Urine Formation by the Kidneys II. Tubular Reabsorption and Secretion

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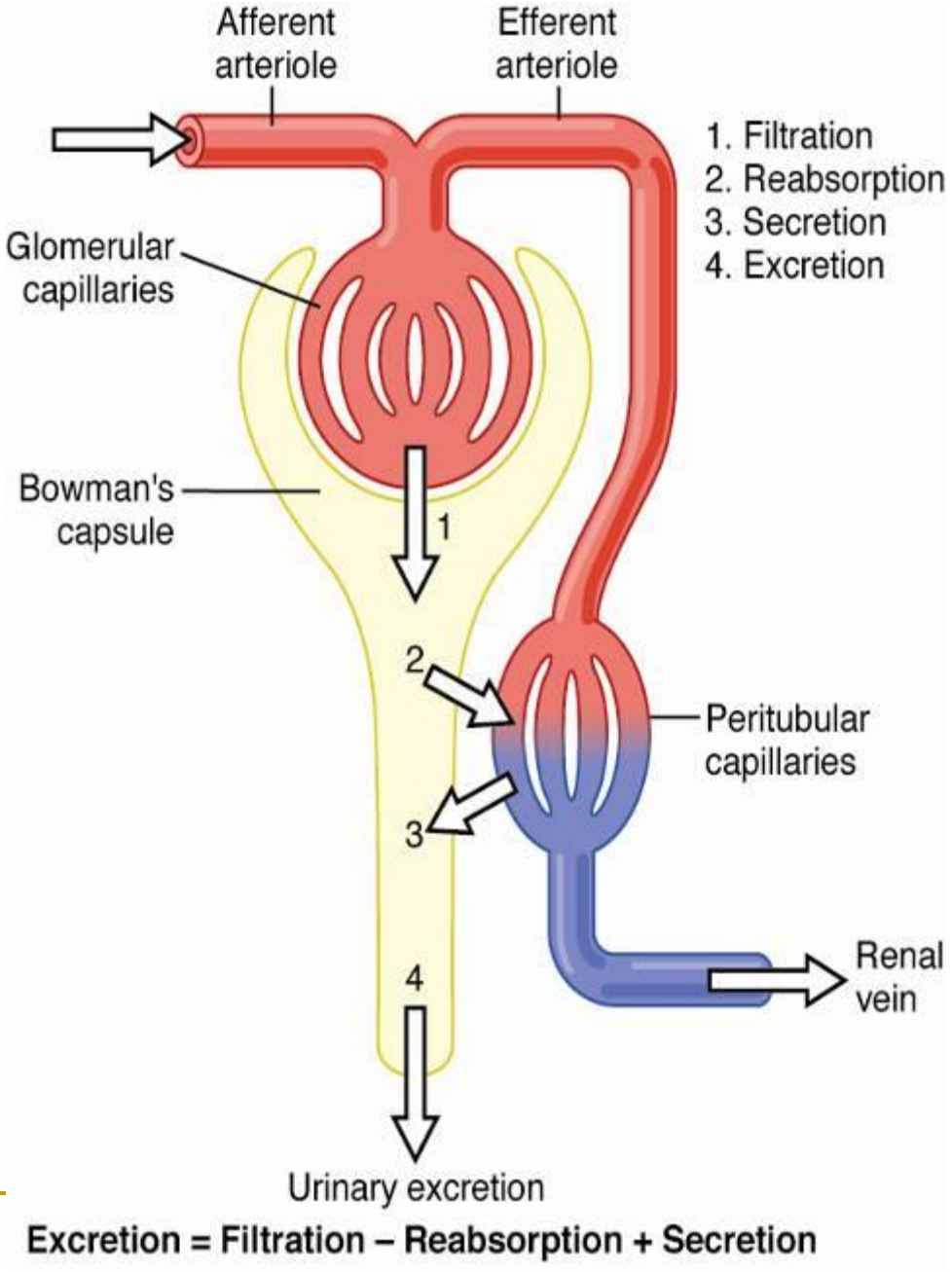
Basic Mechanisms of Urine Formation



Example: Given the following data, calculate the rate of Na^+ filtration, excretion, reabsorption, and secretion

GFR =100 ml/min or (180L/D)

P_{Na} = 140 mEq/L

urine flow = 1 ml/min

urine [Na+] = 100 mEq/L

Filtered load of Na = GFR x P_{Na}

= 180 L/D x 140 mEq/L = 25,200 mEq/D

Excretion Na = Urine flow rate x Urine Na conc

=.1.5 L/D x 100 mEq/L

= 150 mEq/D

Example: Given the following data, calculate the rate of Na^+ filtration, excretion, reabsorption, and secretion

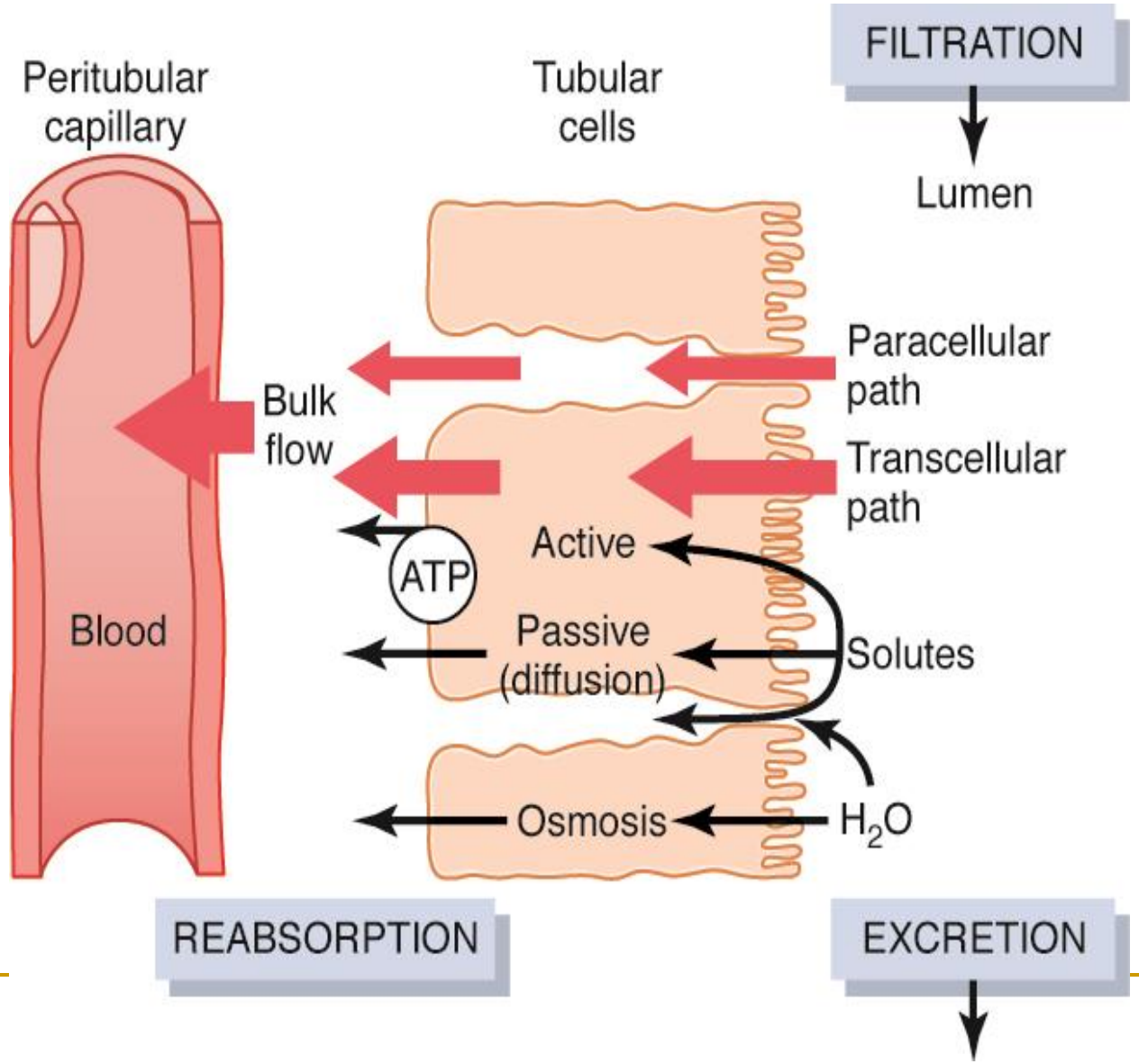
GFR =100 ml/min;
P_{Na} = 140 mEq/L
urine flow = 1 ml/min;
urine Na conc = 100 mEq/L

Filtration Na = 0.1 L/min x 140 mEq/L = 14 mEq/min
Excretion Na = .001 L/min x 100 mEq/L = 0.1 mEq/min
Reabsorption Na = Filtration Na - Excretion Na

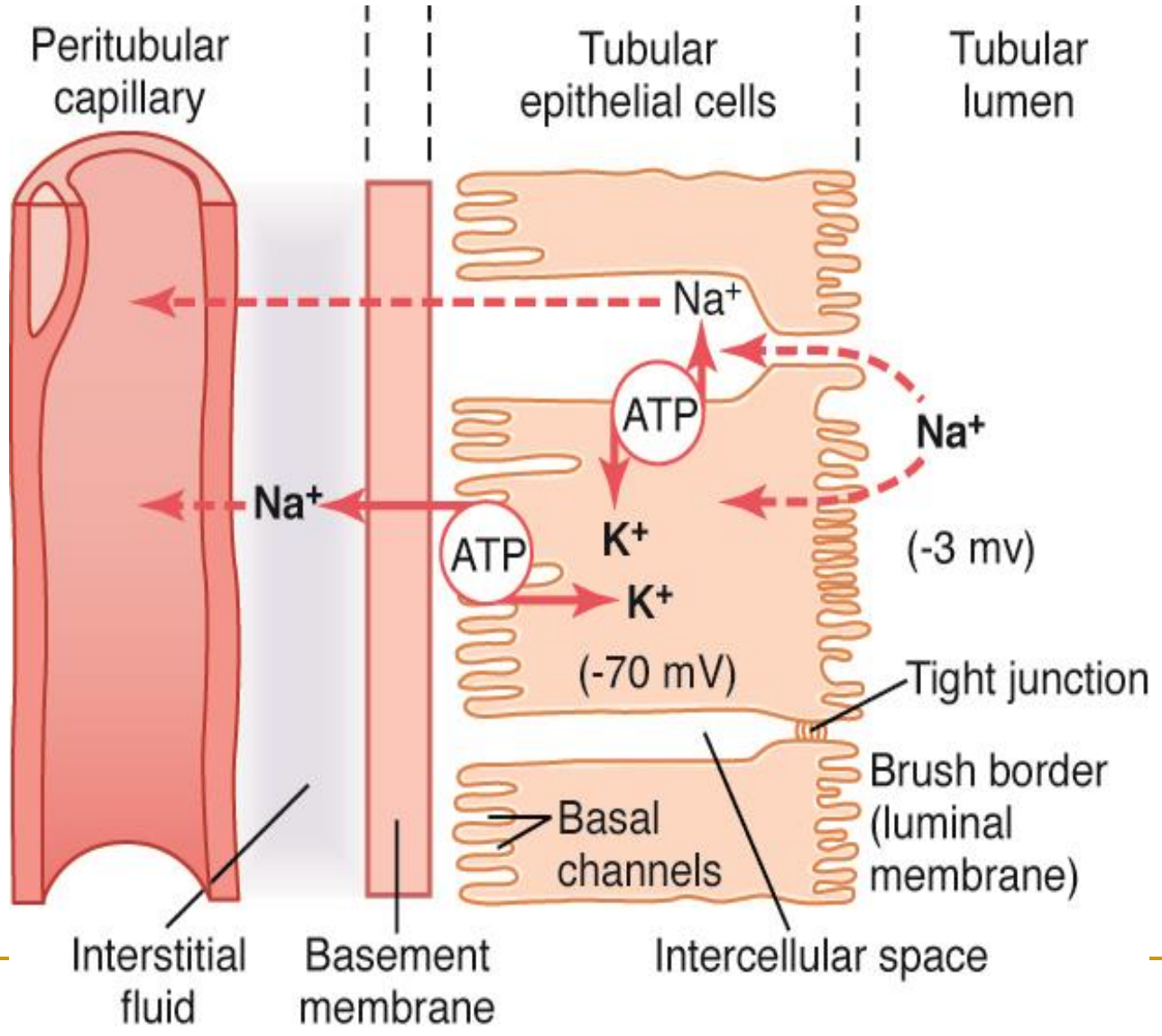
Reabs Na = 14.0 - 0.1 = 13.9 mEq/min

Secretion Na = There is no net secretion of Na since Excret Na < Filt Na

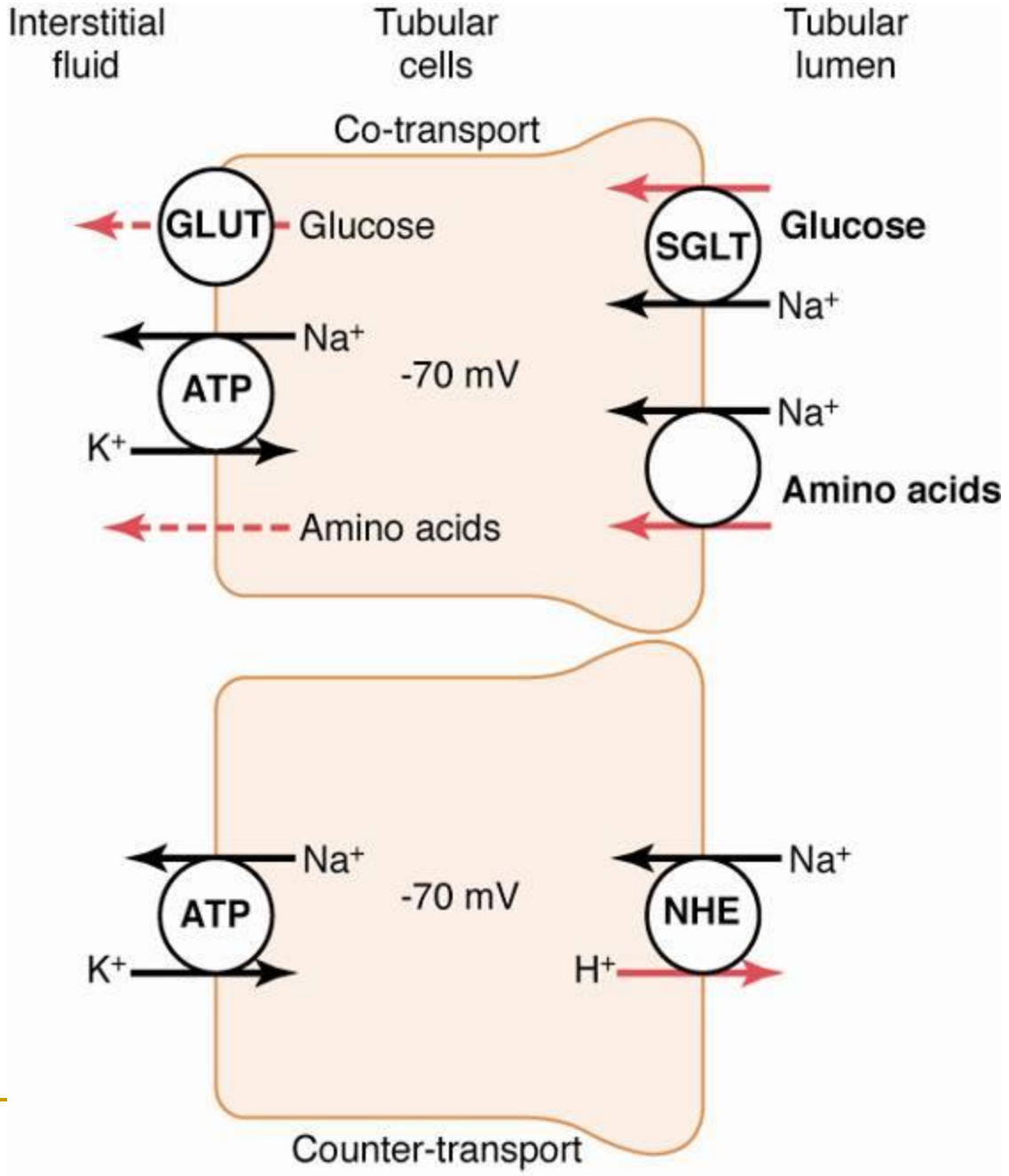
Reabsorption of Water and Solutes



Primary Active Transport of Na^+



Mechanisms of secondary active transport. Dapagliflozin



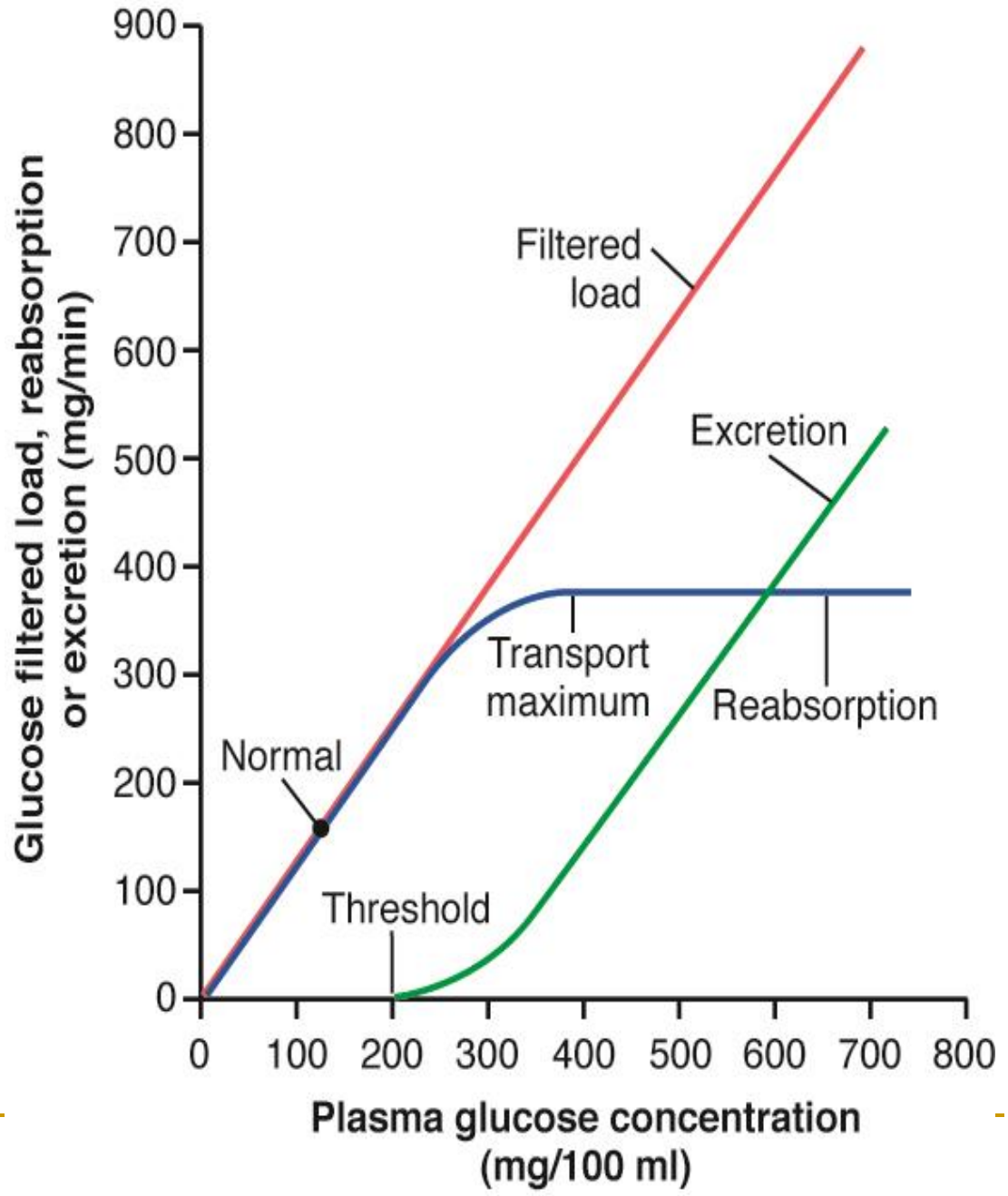
https://youtu.be/wFDtDM4x7jI?si=HIIdSoFik4jR4nRN

Transport Maximum

Some substances have a maximum rate of tubular transport due to saturation of carriers, limited ATP, etc

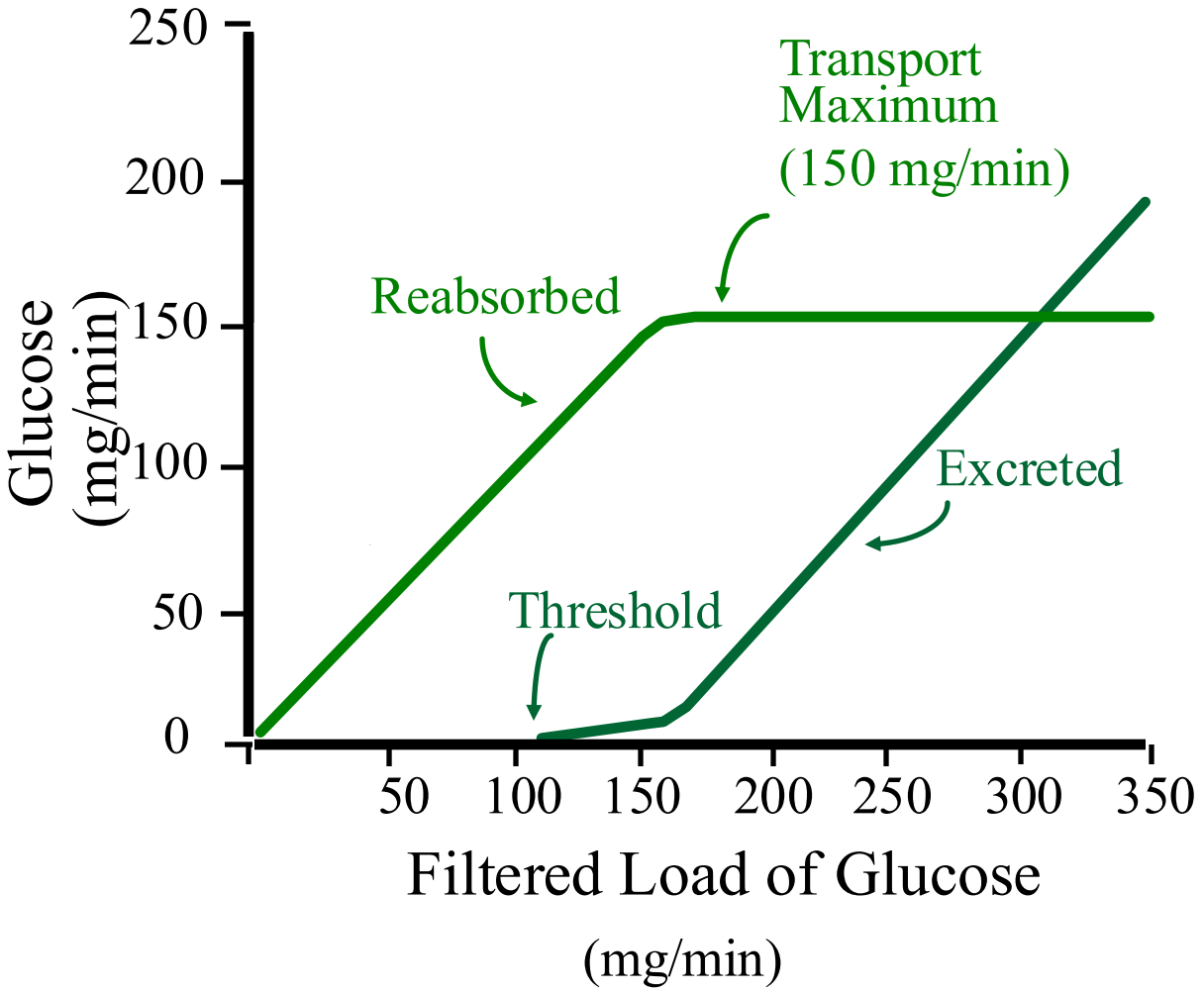
- Transport Maximum: Once the transport maximum is reached for all nephrons, further increases in tubular load are not reabsorbed and are excreted.
- Threshold is the tubular load at which transport maximum is exceeded in some nephrons. This is not the same as the transport maximum of the whole kidney because some nephrons have lower transport max's than others.
- Examples: glucose, amino acids, phosphate, sulphate

Glucose Transport Maximum



A uninephrectomized patient with uncontrolled diabetes has a GFR of 90 ml/min, a plasma glucose of 200 mg% (2mg/ml), and a transport max (Tm) shown in the figure. What is the glucose excretion for this patient?

