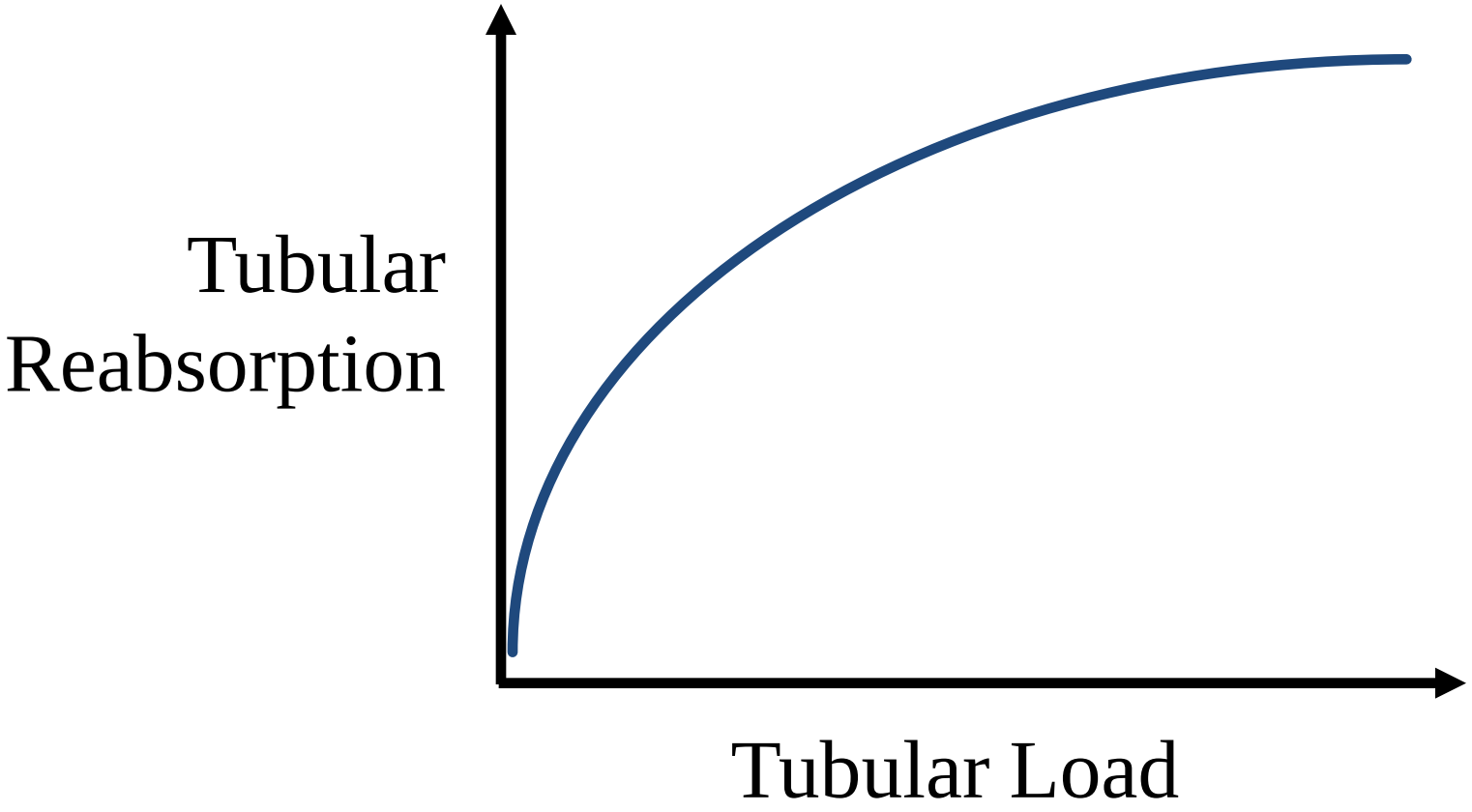
Lecture-5
Regulation of Tubular Reabsorption

- Glomerulotubular Balance
- Peritubular Physical Forces
- Hormones
  - aldosterone
  - angiotensin II
  - antidiuretic hormone (ADH)
  - natriuretic hormones (ANF)
  - parathyroid hormone
- Sympathetic Nervous System
- Arterial Pressure (pressure natriuresis)
- Osmotic factors

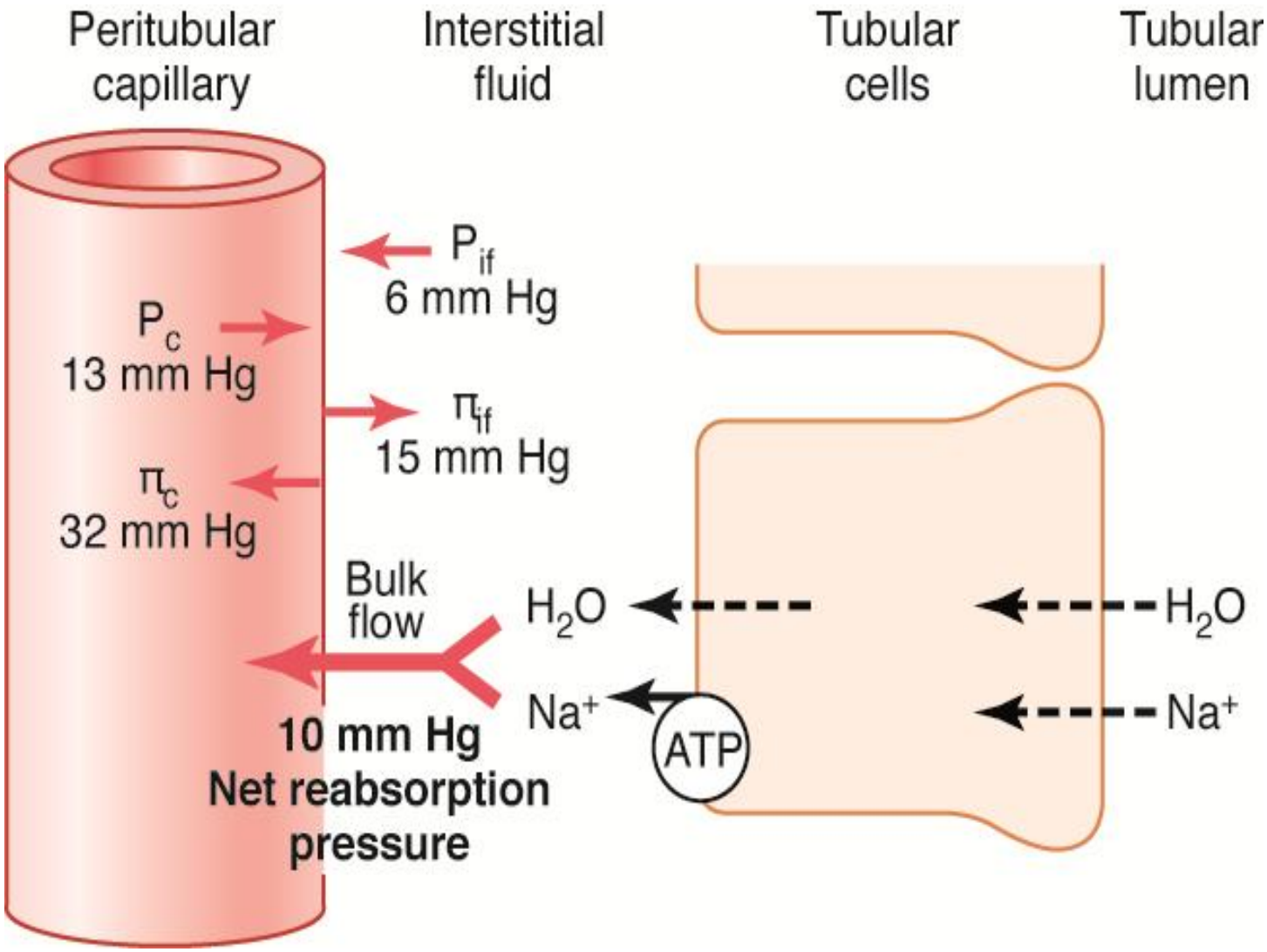
Glomerulotubular Balance



Importance of Glomerulotubular Balance in Minimizing Changes in Urine Volume

GFR	Reabsorption	Urine Volume	% Reabsorption
	no glomerulotubular balance		
125	124	1.0	99.2
150	124	26.0	82.7
	“perfect” glomerulotubular balance		
150	148.8	1.2	99.2

Peritubular capillary reabsorption



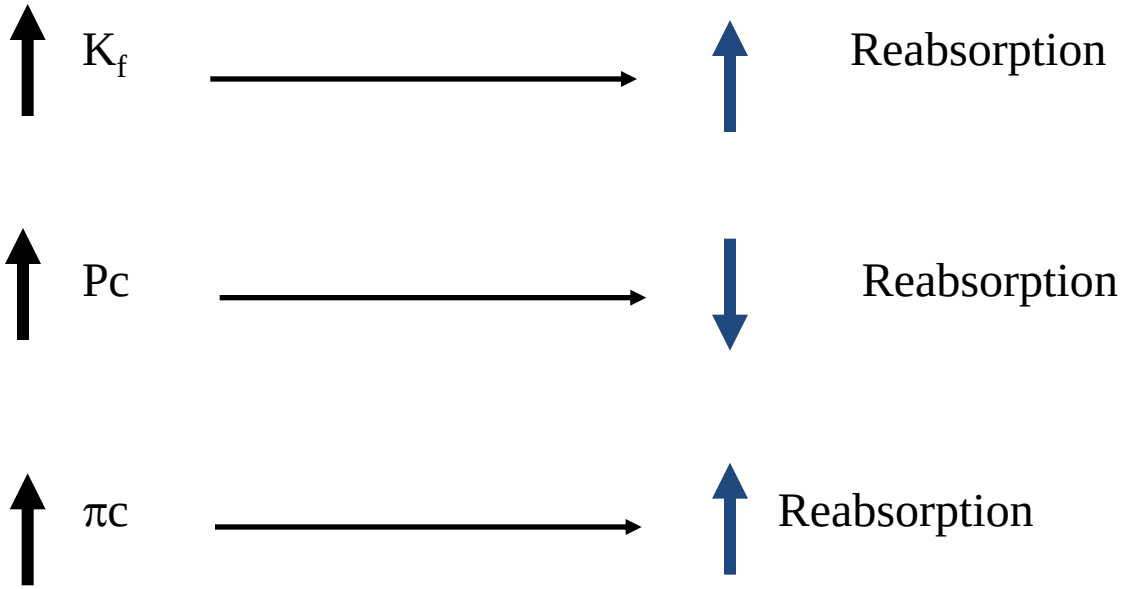
Peritubular Capillary Reabsorption

Reabs = Net Reabs Pressure (NRP) x K_f

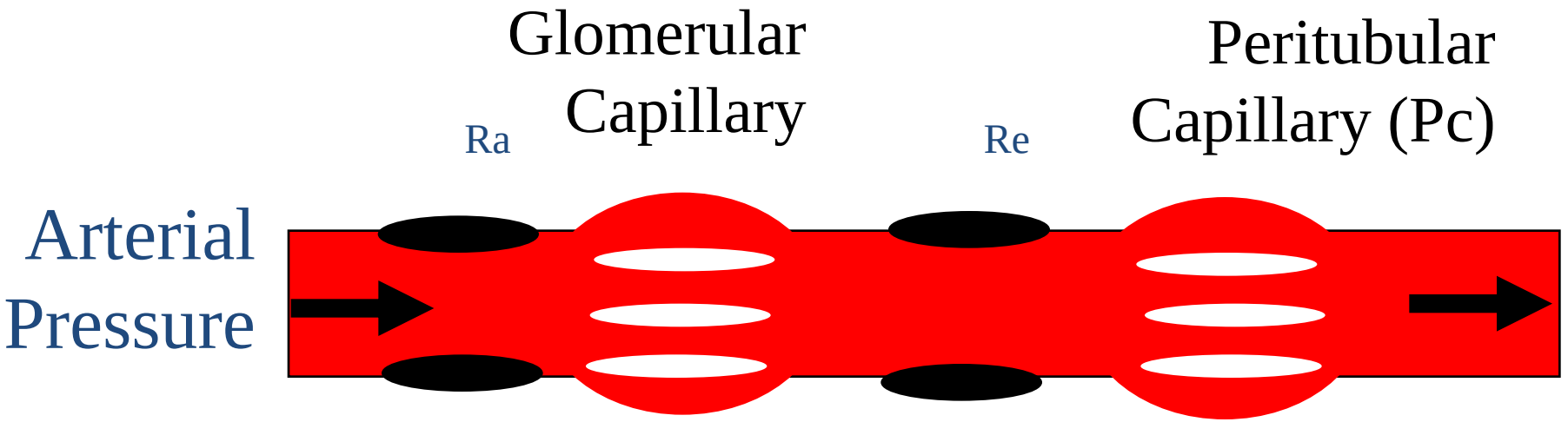
= (10 mmHg) x (12.4 ml/min/mmHg)

