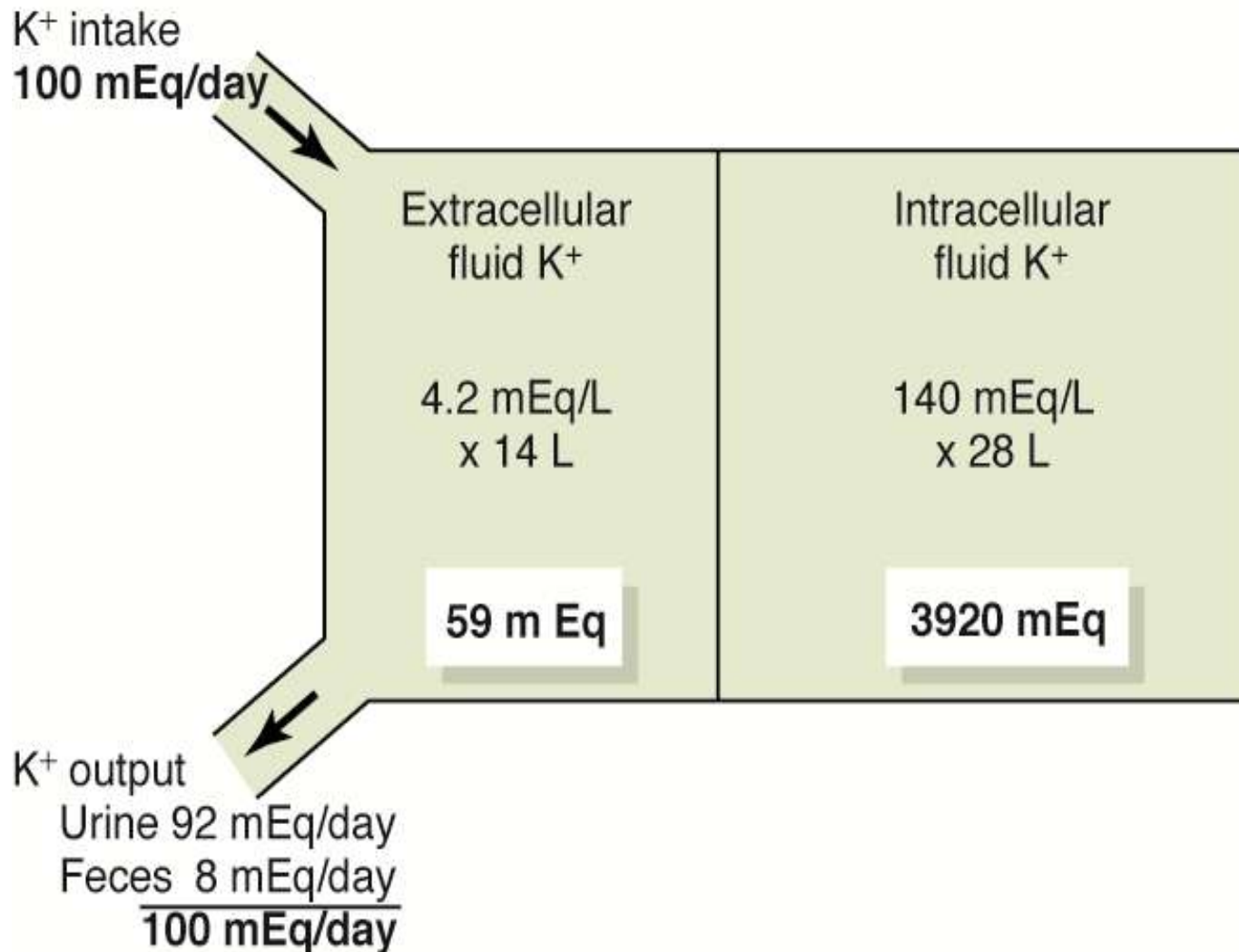


# Potassium regulation.

- Kidney is a **major** regulator for potassium Homeostasis.

# Normal potassium intake, distribution, and output from the body.



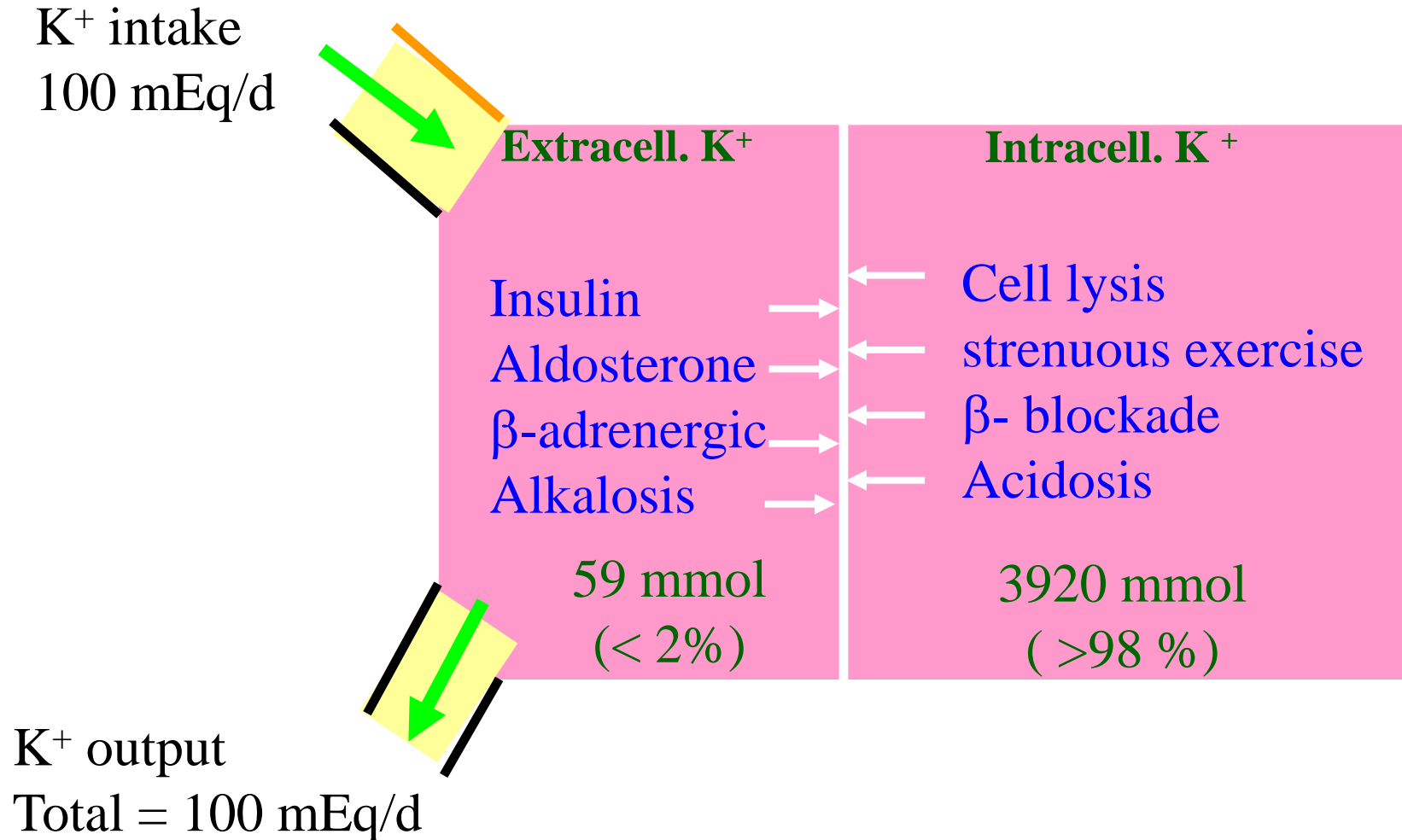
### Effects of severe hyperkalemia

- Partial depolarization of cell membranes
- Cardiac toxicity  
ventricular fibrillation or asystole