1. 0 mg/min
2. 30 mg/min
3. 60 mg/min
4. 90 mg/min
5. 120 mg/min



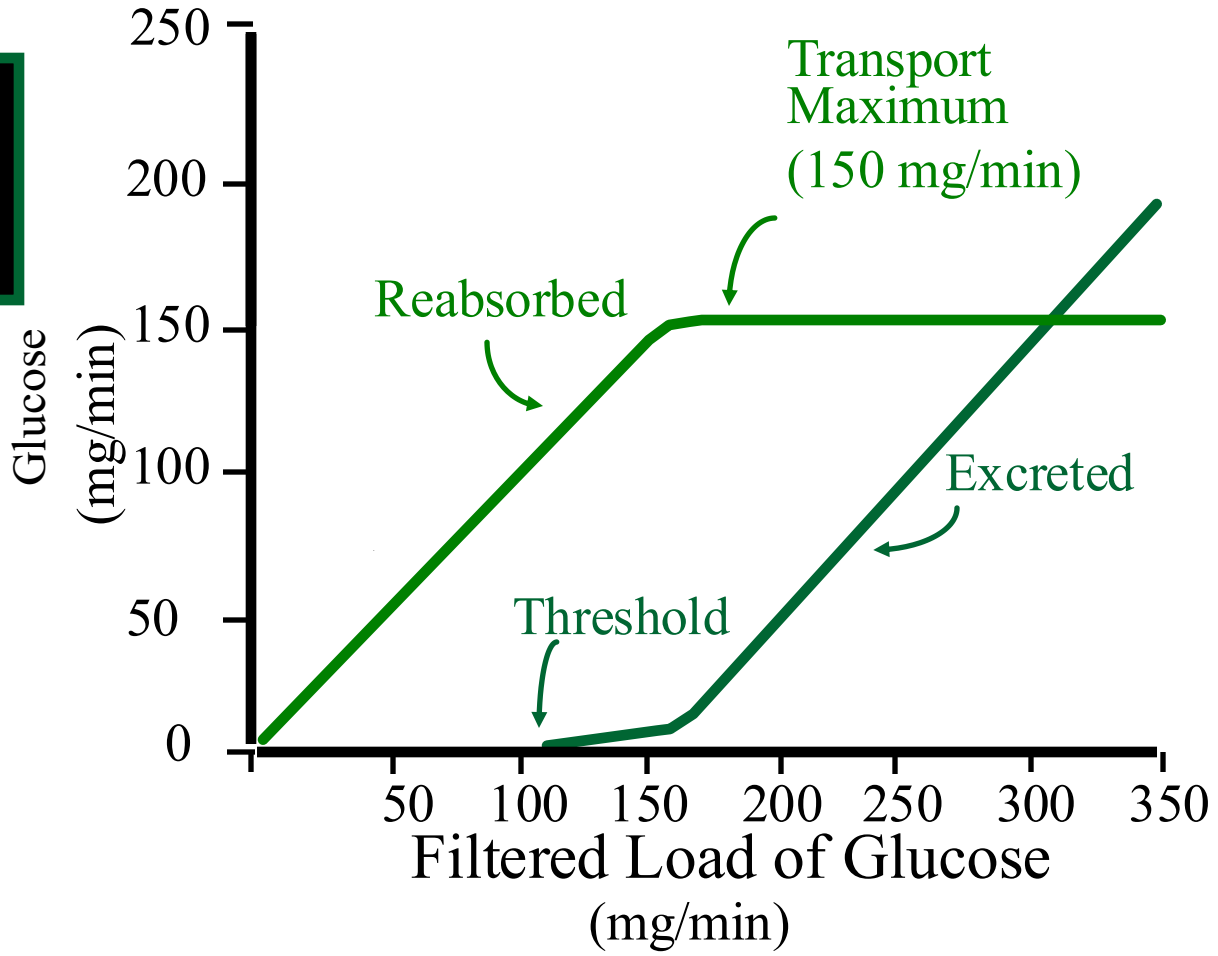
Answer: Filt $_{Glu}$ = (GFR x P_{Glu}) = (90 x 2) = 180 mg/min

Reabs $_{Glu}$ = T_{max} = 150 mg/min

Excret $_{Glu}$ = 30 mg/min

GFR = 90 ml/min
P_{Glu} = 2 mg/ml
T_{max} = 150 mg/min

a. 0 mg/min
b. 30 mg/min
c. 60 mg/min
d. 90 mg/min
e. 120 mg/min



Sodium Homeostasis

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

1. **normal extracellular volume dynamics**

- ↓ Na in ECF → volume contraction. ↑ Na in ECF → volume expansion and edema.

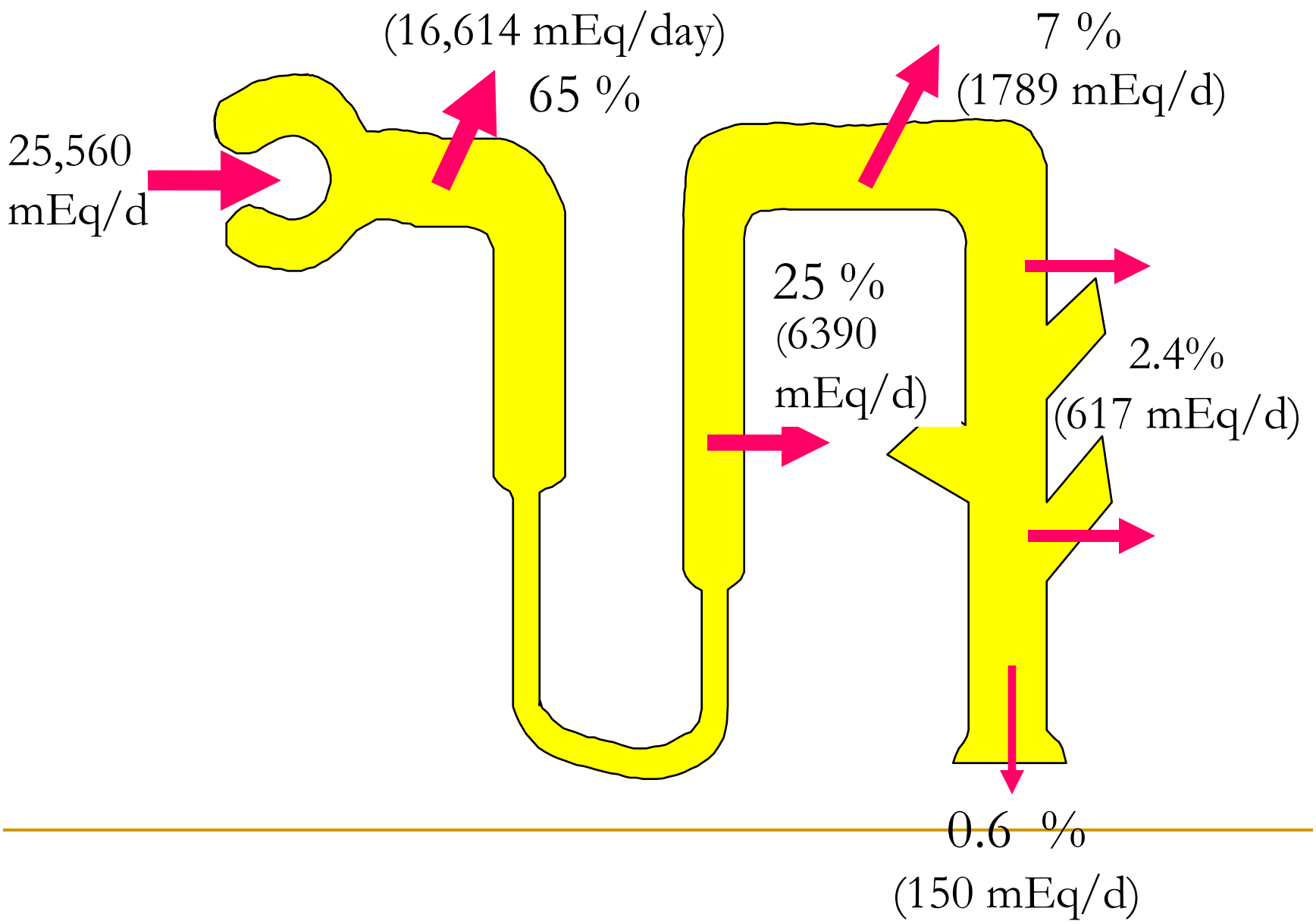
1. **excitability of certain tissues: excitable cells**
2. **cotransport and counter transport…glucose, a.a, H^+**
3. **concentration of urine in thick ascending**
4. **Sodium accounts for a significant portion of plasma osmolarity. Plasma osmolarity can be estimated by multiplying plasma sodium concentration times 2.1.**

Most of the primary active transport in the entire tubular system is to transport Na^+

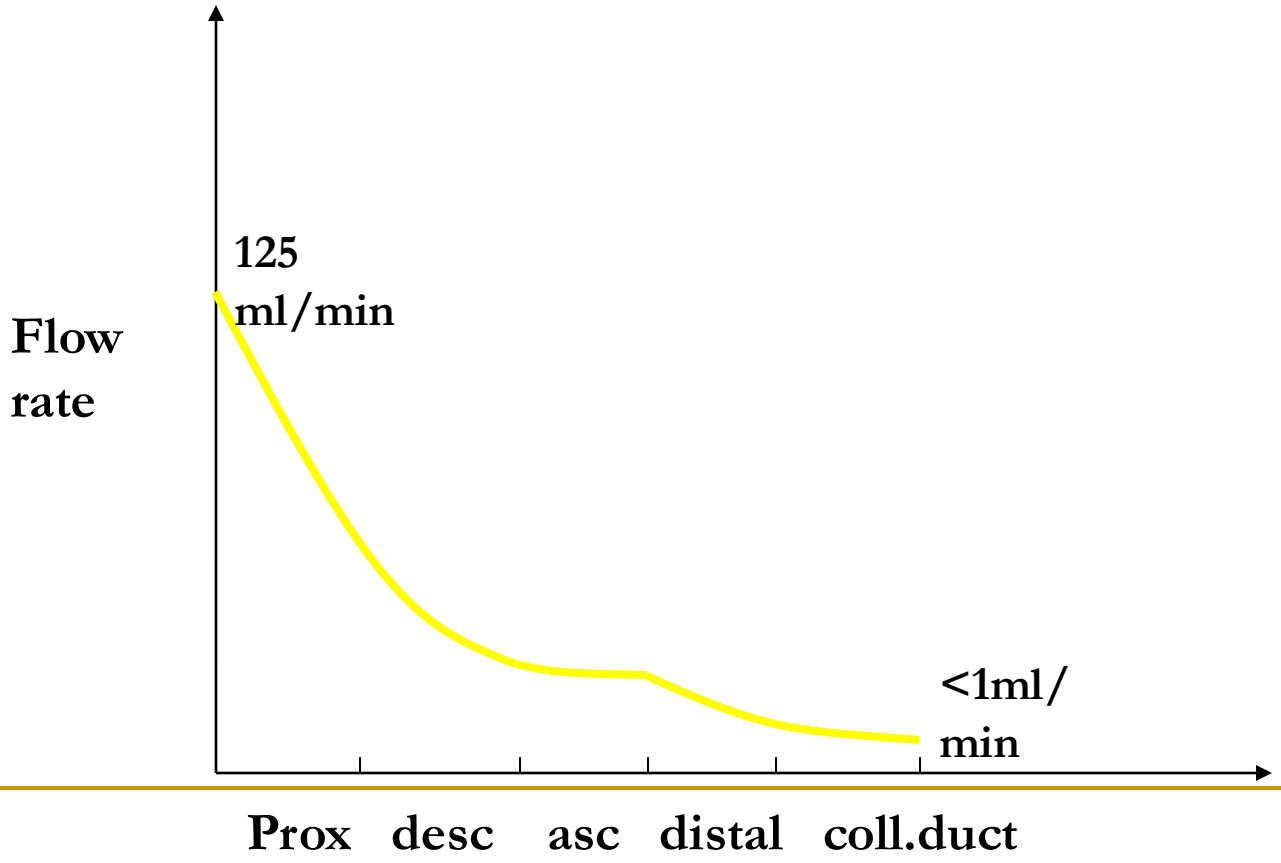
Na^+ & H_2O reabsorption occurs as the following :

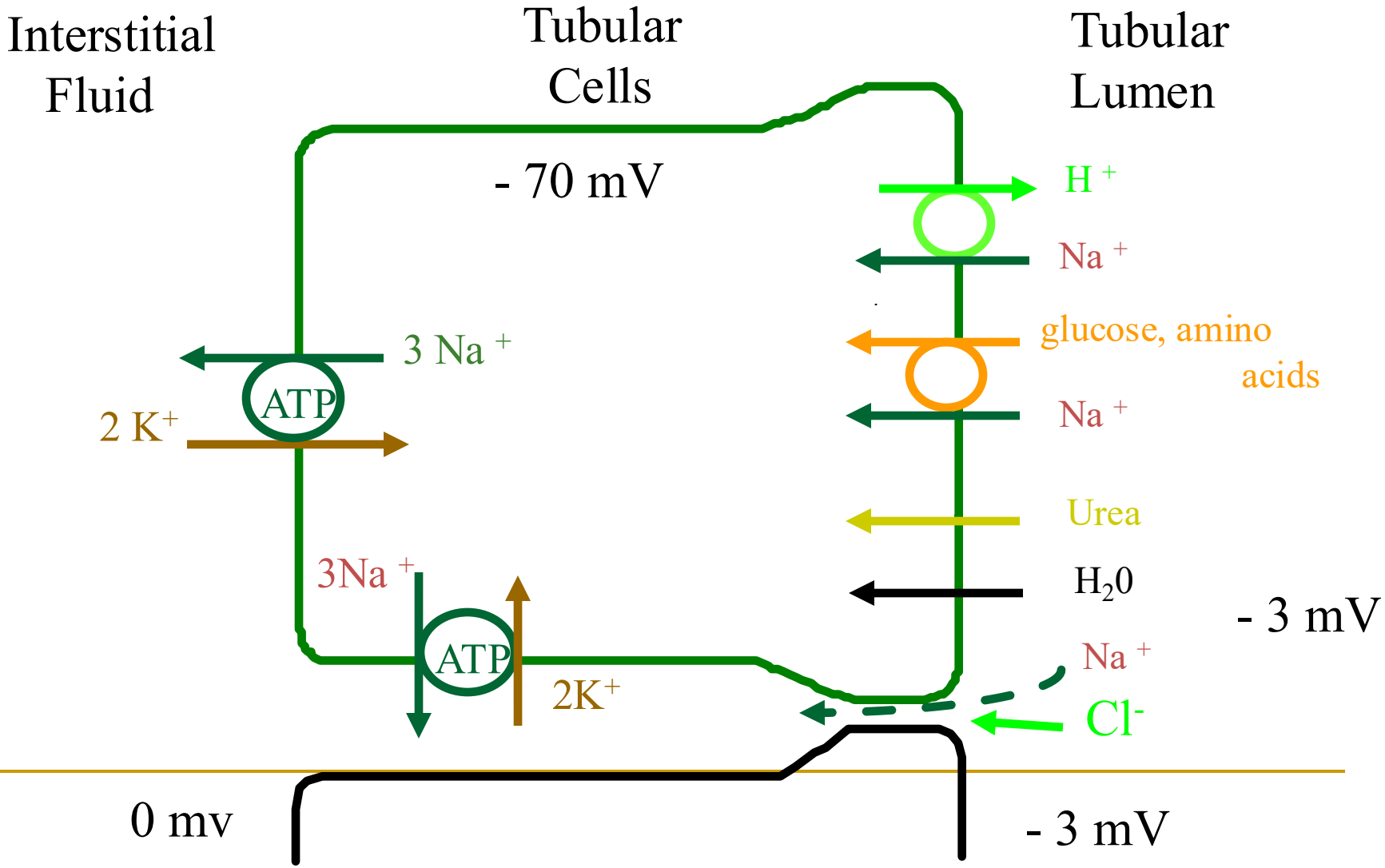
Segment	Na^+%	H_2O%
Proximal tubule	65%	65%
Descend (Henle)	-	15%
Ascending (Henle	25%	-
Distal tubule	7%	10%
Collecting duct	2.4%	9%

Normal Renal Tubular Na^+ Reabsorption



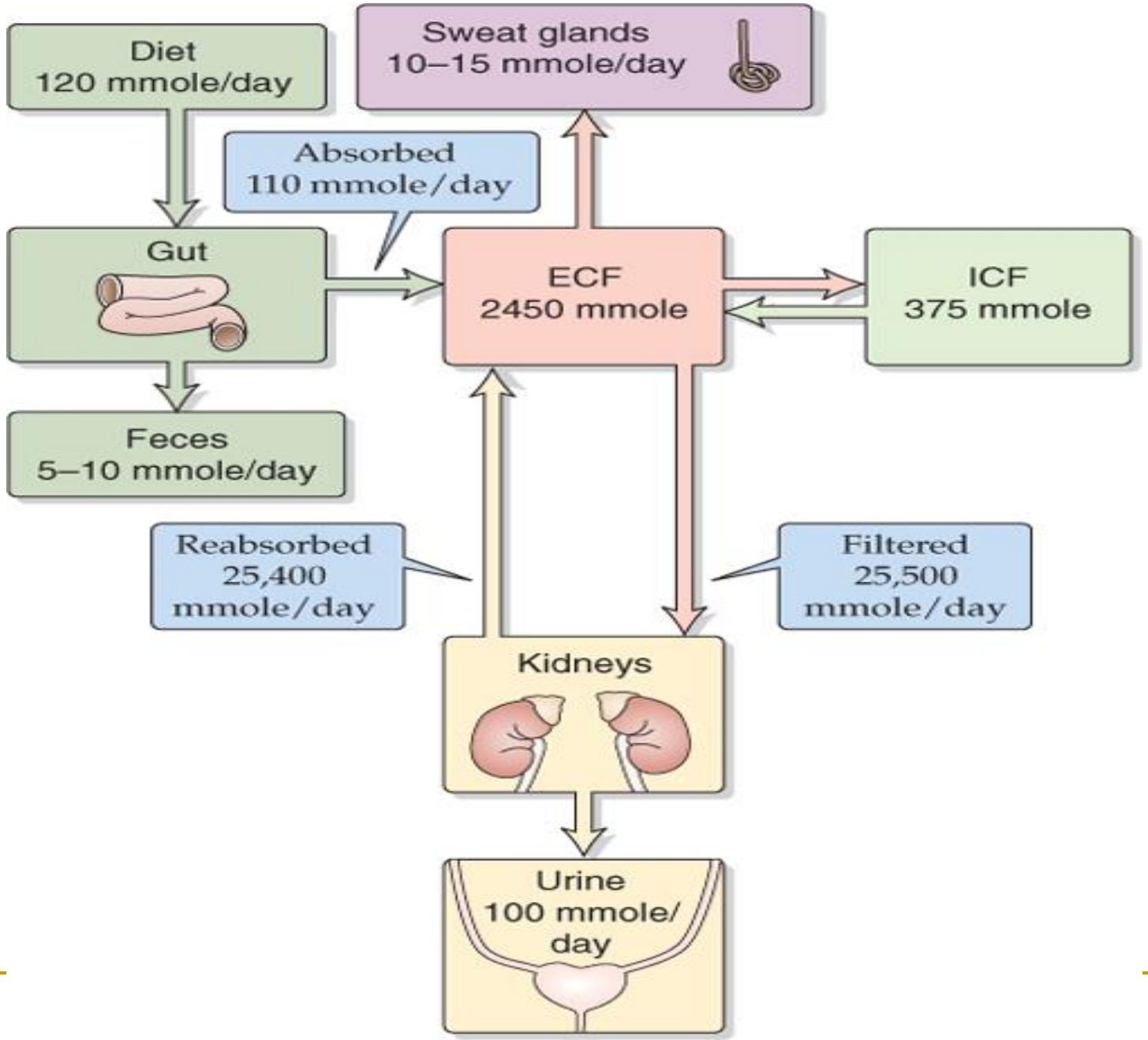
$$C_{Na^+} = [U_{Na^+} / P_{Na^+}] \times V$$
$$= 100/140 \times 1 = < 1 \text{ ml/min}$$