Reabs = 124 ml/min

Determinants of Peritubular Capillary Reabsorption



Determinants of Peritubular Capillary Hydrostatic Pressure

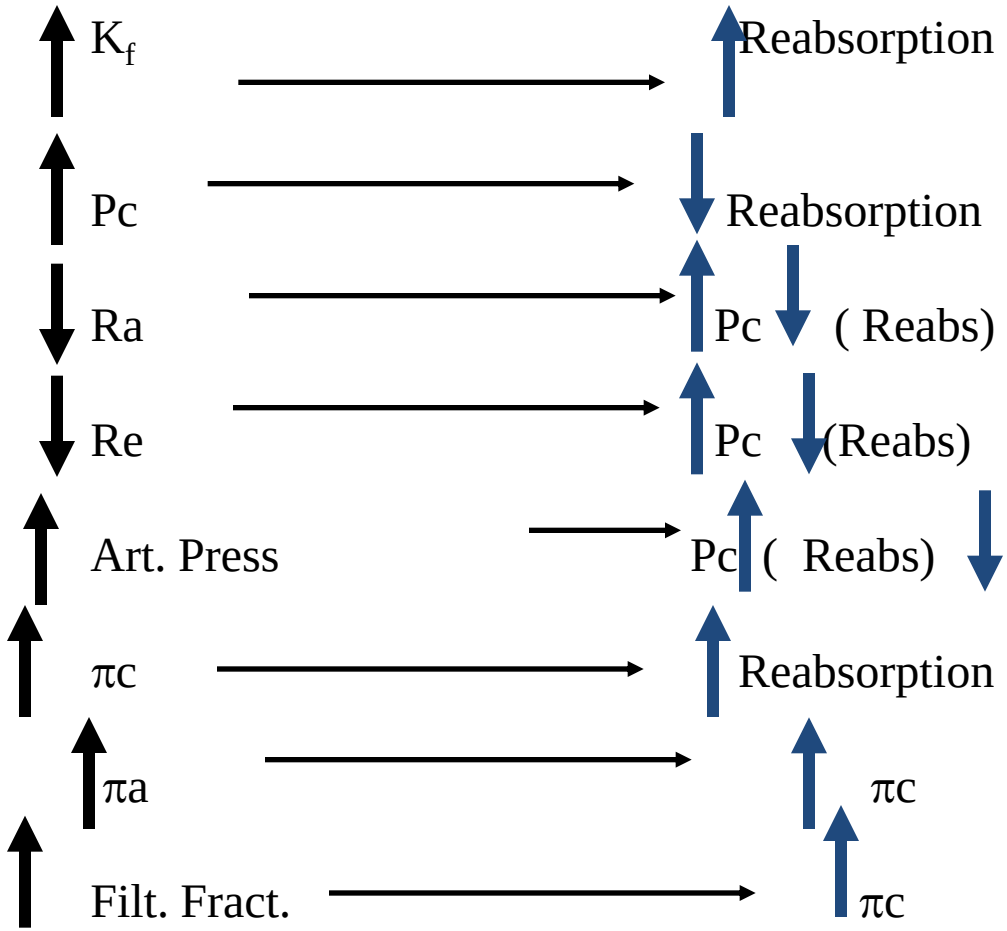


↑ Arterial Pressure → ↑ Pc → ↓ Reabs.

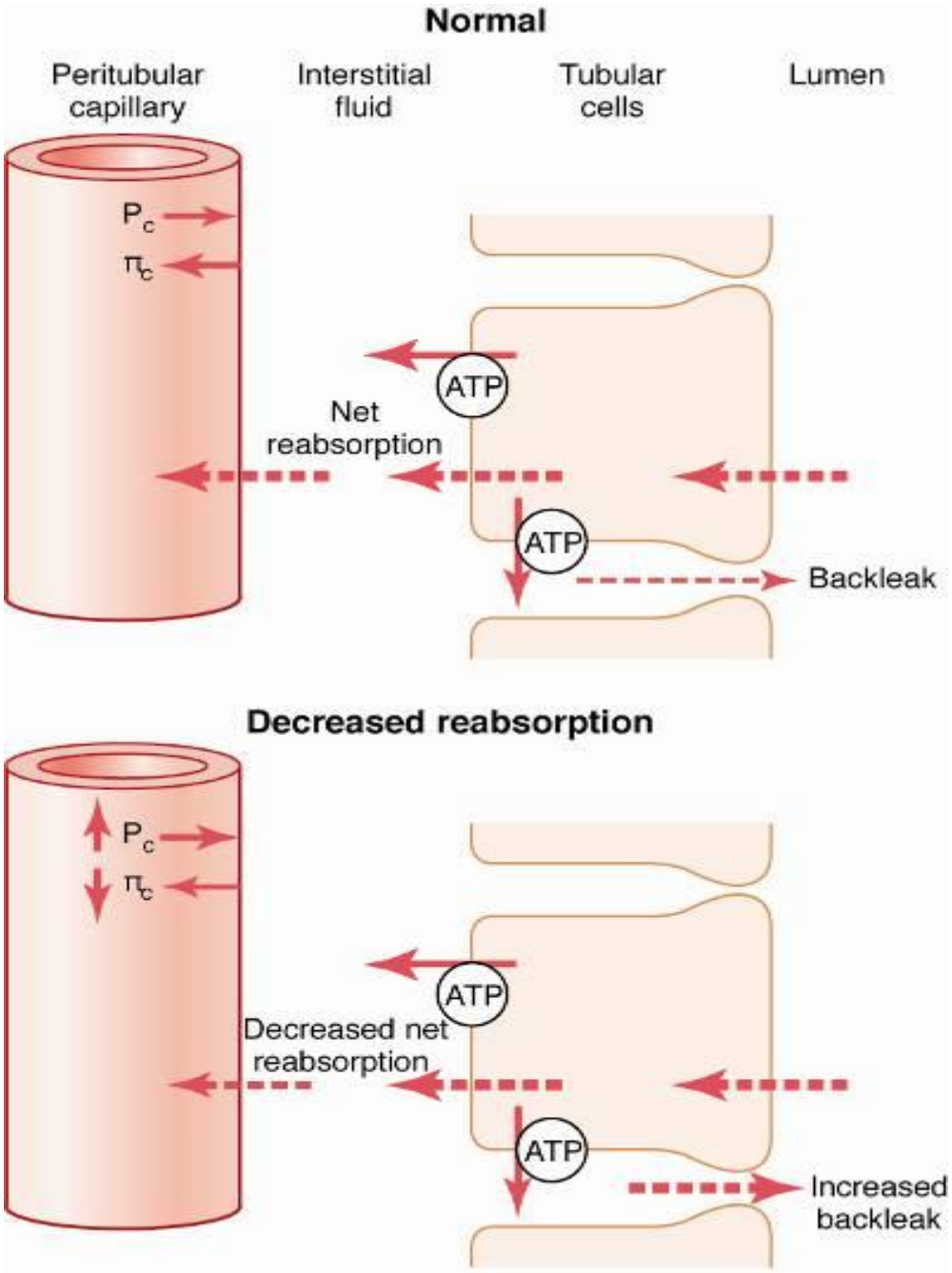
↑ Ra → ↓ Pc → ↑ Reabs.

↑ Re → ↓ Pc → ↑ Reabs.

Factors That Can Influence Peritubular Capillary Reabsorption



Effect of increased hydrostatic pressure or decreased colloid osmotic pressure in peritubular capillaries to reduce reabsorption



Question

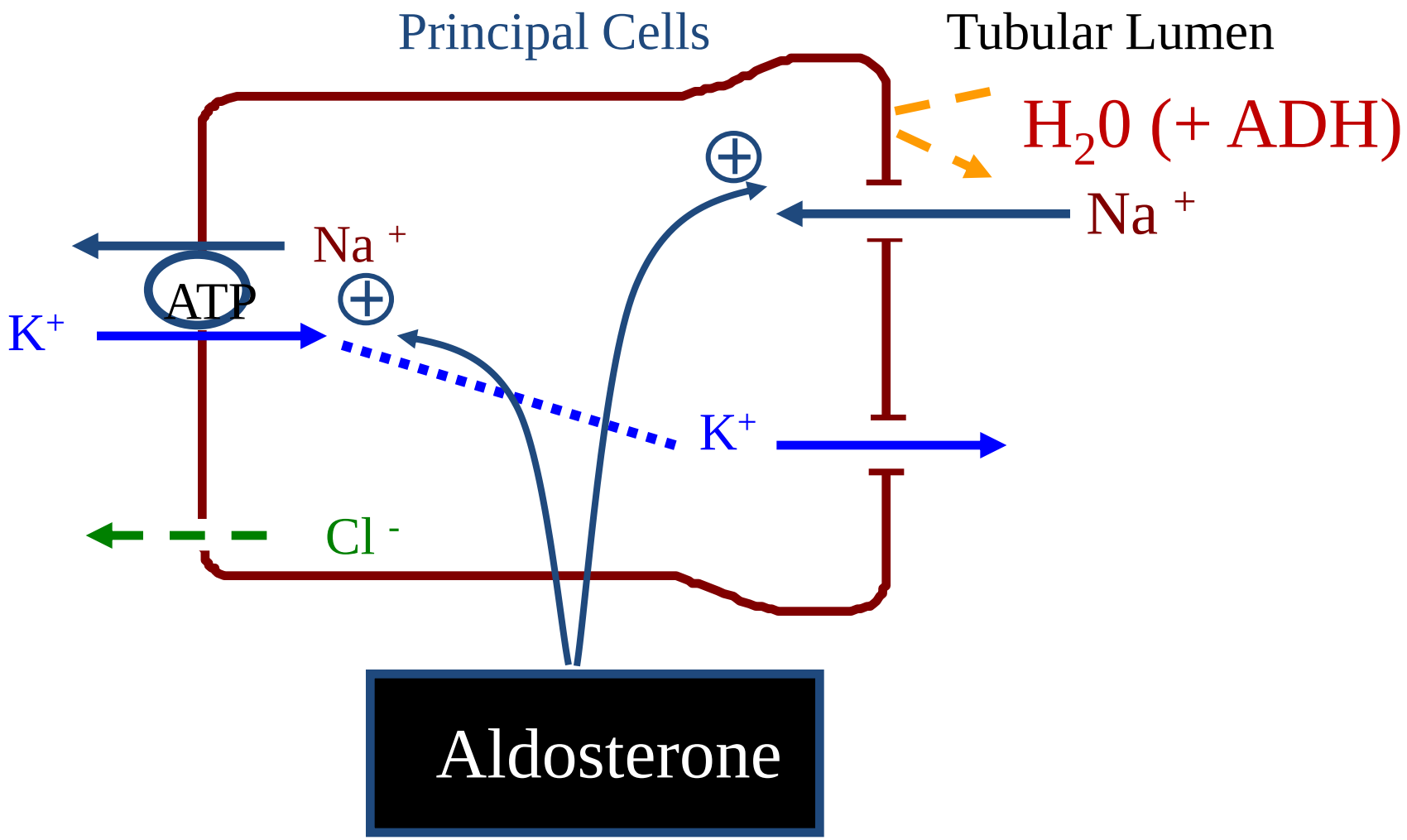
Which of the following changes would tend to increase peritubular reabsorption ?