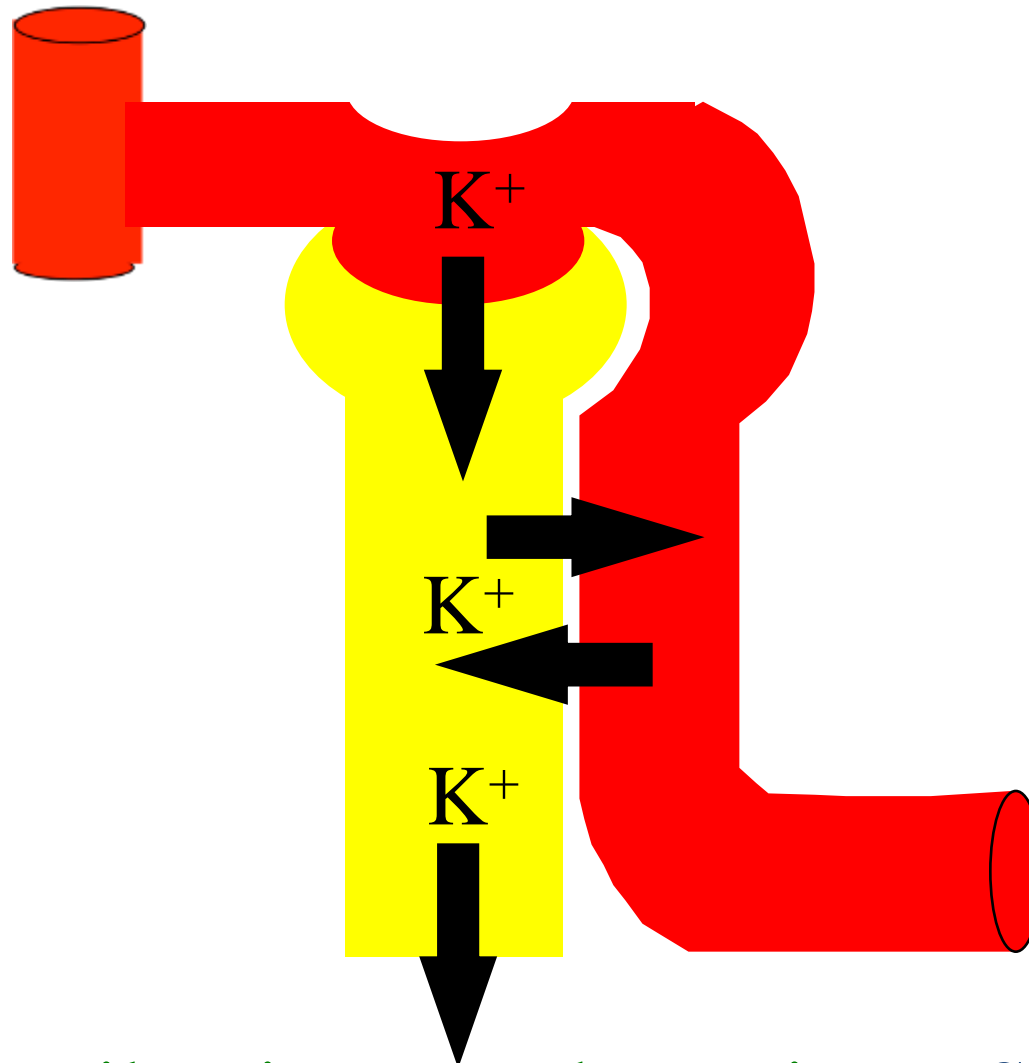
### Effects of severe hypokalemia

- Hyperpolarization of cell membranes
- Fatigue, muscle weakness
- hypoventilation
- delayed ventricular repolarization

## Potassium Regulation: Internal and External

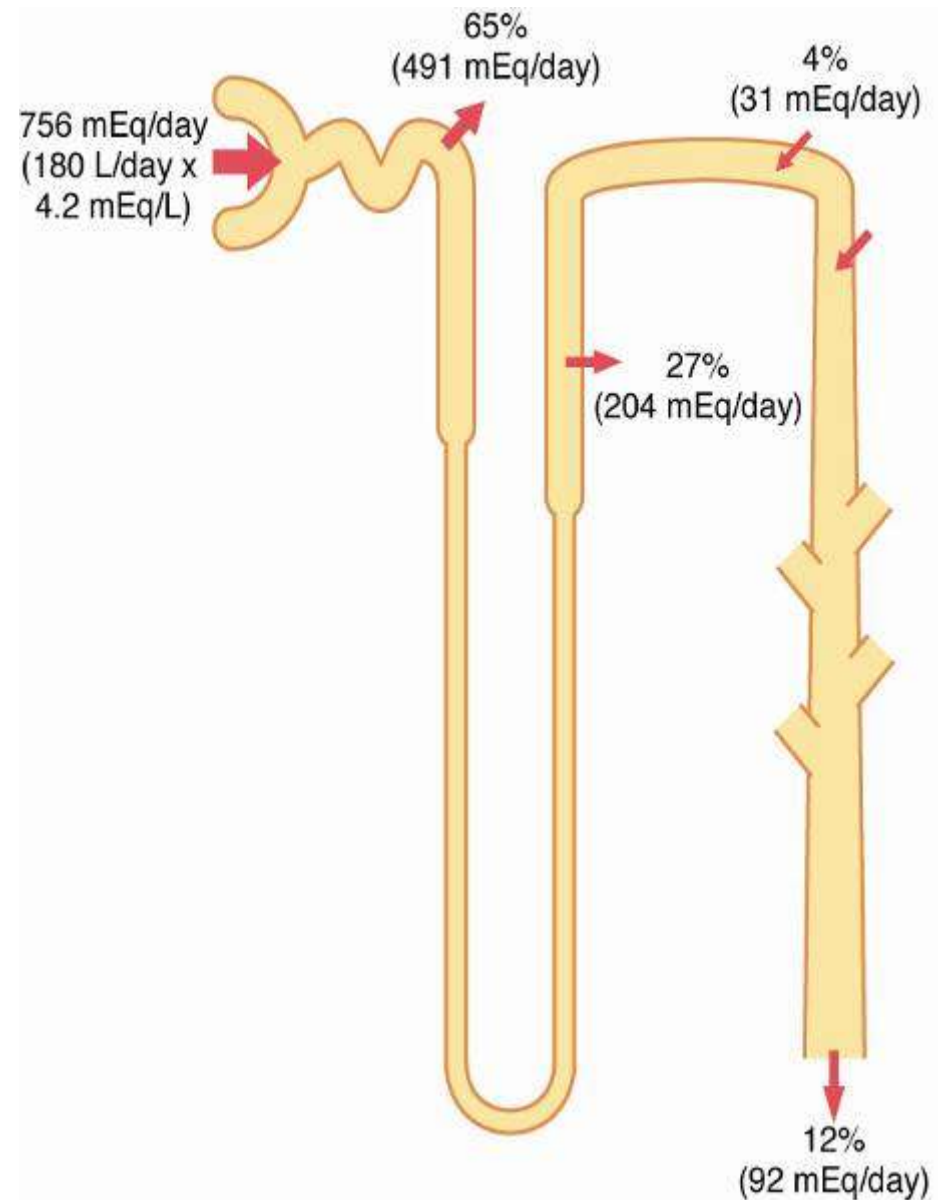


## Control of Potassium Excretion



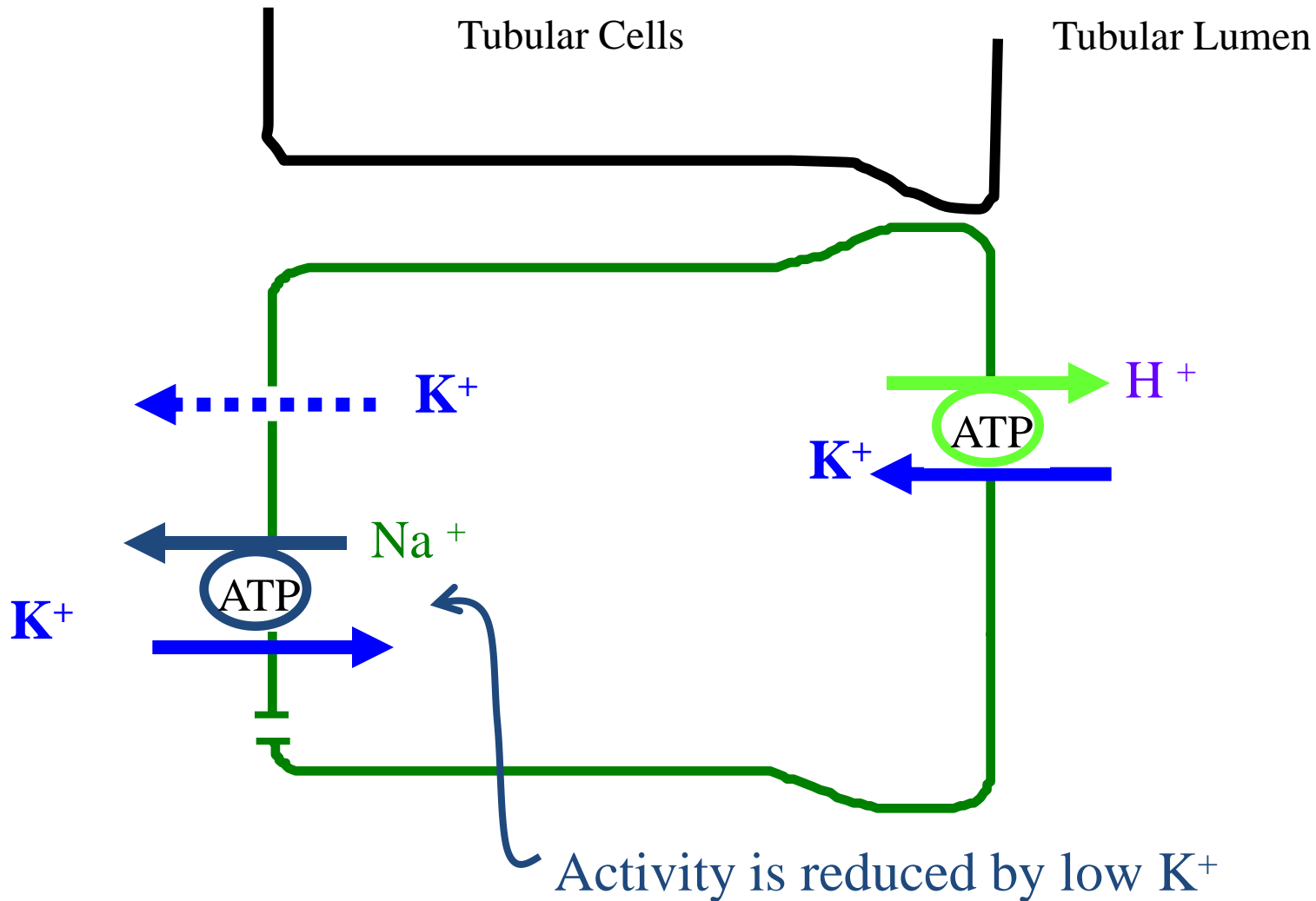
$$\text{Excretion} = \text{Filtration} - \text{Reabsorption} + \text{Secretion}$$

