldosterone secretion

- Changes in volume and RAAS activation
- K^+ concentration
  - Increase in K^+ stimulate opening of Ca^+ channels in adrenal glands that generate more aldosterone

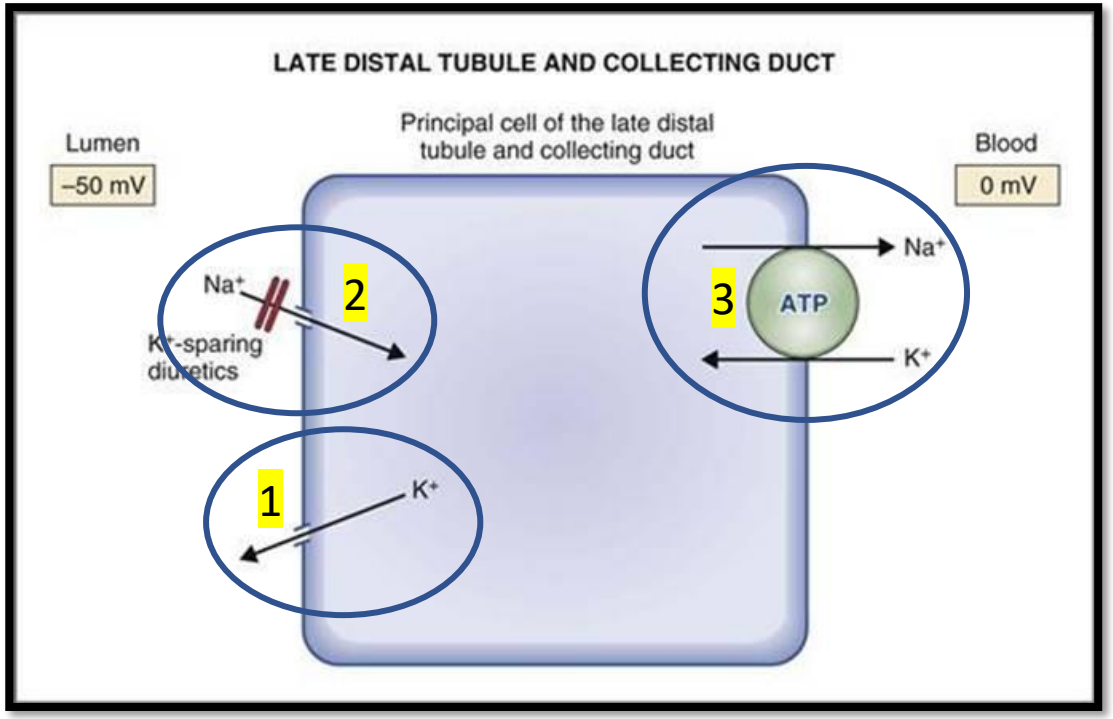


Potassium handling

Aldosterone

1. Increases K^+ secretion by principal cells ($ROMK^+$)
2. Increases Na^+ reabsorption via new ENaCs
3. Induced Na^+-K^+ ATPase

- Increases intracellular Na^+ for Na^+-K^+ ATPase to use
  - As more Na^+ is pumped out of the cell, more K^+ comes into it
  - Raising intracellular K^+, which increases driving force for K^+
- Increases the number of $ROMK^+$



Potassium handling

Diuretics and K^+

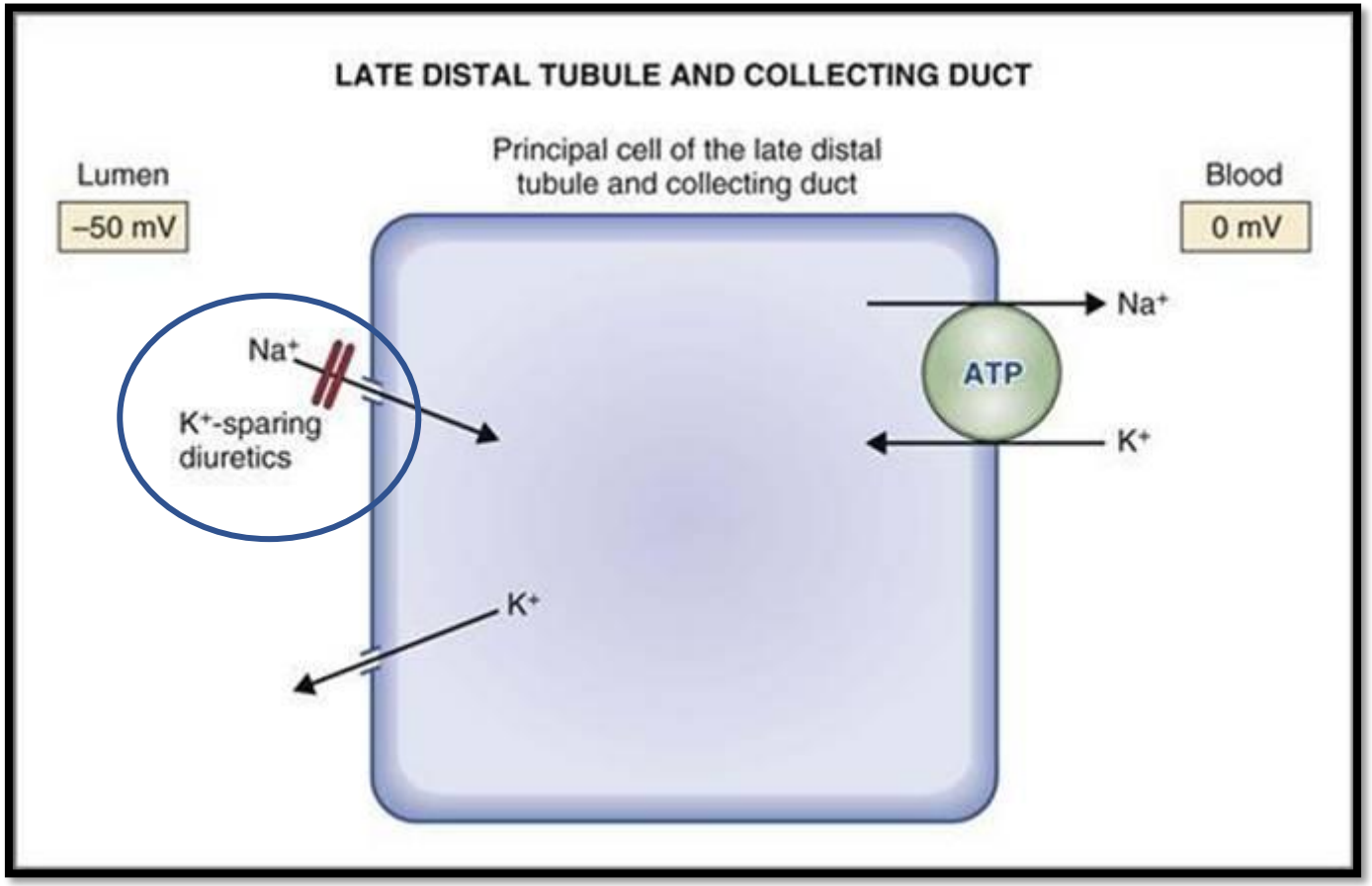
Loop diuretics and thiazides

- Inhibit Na^+ and K^+ reabsorption upstream to the site of K^+ secretion thereby delivering more Na^+ to principal cells
- More Na^+ enters the cells, more Na^+ is extruded via Na^+-K^+ ATPase
- More K^+ is pumped into the cells, higher driving force for secretion
- The increase in flow rate keeps luminal gradient active by diluting luminal K^+
- Loop diuretics also inhibit K^+ absorption via pump