1. increased arterial pressure
2. decreased afferent arteriolar resistance
3. increased efferent arteriolar resistance
4. decreased peritubular capillary K_f
5. decreased filtration fraction

Aldosterone actions on late distal, cortical and medullary collecting tubules

- Increases Na^+ reabsorption - principal cells
- Increases K^+ secretion - principal cells
- Increases H^+ secretion - intercalated cells

Late Distal, Cortical and Medullary Collecting Tubules



Abnormal Aldosterone Production

- Excess aldosterone (Primary aldosteronism Conn's syndrome) - Na^+ retention, hypokalemia, alkalosis, hypertension

- Aldosterone deficiency - Addison's disease
  Na^+ wasting, hyperkalemia, hypotension

Control of Aldosterone Secretion

Factors that increase aldosterone secretion

- Angiotensin II
- Increased K^+
- adrenocorticotrophic hormone (ACTH) (permissive role)

Factors that decrease aldosterone secretion

- Atrial natriuretic factor (ANF)
- Increased Na^+ concentration (osmolality)

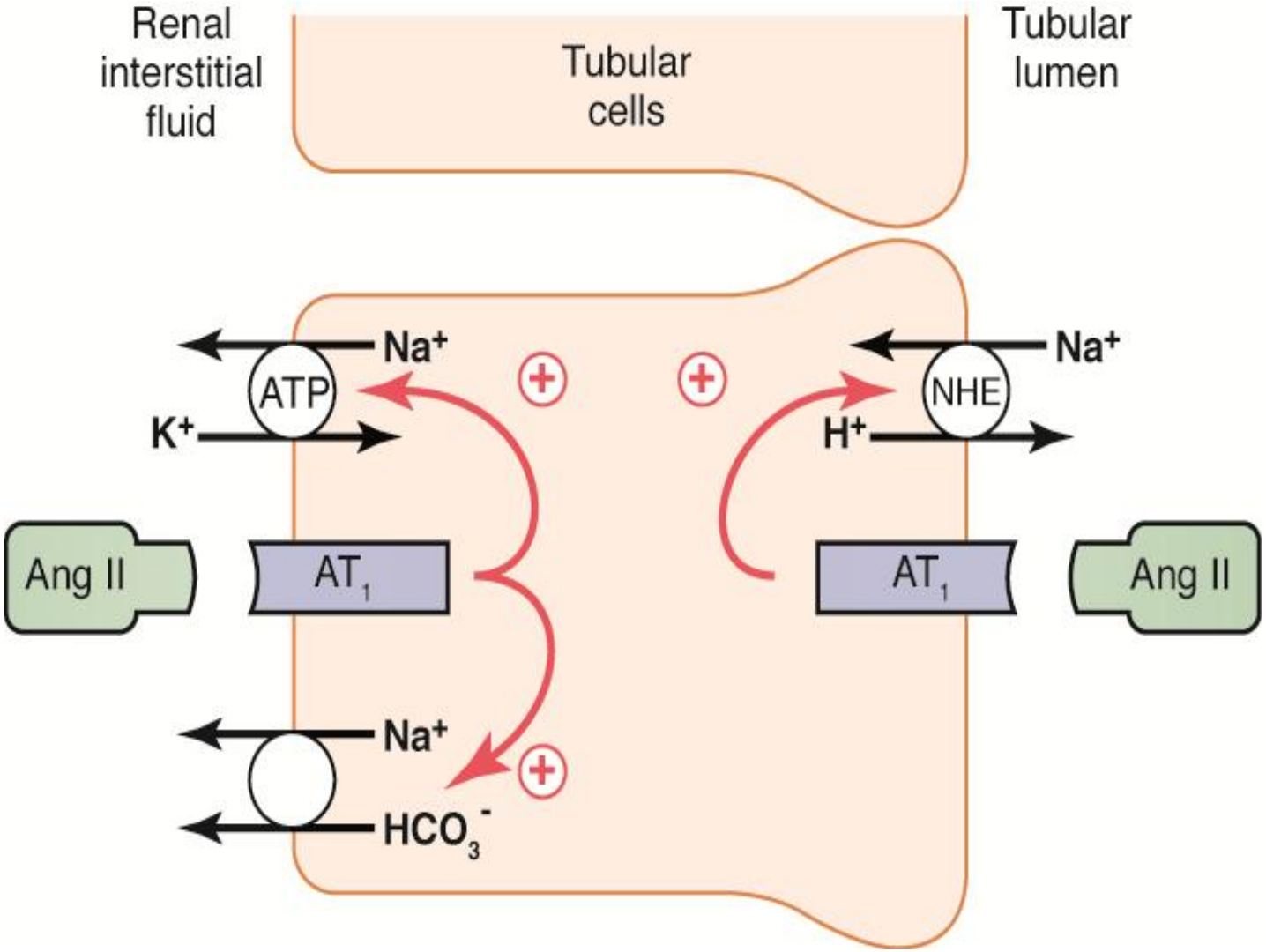
Angiotensin II Increases Na^+ and Water Reabsorption

- Stimulates aldosterone secretion

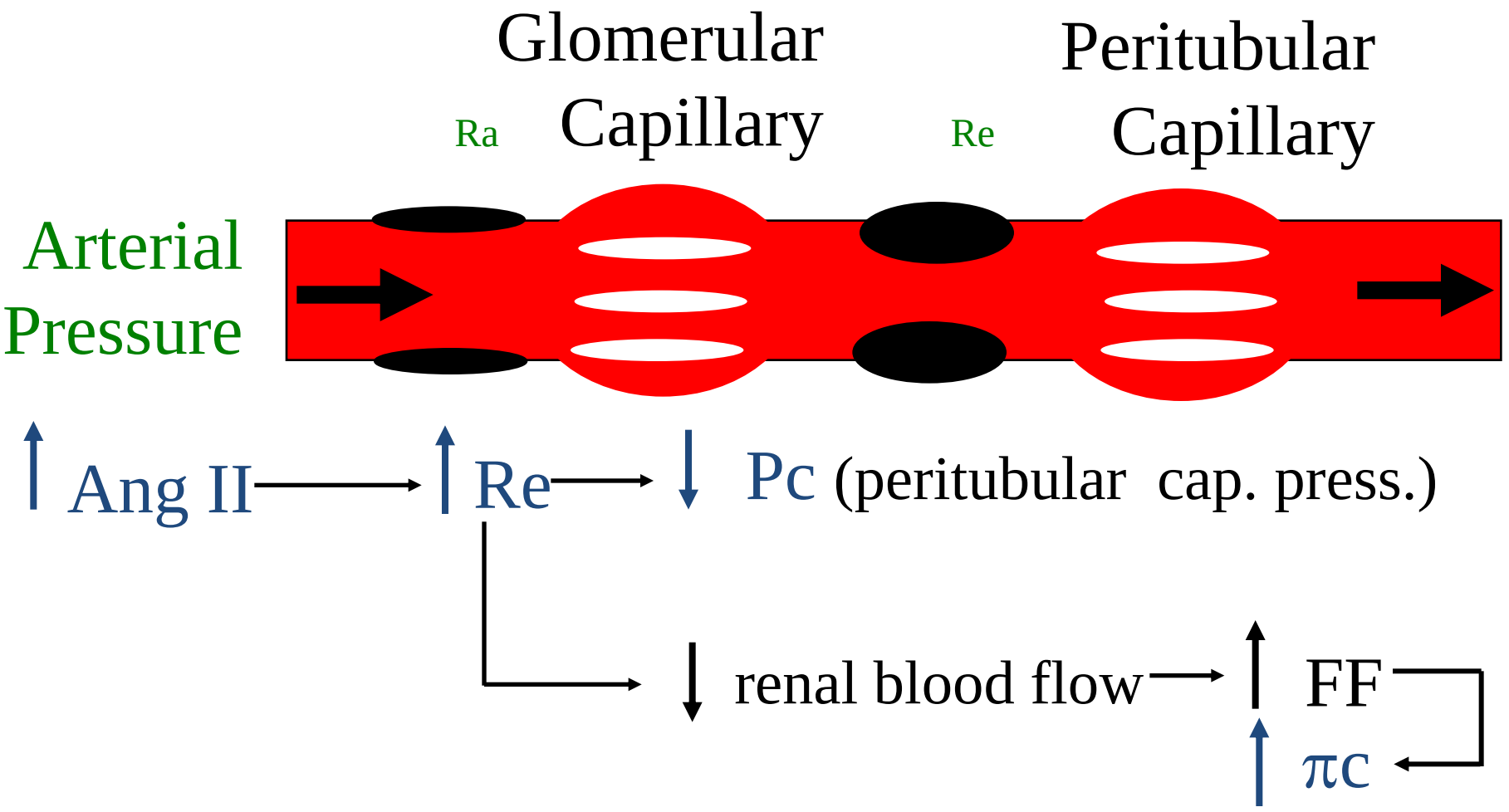
- Directly increases Na^+ reabsorption (proximal, loop, distal, collecting tubules)

- Constricts efferent arterioles
  - decreases peritubular capillar hydrostatic pressure
  - increases filtration fraction, which increases peritubular colloid osmotic pressure

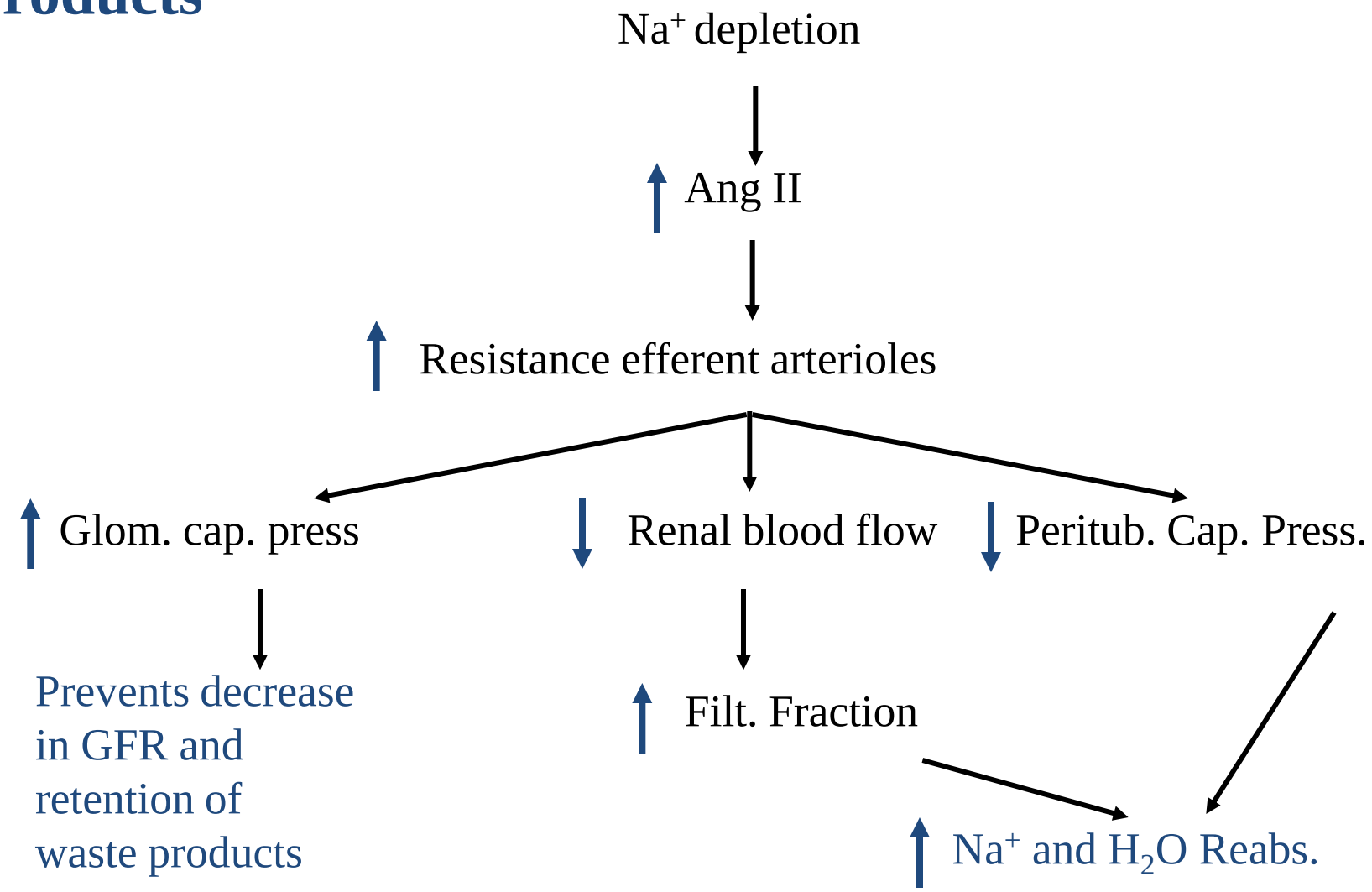
Angiotensin II increases renal tubular sodium reabsorption



Effect of Angiotensin II on Peritubular Capillary Dynamics



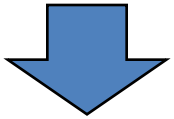
Ang II constriction of efferent arterioles causes Na^+ and water retention and maintains excretion of waste products



Angiotensin II blockade decreases Na^+ reabsorption and blood pressure

- ACE inhibitors (captopril, benazipril, ramipril
- Ang II antagonists (losartan, candesartin, irbesartan
- Renin inhibitors (aliskirin

- decrease aldosterone
- directly inhibit Na^+ reabsorption
- decrease efferent arteriolar resistance