## Renal tubular sites of potassium reabsorption and secretion.

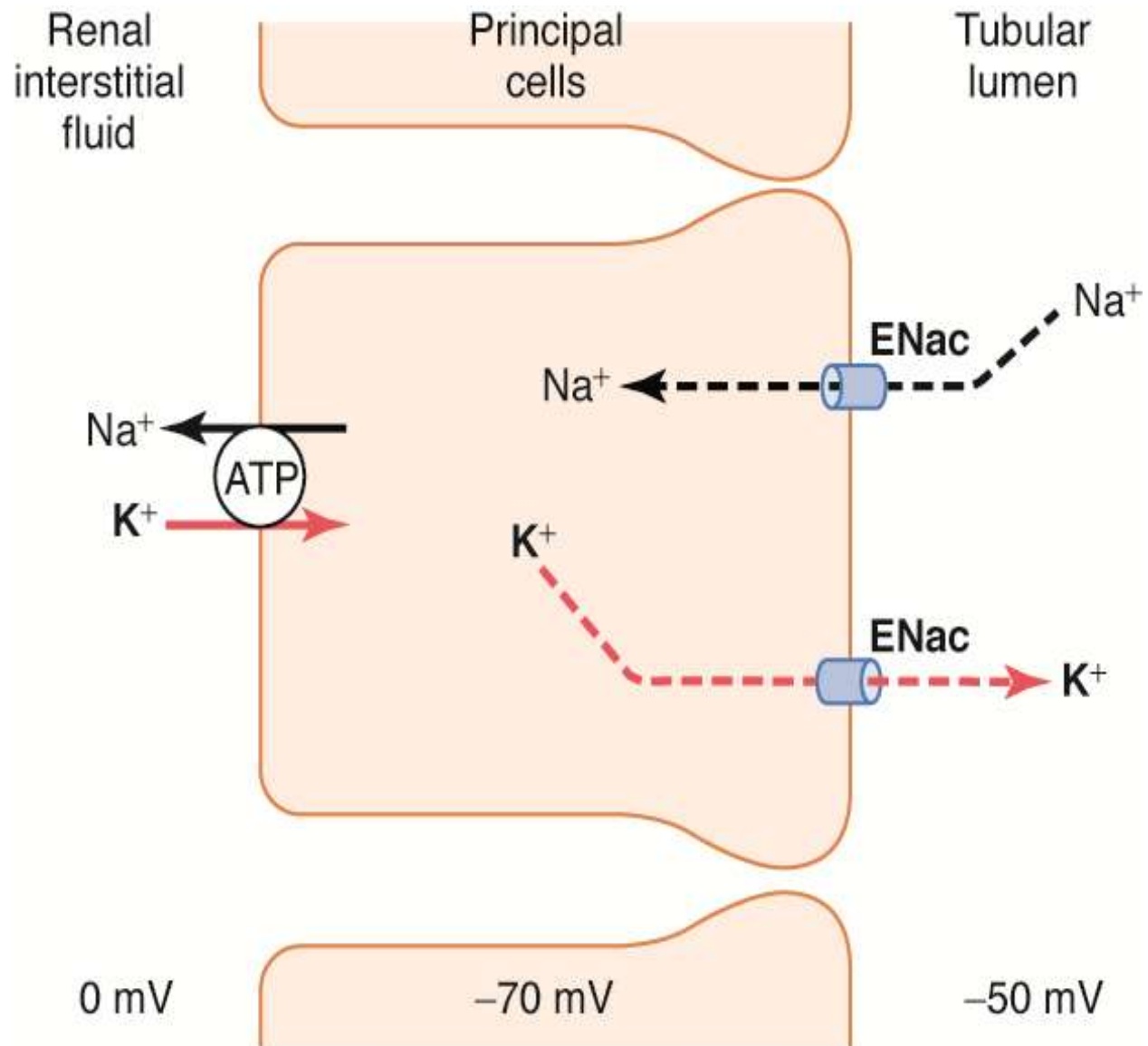


# Late Distal and Cortical Collecting Tubules

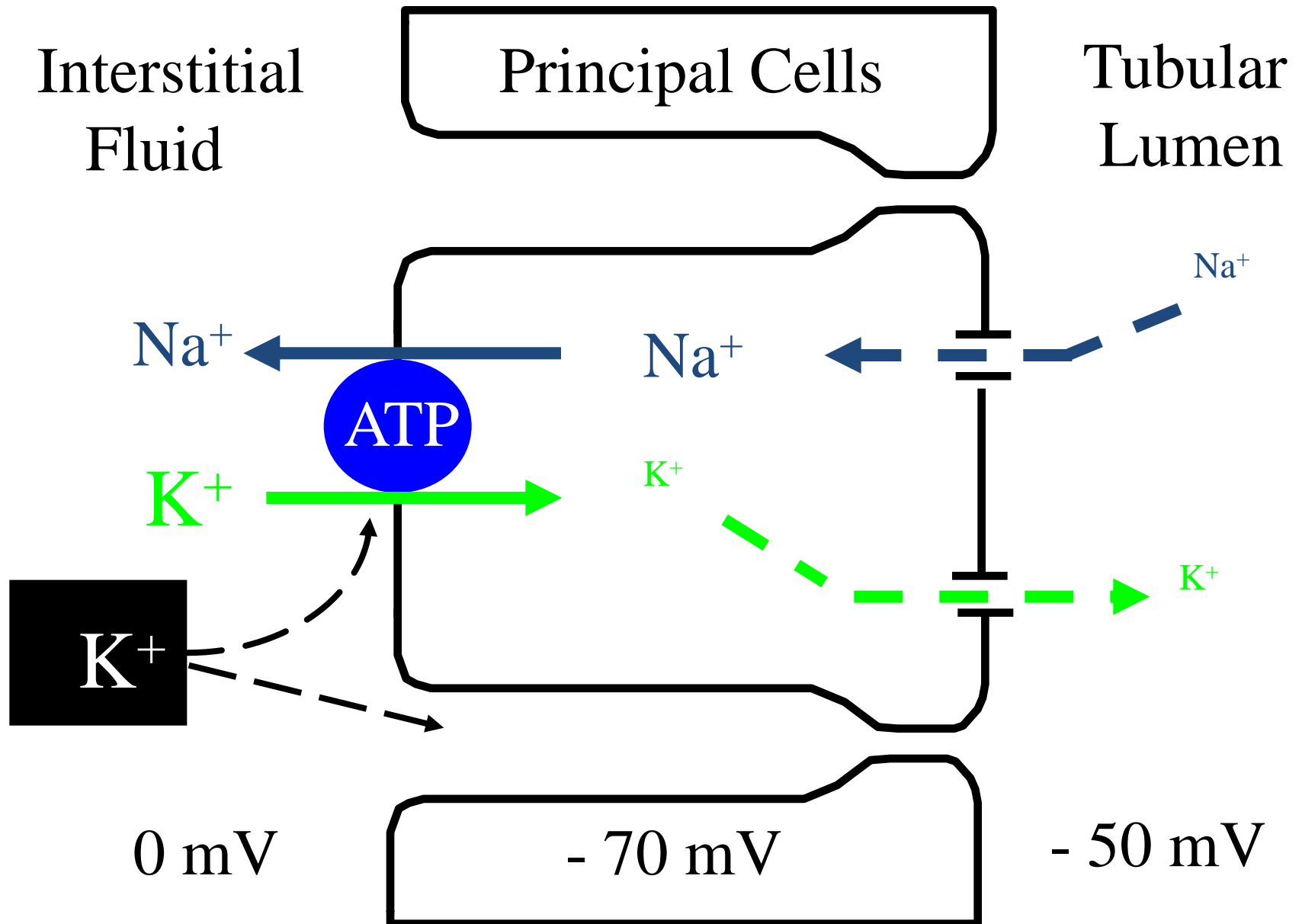