Potassium handling

K^+ sparing diuretics

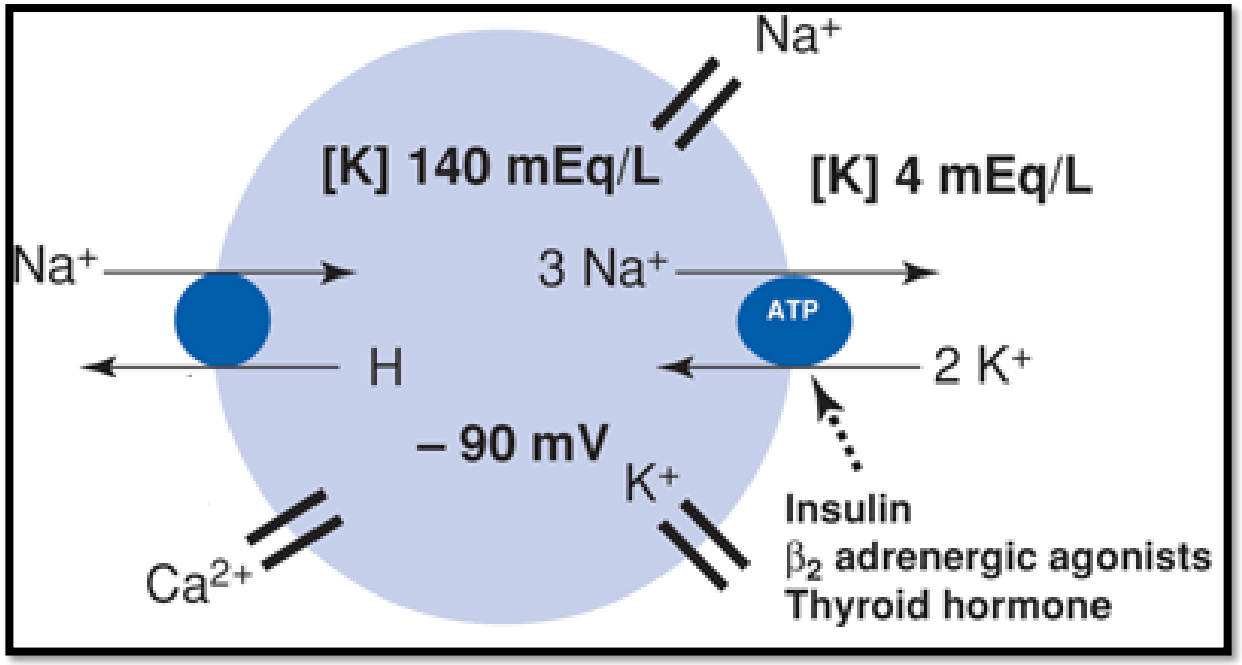
- They do not cause kaliuresis
- Inhibit all actions of aldosterone on principal cells – inhibit K^+ secretion



Potassium handling

Additional regulation of kalemia

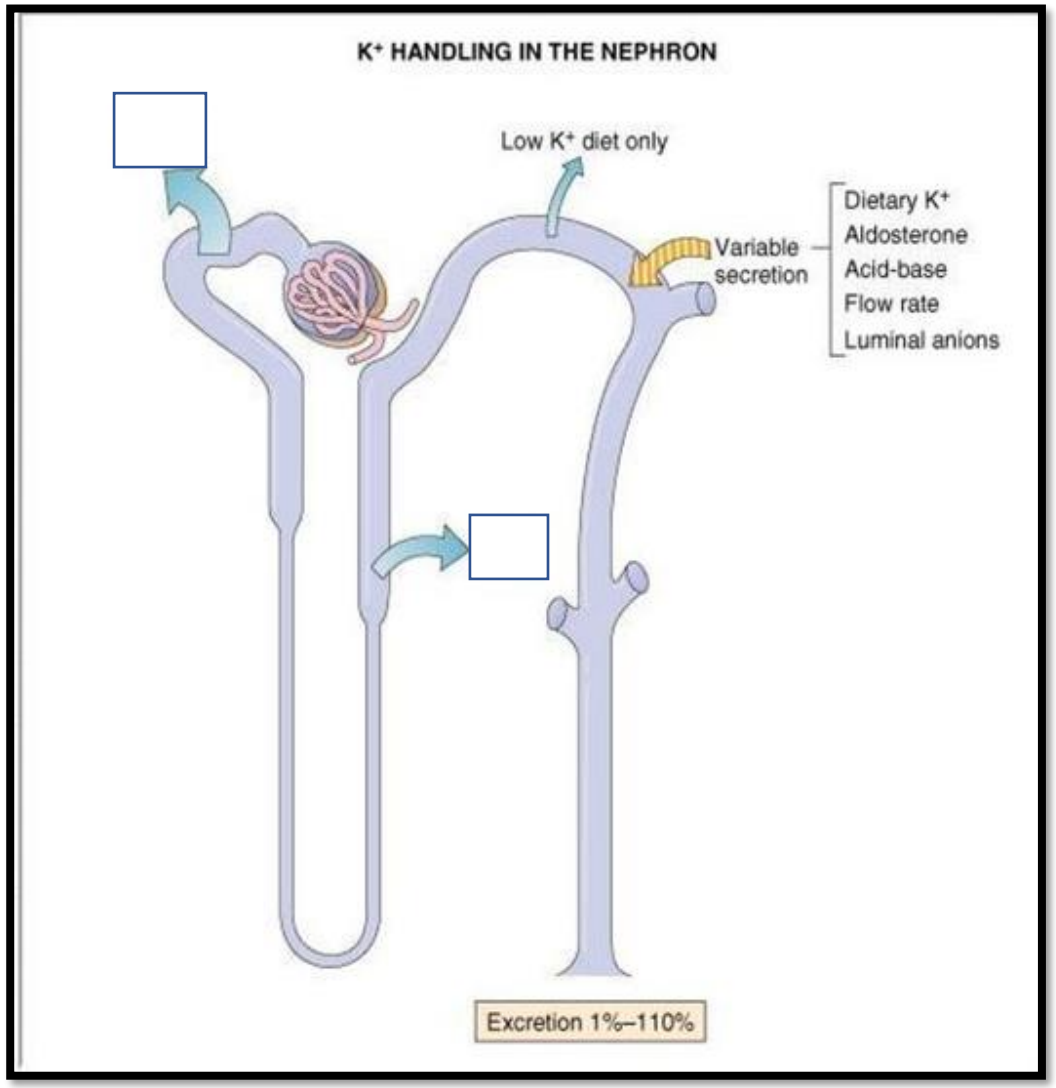
- Insulin – via Na^+-K^+
- Acid-base status – alkalemia causes exchange between H^+ and K^+
- β-adrenergic – increasing Na^+-K^+
- α-adrenergic agonism – K^+ out of the cell
- Osmolarity – increases in osmolarity cause K^+ out of the cell – as water leaves the cells it drags K^+ with it