Natriuresis and Diuresis +  Blood Pressure

Segmental Variation in the Tubular System

- **The ratio of a substance's concentration in the tubular fluid to its levels in the plasma changes along the course of the tubular system depending on how it is handled.**
- **The next Figure describes these changes. Notice how levels of glucose and amino acids drop to extinction even before the tubular fluid completes its passage through the proximal tubule.**
- **The TF/P for sodium remains 1 in the proximal tubule since Na+ and water are reabsorbed in the same proportion.**
- **For inulin, however, TF/P reaches 3 in the proximal tubule since 65% of water and none of the inulin is reabsorbed.**
- **Regarding PAH, its levels in the proximal tubule are higher than those of the others. The reason is that it is not only filtered, but also actively secreted and not reabsorbed.**

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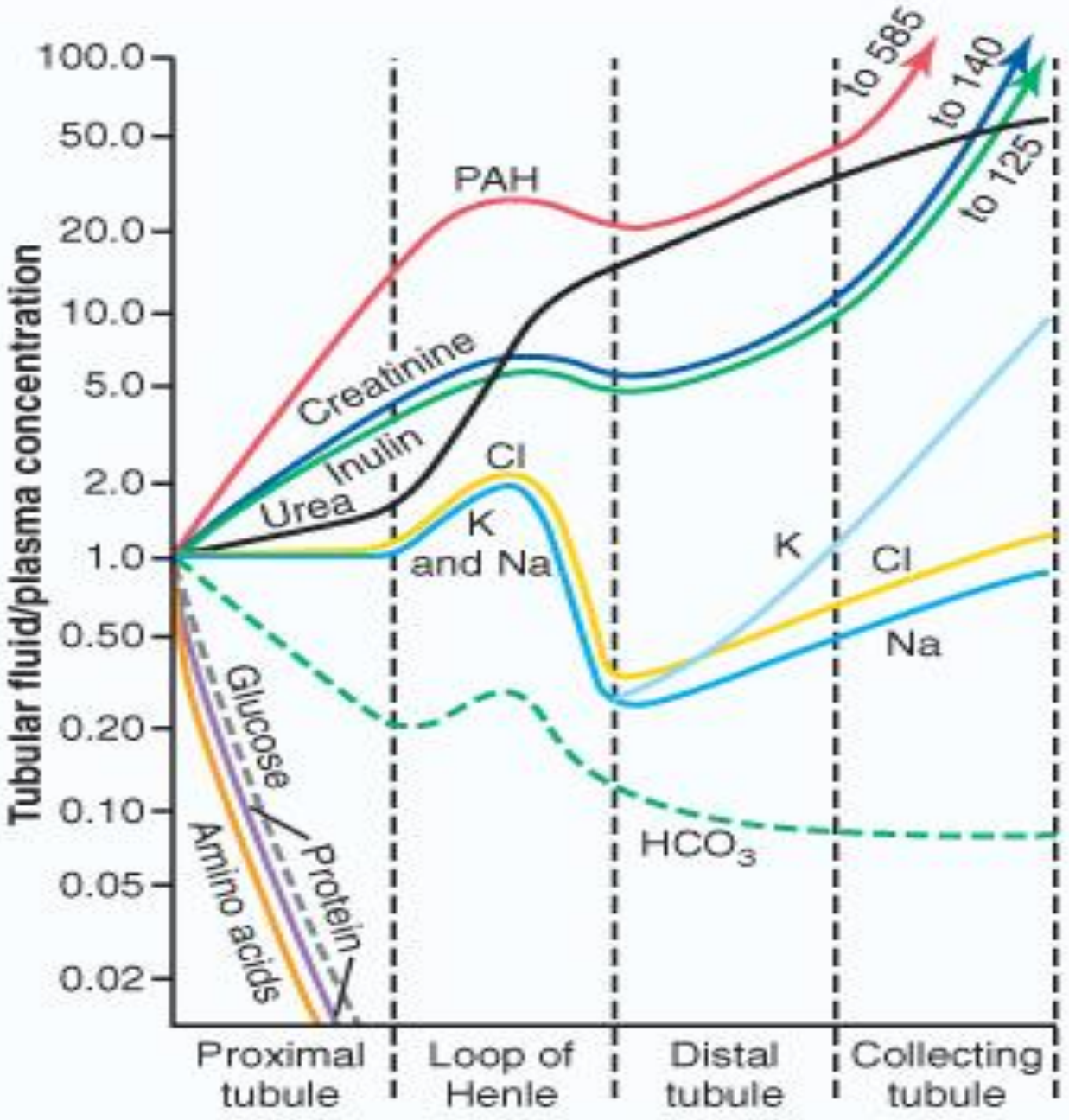

Tubular fluid/plasma concentration
100.0
50.0
20.0
10.0
5.0
2.0
1.0
0.50
0.20
0.10
0.05
0.02
PAH
Creatinine
Inulin
Urea
Cl
K
and Na
Glucose
Amino acids
Protein
HCO_3
K
Cl
Na
To 585
to 140
to 125
Proximal tubule
Loop of Henle
Distal tubule
Collecting tubule

Sodium Homeostasis

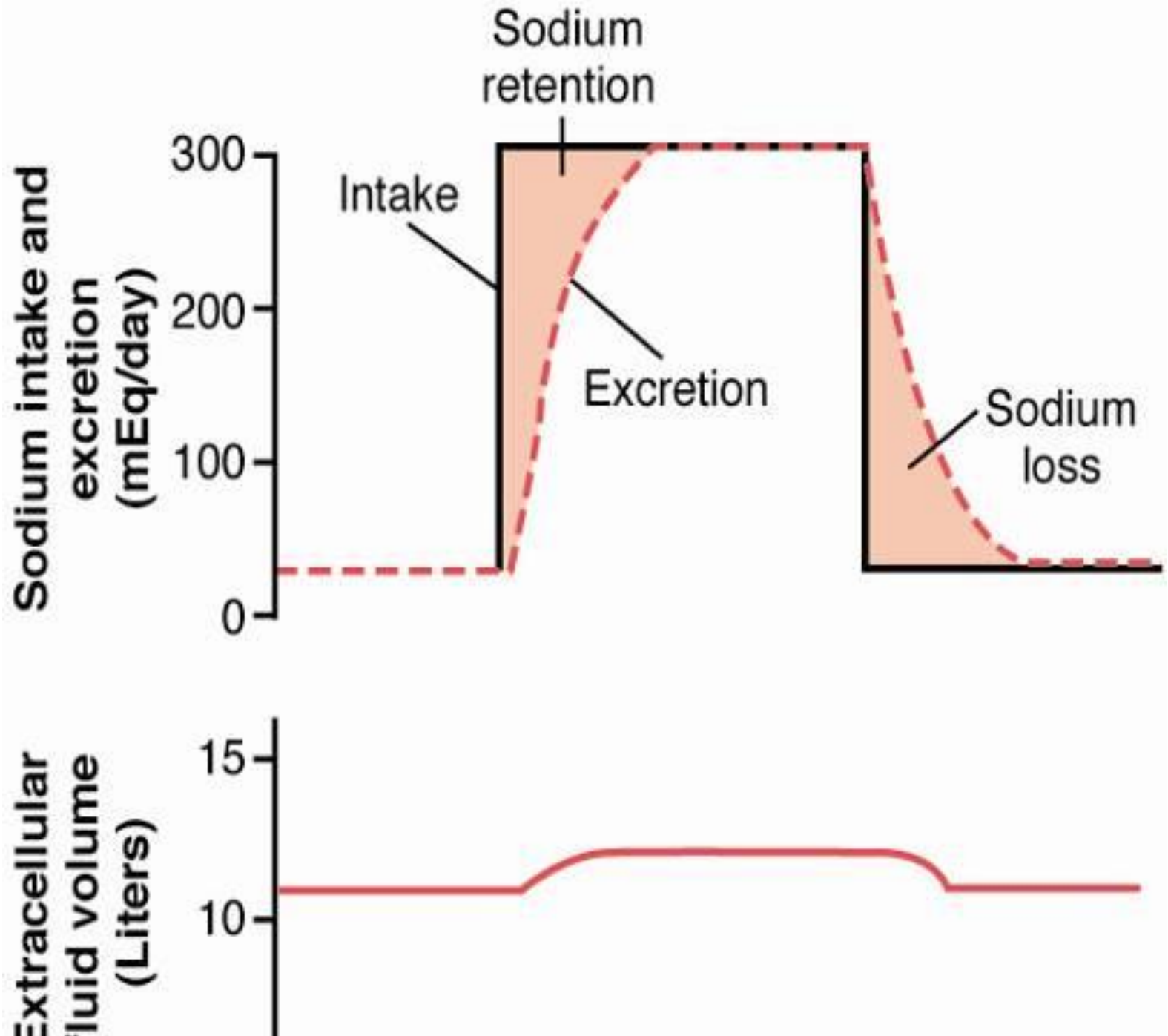
- 65% is in ECF 140 mEq/L.
- 5-10% is in ICF 10-30 mEq/L.
- 25% is in bone nonexchangable.
- ↓ Na in ECF → volume contraction.
- ↑ Na in ECF → volume expansion and edema.
- **- Most of the primary active transport in the entire tubular system is to transport Na^+**

Sodium Homeostasis

- **Sodium is an electrolyte are major importance in the human body. It is necessary for :**

1. **normal extracellular volume dynamics: more Na means volume**
2. **excitability of certain tissues**
3. **cotransport and countertransport**
4. **countercurrent mechanism: the ability of kidney to make concentrated urine**
5. **Sodium accounts for a significant portion of plasma osmolarity. The latter can be estimated by multiplying plasma sodium concentration times 2.1.**
6. **blood pressure**

asing sodium intake 10-fold on urinary sodium excretion and extracellular fluid



Sodium Balance

- **Sodium balance is achieved when intake and output equal each other.**
- **Sodium intake is about 155mmol/d in the average American diet. Logically, the daily output would be 155mmol/d as well.**
- **The kidney accounts for 150mmol of this output. Hence, the kidney is a major organ in sodium homeostasis.**

Na^+ & H_2O reabsorption occurs as the following :

Segment	Na+%	H2O%
Proximal tubule	65%	65%
Descending (Henle)	-	15%
Ascending (Henle	25%	-
Distal tubule	5%	10%
Collecting duct	4%	9%

- There are 2 ways to handle Na+ in the kidney

1) Though altering Glomerular Filtration or

2) Reabsorption

- Ex: when Na+ intake↑→ ↑Na filtered → ↑ reabsorption
- This is called " glomerulotubular balance " to ensure that a constant fraction is reabsorbed (≈ 2/3) → this occurs in the proximal tubules .

A-Reabsorption in proximal tubules

- **There are 2 ways for Na transport through the cells:**

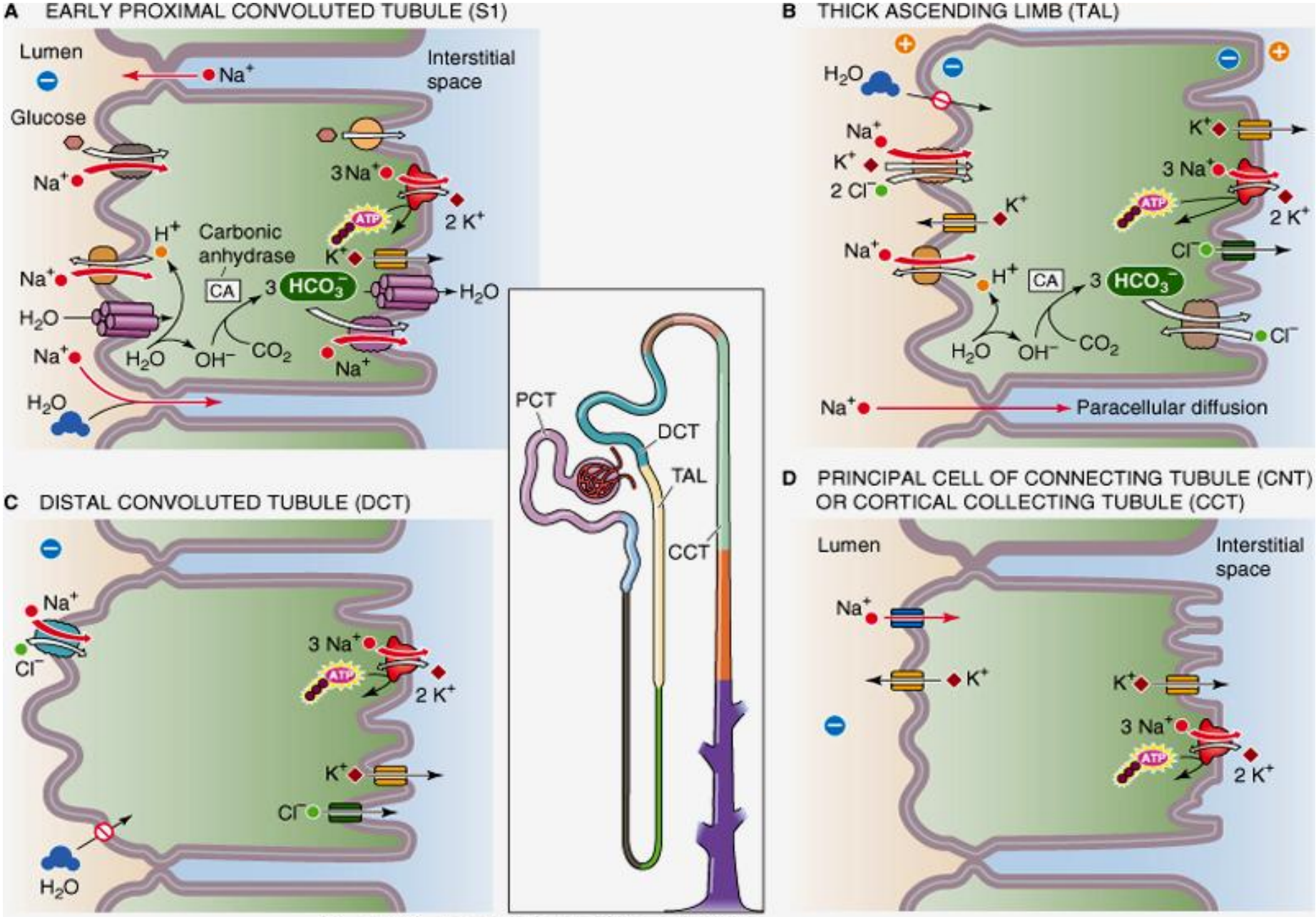
1. transcellular → channels (T-max)