## Intercalated Cells – Reabsorb $K^+$

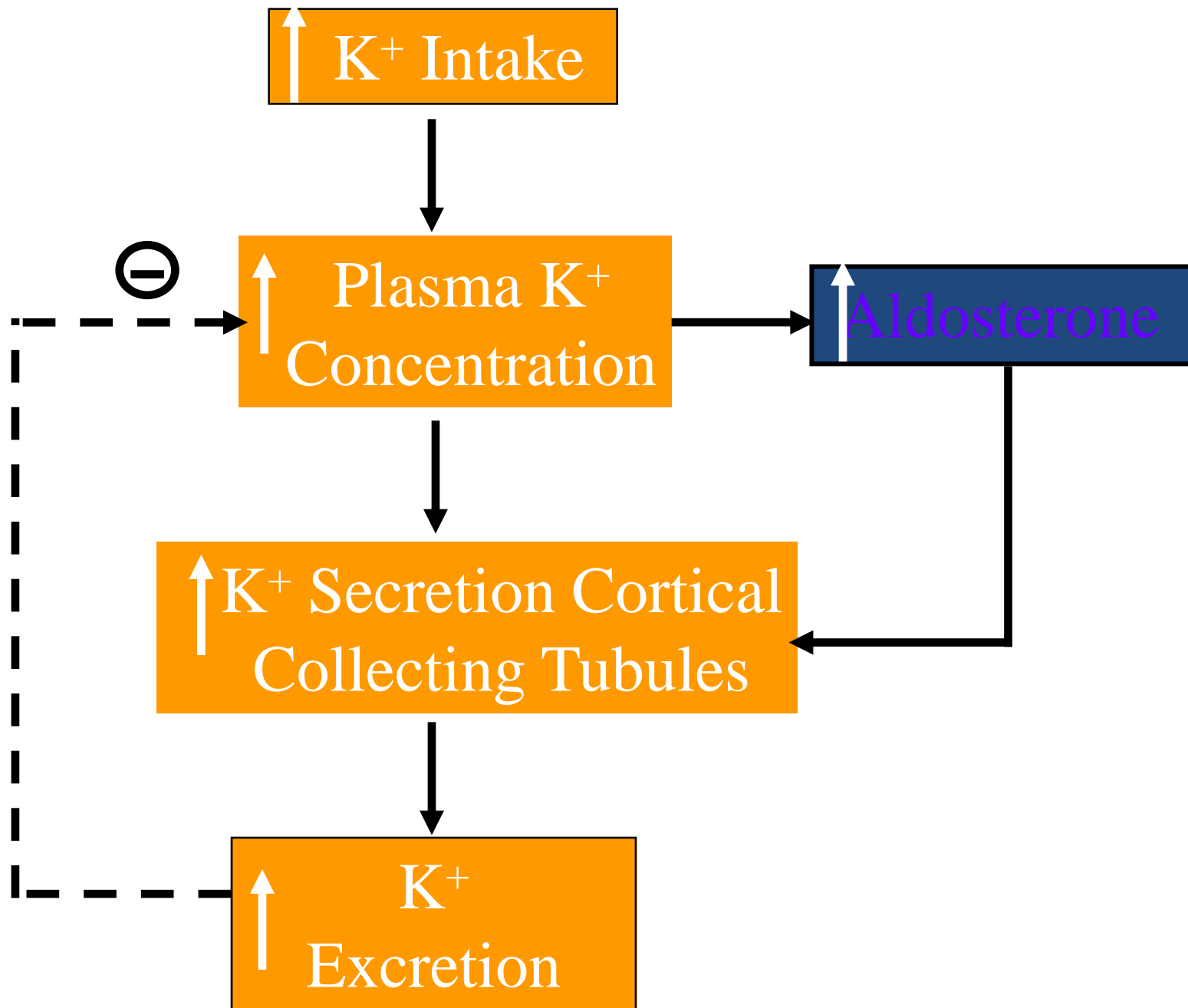


## Potassium Secretion by Principal Cells

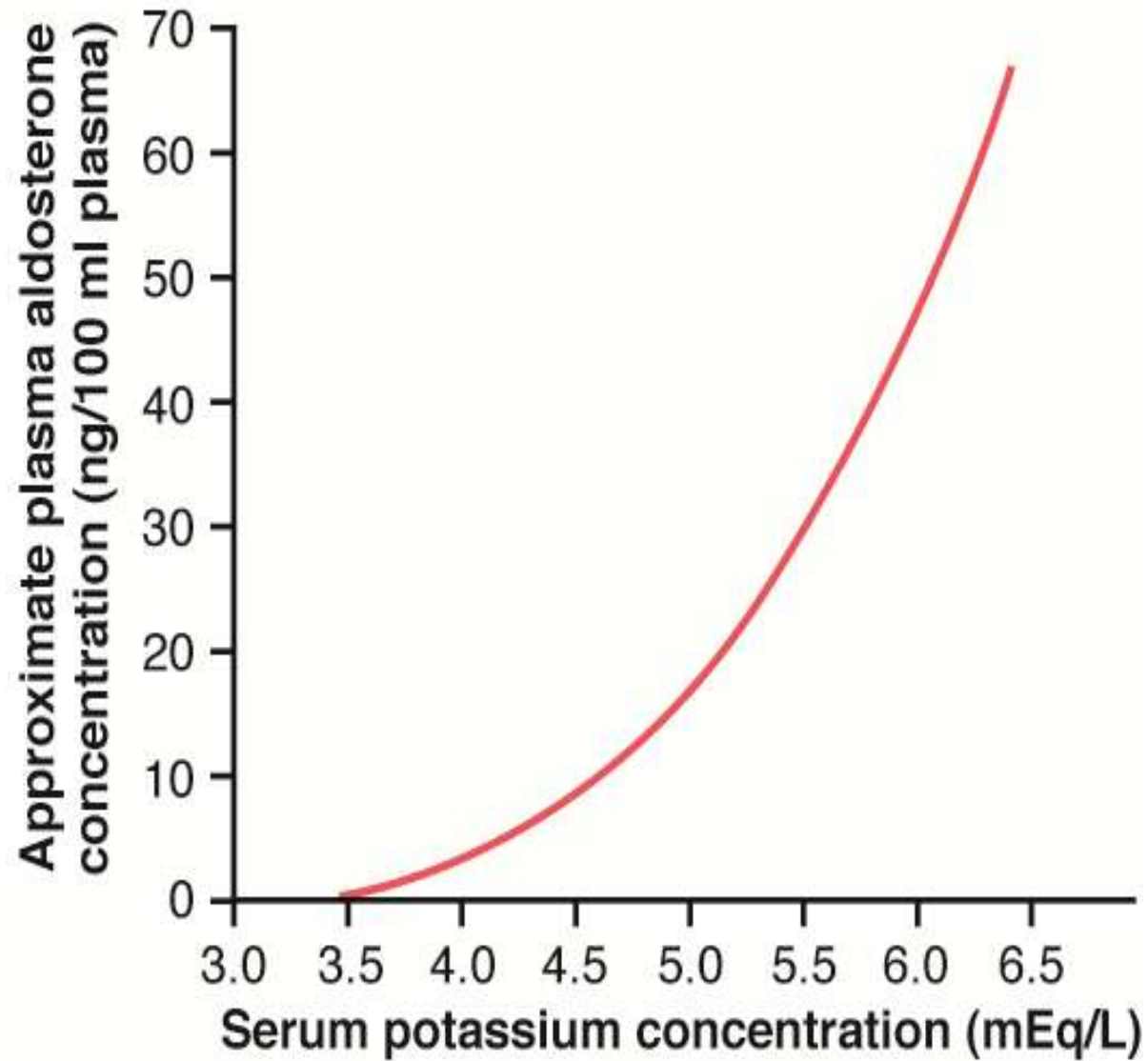




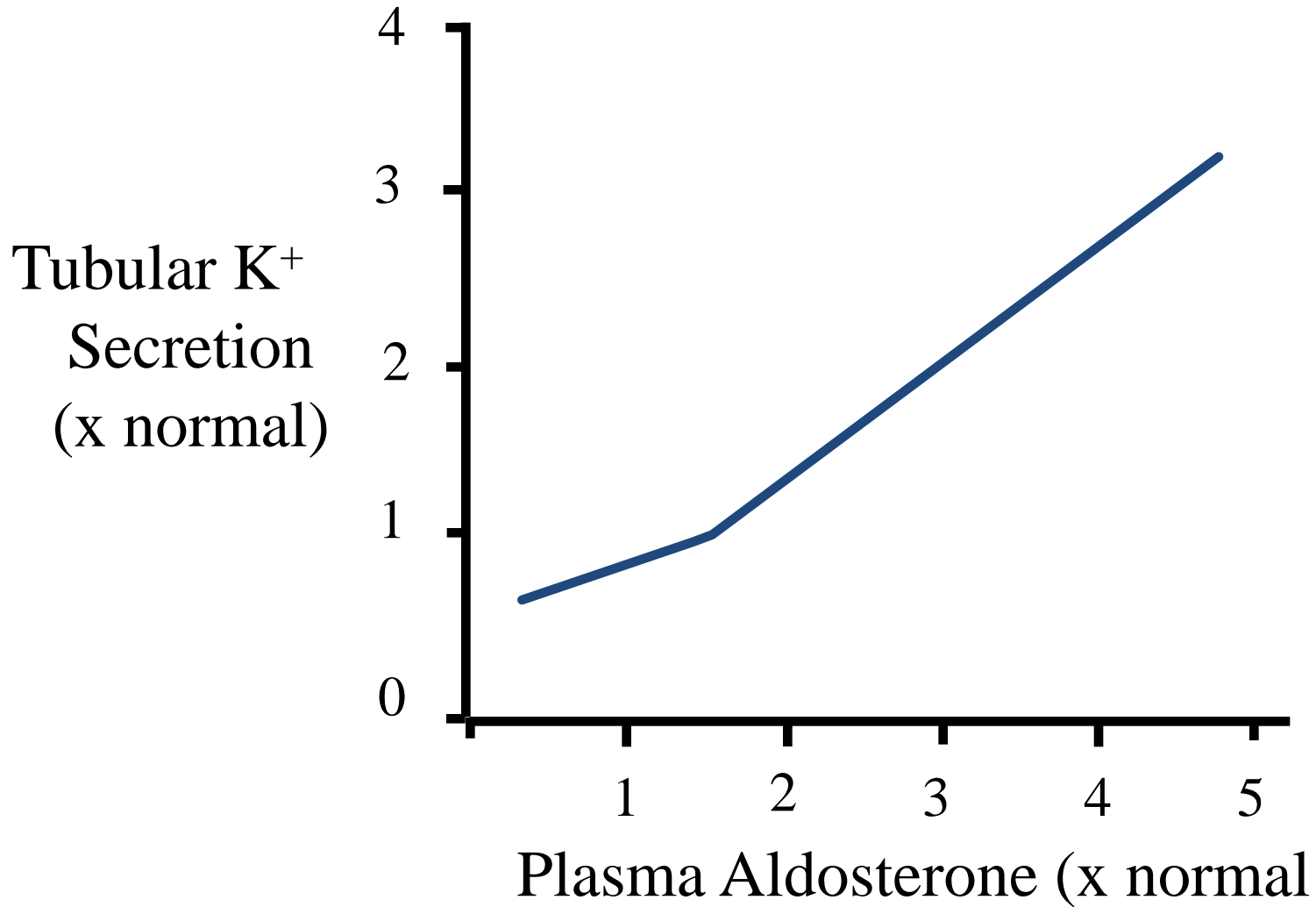