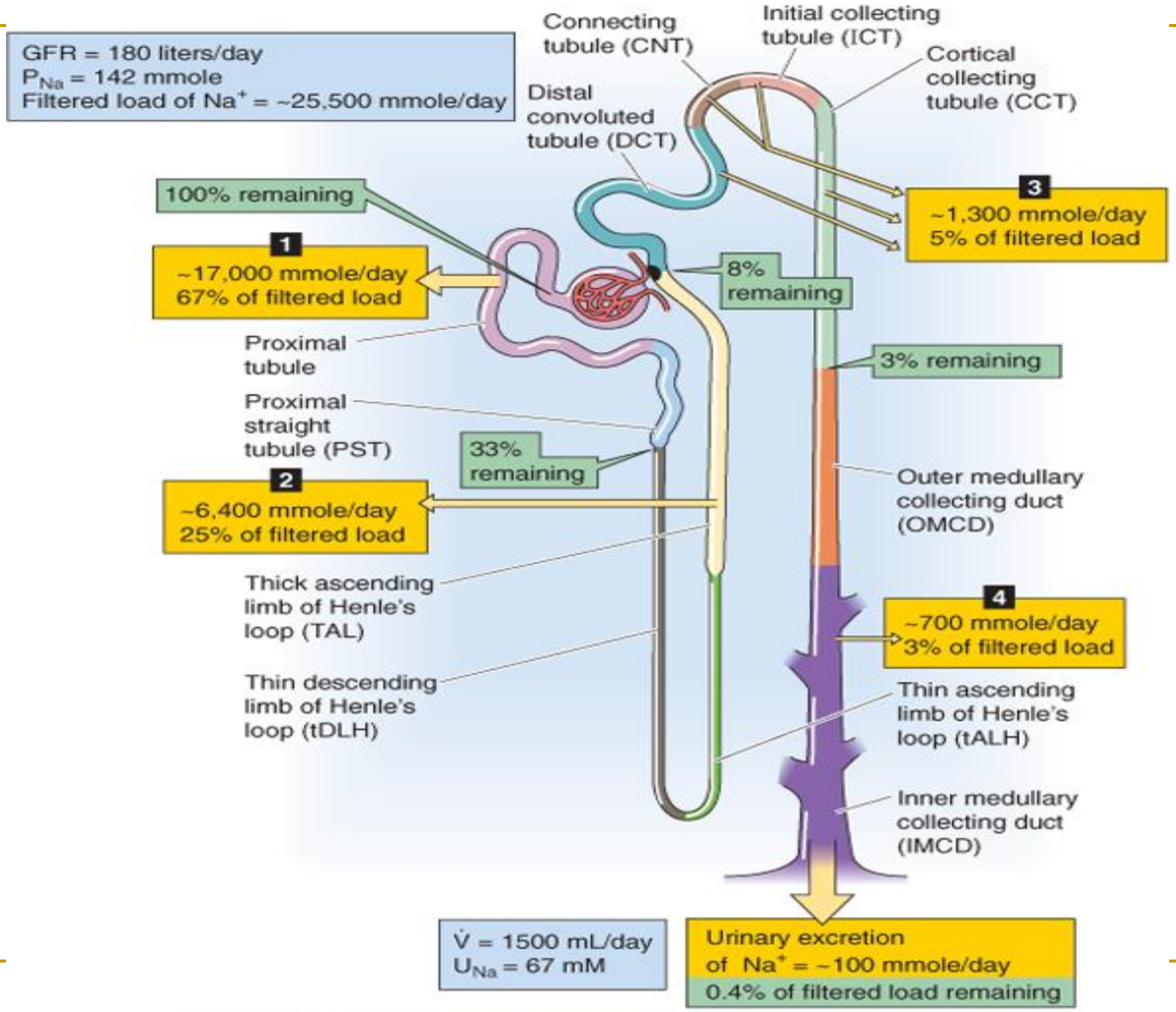



Interstitial Fluid
Tubular Cells
Tubular Lumen
- 70 mV
H +
Na +
glucose, amino acids
Na +
3 Na +
ATP
2 K+
Urea
H20
3Na +
ATP
2K+
Na +
Cl-
- 3 mV
0 mv
- 3 mV

Sodium Homeostasis

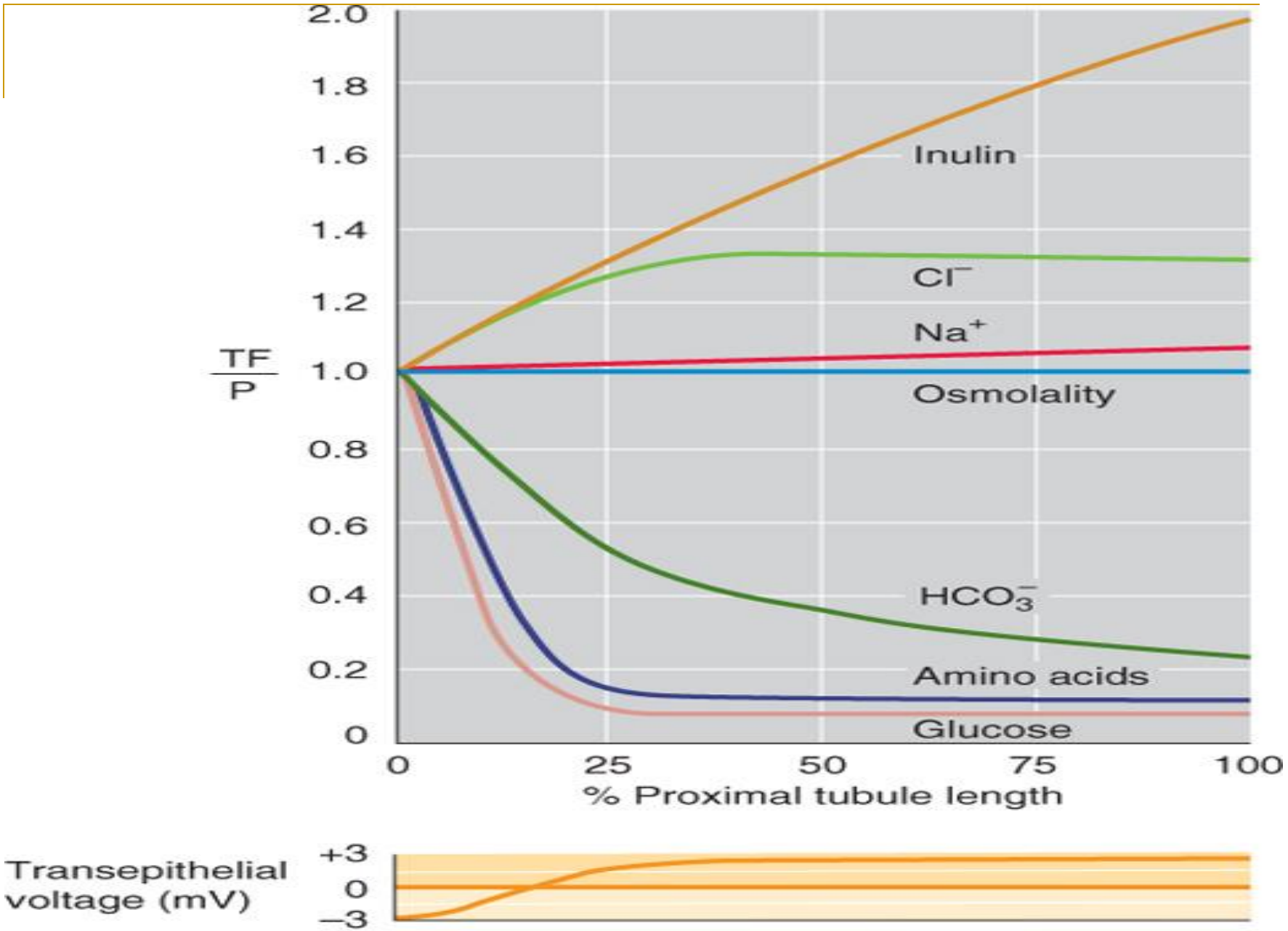
- **Sodium balance is achieved when intake and output equal each other.**
- **Sodium intake is about 120-155 mmol/d in the average American diet (≈ 4 gm). Logically, the daily output would be 120-155mmol/d as well.**
- **The kidney accounts for 115-150 mmol of this output. Hence, the kidney is a major organ in sodium homeostasis.**





Na^+ Clearence

- Sodium clearance can be calculated as follows:
- U_{Na+} = 150mmol/d ÷ 1.5l/d urine per day = 100mmol/l
- $C_{Na+} = (U_{Na+} / P_{Na+}) * V = (100 / 145) * 1 =$ 0.69ml/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 = 180 l/d * 140 mM = 25200mEq
- Amount of sodium excreted by the kidney = 150 mM
- Percent reabsorbed = 25050 / 25200 = 99.4%



sodium homeostasis

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

1. **GFR (1st factor)**
2. **Aldosterone (2nd factor)**
3. **Atrial natriuretic peptide (3rd factor)**

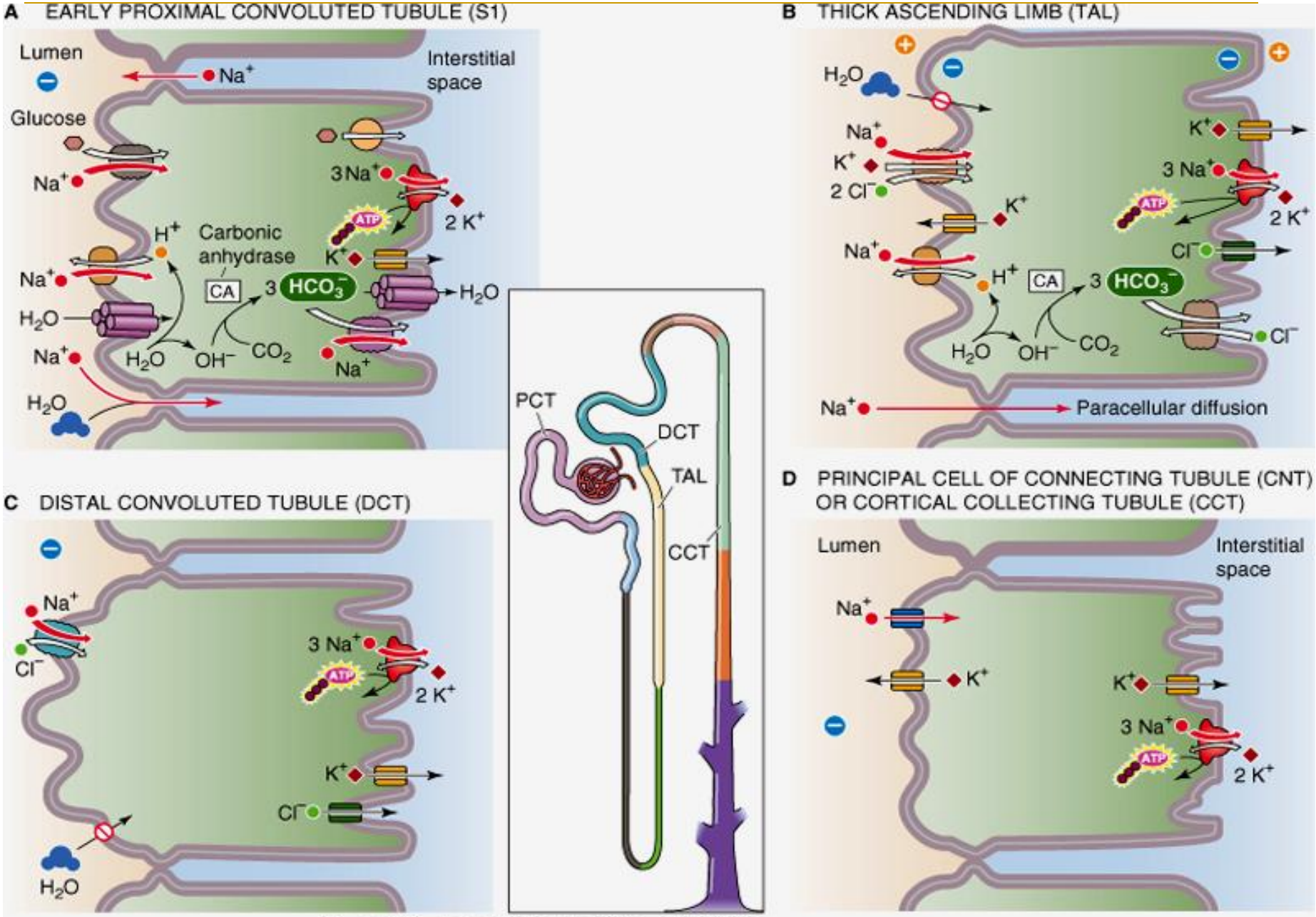
- There are 2 ways to handle Na^+ by the kidneys:

1) Through altering filtration (↑or↓) or

2) altering Na^+ reabsorption (↑or↓)

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

- In distal tubule Na^+ reabsorption is decreased.



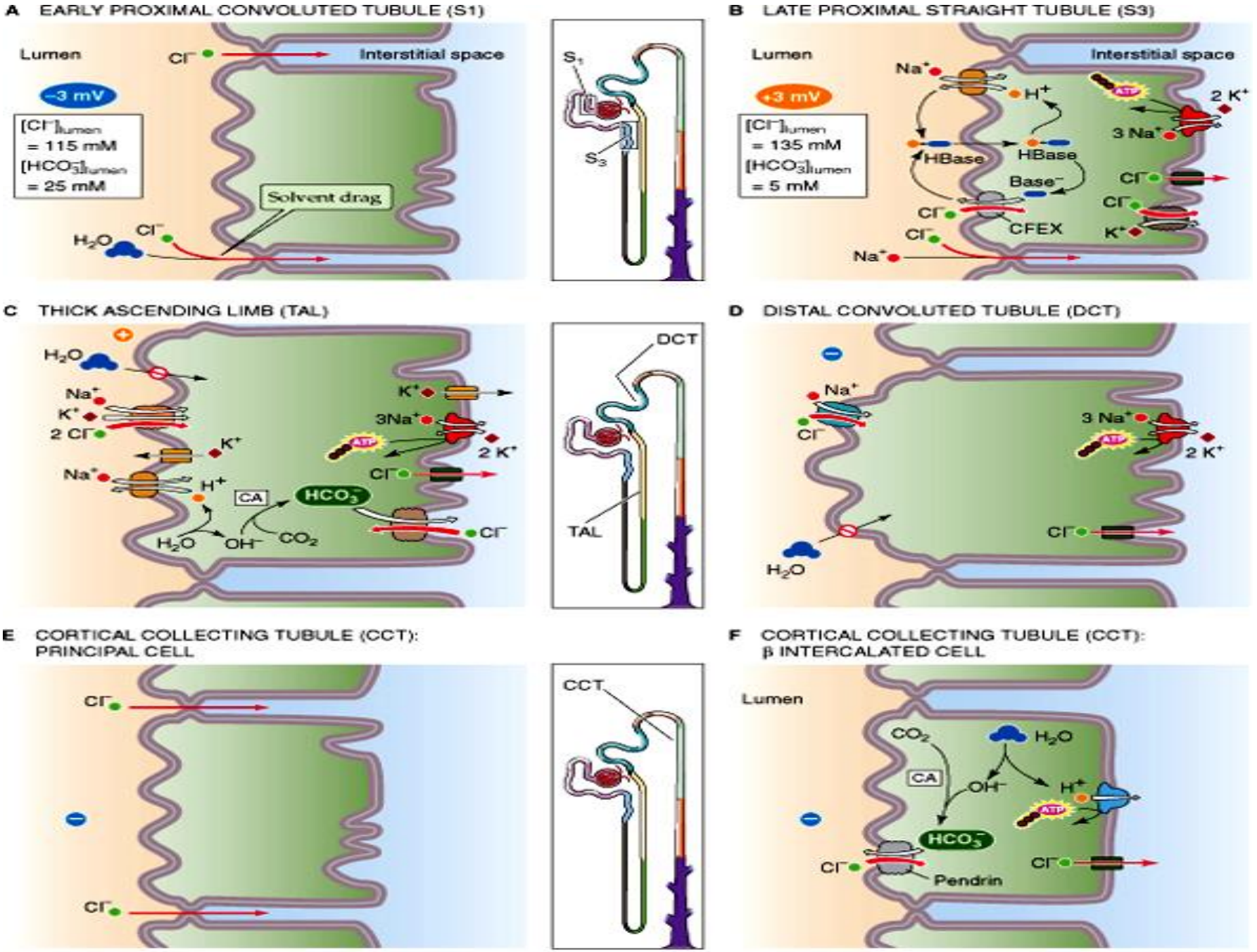
A-Reabsorption at proximal tubules

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

1. transcellular → channels and carriers (T-max)

2. paracellular → tight junction passive and no Tmax

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



A-Reabsorption in proximal tubules

- **In the early part of the proximal tubule , Na^+ & H_2O are reabsorbed with glucose & amino acids by "cotransport process".**
- **$[Na^+]_{out}$ = 140 mEq**
- **$[Na^+]_{in}$ = 14 mEq**
- **So Na^+ moves down gradient from the luminal side to the cell, while it is pumped actively through the basolateral membrane (anti-gradient) .**

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. Later on, Na^+ follows Cl^-.**

- **<u>B. Reabsorption in descending limb of Henle</u>** (no reabsorption).
- **<u>C. Reabsorption in the Ascending limb of Henle.</u>**

  reabsorption involves (Na^{+}-K^{+}-2Cl^{-}) co-transporter **without** H_2O , this is called [single effect] → ↑ osmolarity in the interstitium and ↓ osmolarity in the TF.

Reabsorption of Na^+

- **<u>D. Reabsorption in late distal tubules & cortical collecting duct</u>**.
- Reaborption of Na^+ & secretion of K^+ occur through the principal cells.

Control of Na^+

- When Na^+ intake is increased → increase in GFR through increasing ECV and BP.

When ECV increases → π in peritubular capillary decreases due to dilution

Control of Na^+

- **How does the body control increase in Na^+ intake ?**

1. **Altering GFR**
2. **Altering Reabsorption**

- **1-Altering GFR:**
- **When Na^+ intake increases → Glomerulotubular feedback does not work for unknown reason → increase Na^+ Excretion.**
- **increase Na^+ intake → increase Pa → increase GFR (Pressure Natriuresis)**

Control of Na

2-Altering reabsorption:

When Na^+ intake increases the RFC is shifted to the left to ensure increase Na^+ excretion. This shift means less production of AII which results in less Na^+ reabsorption and thus increase its excretion. In addition less AII means less aldosterone and less Na^+ reabsorption.

- **Aldosterone is also autoregulated….means whenever [Na^+] in plasma increases, Aldosterone production decreases**
- **ANP (Atrial Natriuretic Peptide) increases due to increase in atrial pressure → it induces four things**

1. **Afferent Arterial dilatation → increase GFR → increase Sodium excretion**
2. **inhibit adrenal cortex from secreting Aldosterone →**
3. **inhibit AII production by inhibiting renin secretion**
4. **dercreases Na reabsorption directly**

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**
- **hypokalemia is a serious complication of loop diuretics and thiazide**

Diuretics

Class	Mechanism	Site of Action
Osmo-diuretics	Mannitol	
loop diuretics like furosemide (Lasix), ethacrynic acid and bometanide	inhibit Na-K-2Cl cotransport. Most powerful available. They increase *Ca^{++} and *Mg^{++} elimination	At thick ascending
**Thiazide	Inhibit Na-Cl cotransport.: increase Ca++ reabsorption …can be used in hypercalciuria	At distal
Acetazolamide (Diamox)	C.A inhibitors	Proximal. Used for glaucoma
***Spironolactone	Inhibit Na+ reabsorption	At principal cells
Na^+ channel blockers such as Amiloride and triamterene	Because they inhibit Na+ reabsorption, they also inhibit K+ secretion.	

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** and mannitol is used in brain edema
- **hypokalemia is a serious complication of loop diuretics and thiazide.. We leave this topic to pharmacology**

Clinical point

- 1. **Spironolactone** (aldactone): works on principal cells by decreasing K^+ secretion → aldactone 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 H_2O with it , used in brain edema .