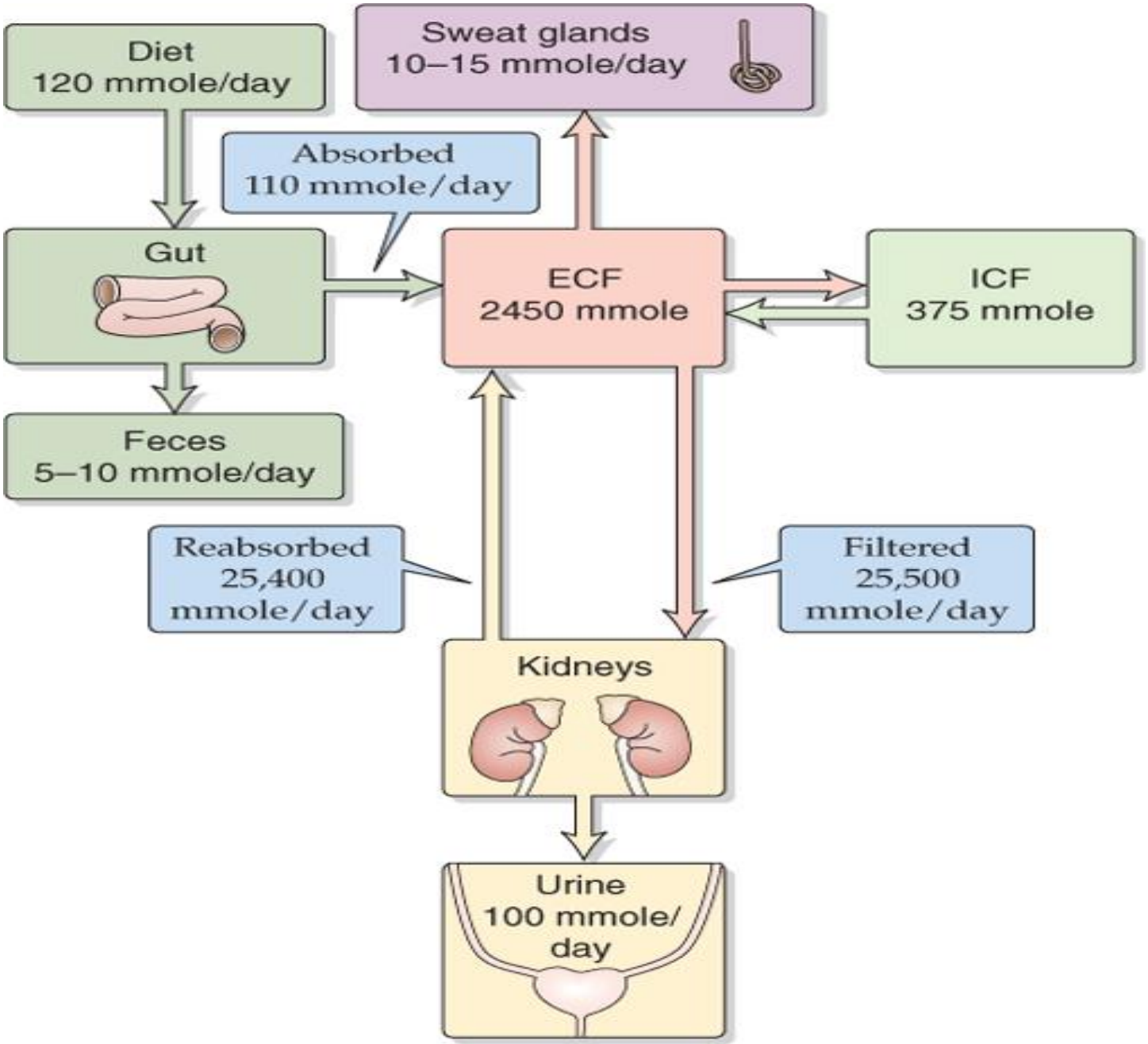
2. paracellular → tight junction

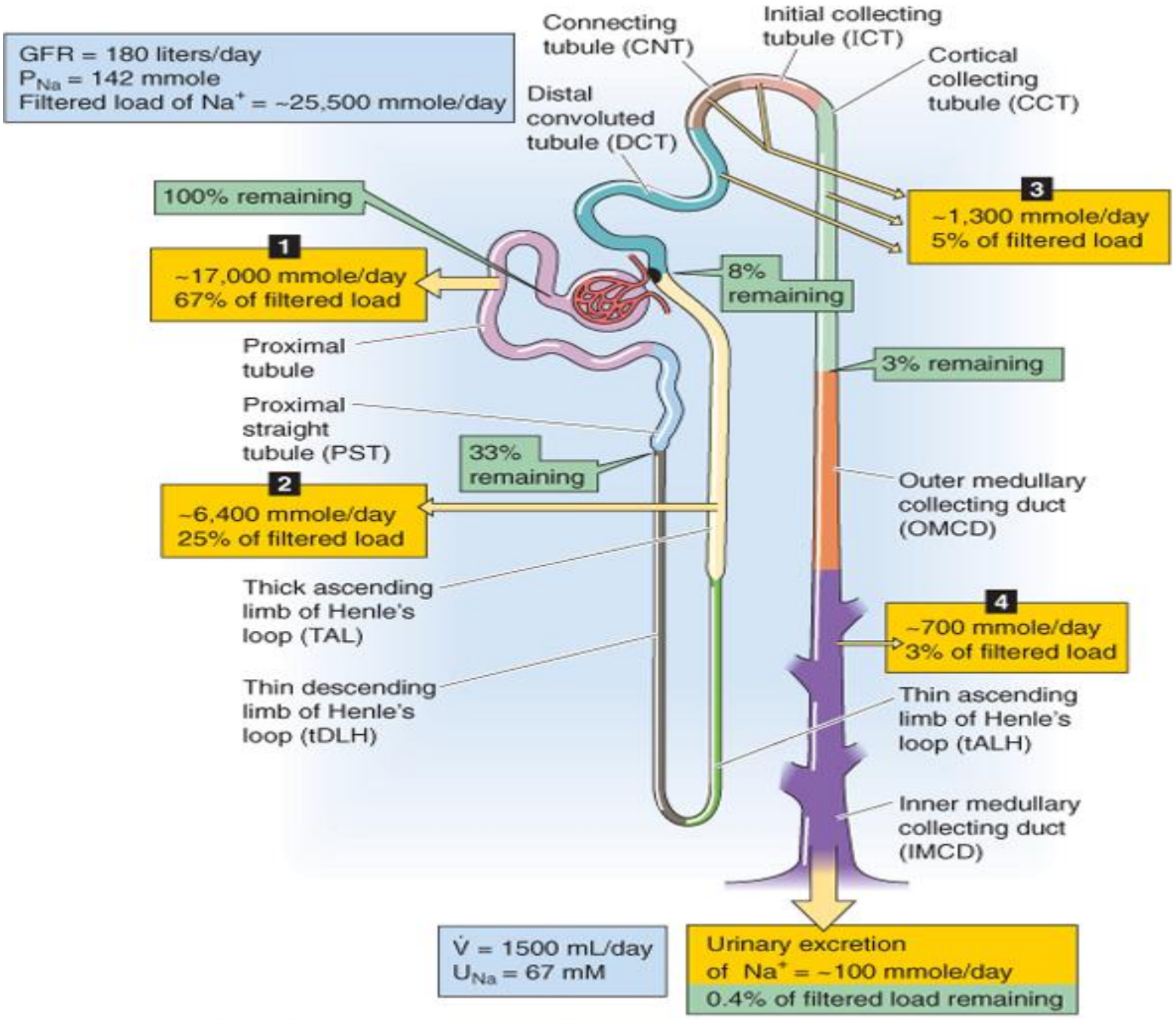
- **In the early proximal tubules, tight junctions are not that tight → paracellular route (+ transcellular route) , so transport is NOT T-max dependant → it is gradient-time dependant .**
- **↑Conc → ↑ time in prox. tubules →more chance to be reabsorbed.**
- **In more distal parts of the nephron , the tight junctions are tighter → T-max dependant transport .**

A-Reabsorption in proximal tubules

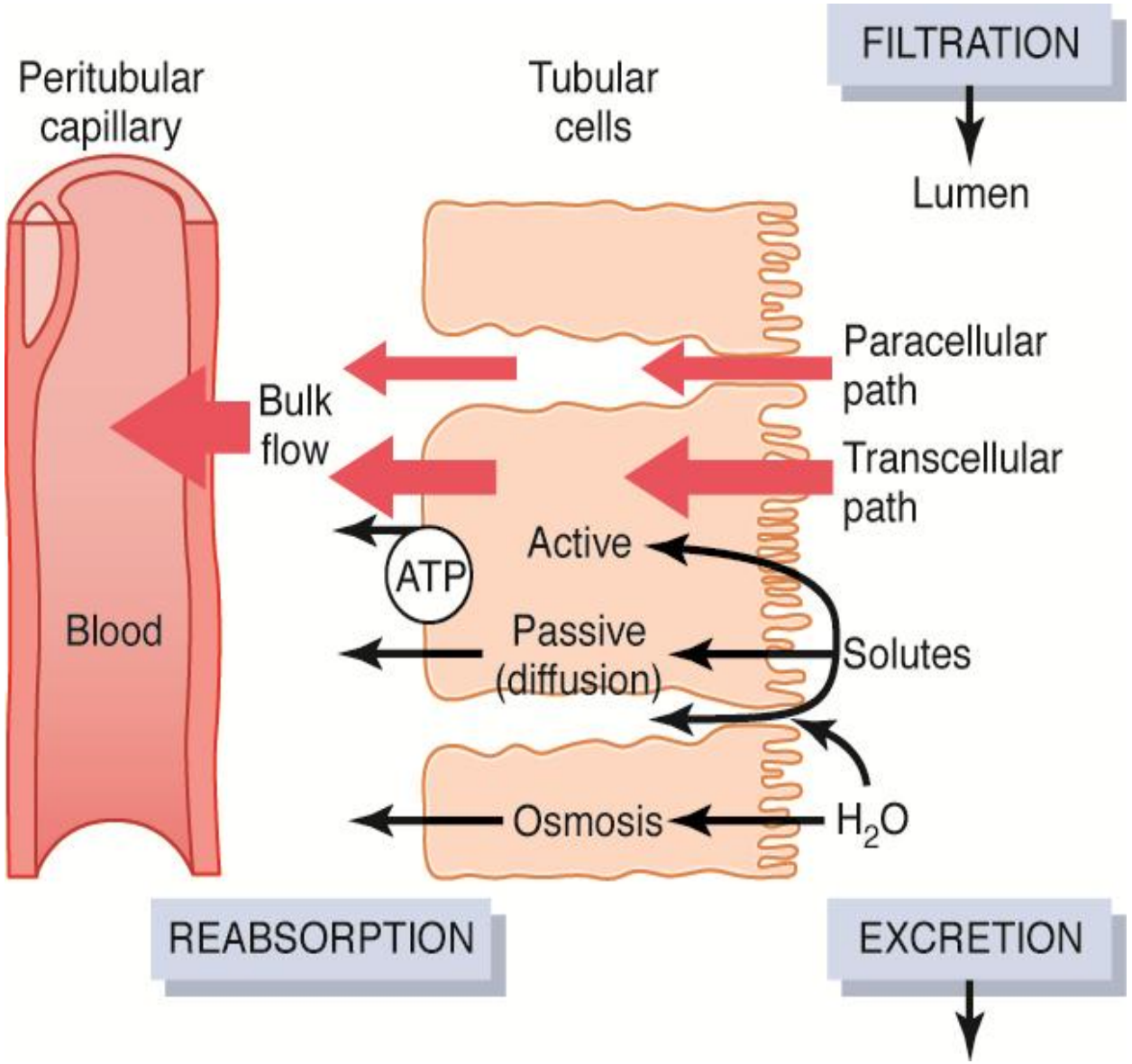
- **In the late proximal tubule , Na+ is reabsorbed with Cl- , because in the early prox.tub. , removal of large amounts of Na+ with glucose creates negativity inside the lumen. so to get back to normal , Cl- is reabsorbed. Na+ follows Cl- .**