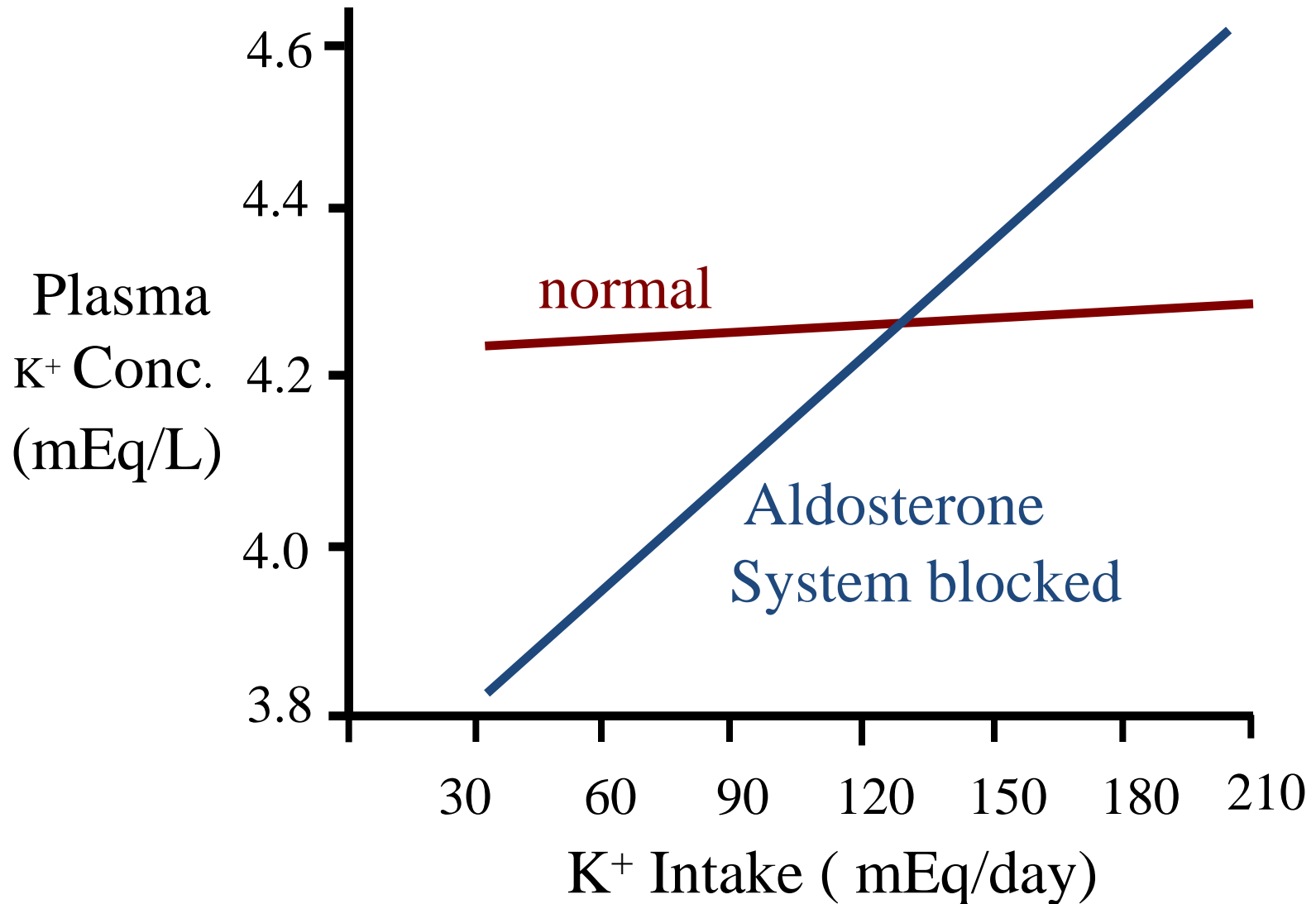
## Increased serum $K^+$ stimulates aldosterone secretion



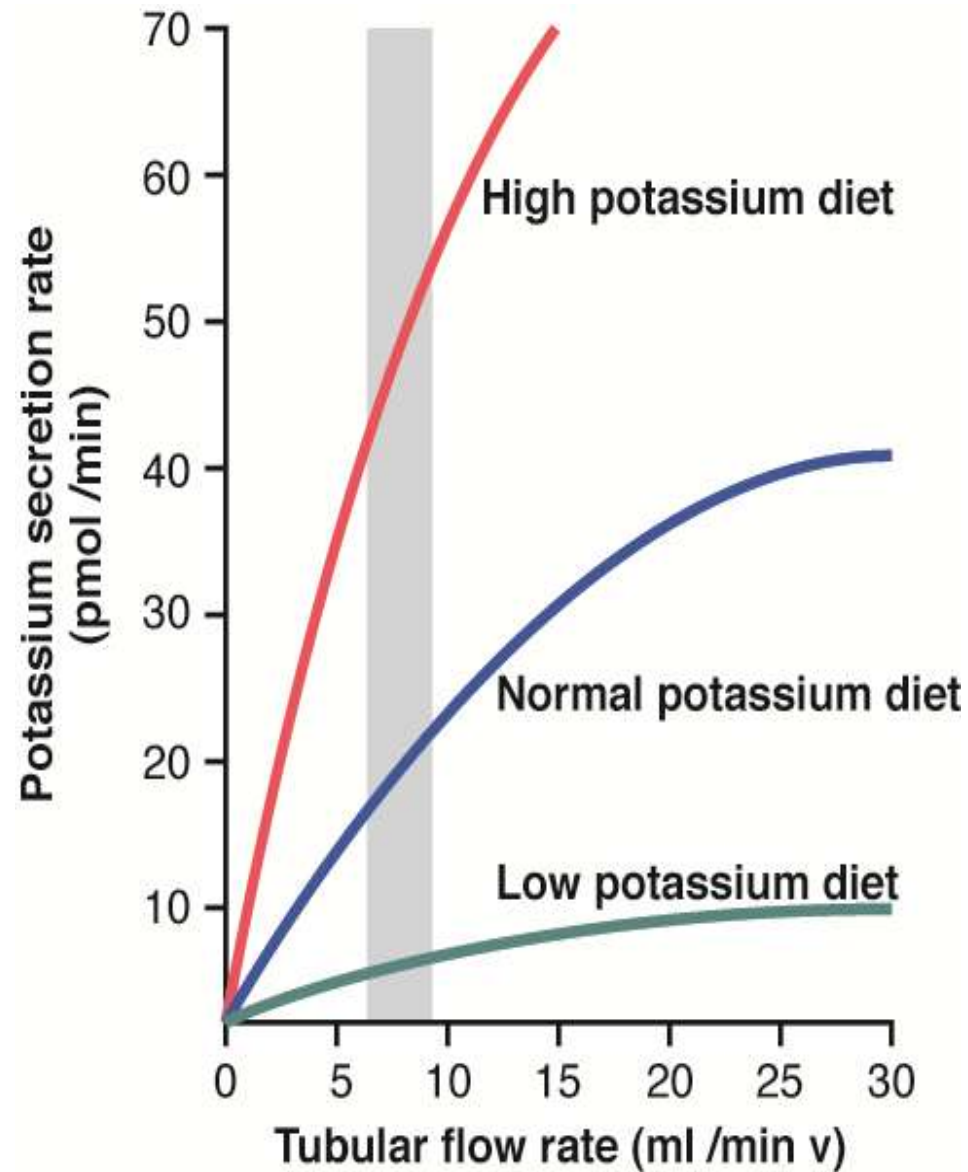
## Effect of Aldosterone on $K^+$ Excretion