Clinical point

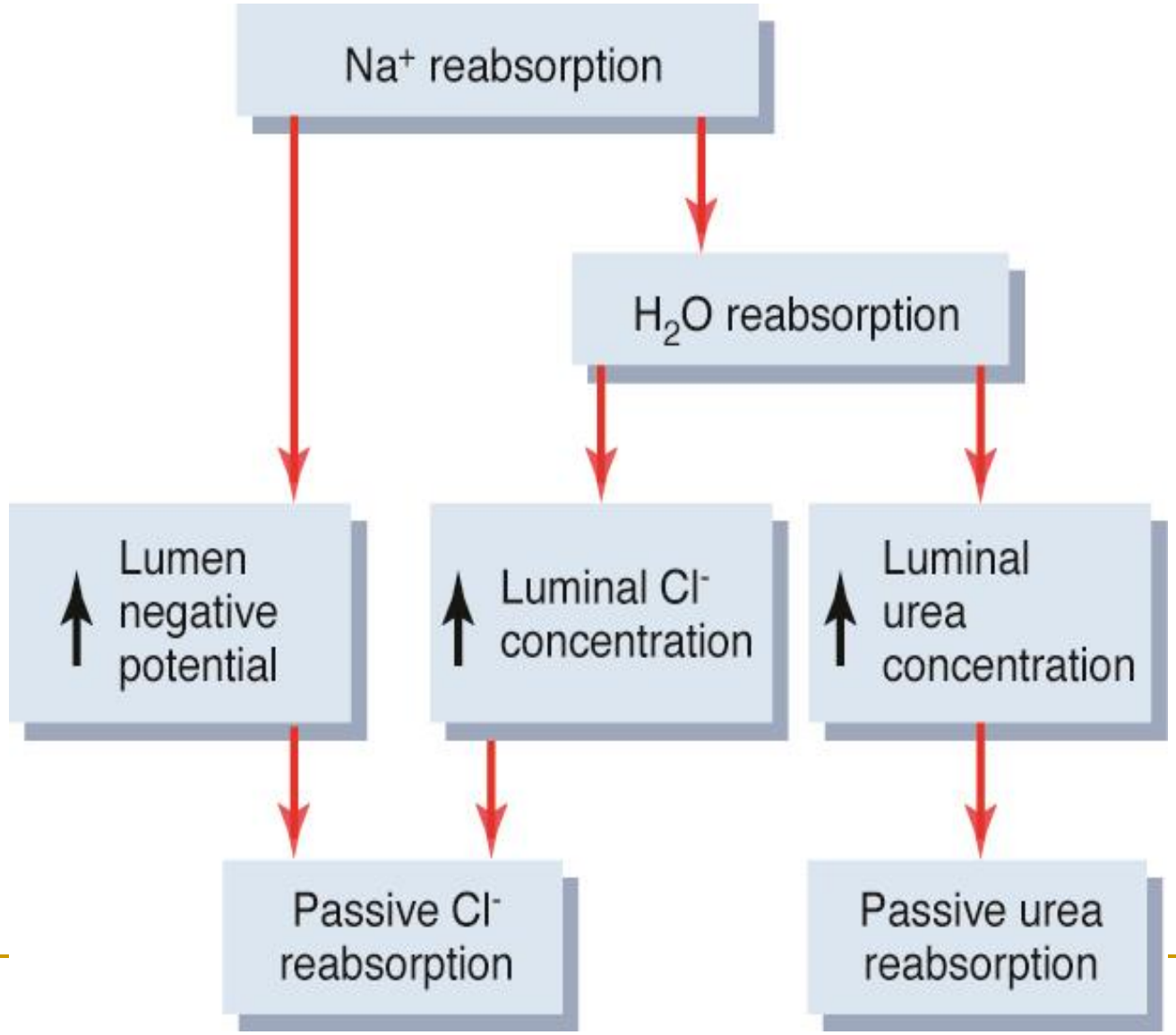
1. **Furesamide (Lasix): a potent loop diuretic acts on the thick ascending limb of Henle TAL where it inhibits Na-2Cl-K → ↑ Na^+ Excretion.**

Lasix is used in pulmonary edema, congestive heart failure & hypertension.

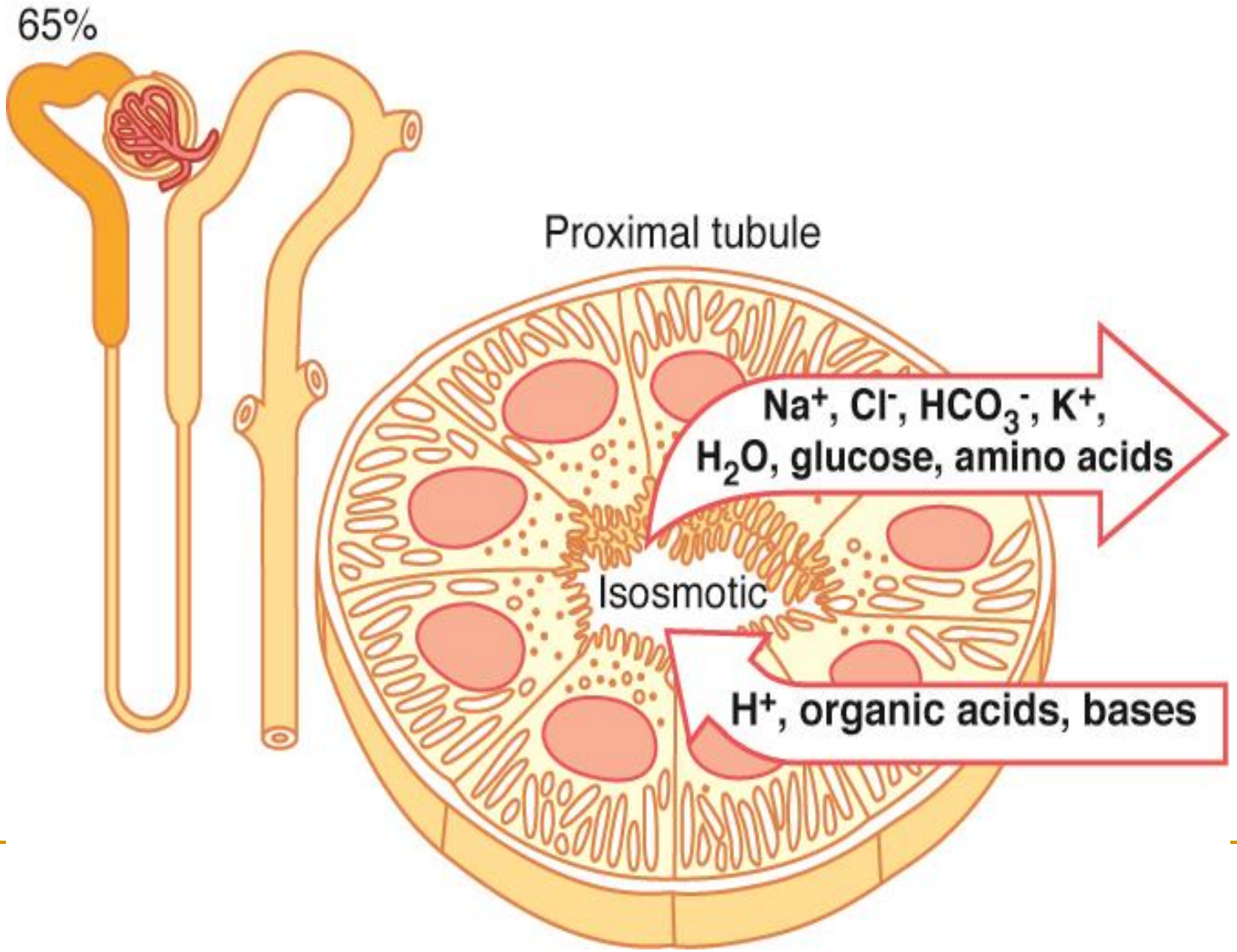
2. **Thiazide/Chlorothiazide (moderate diuretic) acts on distal convoluted tubule DCT inhibiting Na/Cl reabsorption increase Ca++ reabsorption and thus is used in hypercalciuria**

- **Those 2 diuretics are called [potassium-wasting diuretics]…they induce hypokalemia**
-

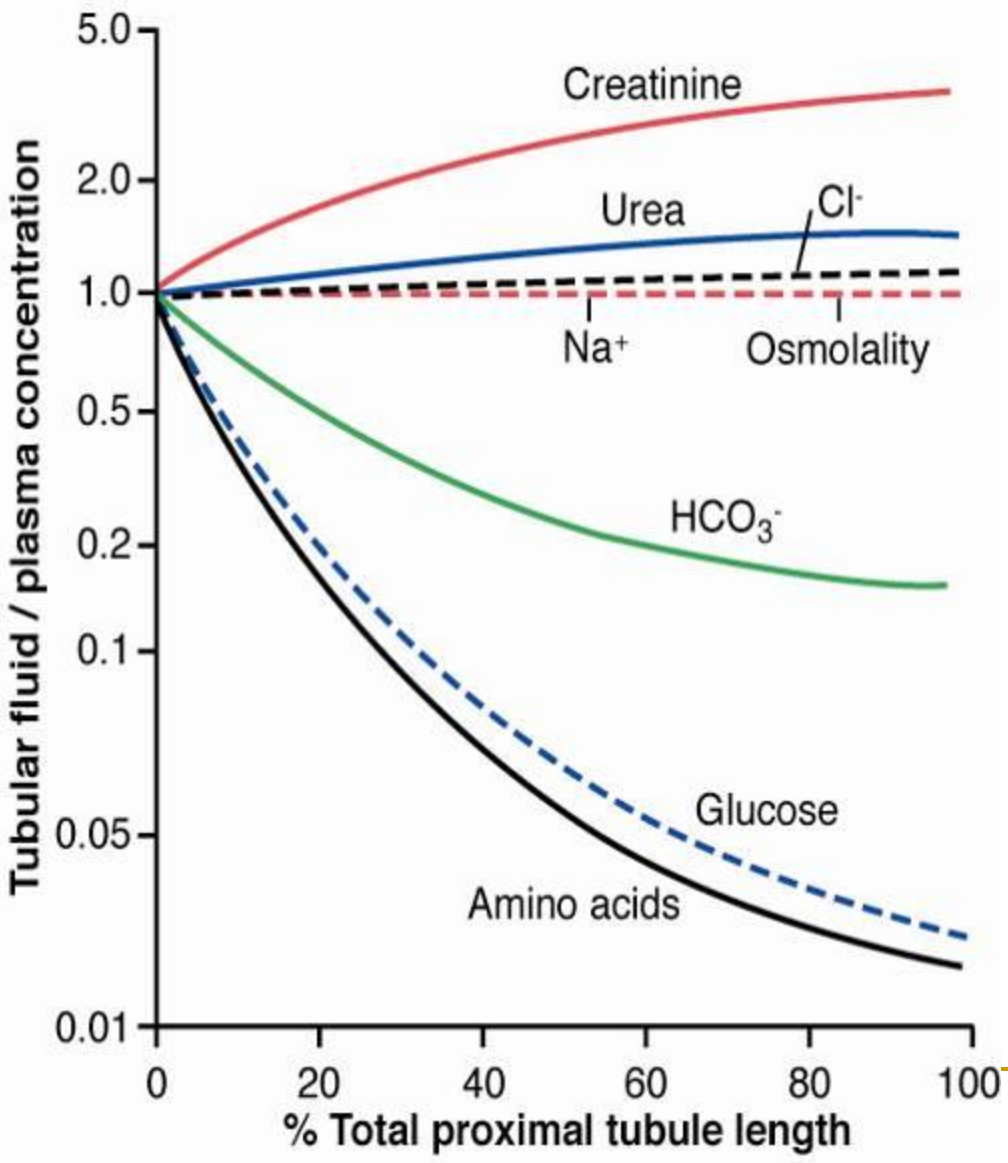
Mechanisms by which water, chloride, and urea reabsorption are coupled with sodium reabsorption



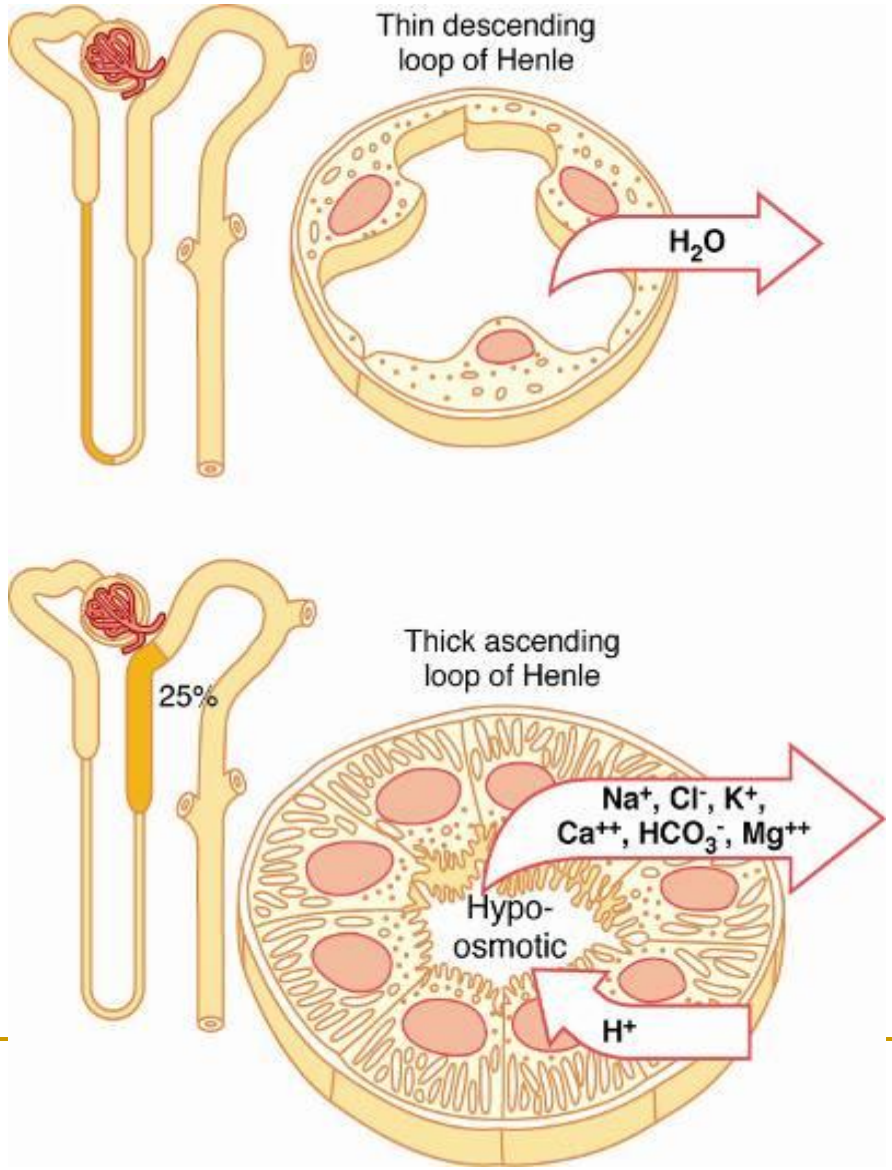
Transport characteristics of proximal tubule.



Changes in concentration in proximal tubule



Transport characteristics of thin and thick loop of Henle.

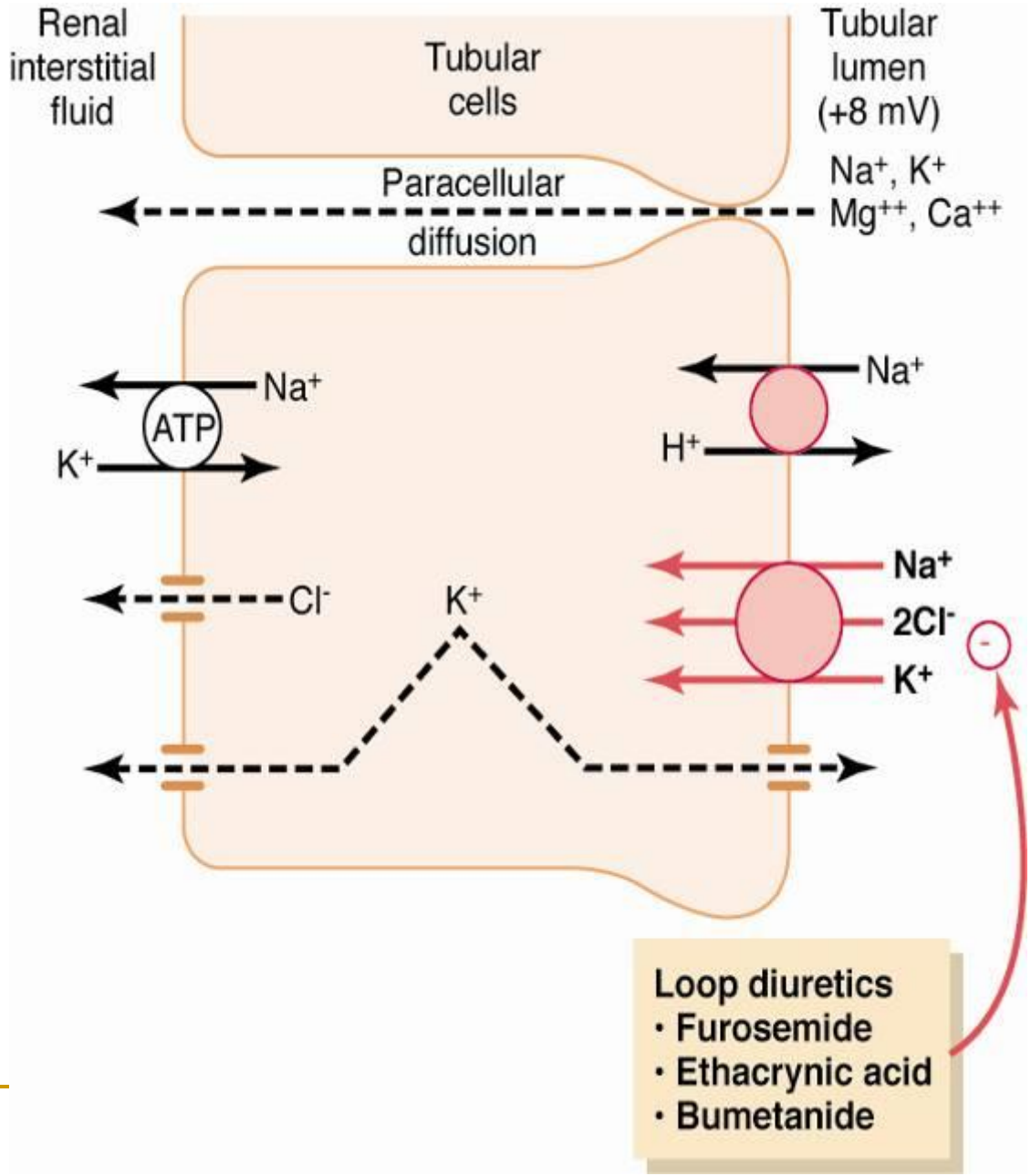


very permeable to H_2O)