Potassium handling

Renal regulation of potassium

Fill in the blanks



Potassium handling

Renal regulation of potassium

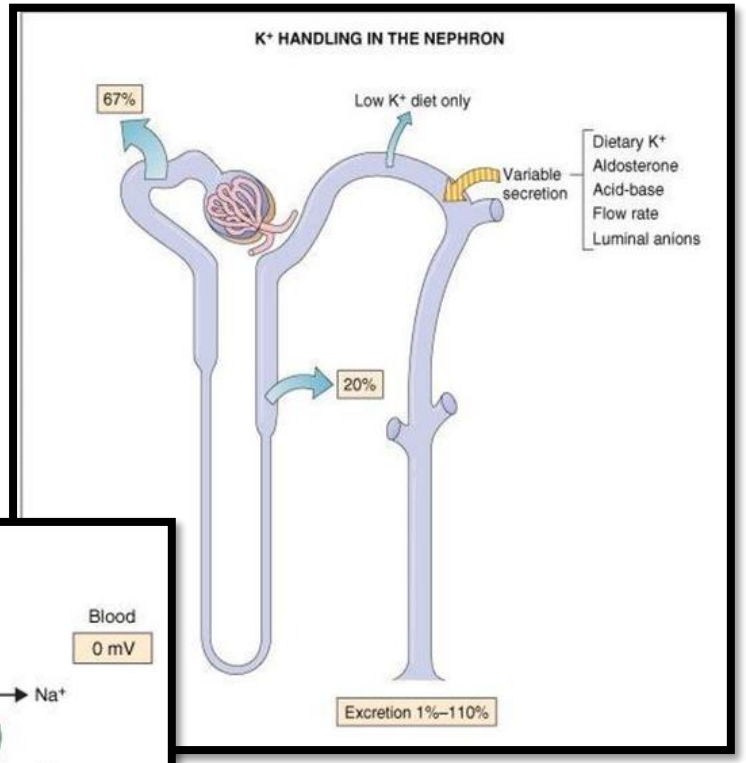
- Urinary excretion of K^+ equals dietary K^+
- K^+ is freely filtered, reabsorbed and secreted

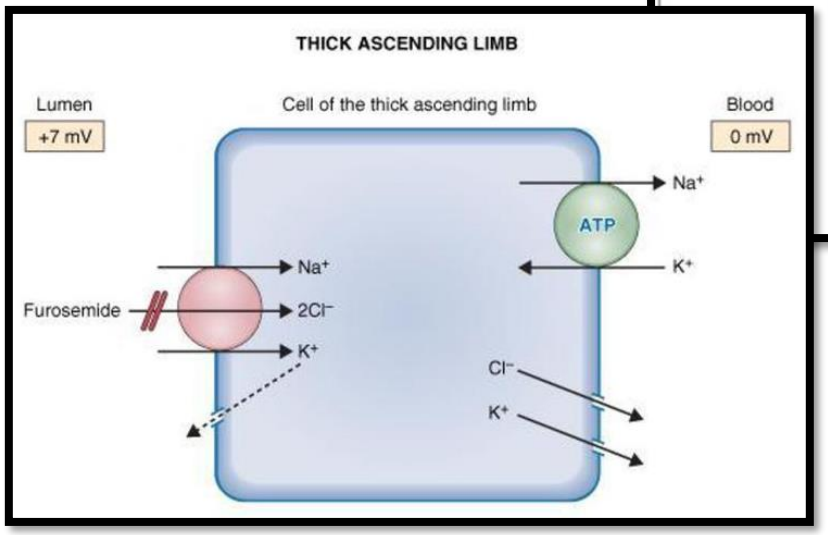
PCT

- Reabsorbs 67%
- Mainly by solvent drag (Na^+)

Thick ascending LOH

- Reabsorbs 20% Na^+-K^+-$2Cl^-$
- Paracellular reabsorption

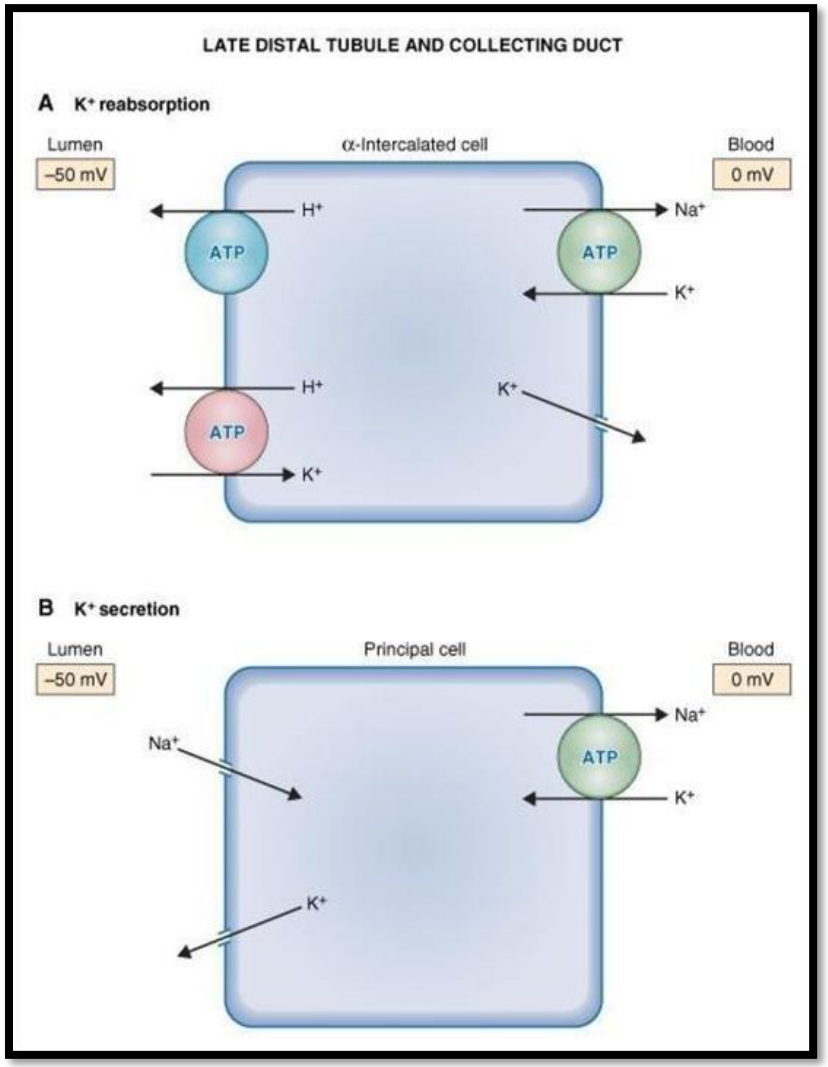




Potassium handling

DCT and CD

- Fine tuning of K^+
- α-intercalated cells – reabsorb K^+ when hypokalemia
  - Via H^+-K^+ ATPase in luminal membrane
  - Urinary excretion can go as low as 1%
- Principal cells - Normal or High K^+ - increase excretion
  - Via ROMK$^+$
  - Excretion can be as high as 110%



Potassium handling

Renal response to hyperkalemia

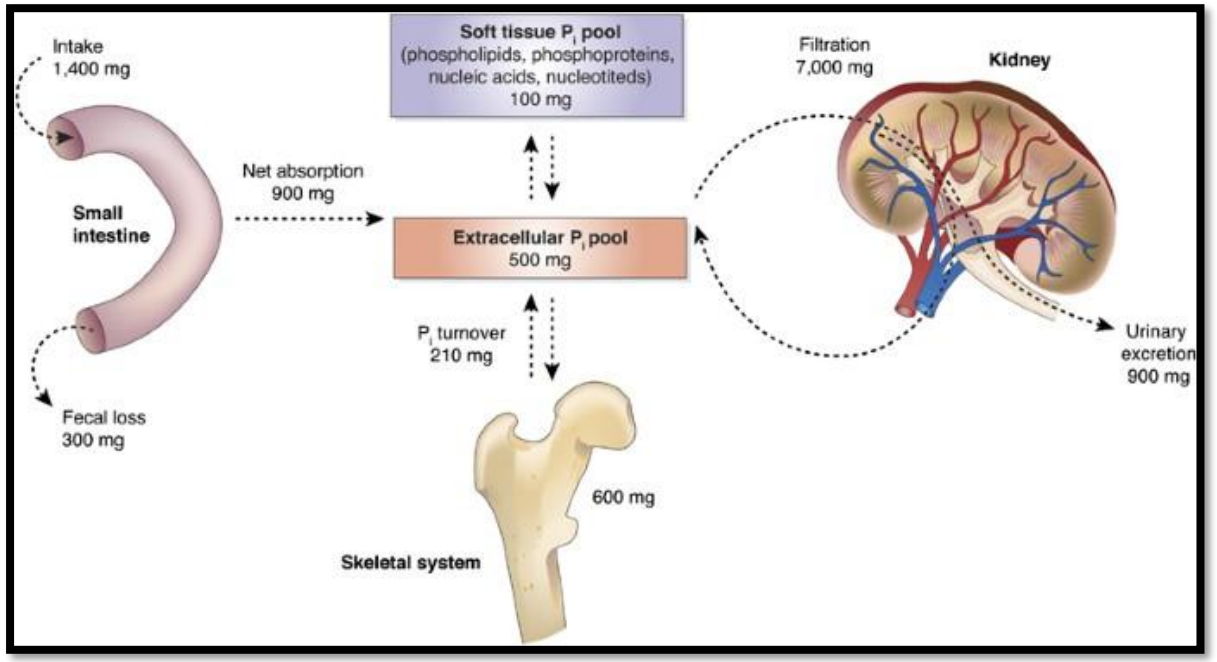
- Na^+-K^+-$2Cl^-$ pump continue to reabsorb K^+
- Increased K^+ presented to tubular cells
- Decreased gradient for K^+ excretion