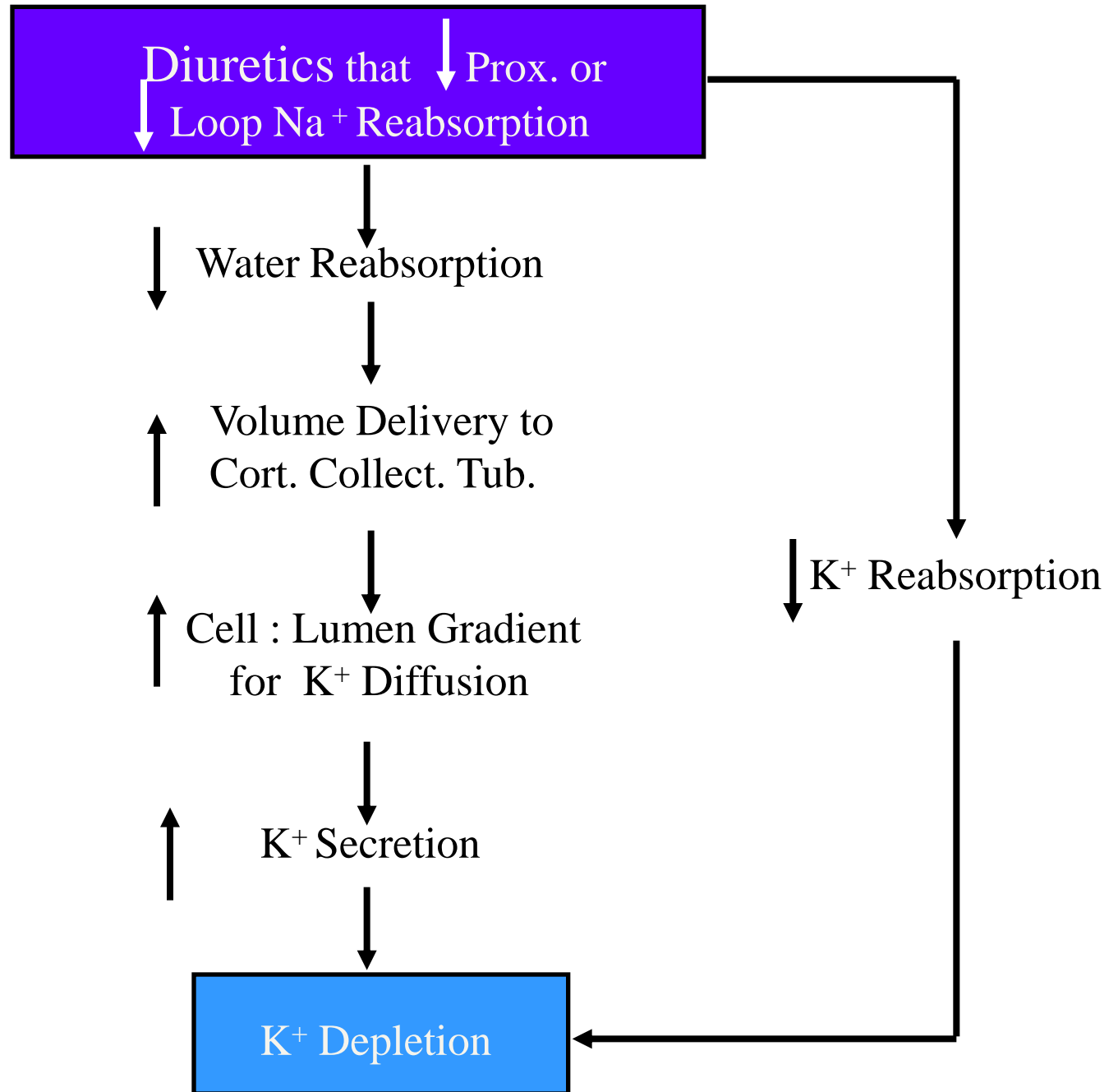


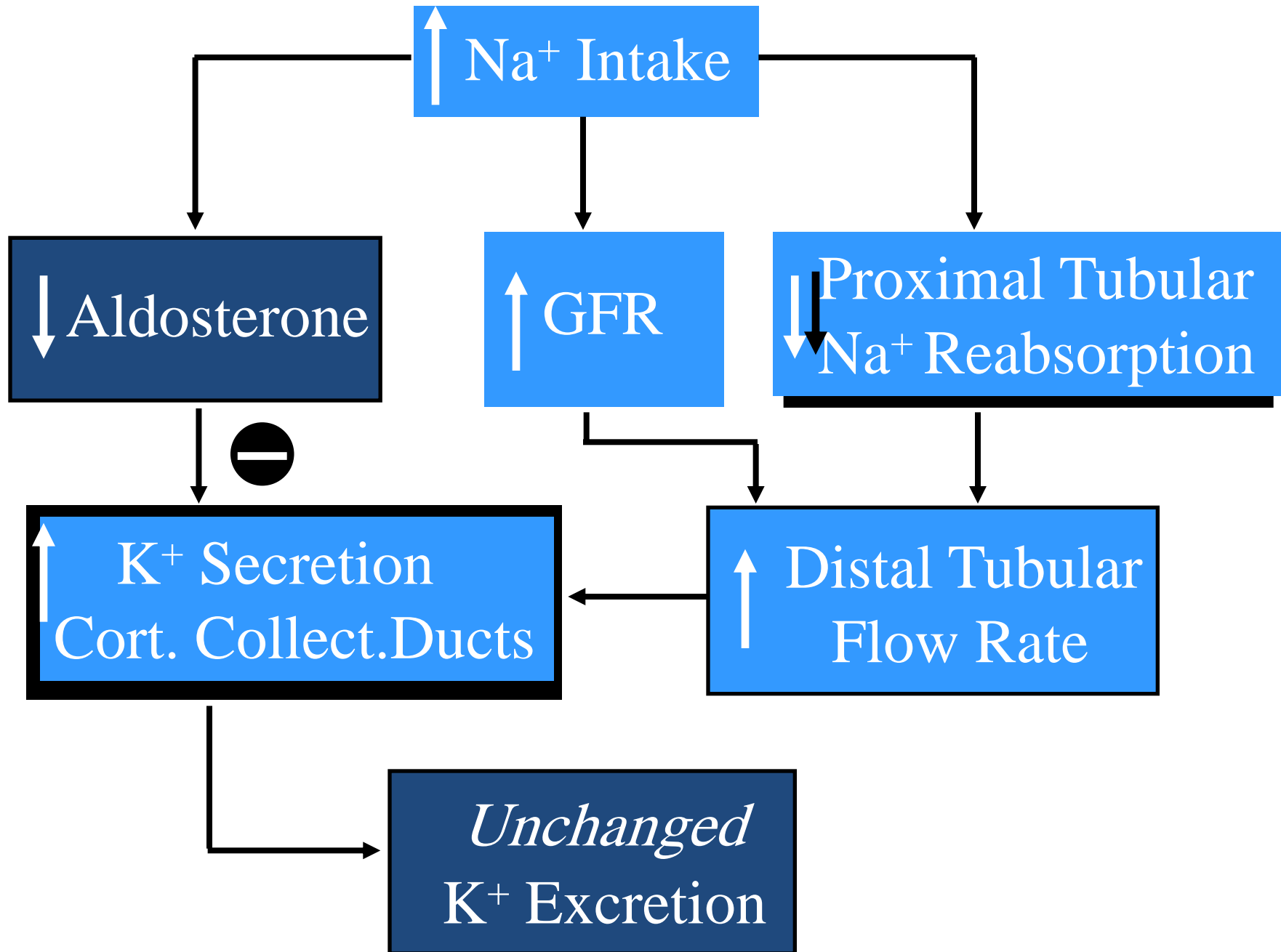
# Effect of Changes in $K^+$ Intake on Plasma $K^+$ After Blocking Aldosterone System