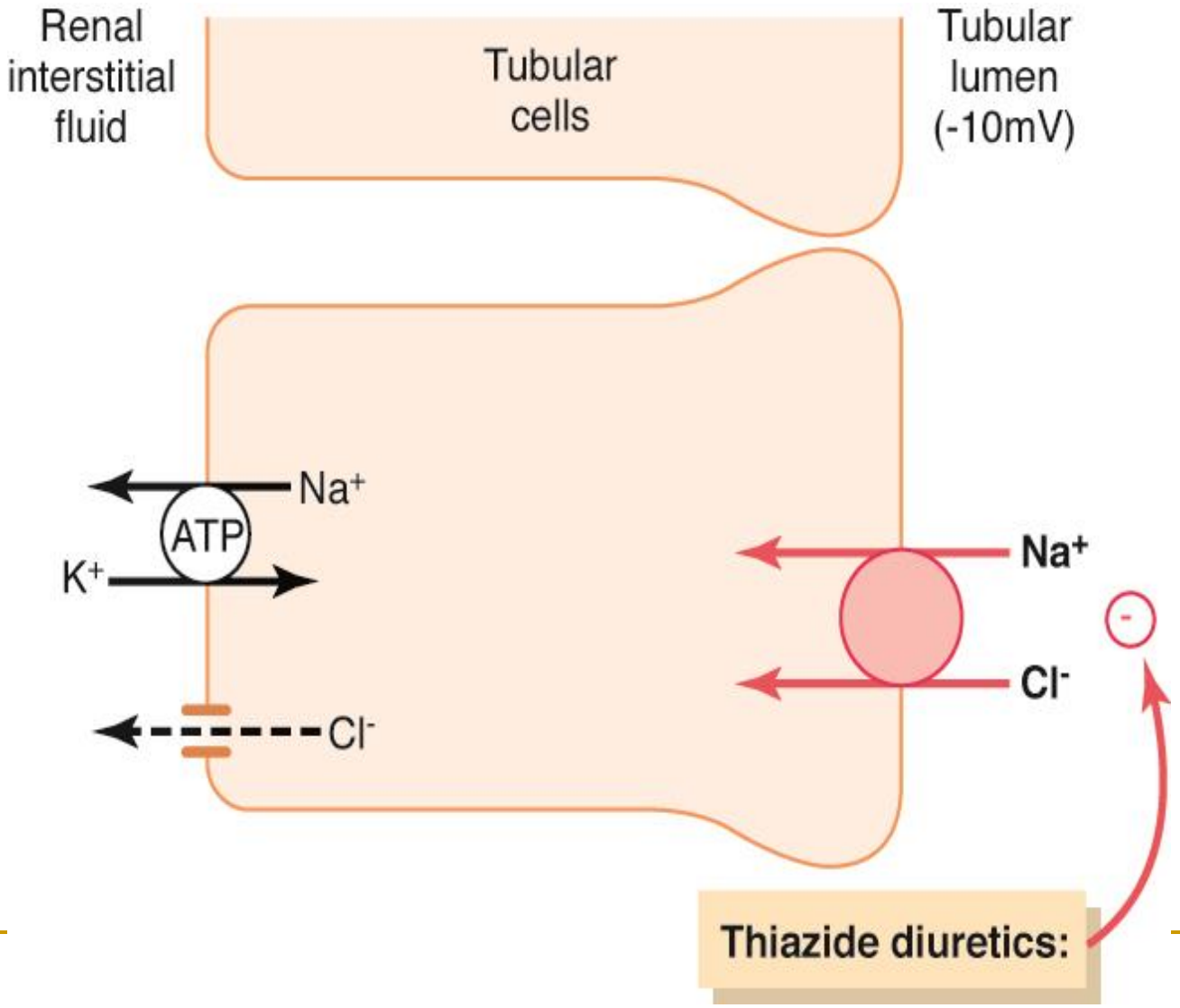
~ 25% of filtered load

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

Sodium chloride and potassium transport in thick ascending loop of Henle



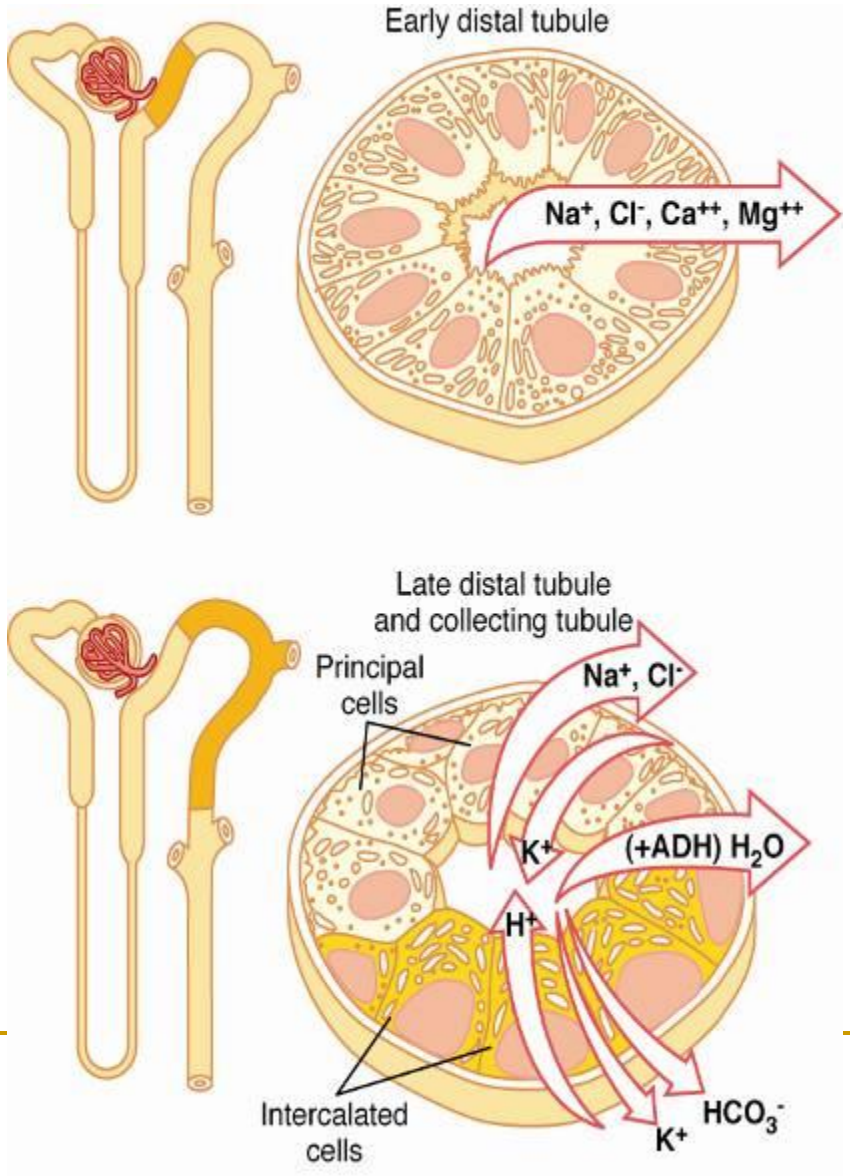
Early Distal Tubule



Early Distal Tubule

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

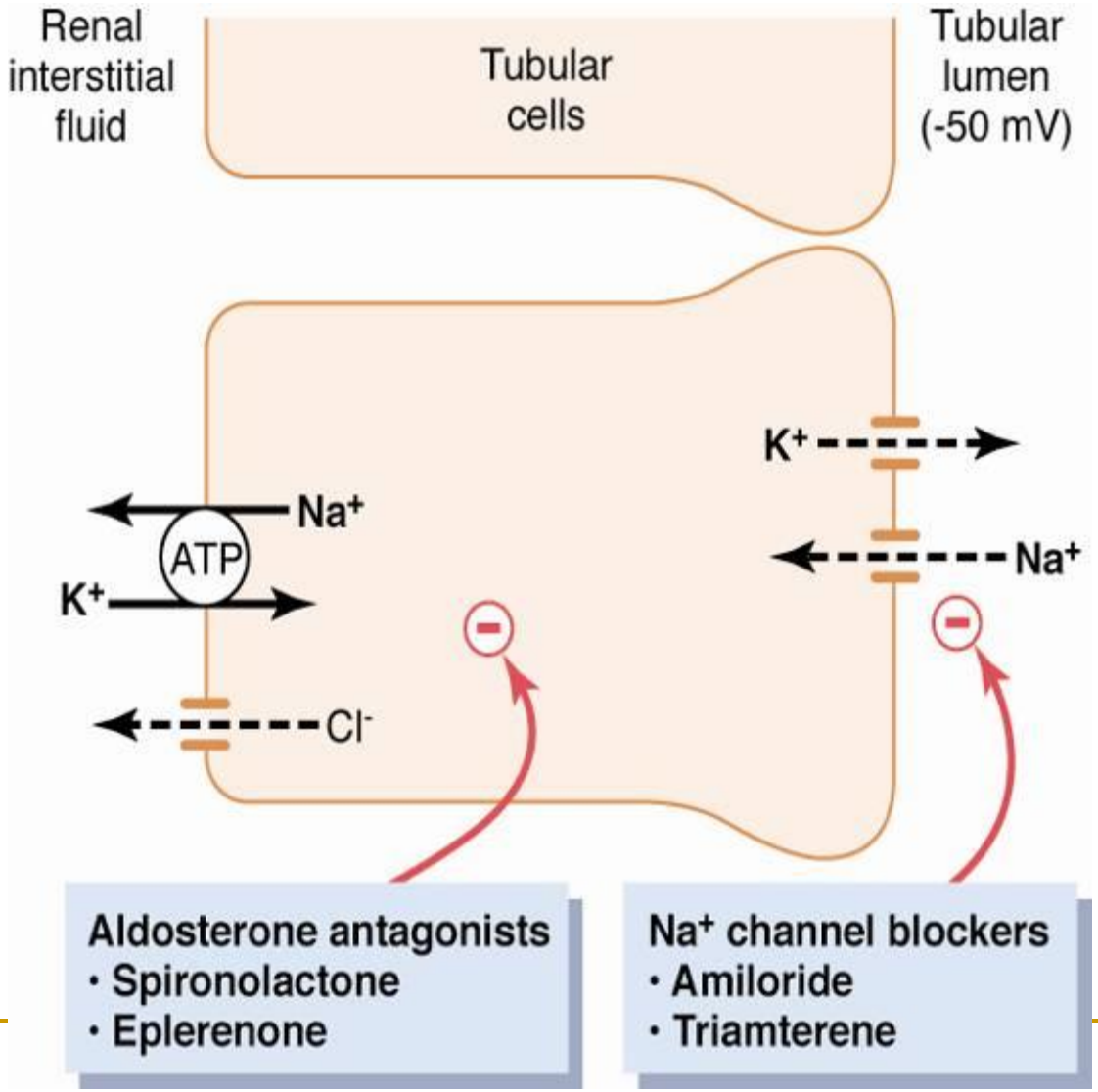
Early and Late Distal Tubules and Collecting Tubules.



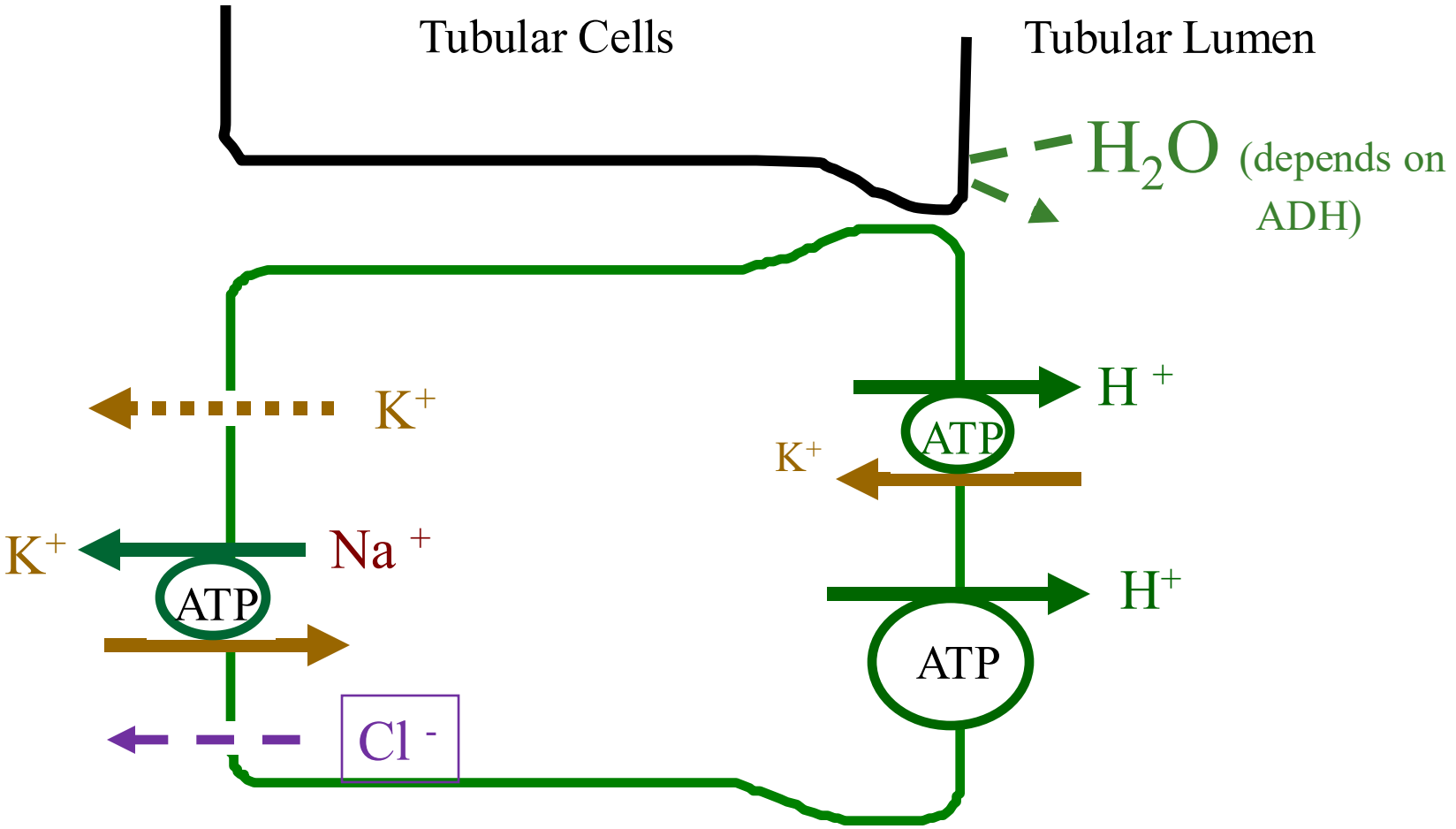
~ 5% of filtered load
NaCl reabsorbed

- not permeable to H_2O
- not very permeable to urea
- permeablility to H_2O depends on ADH
- not very permeable to urea

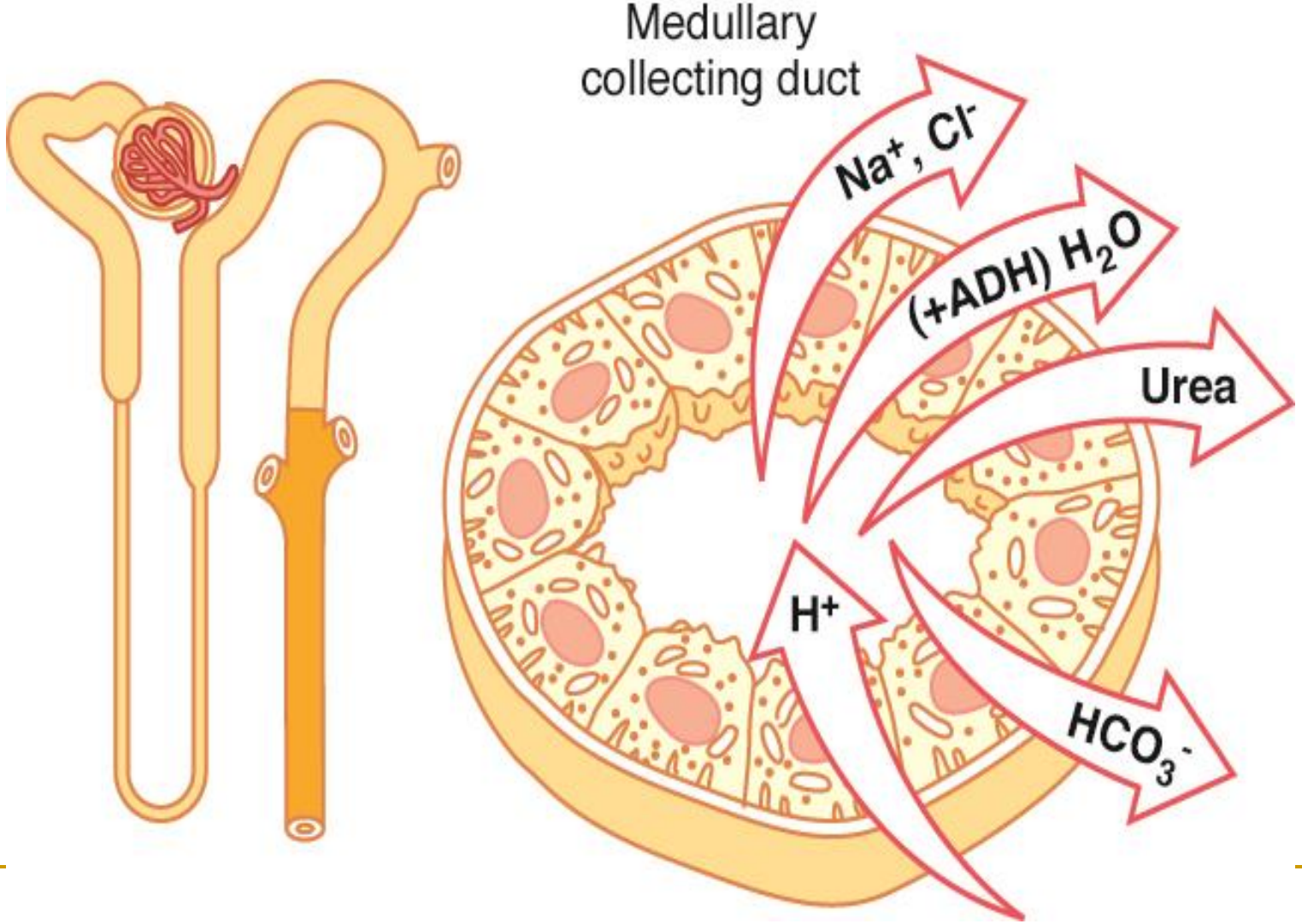
Late Distal and Cortical Collecting Tubules Principal Cells – Secrete K^+



Late Distal and Cortical Collecting Tubules Intercalated Cells –Secrete H^+



Transport characteristics of medullary collecting ducts

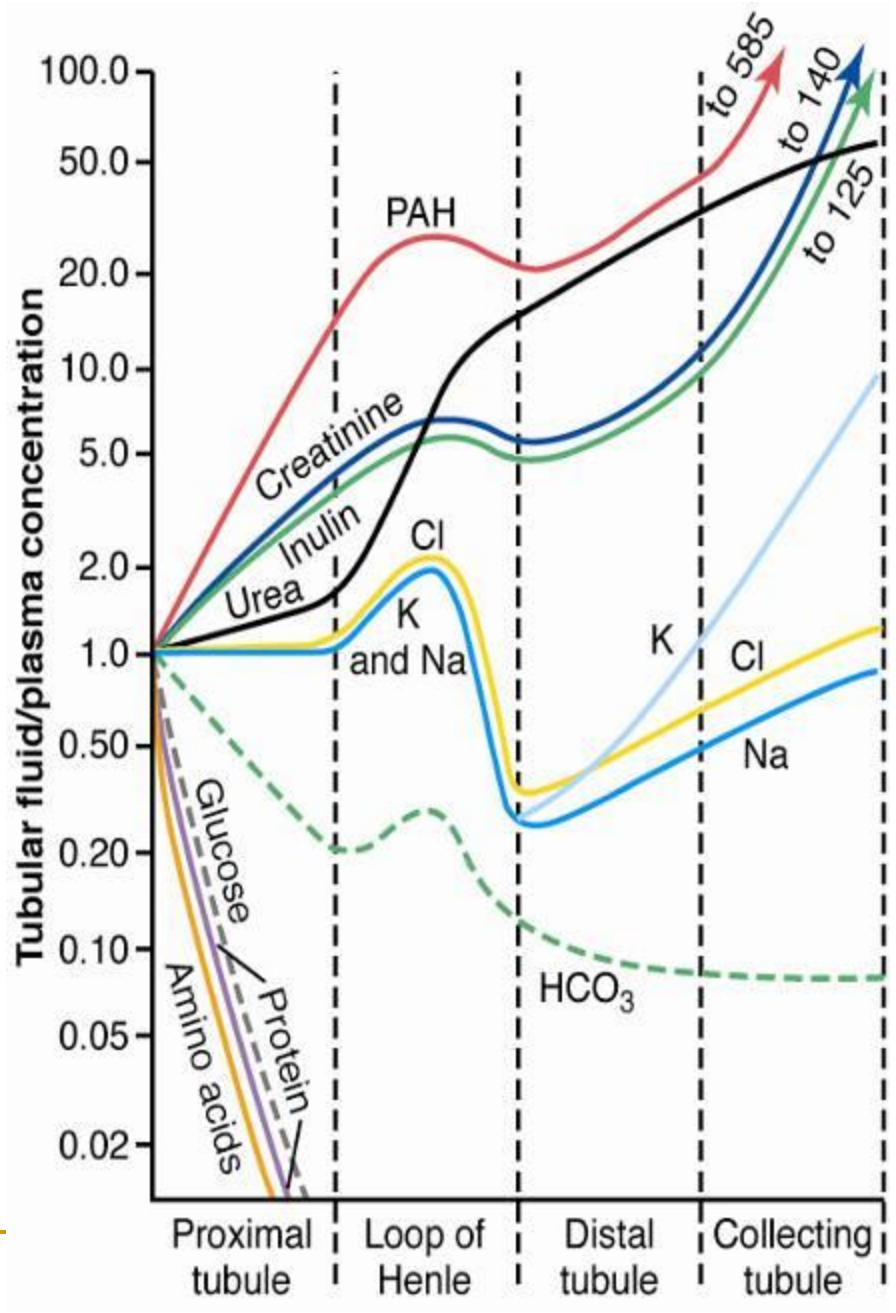


Concentrations of solutes in different parts of the tubule depend on relative reabsorption of the solutes compared to water

- If water is reabsorbed to a greater extent than the solute, the solute will become more concentrated in the tubule (e.g. creatinine, inulin)

- If water is reabsorbed to a lesser extent than the solute, the solute will become less concentrated in the tubule (e.g. glucose, amino acids)

Changes in concentrations of substances in the renal tubules

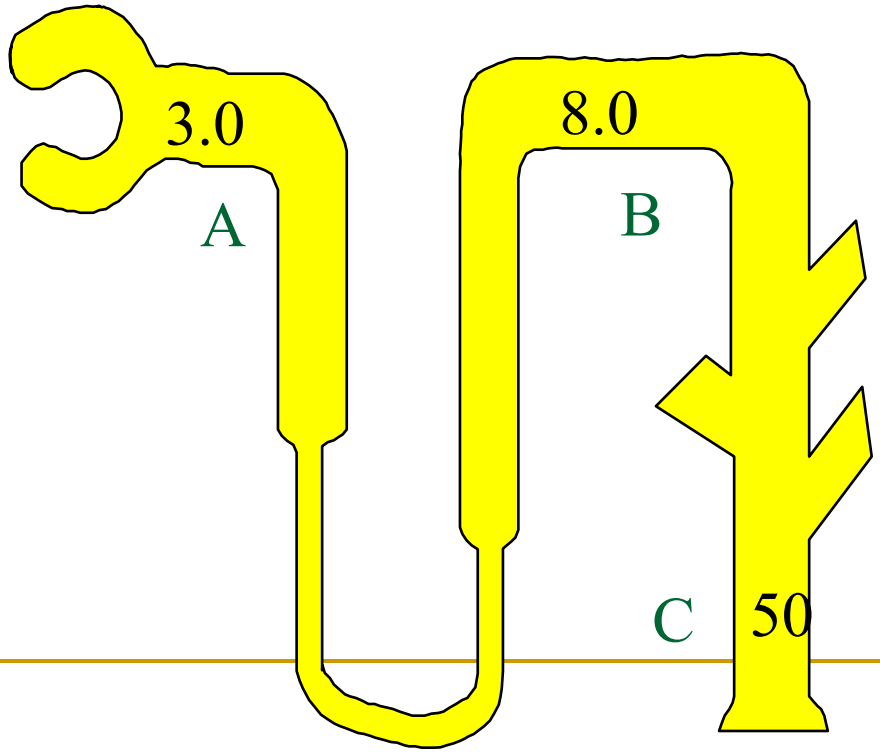


The figure below shows the concentrations of inulin at different points along the tubule, expressed as the tubular fluid/plasma (TF/P_{inulin}) concentration of inulin. If inulin is not reabsorbed by the tubule, what is the percentage of the filtered water that has been reabsorbed or remains at each point ? What percentage of the filtered waterhas been reabsorbed up to that point?

A = 1/3 (33.33 %) remains
66.67 % reabsorbed

B = 1/8 (12.5 %) remains
87.5 % reabsorbed

C = 1/50 (2.0 %) remains
98.0 % reabsorbed



$C_x = C_{Inulin}$ X neither reabsorbed nor secreted.