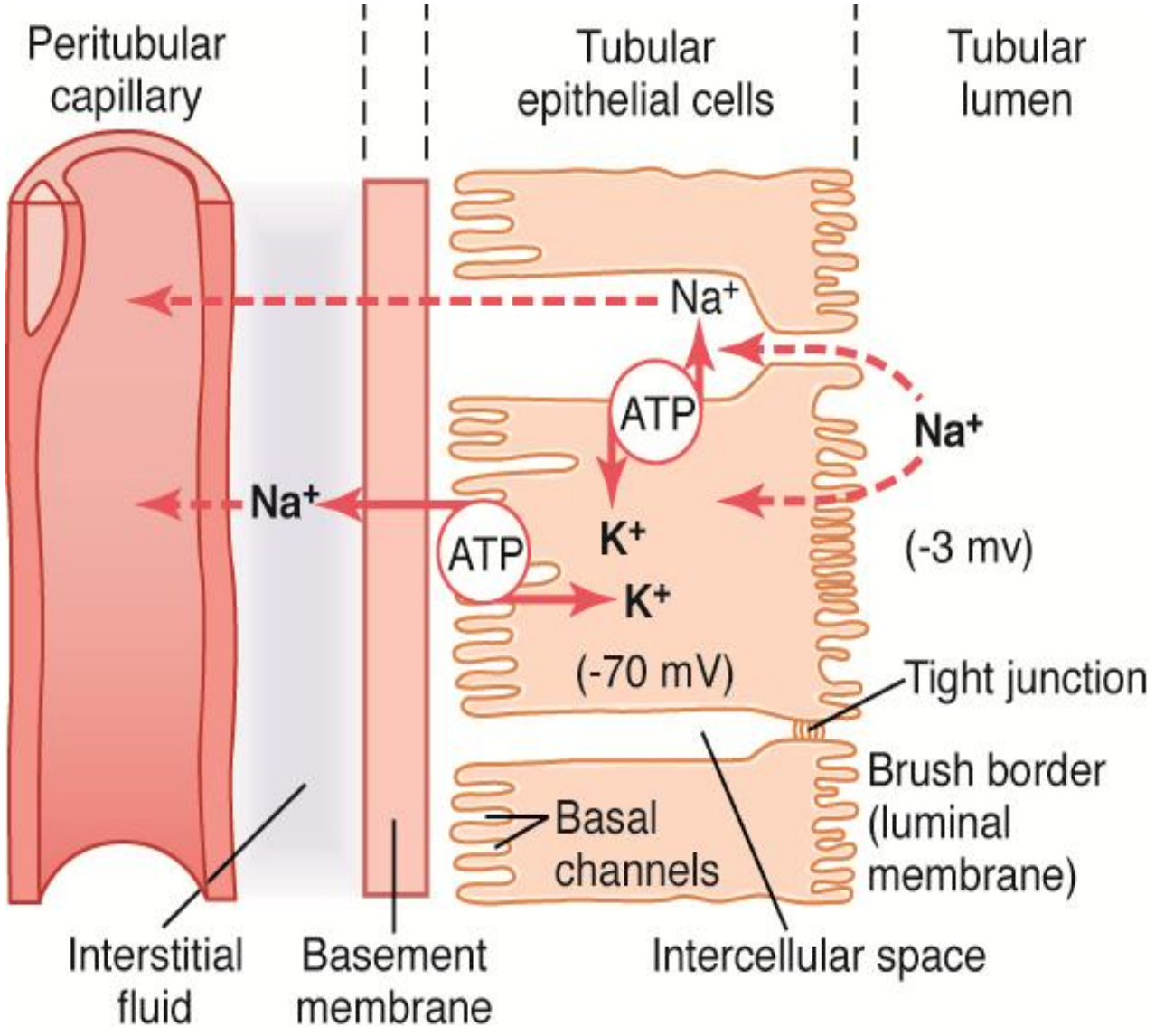




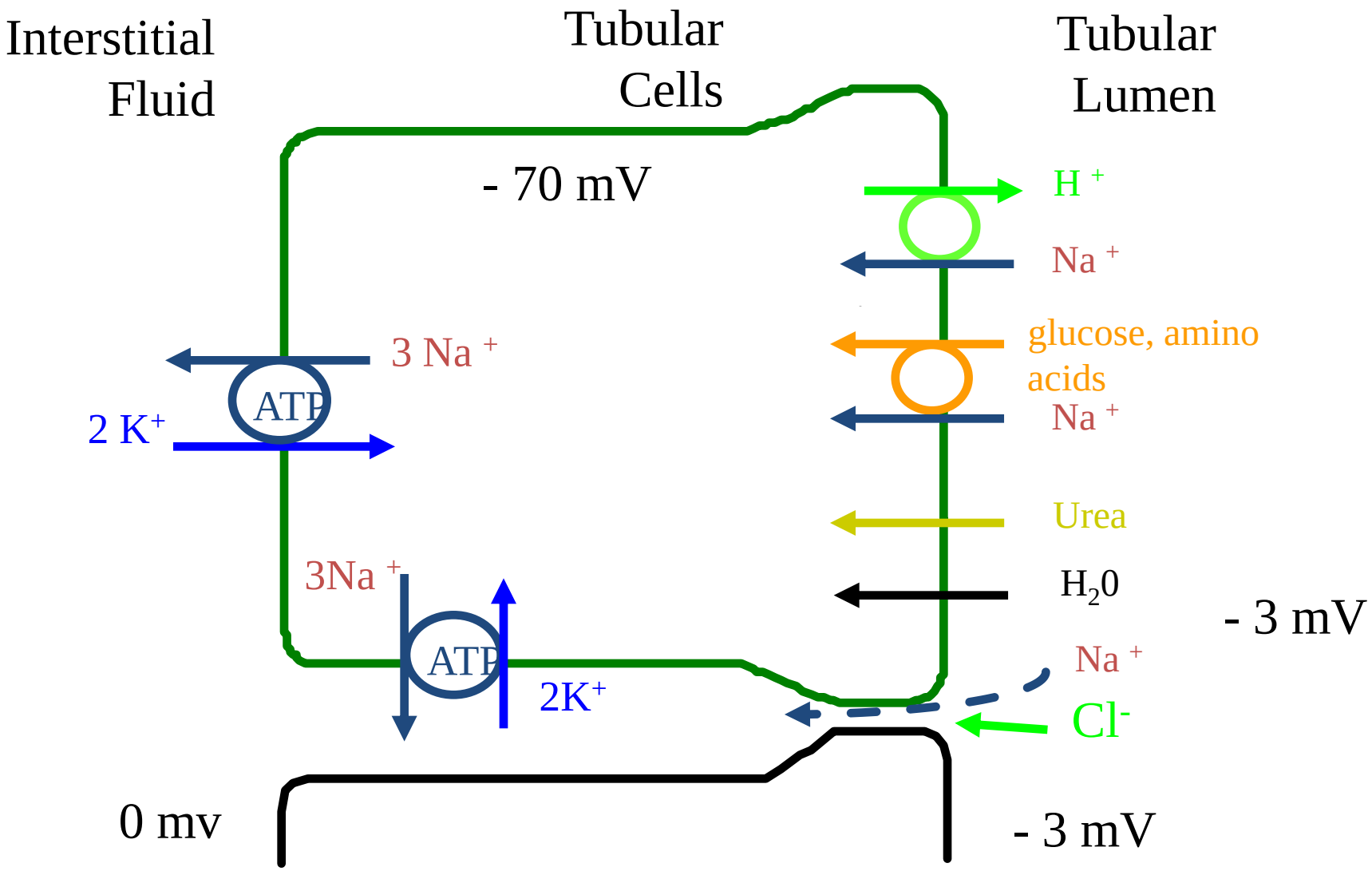
Reabsorption of Water and Solutes



Primary Active Transport of Na^+



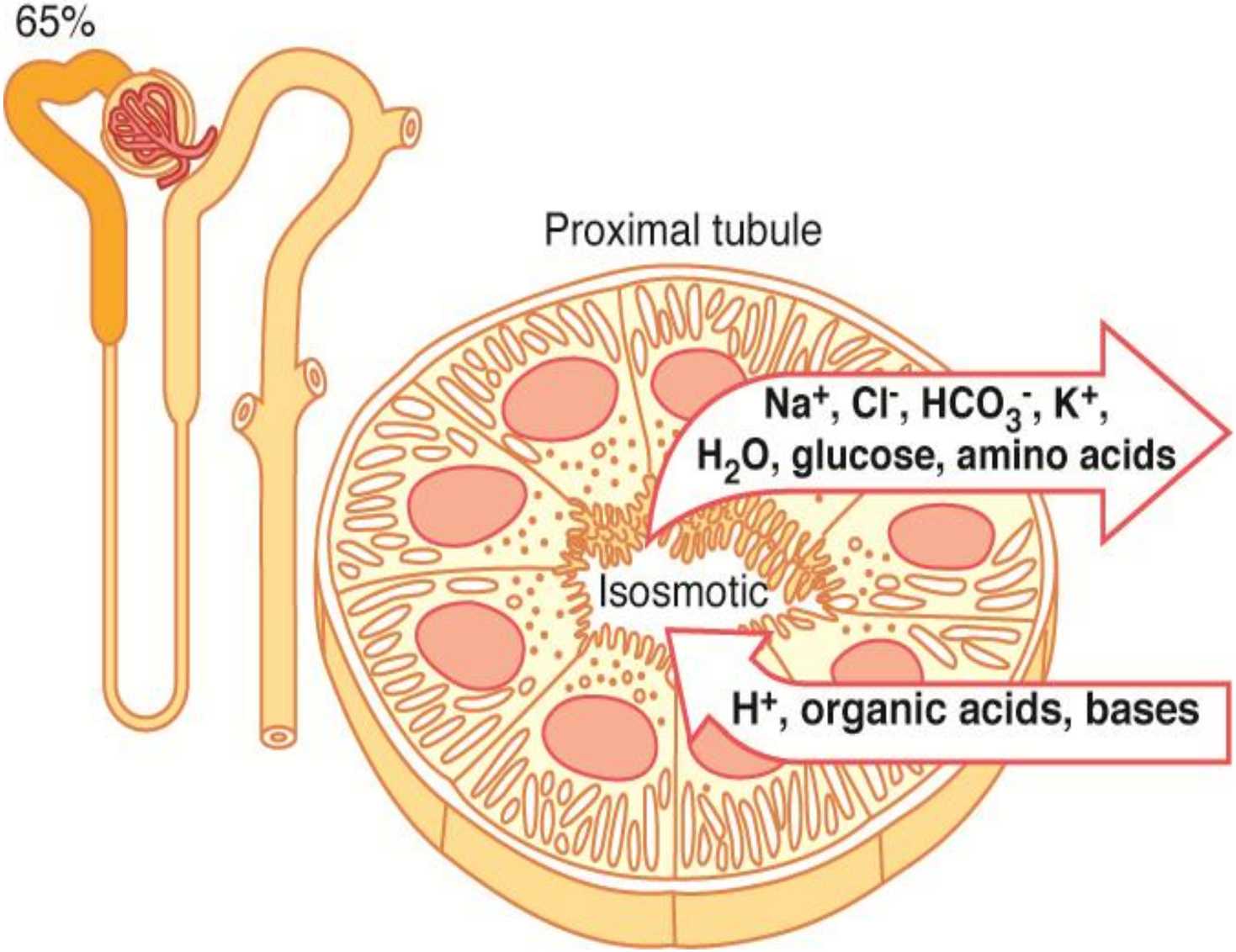
Reabsorption of Water and Solutes is Coupled to Na^+ Reabsorption