## Effect of collecting tubule flow rate on $K^+$ secretion

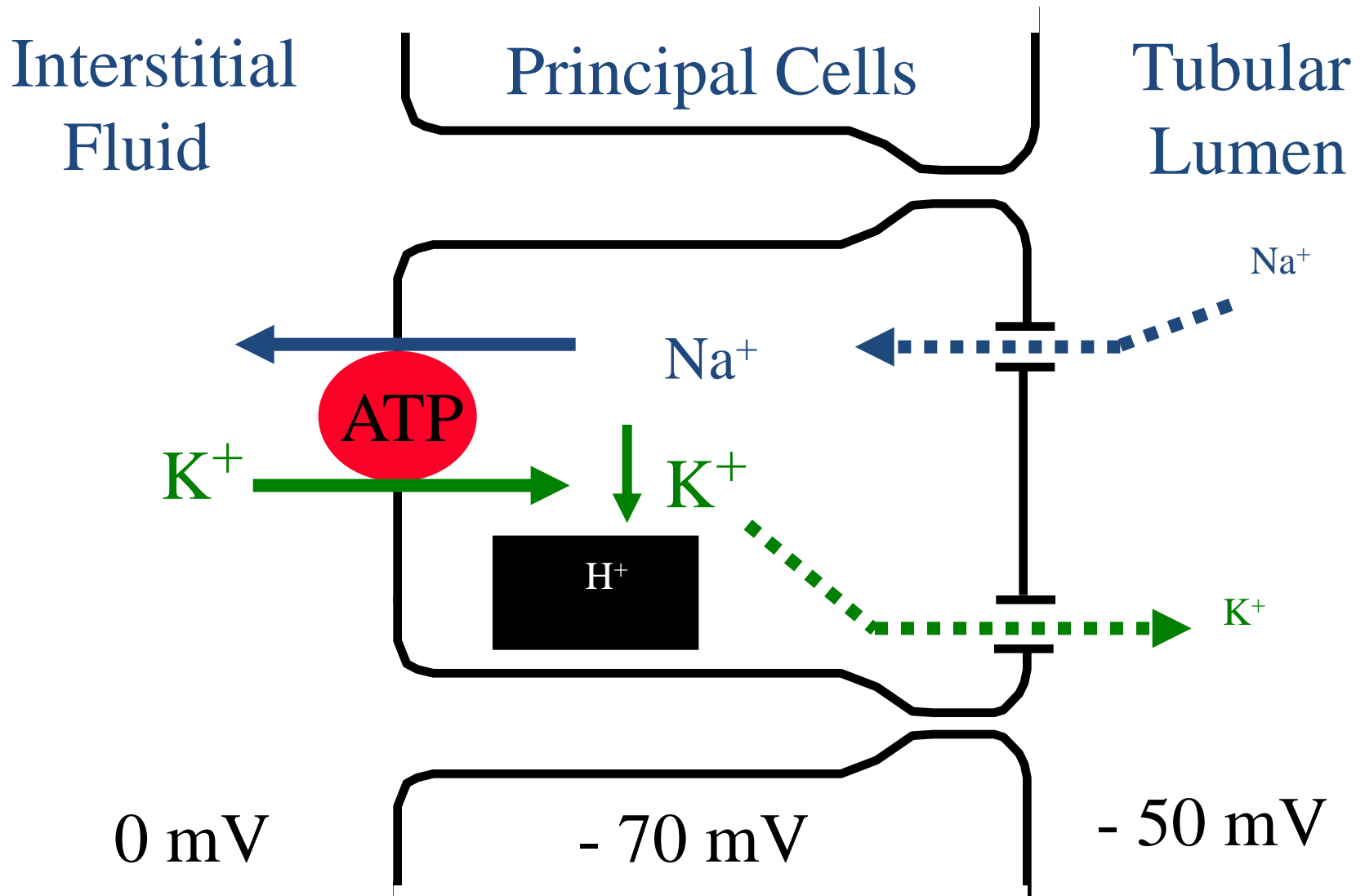








# Acidosis Decreases Cell $K^+$



Alkalosis



$K^+$  in Cells



$K^+$  Secretion



$K^+$  Excretion



$K^+$  Depletion



## Causes of Hyperkalemia

- Renal failure
- Decreased distal nephron flow (heart failure, severe volume depletion, NSAID, etc)
- Decreased aldosterone or decreased effect of aldosterone
  - adrenal insufficiency
  - $K^+$  sparing diuretics (spironolactone, eplerenone)
- Metabolic acidosis (hyperkalemia is mild)
- Diabetes (kidney disease, acidosis, ↓ insulin)

## Causes of Hypokalemia

- Very low intake of  $K^+$
- GI loss of  $K^+$  - diarrhea
- Metabolic alkalosis
- Excess insulin
- Increased distal tubular flow /
  - salt wasting nephropathies
  - osmotic diuretics
  - loop diuretics
- Excess aldosterone or other mineralocorticoids

# K<sup>+</sup> - Reabsorption

- K contributes to RMP so
-  k → hypopolarization and cardiac arrest
-  k → decreased excitability and paralysis

Clearance:

$$C_{K^+} = \frac{60 \text{ mEq/L} * 1 \text{ ml/min}}{4 \text{ mEq}}$$

$$= 15 \text{ ml/min}$$

Which is more than C<sub>Na<sup>+</sup></sub>

# Potassium regulation

- Kidney failure → hyperkalemia which predispose for severe arrhythmias.
- On the other hand sodium concentration usually not to be affected too much because when we have increase in sodium concentration we will have a relative increase in water reabsorption which make no effect in sodium concentration (sometimes we may have a decrease in sodium concentration).

# Potassium regulation

- Potassium concentration in the plasma equals 4mEq/L (3.5-5.5 mEq/l).
- Hyperkalemia >5.5
- Hypokalemia <3.5
- When reaches 7-8mEq\l plus ECG changes → dialysis

# Potassium regulation

- Potassium daily intake is from 50-200mEqv, the average is about 100mEqv/day
- 92% of potassium daily intake is excreted by the kidneys, the rest 8% by other mechanisms like feces.
- Potassium is found mainly as INTRACELLULAR ion in a concentration of 150mEqv/L, while the extracellular concentration is about 4 mEq/L.
- If we want to calculate how much the total potassium inside the cell, we simply multiply 28L (the intracellular volume) with 150mEqv, while to calculate the extracellular total potassium we multiply 4mEqv/L with 14L(the extracellular volume)
- The total mEq of potassium OUTSIDE the cell (extracellular) equals about 56 mEq (generally speaking =60mEq).



# Potassium regulation

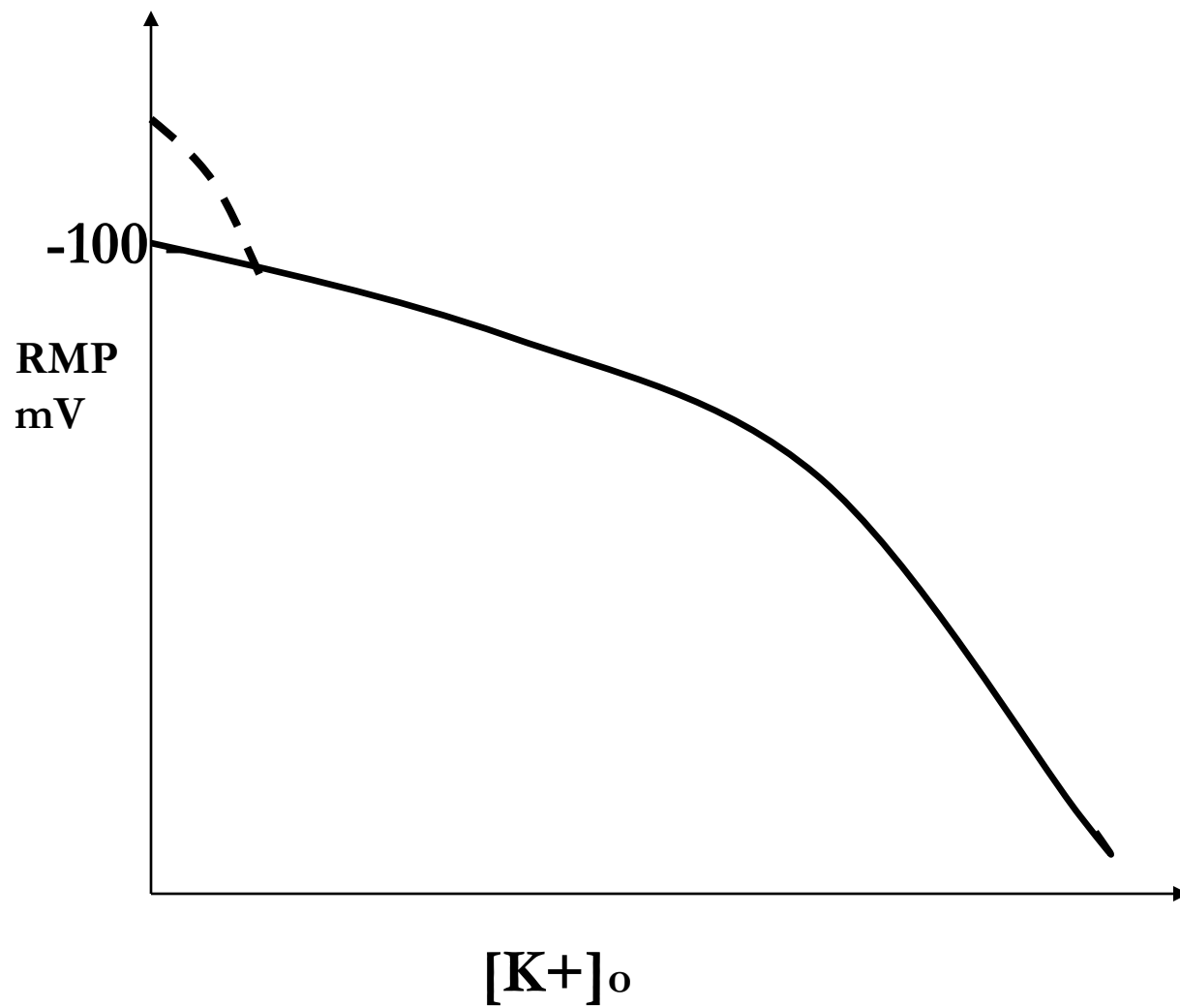
- **suppose that you ingest 50mEqv of potassium in one meal, they will distribute in the 14L this will increase plasma  $K^+$  by 3.6mEqv/L.**
- **Total potassium of extracellular concentration which will reach 7.6mEqv/L!!**

# Potassium regulation

- 1) We can push the extra amount of potassium inside the cell which acts as a BANK for potassium. Note that the increase in intracellular concentration of potassium is LESS important than extracellular increase which will affect the excitability of the tissues

Look at the figure below and notice the following:

- This resembles the relationship between potassium outside the cell and the resting membrane potential given by Nernst equation
- The dotted line is a deviation from the calculated Nernst equation.
- The more the potassium, the less the negativity of the resting membrane potential and vice versa
- Immediately after we start eating, the pancreas secretes INSULIN which stimulates the uptake of potassium by the cells.
- $K^+$  does not remain in the ECF



## Clinical note:

- **A patient with Diabetic Ketoacidosis (a life-threatening complication in patients with untreated diabetes mellitus especially type 1 DM) came to your clinic with hyperkalemia, how you manage him/her?**
- **We know that deficiency of insulin will cause hyperkalemia when the body ingests a meal containing potassium.**
- **When insulin is given → hypokalemia**
- **Give K<sup>+</sup> supplement with insulin.**
- **Management of diabetic ketoacidosis is by giving INSULIN and POTASSIUM**

# Potassium regulation

- 2) kidney management

remember that clearance of potassium is *about* 15 ml/min (depends on the intake)