If $C_x > C_{Inulin}$ X undergoes net secretion

If $C_x < C_{Inulin}$ X underwent net reabsorption

$$Concentration = \left[\frac{relative' reabsorbtion + \sec retion}{relative' reaborbion' of' H_2O} \right]$$

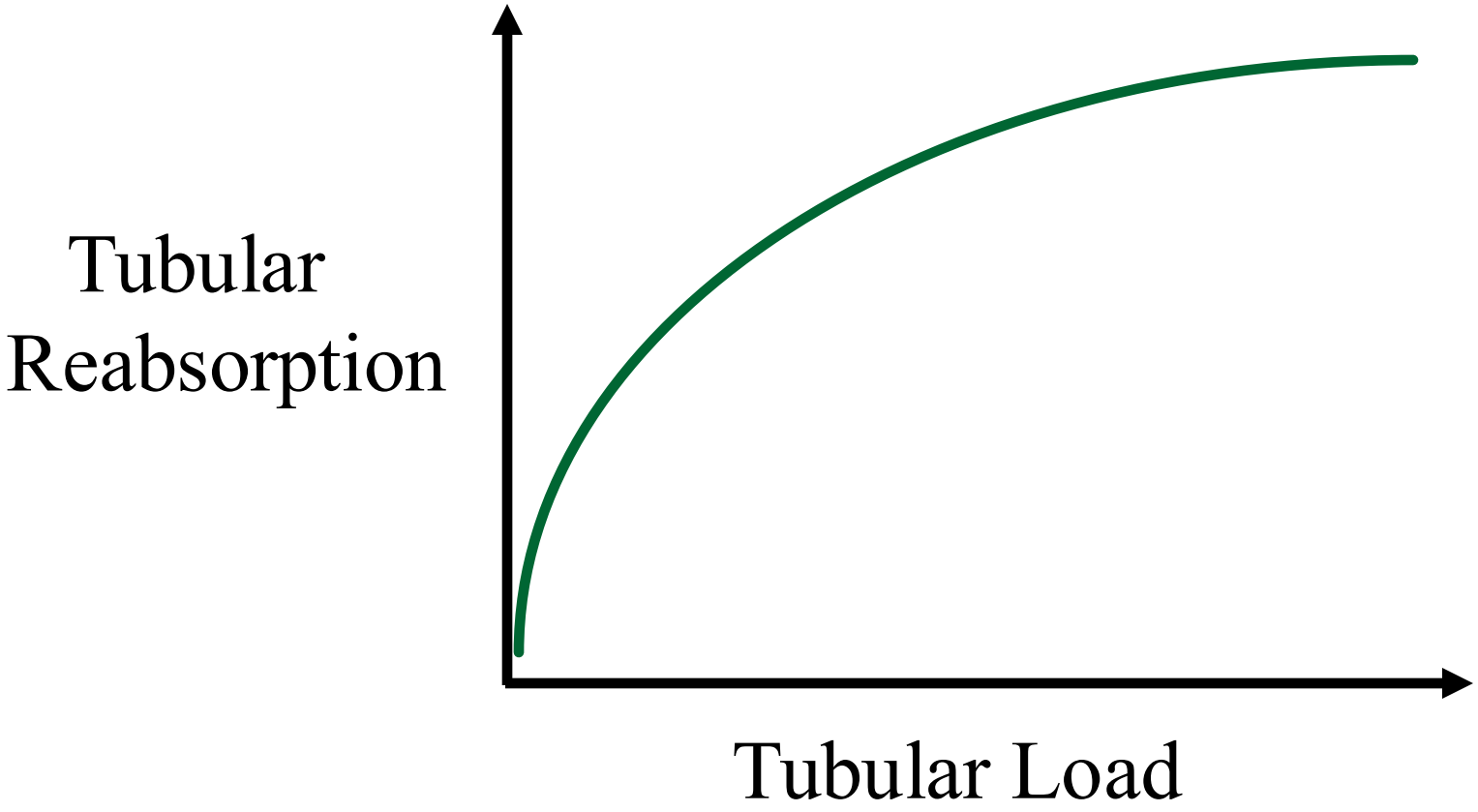
By using Micropunture technique: $\left[\frac{(TF/P)_x}{(TF/P)_{Inulin}} \right] =$

1. $[TF/P]_{inulin}$ indicate how much water reabsorbed at that segment
2. $[TF/P]_X$
   if = 1 then X is reabsorbed at the same fraction as water.
   If > 1 then X is reabsorbed less than water.
   If < 1 then X is reabsorbed more than water.

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

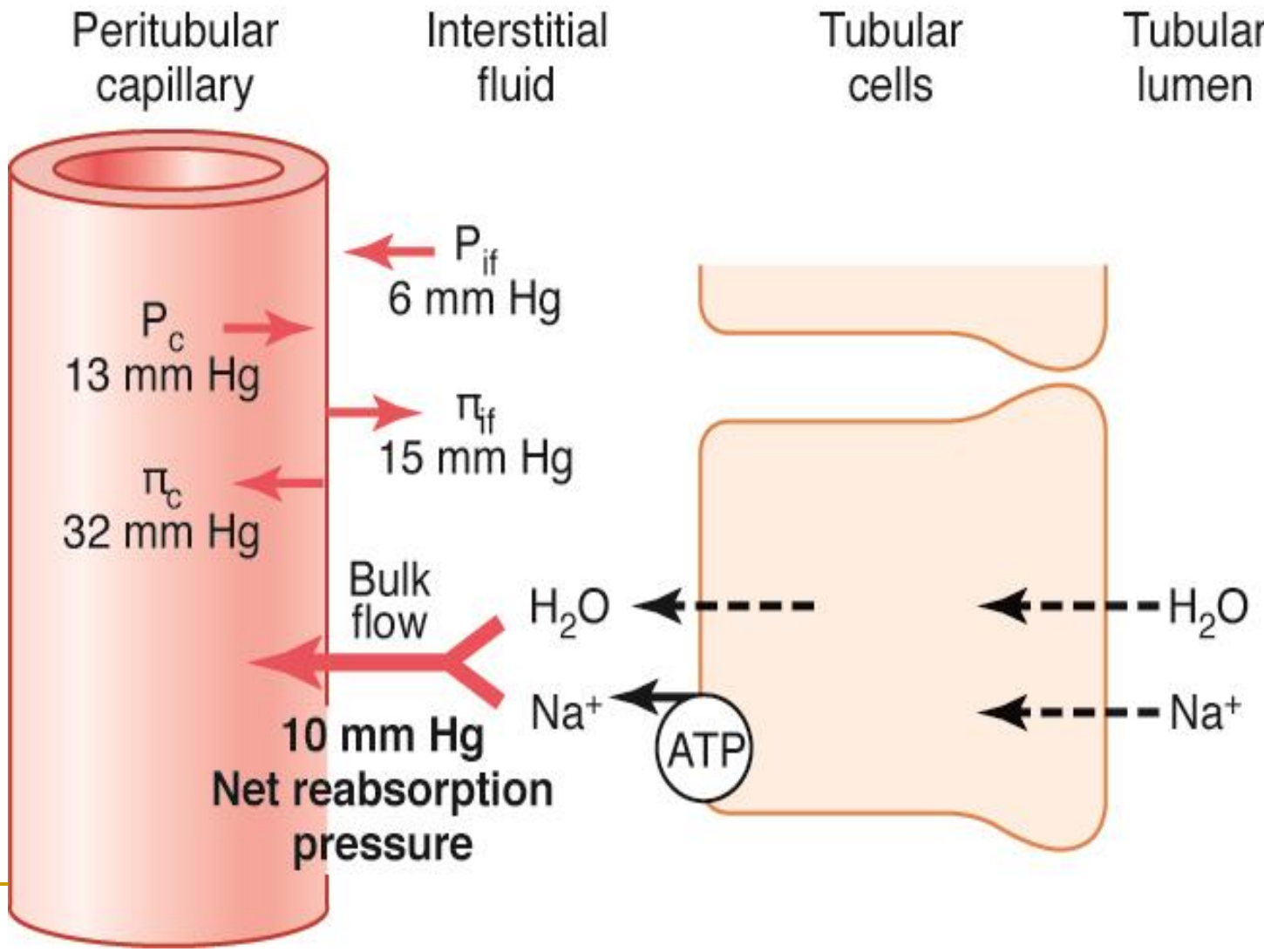
Glomerulotubular Balance



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



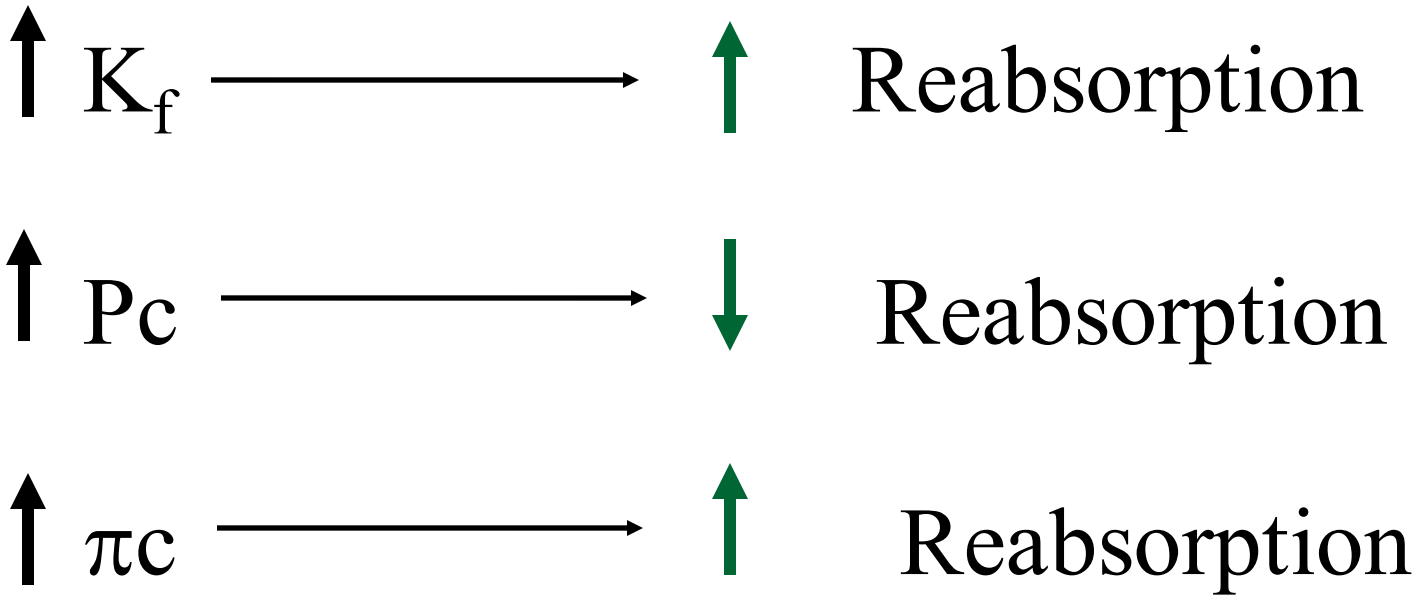
Peritubular Capillary Reabsorption

Reabs = Net Reabs Pressure (NRP) x K_f

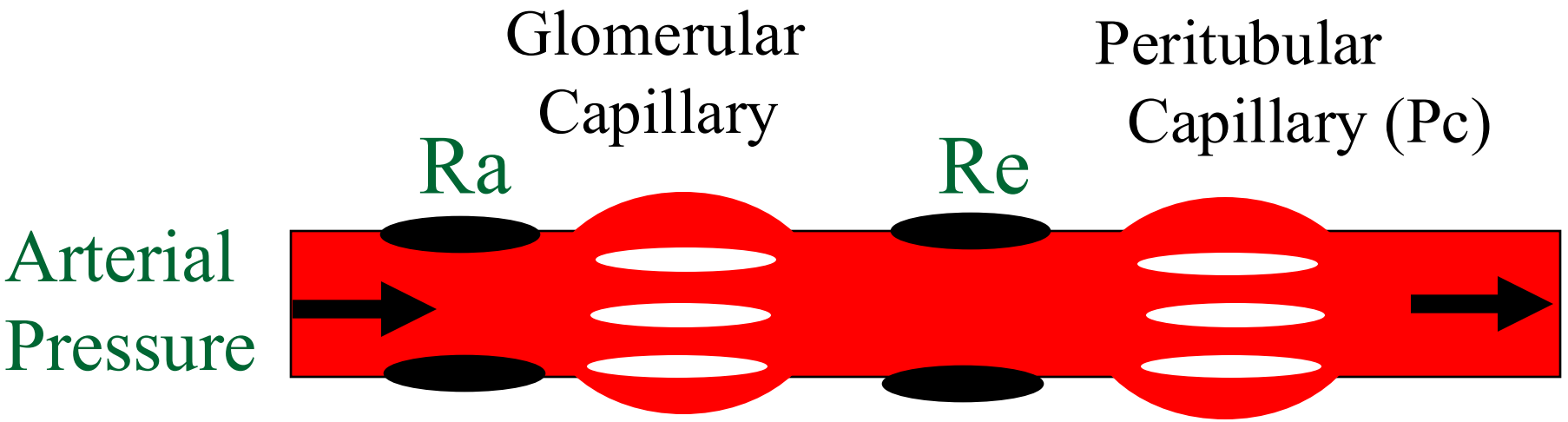
= (10 mmHg) x (12.4 ml/min/mmHg)

Reabs = 124 ml/min

Determinants of Peritubular Capillary Reabsorption



Determinants of Peritubular Capillary Hydrostatic Pressure

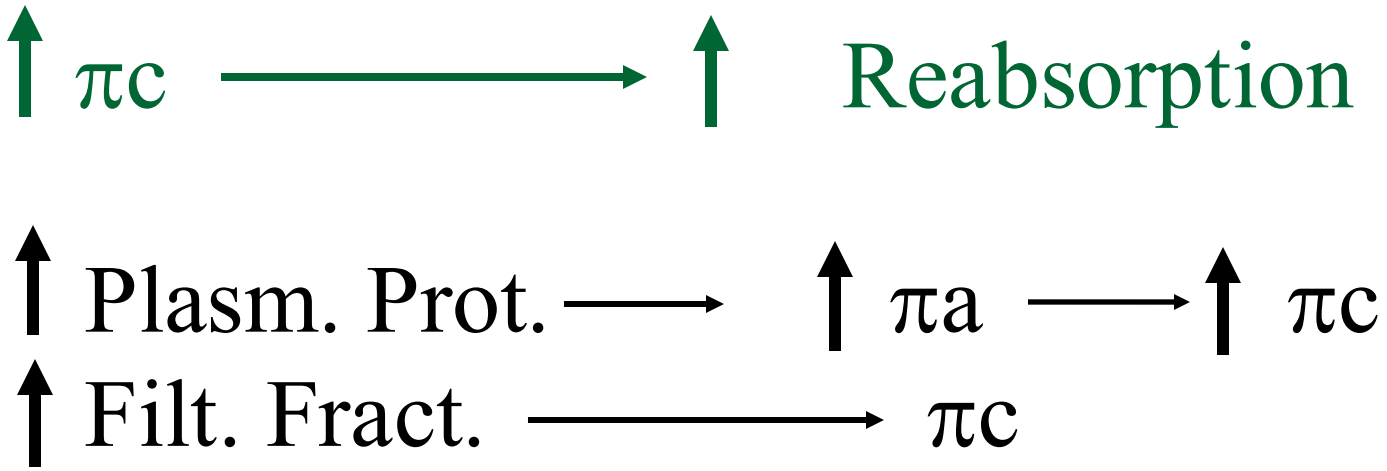


↑ Arterial Pressure → ↑ Pc → ↓ Reabs.

↑ Ra → ↓ Pc → ↑ Reabs.

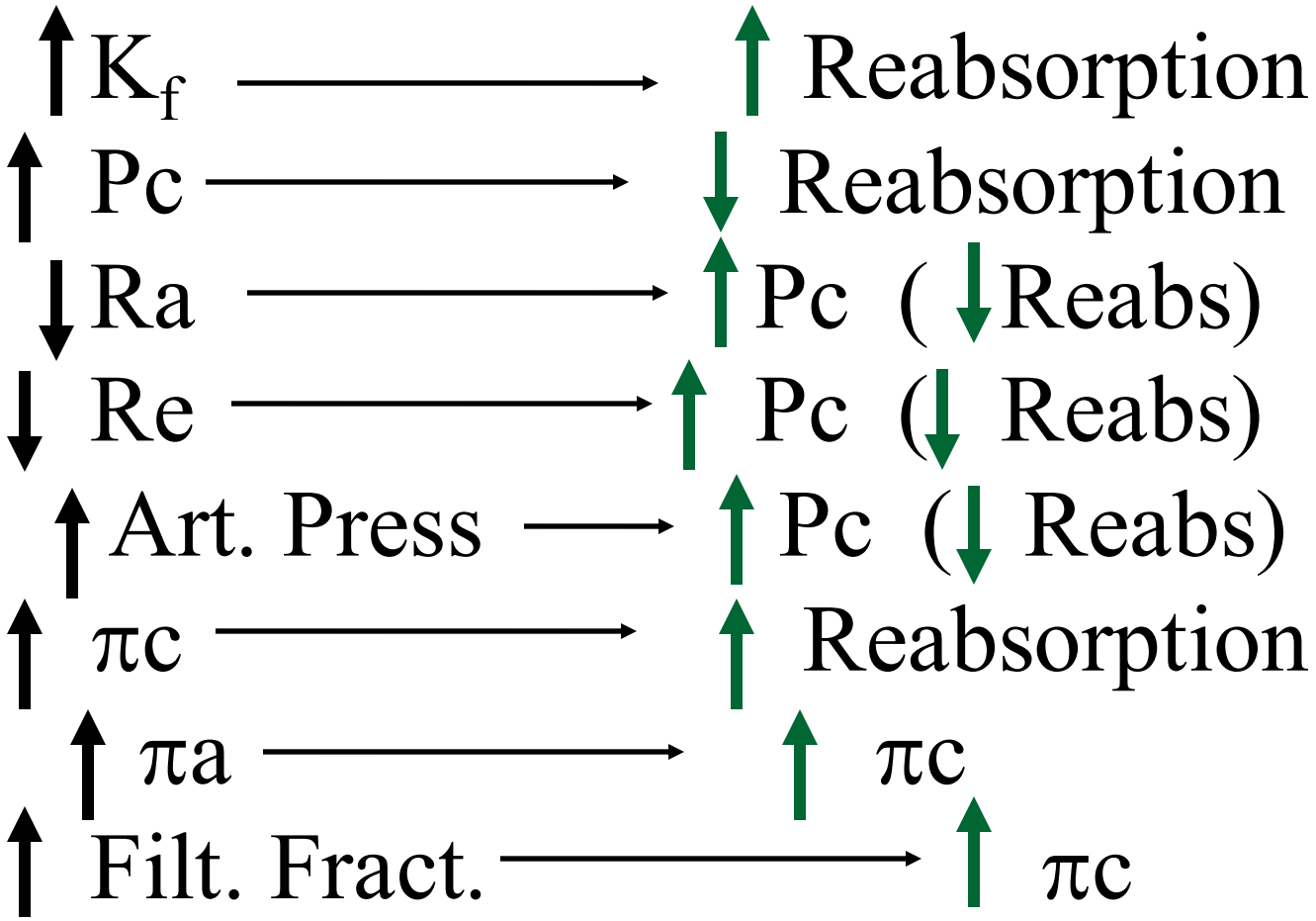
↑ Re → ↓ Pc → ↑ Reabs.