Phosphate handling

Phosphate handling

Phosphate homeostasis

- P^+ primarily localized in bone matrix (85%)
- Remainder between ICF (15%) and ECF (<0.5%)
- 90% of P^+ is not bound to plasma proteins – filtered across glomerulus



Phosphate handling

Regulation of Phosphatemia

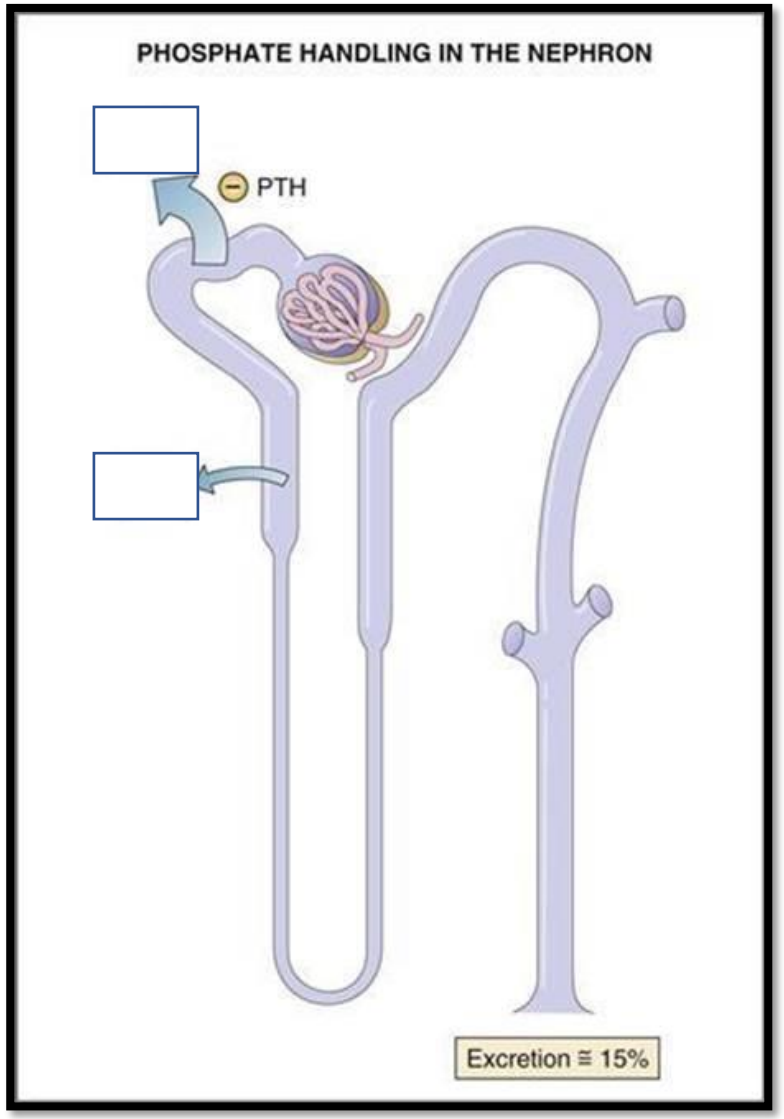
- PTH regulates P^+ reabsorption
  - Binds to its receptor on basolateral membrane of Proximal tubule
  - Inhibits Na^+- P^+ cotransport
  - Causes phosphaturia

- GH increases P^+ reabsorption by PCT
- Insulin and thyroxine also increase reabsorption
- Calcitonin and ANP inhibit reabsorption

Phosphate handling

Renal handling of P^+

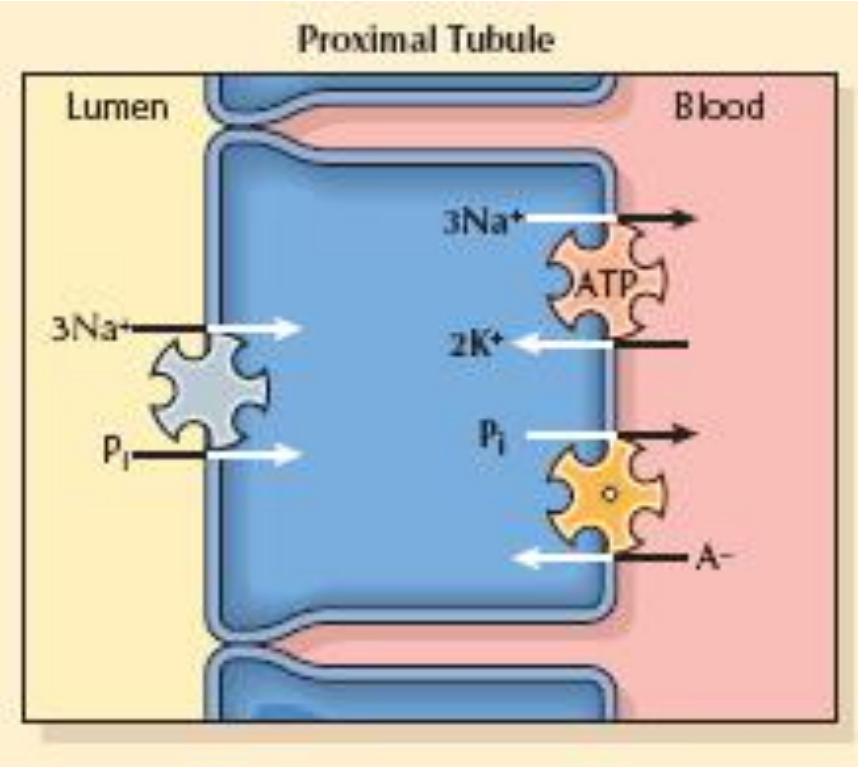
Fill in the blanks



Phosphate handling

Renal handling of P^+

- PCT reabsorbs 70%
  - Proximal straight tubule reabsorbs 15%
- Via Type II Na^+-P^+ cotransporter
- Pumps that reabsorb P^+ have a max capacity (Tm)
- Non-reabsorbed P^+ serves as urinary buffer

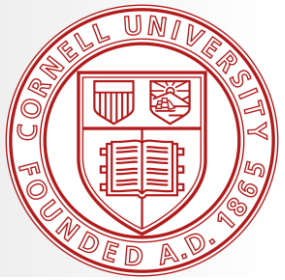


Phosphate handling

Why does kidney damage cause hyperphosphatemia?