- Potassium is FREELY filtered. We have a total GFR of 180L/day ... every liter have 4 mEqv... so the total is 720 mEqv of potassium is filtered.
- Now how much is excreted??
- As we said 92 mEqv will be excreted by the kidney if the intake was 100 mEqv
- So we have a reabsorption of  $(720-92=628 \text{ mEqv})$ ...where does this reabsorption occurs??
  - a) 2/3 of total filtered potassium is absorbed in proximal tubules (65%)
  - b) 25% from thick ascending part of Henle's loop

# Potassium regulation

- note that the left filtered and NOT reabsorbed is 10% which equals 72 mEqv....but we said that the amount found in the urine (excreted) is 92mEqv...how this is reached?
- So the amount of potassium in the urine has 2 sources:
- (1) filtered NOT reabsorbed ( $\frac{2}{3}$ )
- (2) secreted ( $\frac{1}{3}$ )
- -We have a type of cells called principal cells found in late distal tubules and collecting ducts, these cells will secrete potassium by the following mechanism:

- increased sodium entry into the cell across the luminal side will activate  $\text{Na}^+\text{-K}^+$  pump to pump  $\text{Na}^+$  outside the cell from the basolateral side and to pump  $\text{K}^+$  inside the cell which will increase the intracellular concentration of  $\text{K}^+$   $\rightarrow$  make a driving force for  $\text{K}^+$  secretion

# Potassium regulation

- How can we increase the  $K^+$  outflow (secretion)??
- 1)activate  $Na^+-K^+$  pump
- 2)make more  $K^+$  channels at the luminal side
- 3)keep the gradient by the fact that  $K^+$  which is secreted is continuously removed
- These are the 3 mechanisms by which potassium secretion is affected.



# Potassium regulation

- **When you eat too much potassium, most of the potassium coming in the urine is from the secreted part because the filtered and reabsorbed part are constant regardless the intake of potassium**
- **-Back to our example of eating a meal containing  $K^+$  which will have a potential of increasing ECF- $K^+$ ...remember that the first mechanism was to push  $K^+$  inside the cell with the effect of insulin secretion...now is the role of the kidney!!**
- **-Increase  $K^+$  in ECF will activate  $Na^+-K^+$  pump and will activate aldosterone secretion which in turn increases potassium secretion**

# Potassium regulation

- **How does aldosterone works?**
- Simply it **enhances sodium entry** (reabsorption) to the principal cell initiating the steps for increasing potassium secretion as mentioned earlier.

# Clinical notes:

- Acute Acidosis inhibit potassium secretion causing hyperkalemia
- $H^+$  exchanges with  $K^+$  so hydrogen ions will enter and potassium ions will exit through the basolateral membrane causing hyperkalemia.
- For every  $\downarrow$  in pH of 0.1 unit  $\rightarrow \uparrow K^+$  0.2 to 1.7 mEq/L.

Note that the term hyperkalemia may not mean a total increase in the  $K^+$  in the body, *but it means that it will increase in the blood*

- Chronic acidosis: we have inhibition of *sodium-chloride reabsorption* which will inhibit water absorption indeed...so we will have increase in flow and wash out (the same effect of diuretics) which will end up with hypokalemia
- Addison's disease which means insufficient amount of adrenal gland secretions including aldosterone will make hyperkalemia

# Clinical notes:

- Conn syndrome which is characterized by increase amount of aldosterone will cause hypertension and hypokalemia
- Hyperosmolality will drive water outside the cells and that's make the potassium concentration inside the cell higher (the cell actually will shrink) the thing that will drive potassium outside the cell causing hyperkalemia
- *For each 10 mOsm increase in osmolality, this will make 0.4-0.8 mEqv increase in potassium extracellular concentration*
- Remember that the normal osmolality in the plasma is 284mOsm
- -Epinephrine pushes potassium inside the cells, so giving beta blocker as propranolol will cause hyperkalemia.
- Exercise through alpha receptors causes hyperkalemia. Thus, Those who take beta-blockers and do severe exercise might suffer from serious hyperkalemia.
- Burns and cell lysis would increase  $K_o$

# Diuretics

- **They are actually 7 groups each work on a specific cell and with a different mechanism.**
- **some of these groups are used for specific indications like carbonic anhydrase inhibitors which is used in glaucoma**
- **Loop diuretics will cause hypokalemia**

Class	Mechanism	Site of Action
osmotic diuretics	Mannitol	
loop diuretics like furosemide, ethacrynic acid and bometanide	inhibit $\text{Na-K-2Cl}$ cotransport. Most powerful available. They increase $\text{Ca}^{++}$ and $\text{Mg}^{++}$ elimination	At thick ascending
**Thiazide	Inhibit $\text{Na-Cl}$ cotransport.: <u>increase</u> $\text{Ca}$ reabsorption	At distal
Acetazolamide (Diamox)	C.A inhibitors	
***Spironolactone	Inhibit $\text{Na}$ reabsorption	At principal cells
$\text{Na}^+$ channel blockers such as Amiloride and triamterene	Because they inhibit $\text{Na}^+$ reabsorption, they also inhibit $\text{K}^+$ secretion. Therefore, they are also $\text{K}^+$ sparing.	

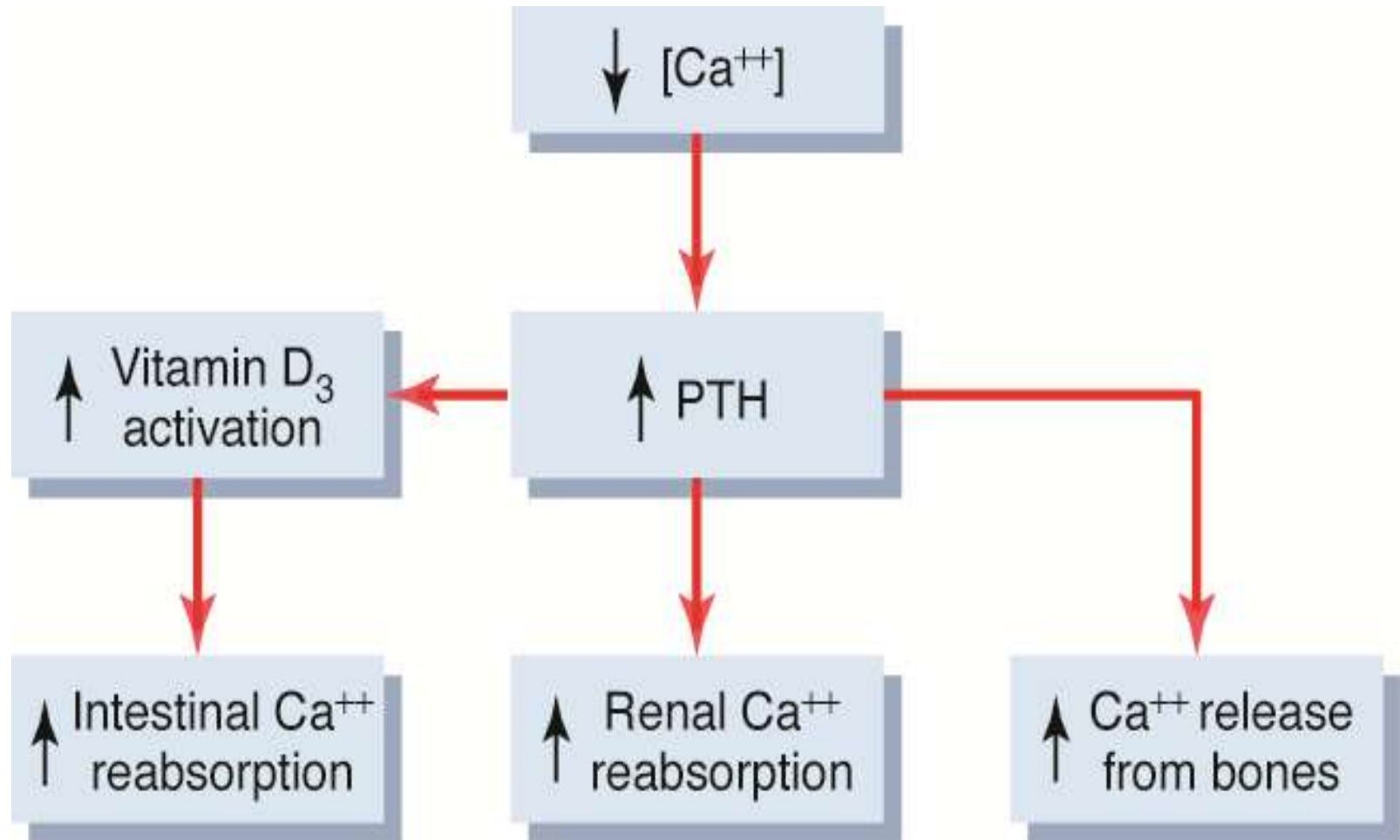
# Ca++ Homeostasis

- **\*PTH is the most important hormone for regulating Ca++ reabsorption**
- **\*Most of the Ca++ is in the bone which serve as a reservoir**
- **\*98% in the bones, 2%in the plasma. Of the 2% of the plasma almost 50%bound and 50%free.**
- **\*we concern about the free part of which 99% is reabsorbed and 1% is excreted**
-

<b>Calcium</b>		Increase Reabsorption	Decrease Reabsorption
Proximal	65%	Volume Contraction	Volume Expansion
TAL	25%	PTH, Clacitonin	Furosemide
DCT	8%	PTH VitD AVP (ADH) Alkalosis Thiazide	Phosphate depletion
Coll Ducts	1%	Amiloride	



# COMPENSATORY RESPONSES TO DECREASED PLASMA IONIZED CALCIUM



## Proximal tubular calcium reabsorption