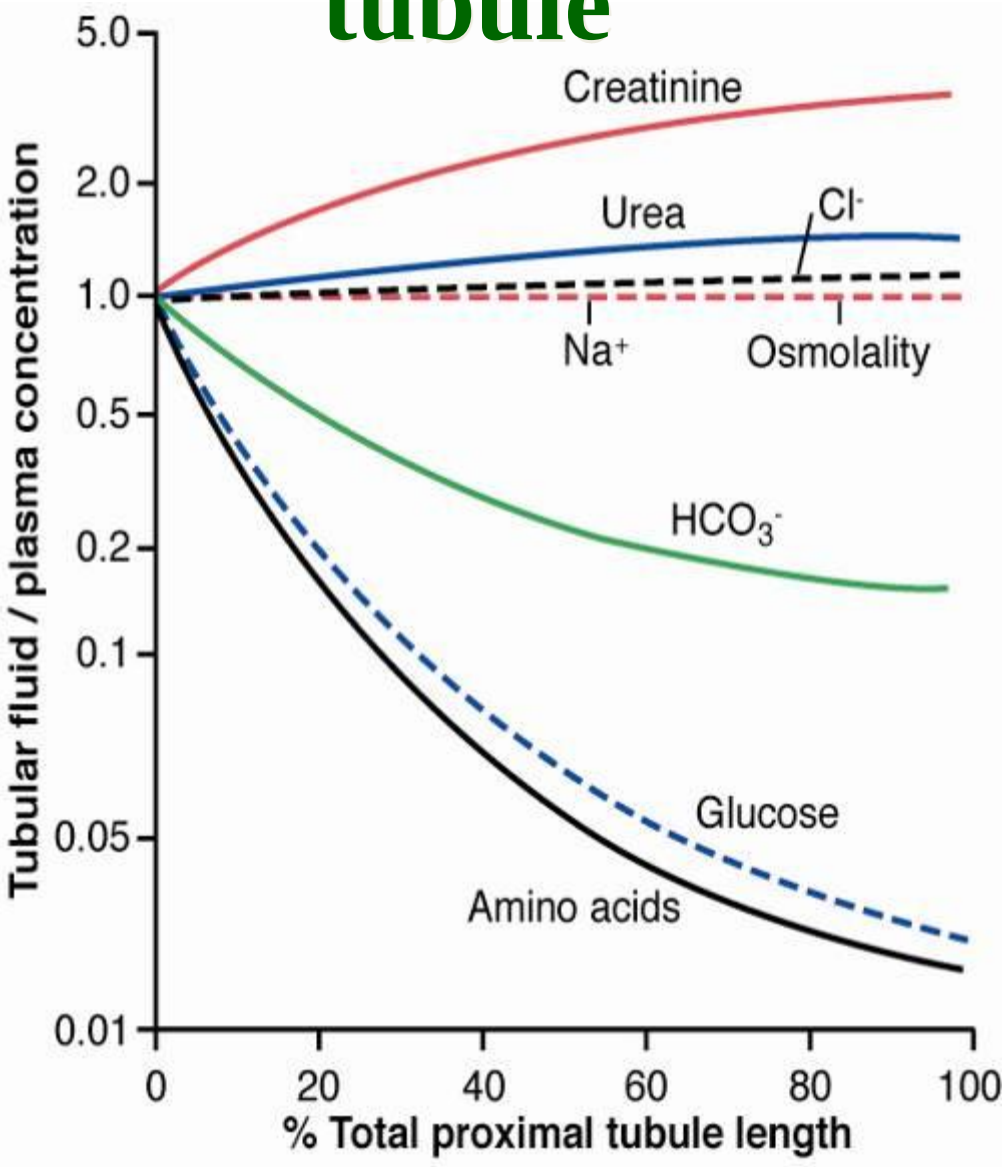
Na^+ Clearence

- Sodium clearance can be calculated as follows:
- U_{Na+} = 150mmol/d ÷ 1.5l/d = 100mmol/l
- $C_{Na+} = (U_{Na+} / P_{Na+}) * V = (100 / 145) * 1 = 0.69$ml/min
- Notice that the value is less than 1 ml/min, which indicates that sodium is mostly reabsorbed.
- Sodium reabsorption is rather extensive. In order to appreciate this, let's do the math.
- Amount of sodium filtered per day = 180l/d * 140mM = 25200mEq
- Amount of sodium excreted by the kidney = 150mEq
- Percent reabsorbed = 25050 / 25200 = 99.4%

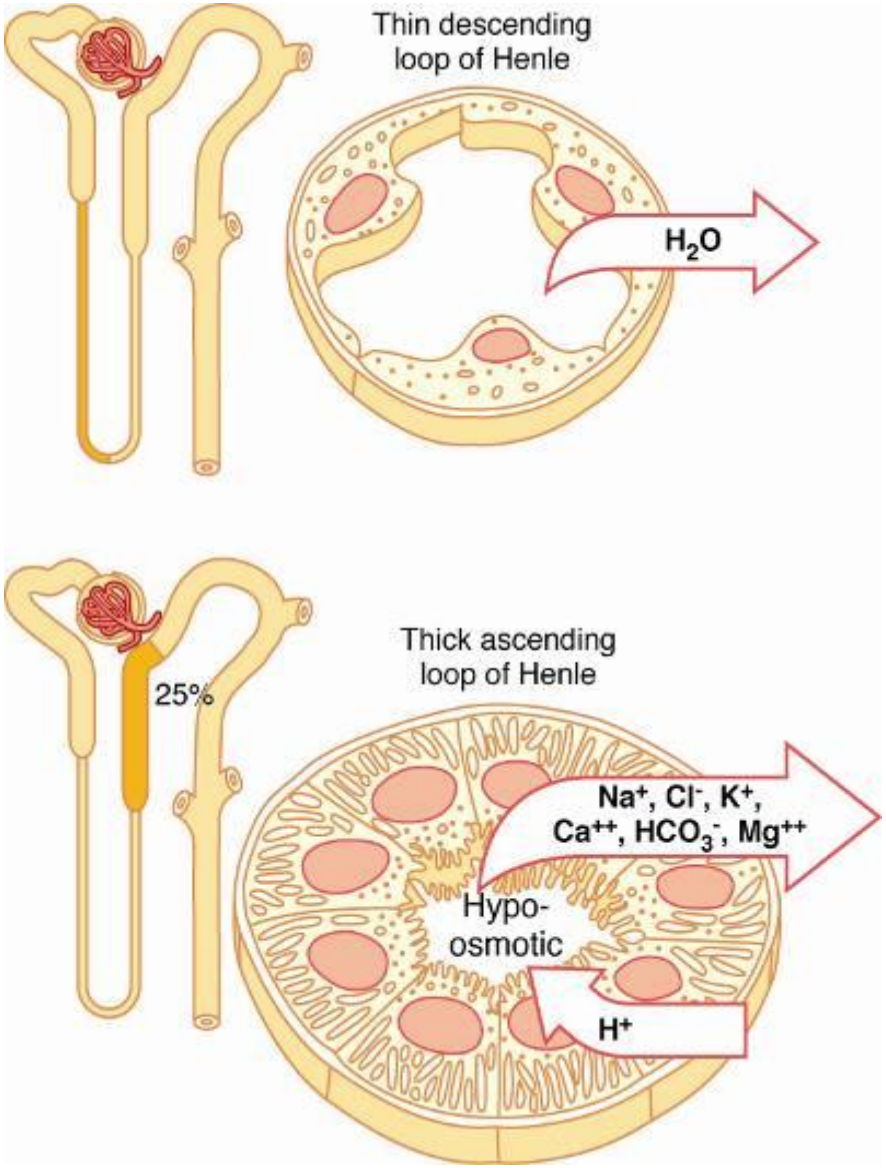
Transport characteristics of proximal tubule.



Changes in concentration in proximal tubule



Transport characteristics of thin and thick loop of Henle.



very permeable to H_2O

~ 25% of filtered load

- Reabsorption of Na^+, Cl^-, K^+, HCO_3^-, Ca^{++}, Mg^{++}
- Secretion of H^+
- not permeable to H_2O

Clinical point

1. **Furesamide (Lasix): a potent loop diuretic acts on the thick ascending limb of Henle TAL where it inhibits Na-2Cl-K → ↑ Na Excretion.**

   Indicated in pulmonary edema & hypertension.

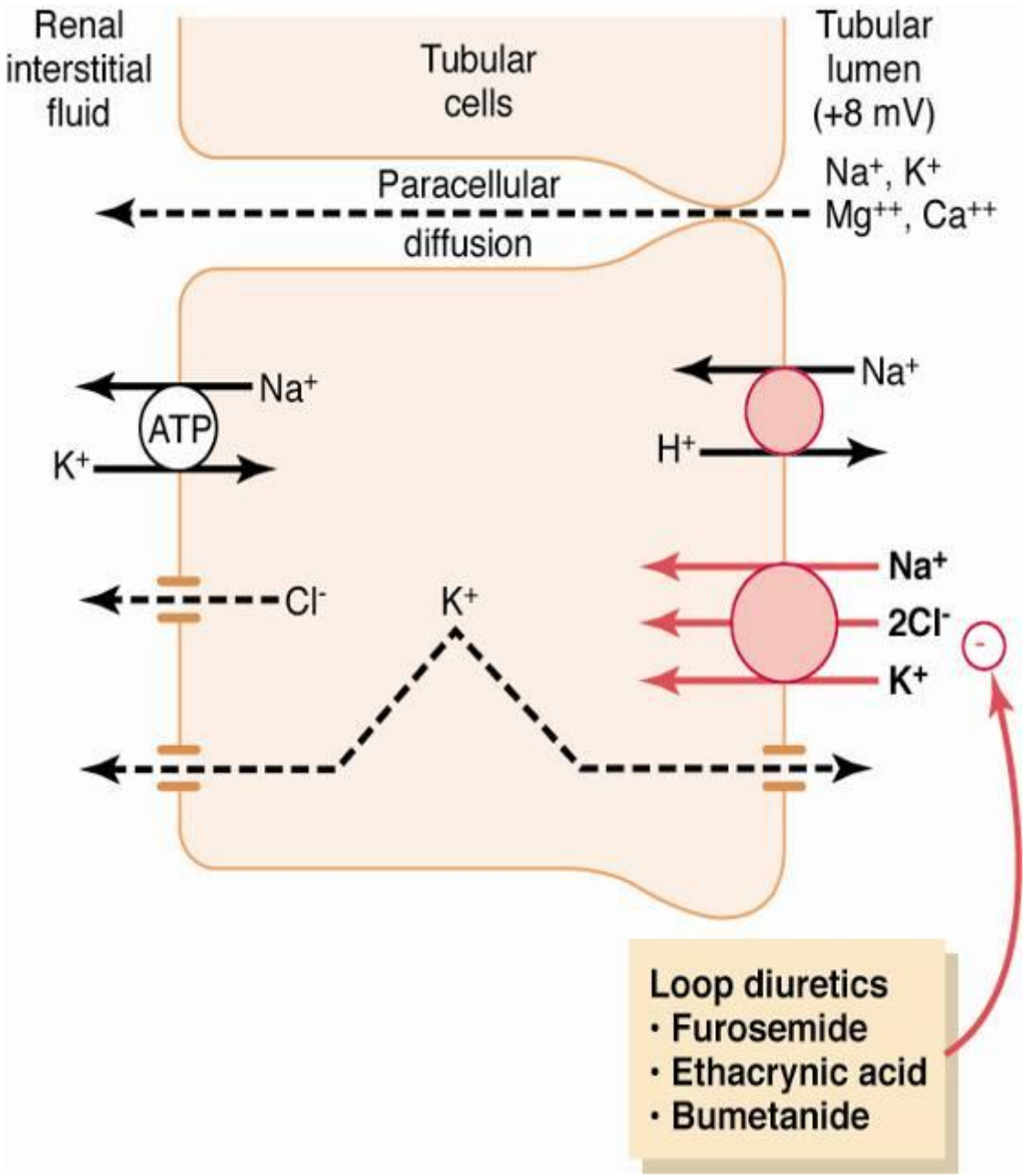
2. **Thiazide/Chlorothiazide (moderate diuretic) acts on distal convoluted tubule DCT inhibiting Na/Cl reabsorption**