- Decreased GFR leads to decrease in filtered P^+ loads

Calcium handling



Calcium handling

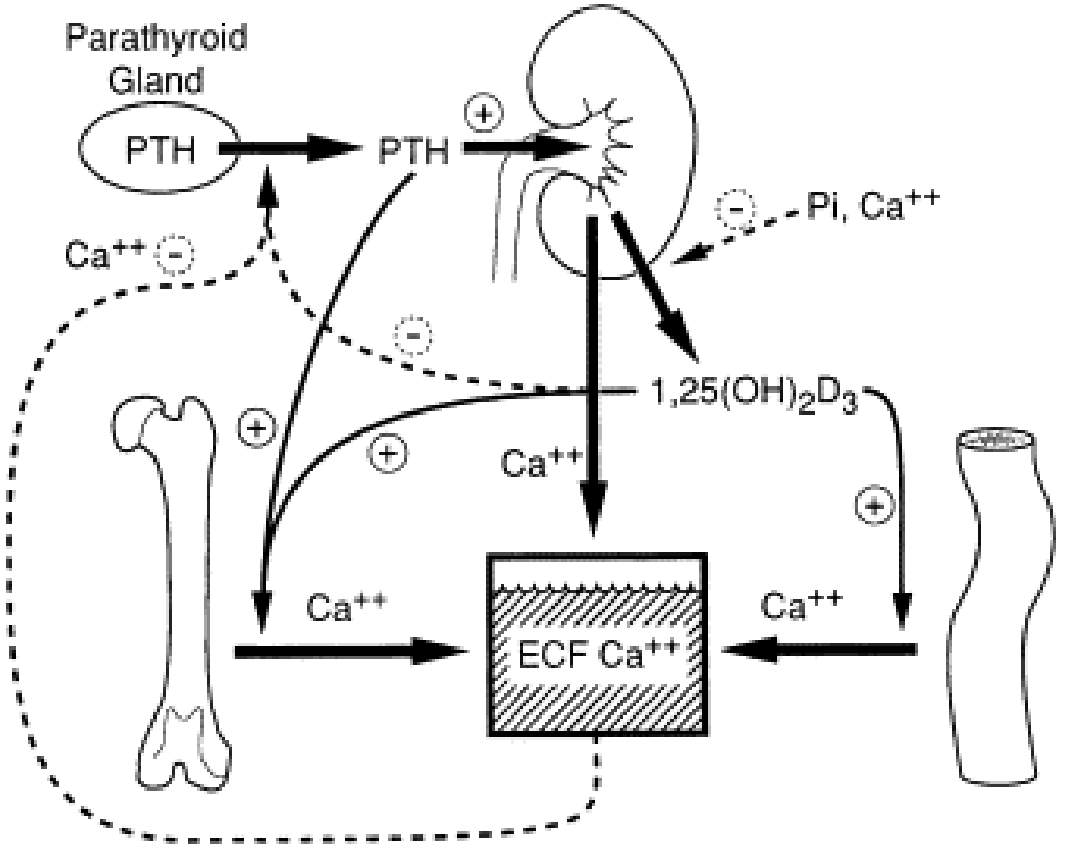
Calcium homeostasis

PTH responsible for minute-to-minute regulation

Calcitriol controls day-to-day regulation

- Target organs:
  - Intestine
  - Kidney
  - Bone

- 99% of Ca^{+} in bone
- Remaining 1% between ECF and ICF
  - 40% of plasma Ca^{+} protein bound
  - 10% bound to other ions (P^{+} and citrate)
  - 50% free (ionized)



Calcium handling

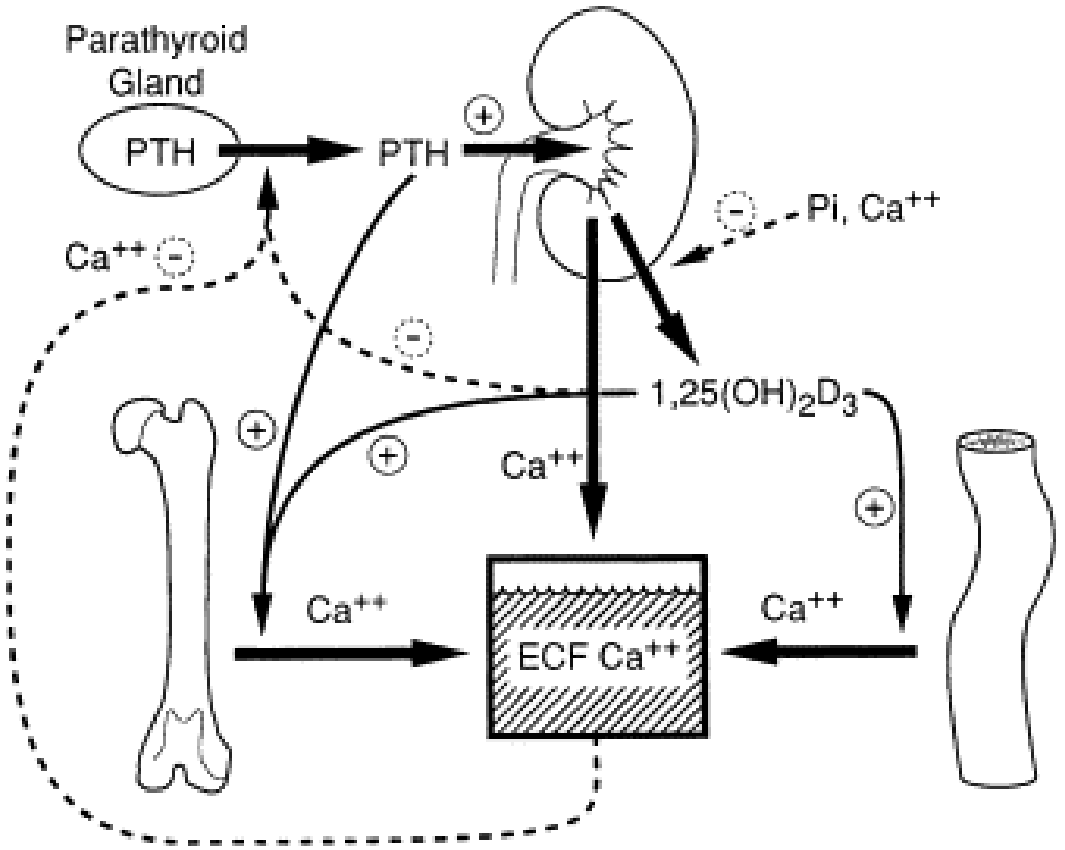
Regulation of Calcemia

PTH

- Released during hypocalcemia
- Increase iCa^{+}
  - Mobilizing Ca^{+} from bone
  - Increase Ca^{+} reabsorption
  - Increase calcitriol synthesis