Determinants of Peritubular Capillary Colloid OsmoticPressure

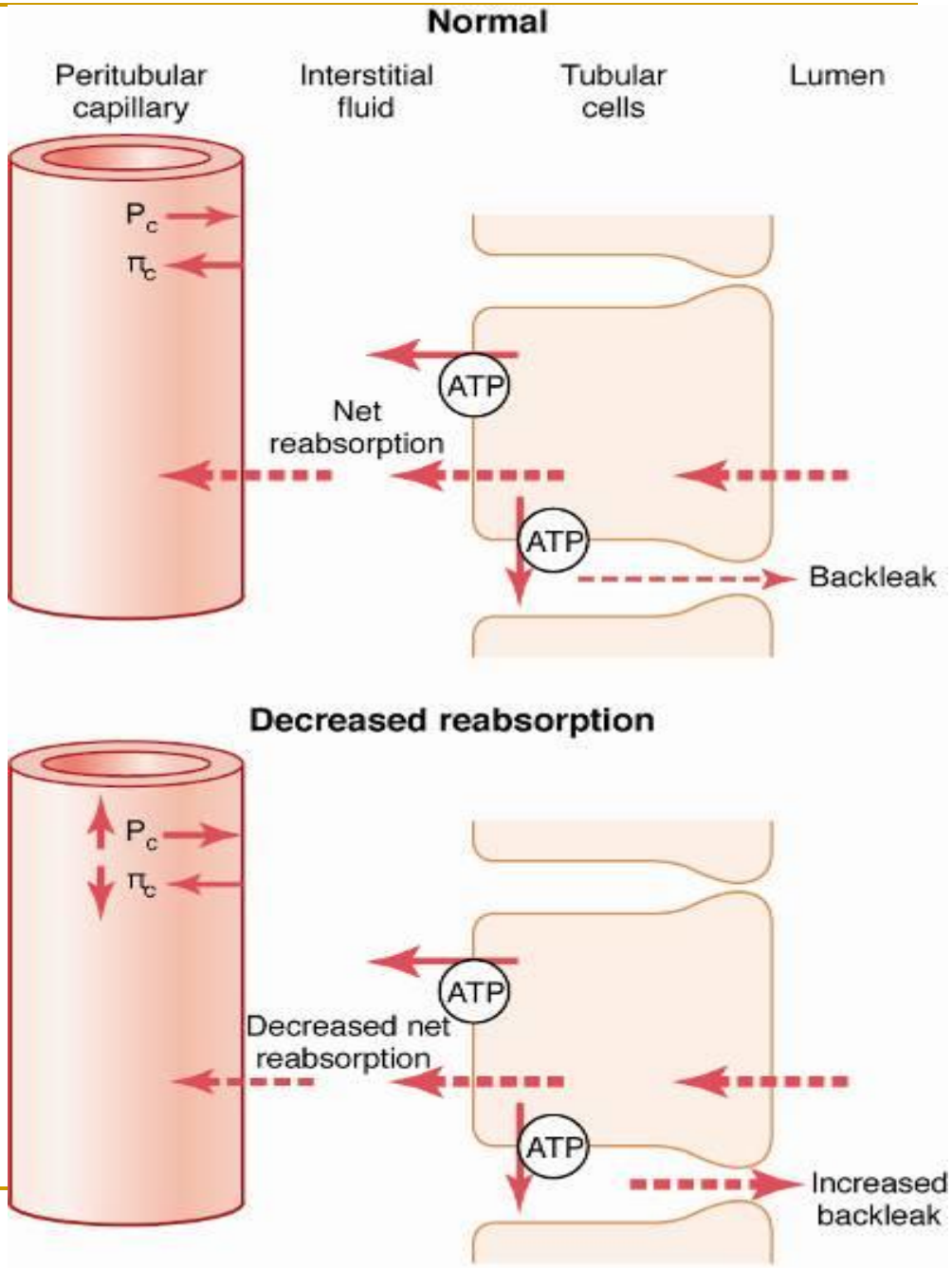


Filt. Fract. = GFR / RPF

Factors That Can Influence Peritubular Capillary Reabsorption



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



Question

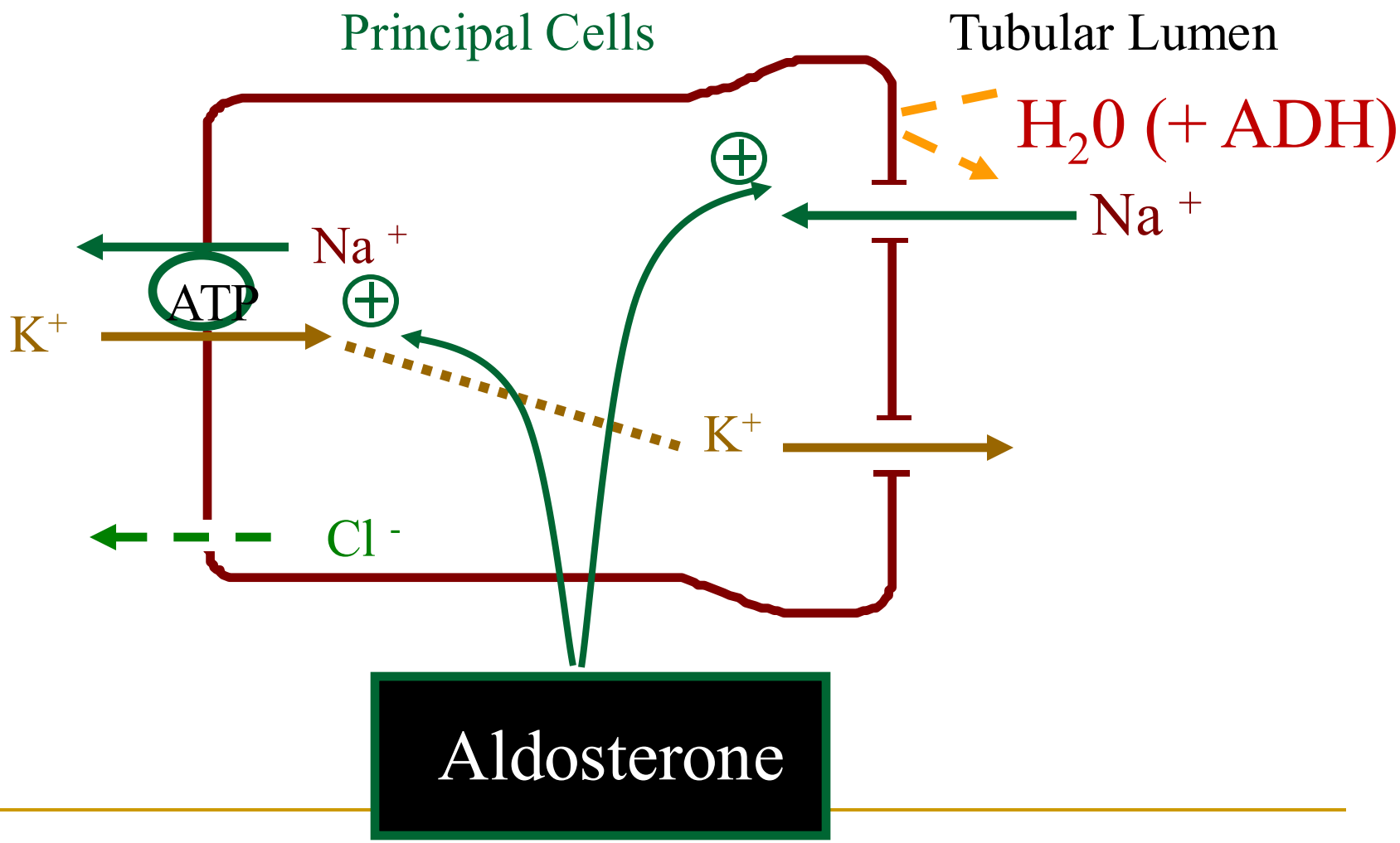
Which of the following changes would tend to increase peritubular reabsorption ?

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)

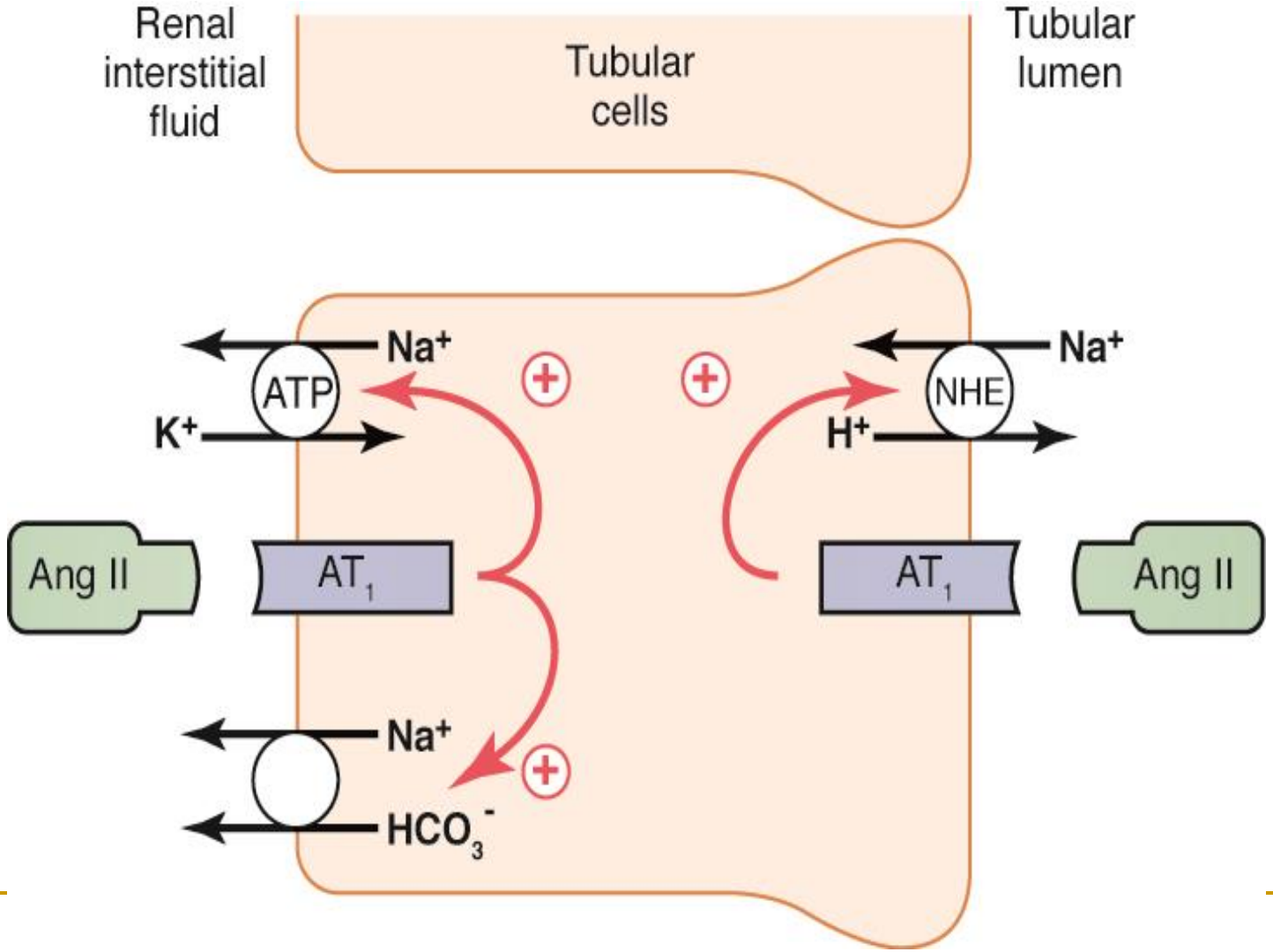
Factors that decrease aldosterone secretion

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

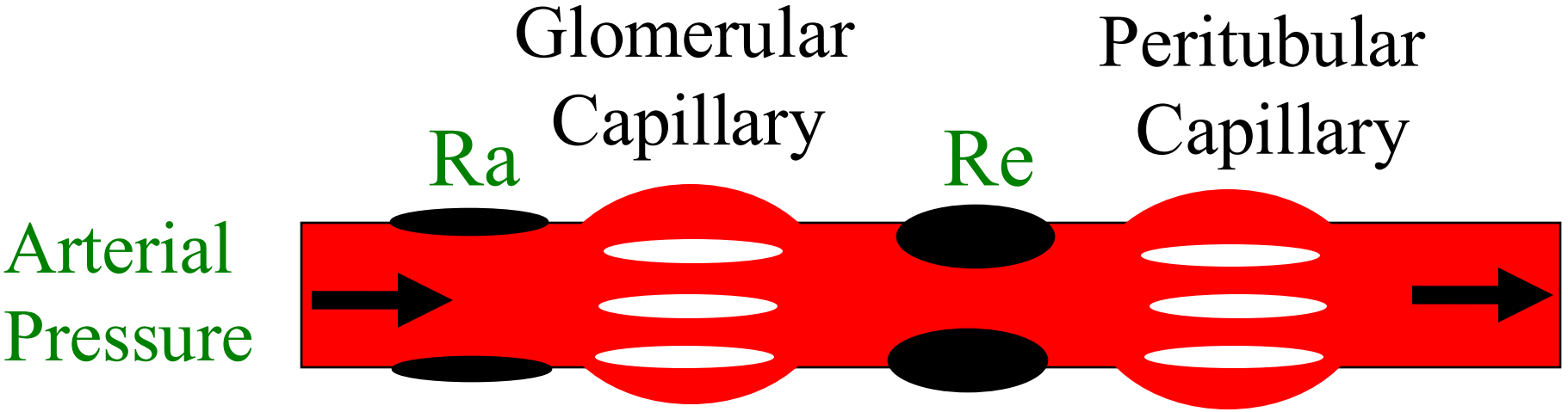
Angiotensin II Increases Na^+ and Water Reabsorption

- Stimulates aldosterone secretion
- Directly increases Na^+ reabsorption
  (proximal, loop, distal, collecting tubules)
- Constricts efferent arterioles
  - decreases peritubular capillary 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

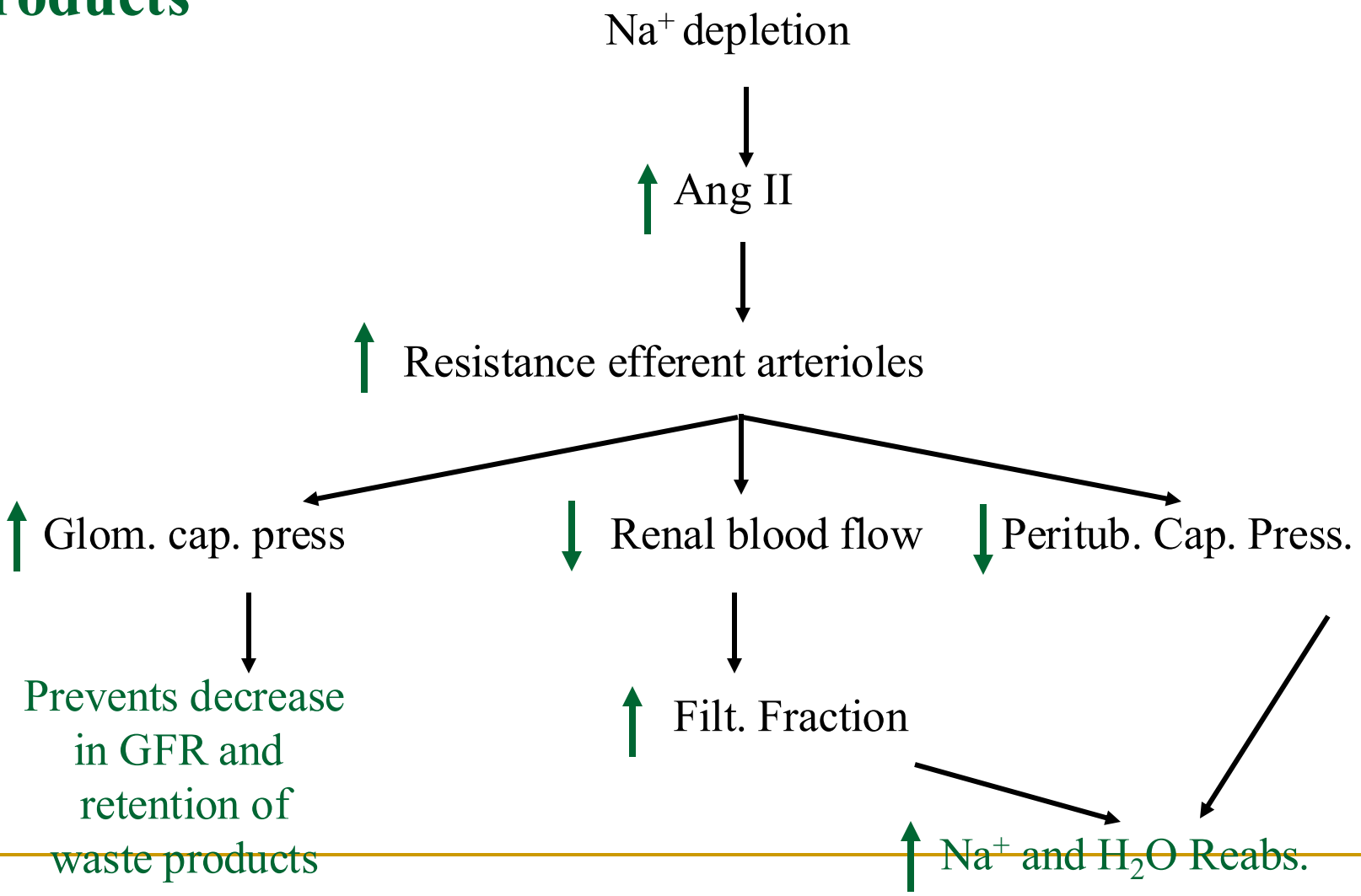


↑ Ang II → ↑ Re → ↓ Pc (peritubular cap. press.)

↓ renal blood flow → ↑ FF

↑ πc

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

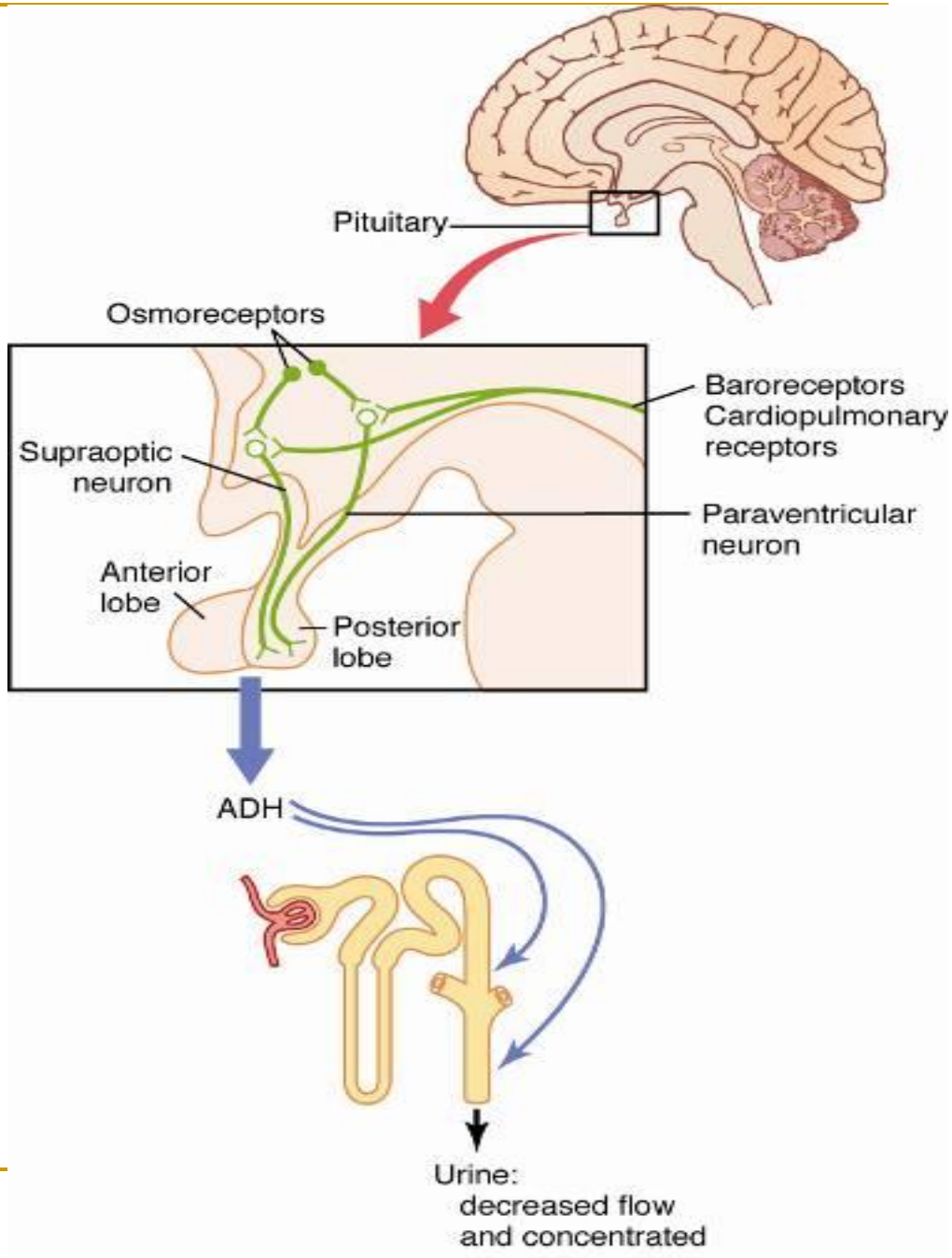
- ACE inhibitors (captopril, benazipril, ramipril)
- Ang II antagonists (losartan, candesartin, irbesartan)
- Renin inhibitors (aliskirin)
  - decrease aldosterone
  - directly inhibit Na^+ reabsorption
  - decrease efferent arteriolar resistance

Natriuresis and Diuresis +  Blood Pressure

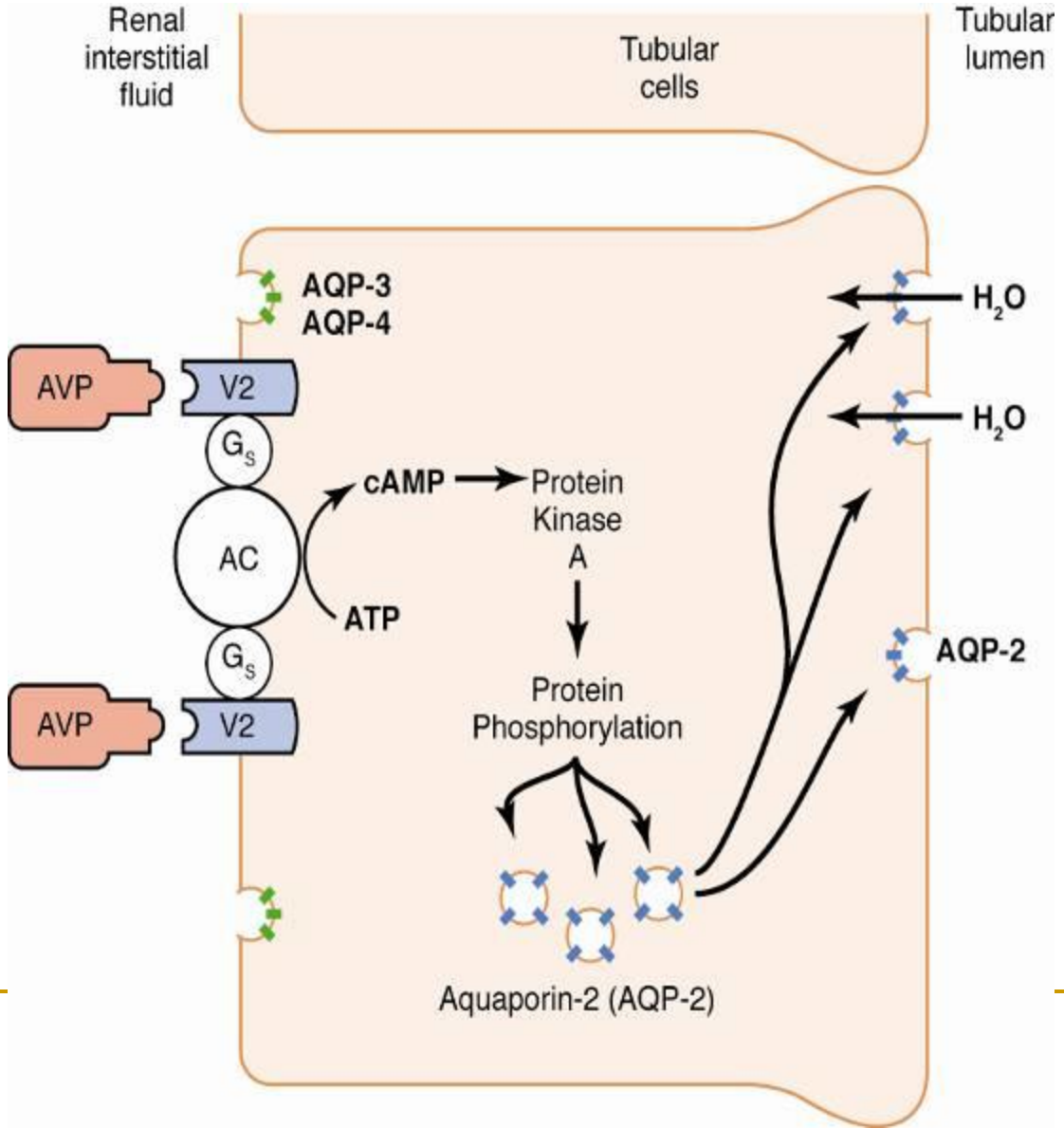
Antidiuretic Hormone (ADH)