- **Those 2 diuretics are called [k+_ wasting diuretics]**
-

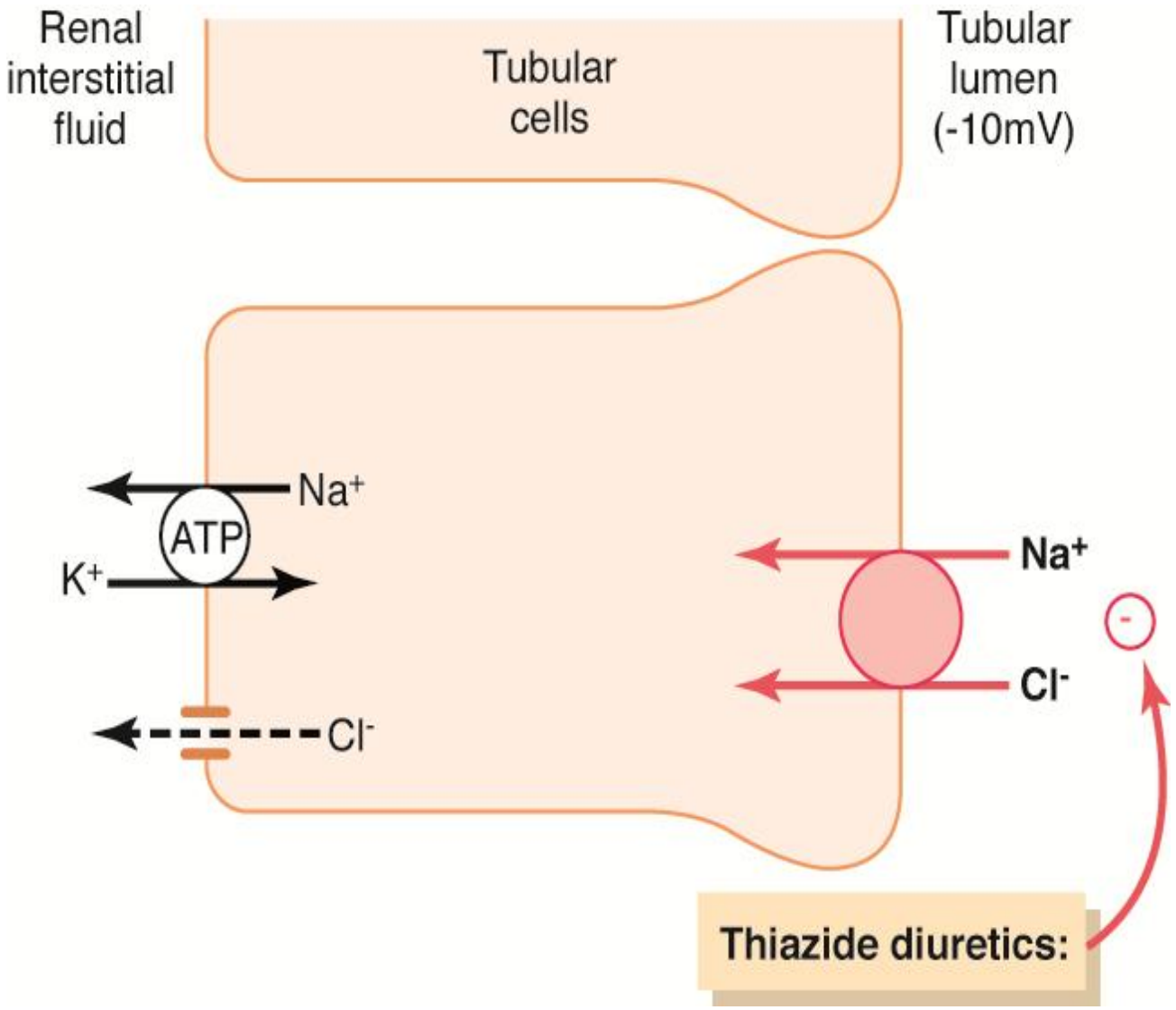
Clinical point cont.

- 1. **Spironolactone** (aldactone): works on principal cells by decreasing K+ secretion → such diuretics are called [K+ sparing diuretics] or [aldosterone antagonists].
- 2. **Osmotic diuretics** , (ex: Mannitol) is a glomerular marker & has an osmotic effect i.e. it's not reabsorbed so it drives H2O with it , used in brain edema .

Sodium chloride and potassium transport in thick ascending loop of Henle



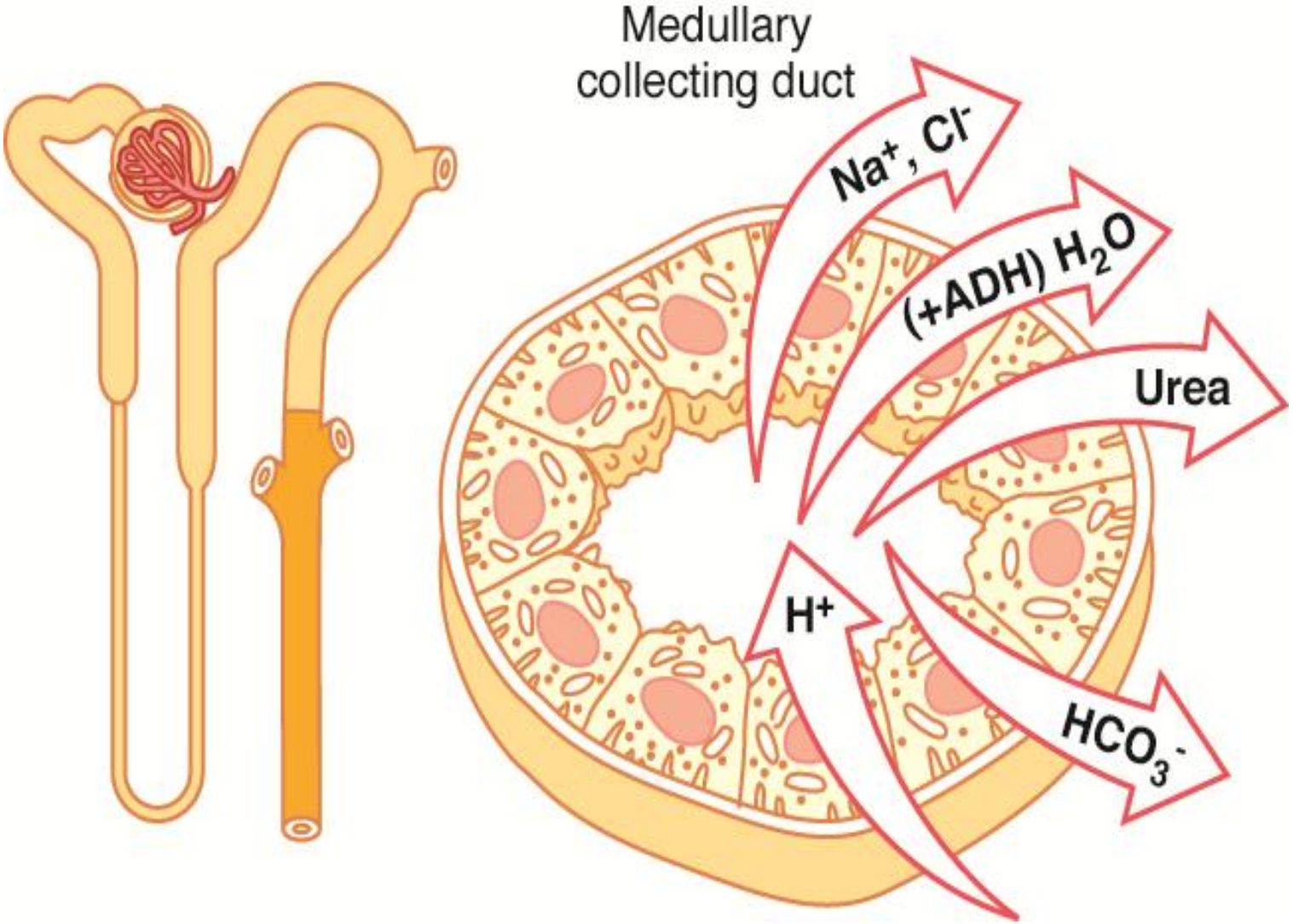
Early Distal Tubule



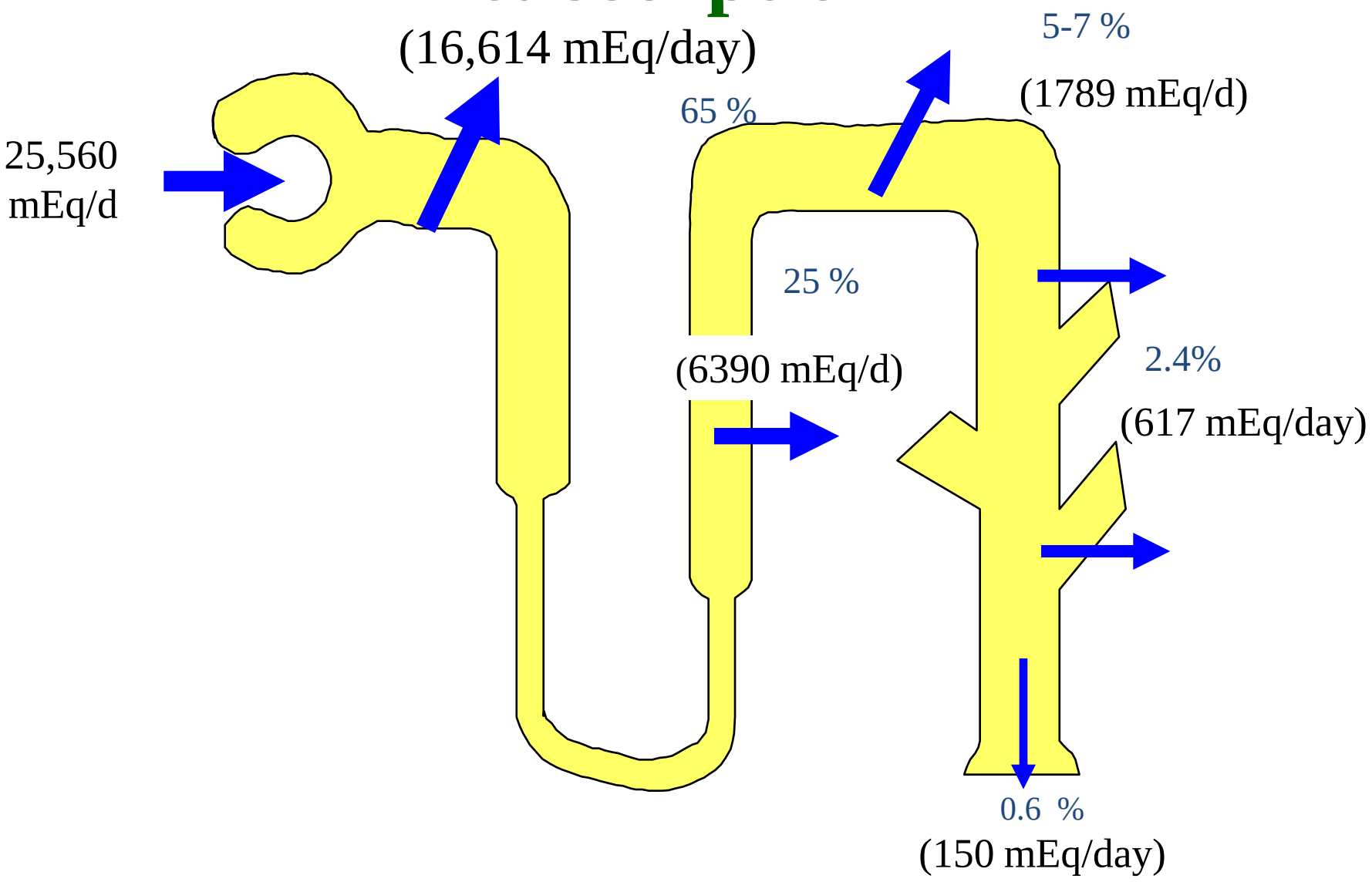
Early Distal Tubule

- Functionally similar to thick ascending loop
- Not permeable to water (called diluting segment)
- Active reabsorption of Na^{+}, Cl^{-}, K^{+}, Mg^{++}
- Contains macula densa

Transport characteristics of medullary collecting ducts



Normal Renal Tubular Na^+ Reabsorption



sodium homeostasis

- **Three factors are principally involved in sodium homeostasis:**

1. **GFR,**
2. **Aldosterone,**
3. **Atrial natriuretic peptide.**

Control of Na^+

- when Na+ intake ↑ → ↑GFR by : -
  - ↑ECV
  - ↑ BP
  - ↓ peritubular π
- when ECV ↑ → ↓ π peritubular capillary due to dilution → ↓ Reabsorption.

- **When Na^+ intake ↑ Glomerulotubular feedback is not working for unknown reason→ ↑ Na Excretion.**

↑ Na intake → ↑ pressure→ ↑ filtration & this is called (Pressure Natriuresis)