Calcitriol

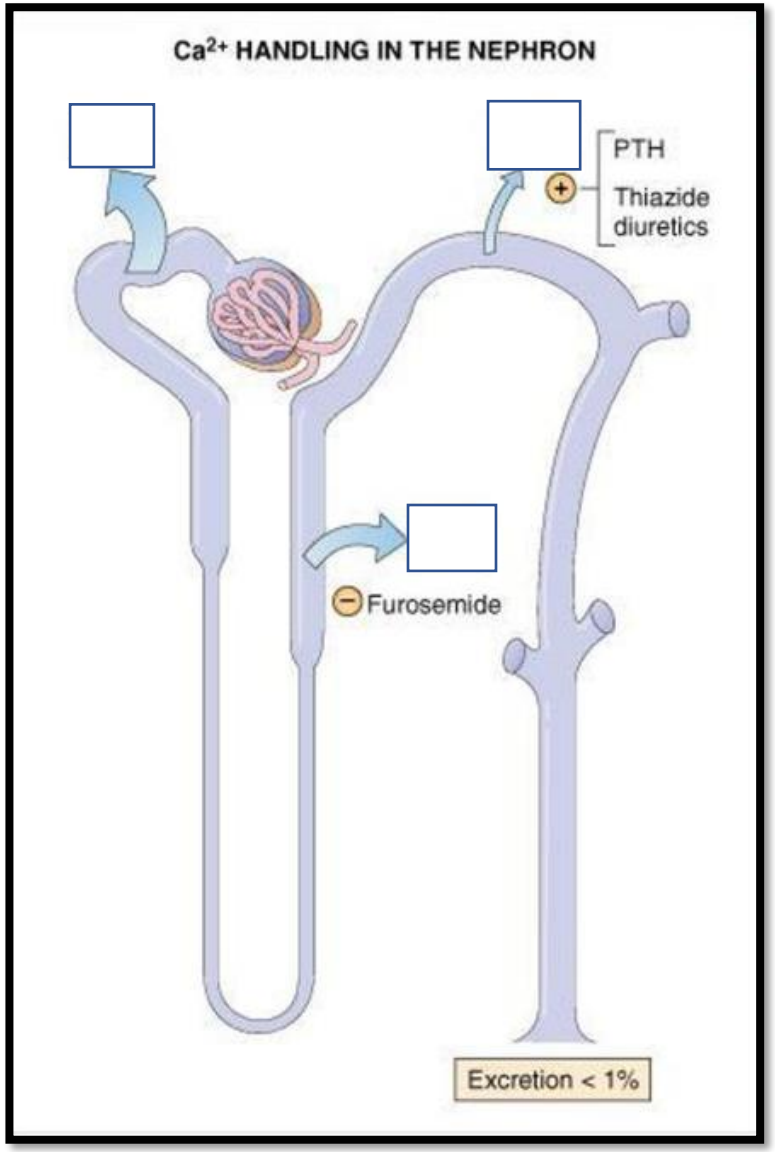
- Increase intestinal absorption
- Inhibits PTH and calcitriol synthesis



Calcium handling

Renal handling of Ca+

Fill in the blanks



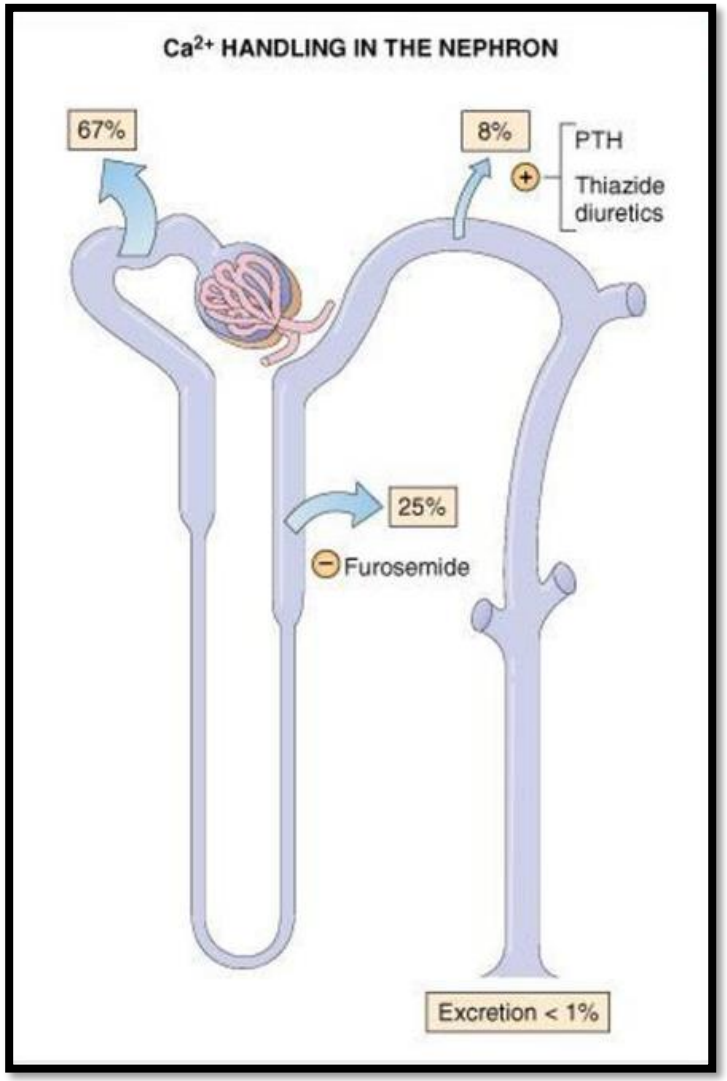
Calcium handling

Renal handling of Ca+

- 99% of Ca^+ is reabsorbed
  - Tightly coupled to Na^+ reabsorption in PCT and Loop of Henle
  - In DCT reabsorption is not coupled with Na^+

PCT

- Ca^+ parallels Na^+ reabsorption
- 67% reabsorbed – coupled to Na^+
- If Na^+ absorption is inhibited, Ca^+ is too

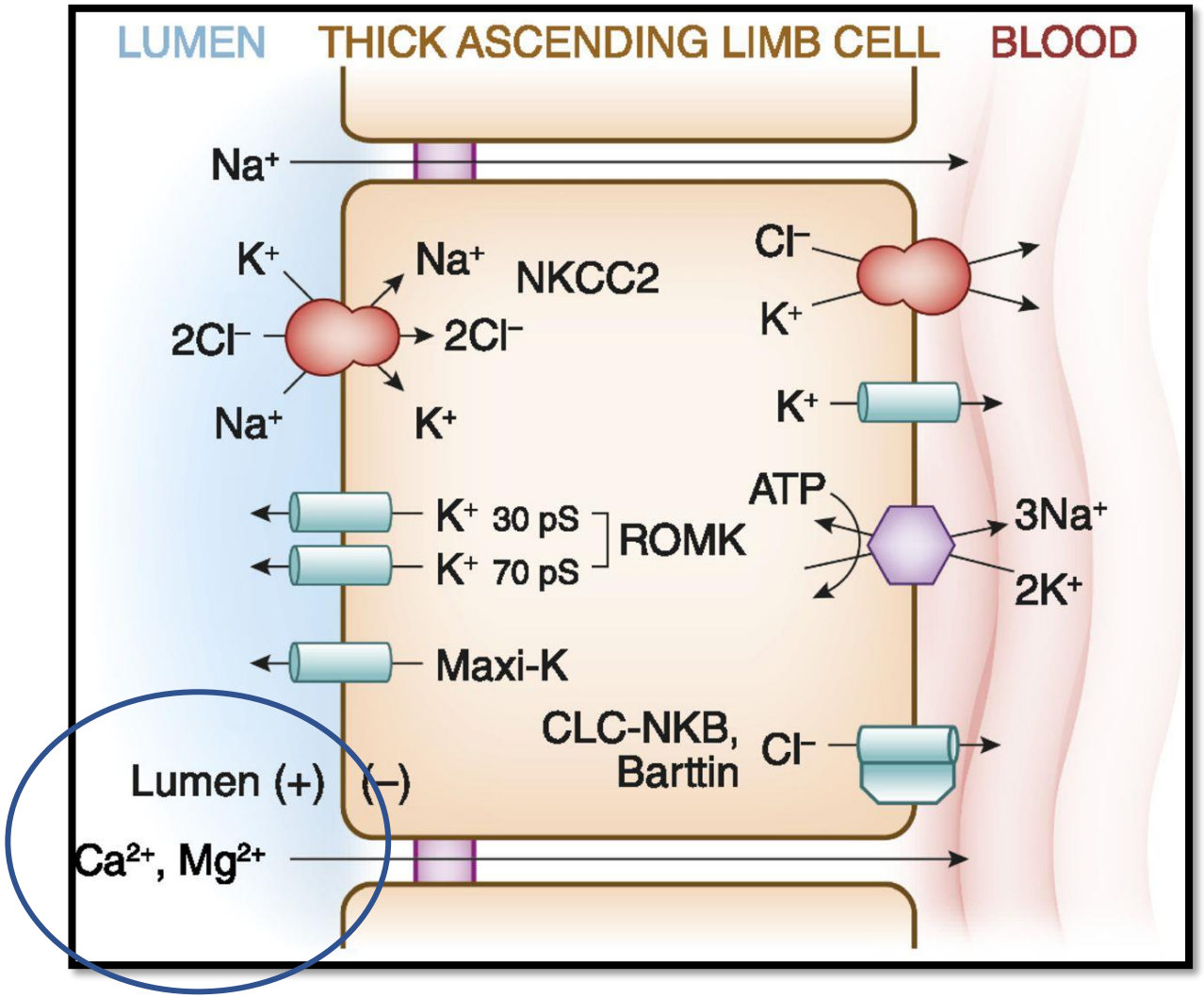


Calcium handling

Thick ascending limb

- 25% reabsorbed
- Paracellular route
- Depends on lumen positive potential (Na^+-K^+-$2Cl^-$)
- Drives reabsorption of divalent cations

- Loop diuretics inhibit Ca^+ reabsorption



Calcium handling

Distal tubule

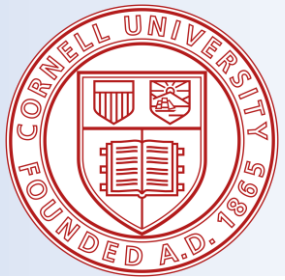
- 8% of Ca^{+}
- Site of regulation of Ca^{+} reabsorption
- Ca^{+} reabsorption not coupled with Na^{+}
- Site of action of PTH

Calcium handling

Treating hypercalcemia

1. Fluid therapy: dilutes Ca^+
   - Hypercalcemia induced nephrogenic DI
   - 0.9% NaCl – Ca^+ free and promotes Ca^+ loss in urine
     - Escape phenomenom leads to decreased Ca^+ reabsorption
   - LRS contains physiologic levels of Ca^+ and less acidifying than NaCl
2. Diuretics enhance Ca^+ loss by abolishing Na^+ gradient
3. Steroids: reduce bone reabsorption, intestinal absorption and increase renal excretion
4. Bisphosphonates: inhibit bone reabsorption

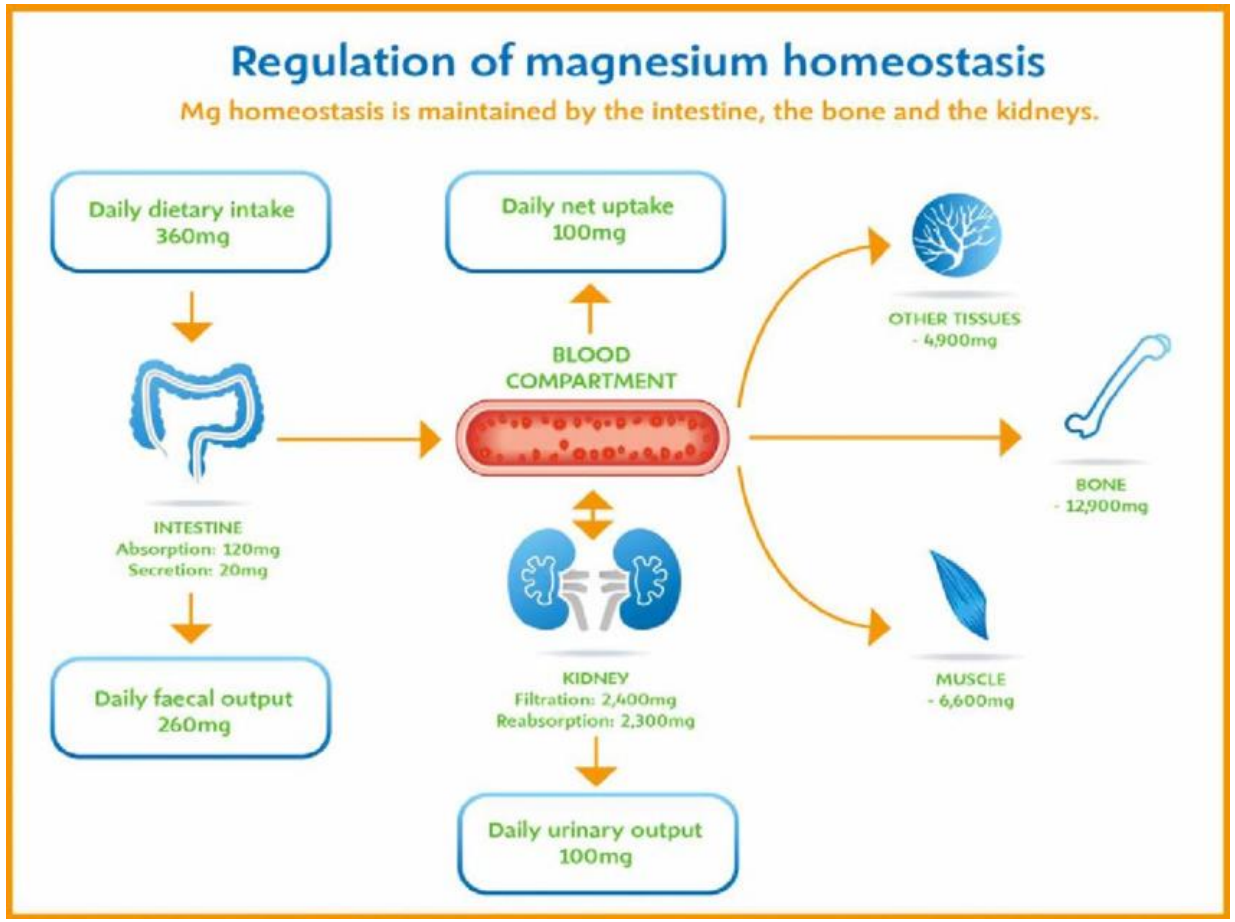
Magnesium handling



Magnesium handling

Magnesium homeostasis

- Intracellular cation
- Housekeeping functions
- 20% of plasma Mg^{+} is bound to proteins
- 80% filtrable



Magnesium handling

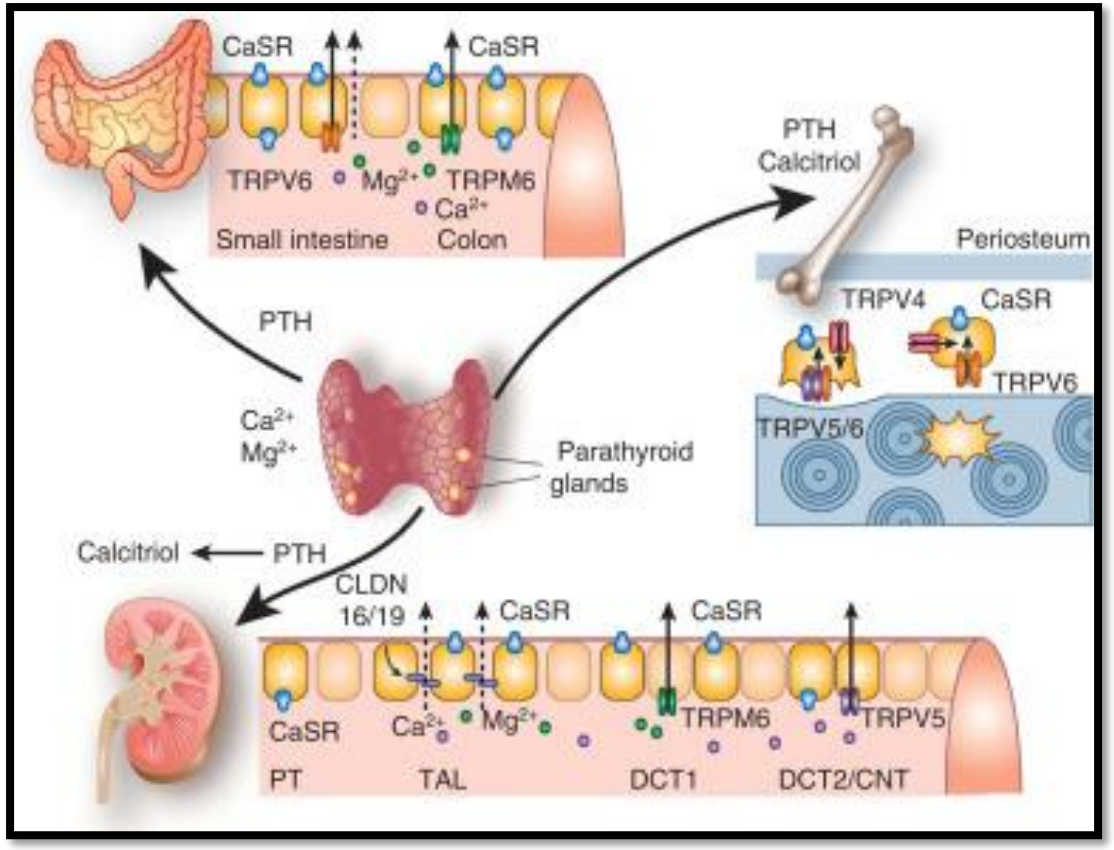
Regulation of magnesemia

Reabsorption stimulated by

- PTH
- Calcitonin
- Glucagon
- ADH
- Aldosterone

Antagonized by

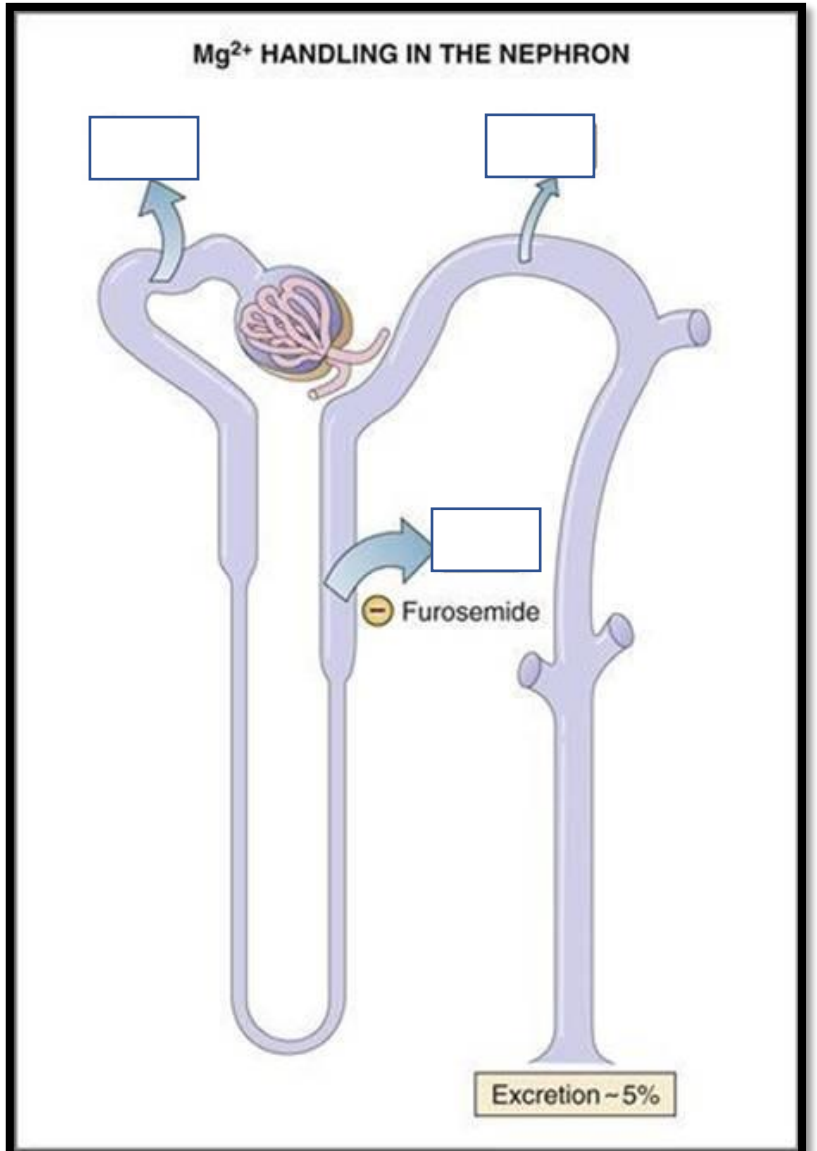
- Hypokalemia
- Hypophosphatemia
- Acidosis



Magnesium handling

Renal handling of Mg^{+}

Fill in the blanks



Magnesium handling

Renal handling of Mg^{+}

PCT

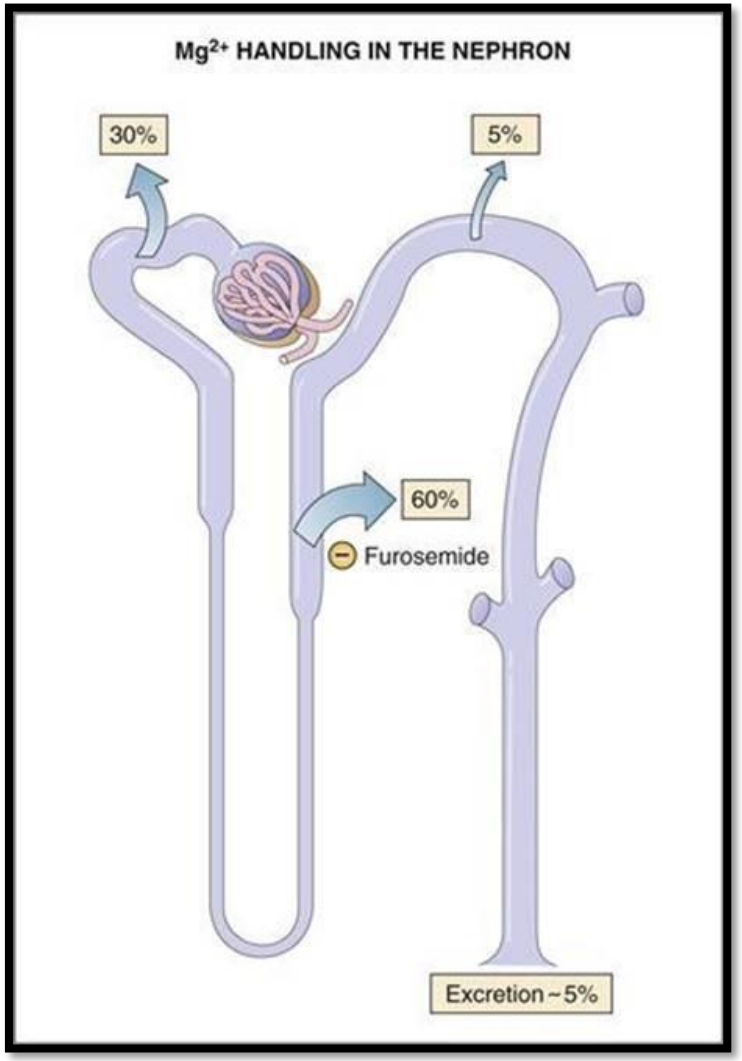
- 30% reabsorbed
  - (10-15% per DiBartola)
- Passive absorption

Thick ascending limb

- 60-70% reabsorbed
- Driven by lumen positive potential difference
- Paracellular pathway
- Loop diuretics inhibit absorption

Distal tubule

- 5% reabsorbed




Wiedikon
Zürich
Wiedikon
Perfetto.
GET
GOLD
JR
DEIN MAINSTREAM-PHONE
NEM EX-PHONE
oppo

Thank you!