- Secreted by posterior pituitary
- Increases H_2O permeability and reabsorption in distal and collecting tubules
- Allows differential control of H_2O and solute excretion
- Important controller of extracellular fluid osmolarity

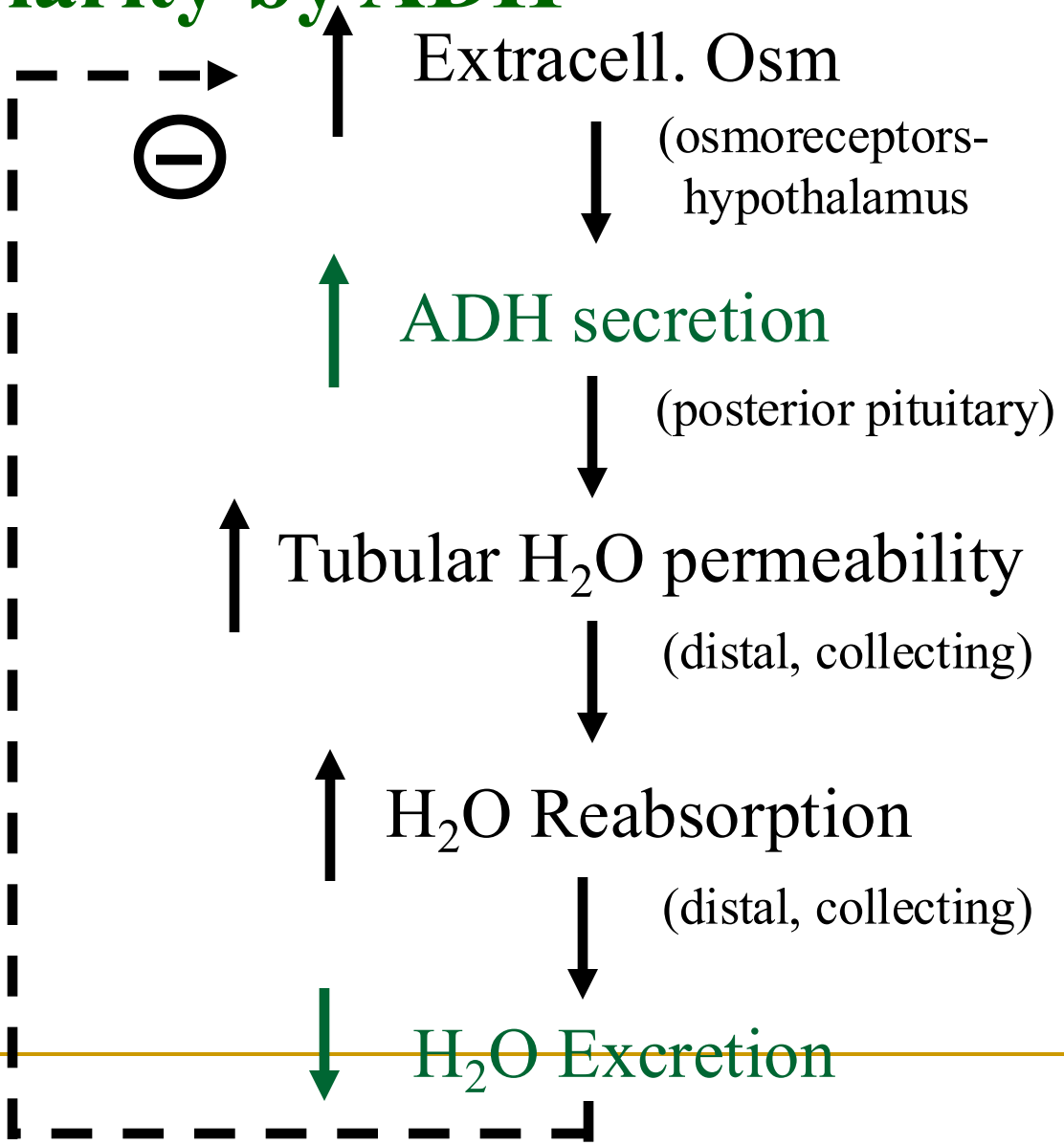
ADH synthesis in the magnocellular neurons of hypothalamus, release by the posterior pituitary, and action on the kidneys



Mechanism of action of ADH in distal and collecting tubules



Feedback Control of Extracellular Fluid Osmolarity by ADH



Abnormalities of ADH

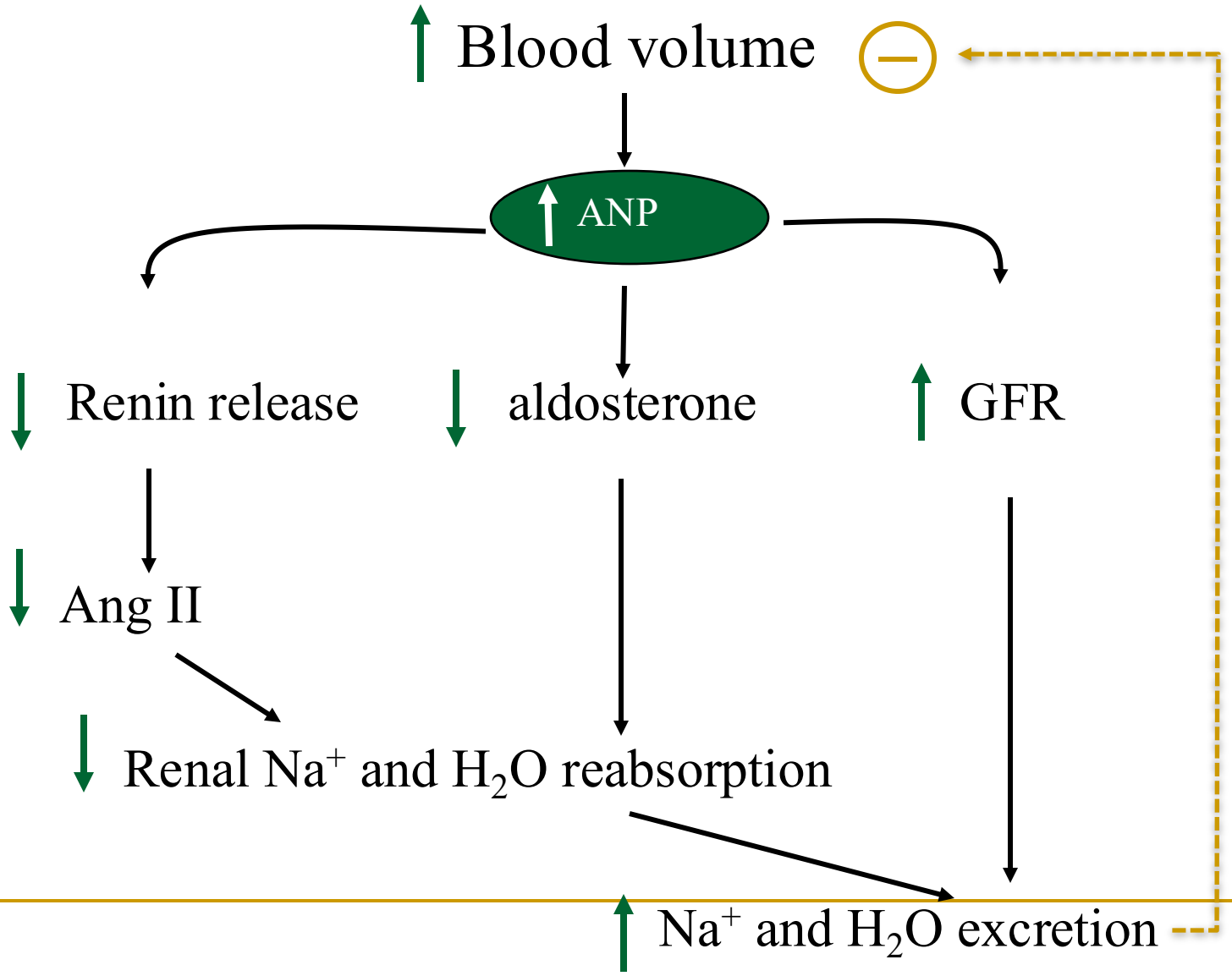
- Inappropriate ADH syndrome (excess ADH)
  - decreased plasma osmolarity, hyponatremia

- "Central" Diabetes insipidus (insufficient ADH)
  - increased plasma osmolarity, hypernatremia, excess thirst

Atrial natriuretic peptide increases Na^+ excretion

- Secreted by cardiac atria in response to stretch (increased blood volume)
- Directly inhibits Na^+ reabsorption
- Inhibits renin release and aldosterone formation
- Increases GFR
- Helps to minimize blood volume expansion

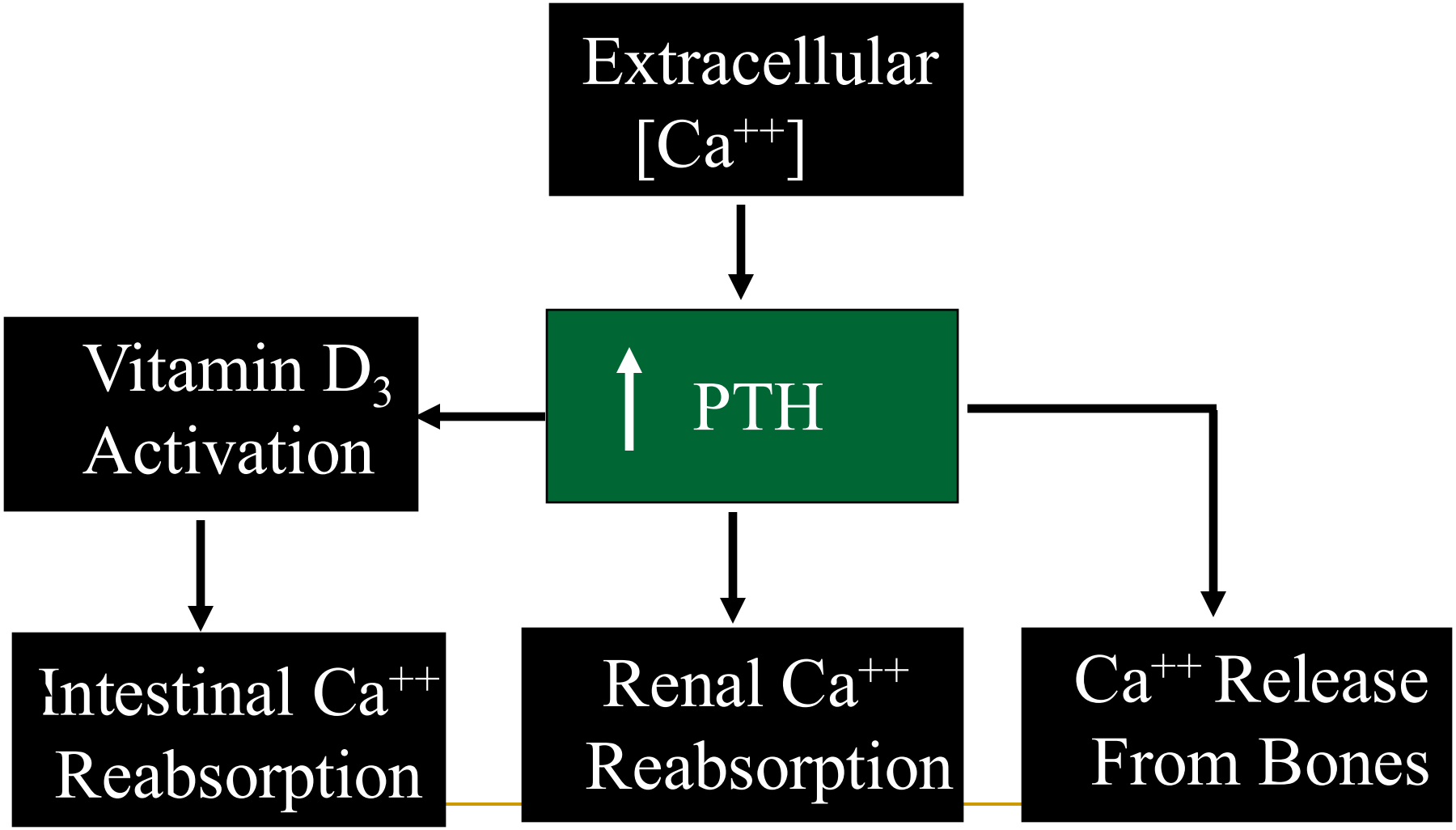
Atrial Natriuretic Peptide (ANP)



Parathyroid hormone increases renal Ca^{++} reabsorption

- Released by parathyroids in response to decreased extracellular Ca^{++}
- Increases Ca^{++} reabsorption by kidneys
- Increases Ca^{++} reabsorption by gut
- Decreases phosphate reabsorption
- Helps to increase extracellular Ca^{++}

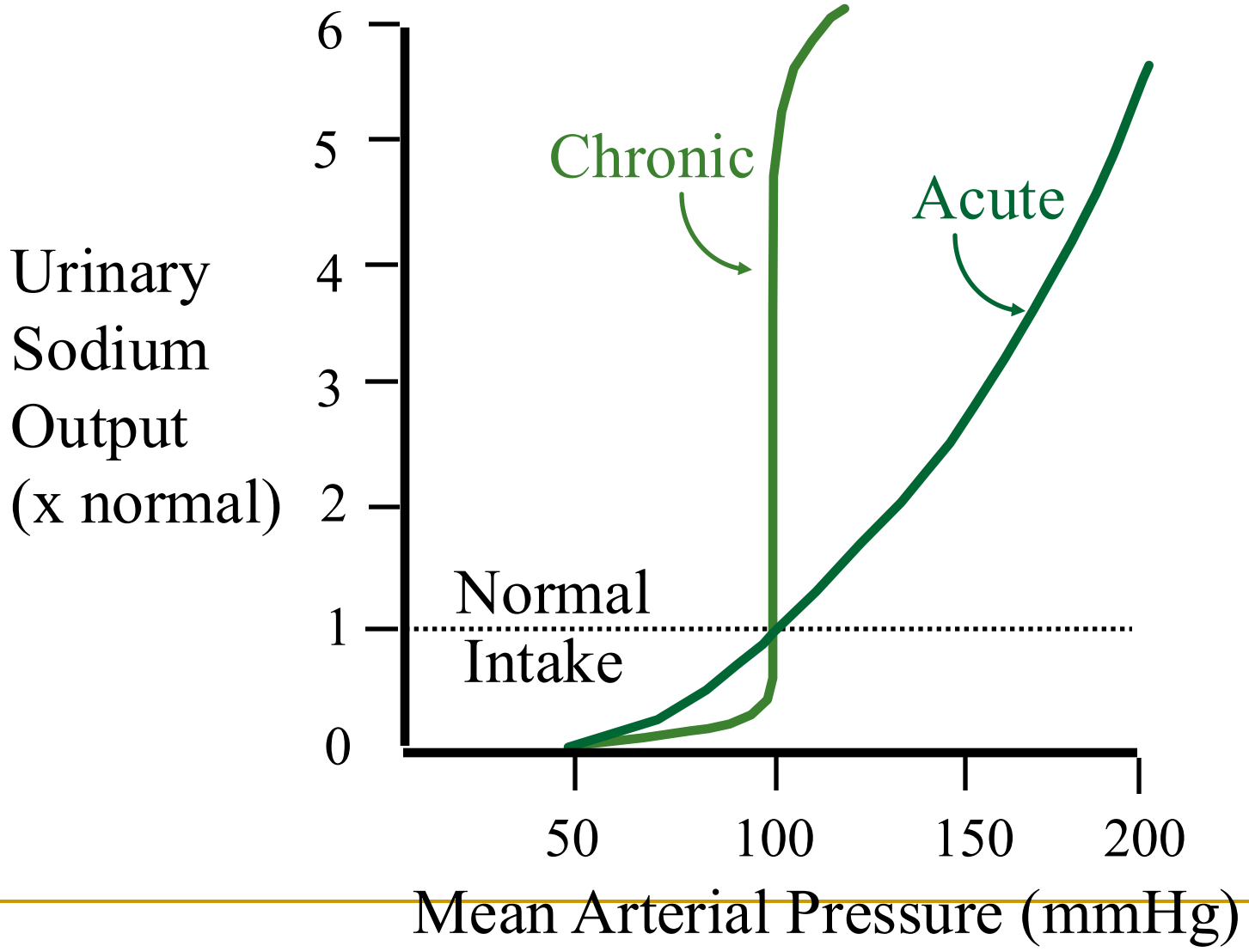
Control of Ca^{++} by Parathyroid Hormone



Sympathetic nervous system increases Na^+ reabsorption

- Directly stimulates Na^+ reabsorption
- Stimulates renin release
- Decreases GFR and renal blood flow (only a high levels of sympathetic stimulation)

Renal Pressure Natriuresis



Increased Arterial Pressure Decreases Na^+ Reabsorption (Pressure Natriuresis)

- Increased peritubular capillary hydrostatic pressure
- Decreased renin and aldosterone
- Increased release of intrarenal natriuretic factors
  - prostaglandins
  - EDRF

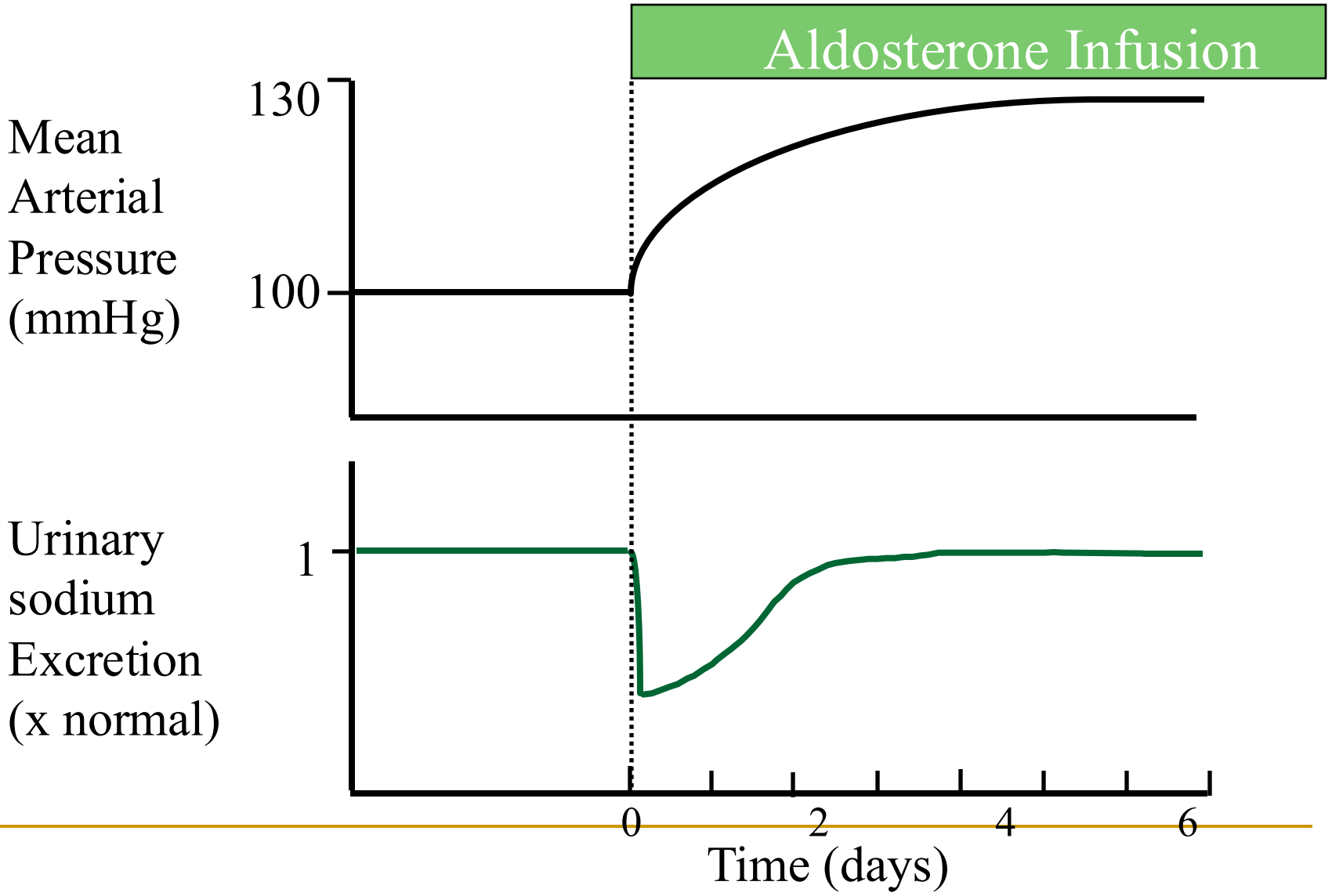
Osmotic Effects on Reabsorption

- Water is reabsorbed only by osmosis
- Increasing the amount of unreabsorbed solutes in the tubules decreases water reabsorption

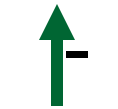
i.e. diabetes mellitus : unreabsorbed glucose in tubules causes diuresis and water loss

i.e. osmotic diuretics (mannitol)

"Escape" from Sodium Retention During Excess Aldosterone Infusion

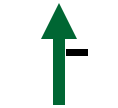


- Conn's syndrome: (primary aldosteronism)



Na^+ reabsorption (distal & coll. tub.)

Na^+ excretion (in steady-state)



K^+ secretion (transient)

K^+ excretion (in steady-state)

plasma K^+

blood pressure

plasma renin

Abnormal Tubular Function:

- Inappropriate ADH syndrome:

↑ water reabsorption

↔ water excretion (urine volume)

↓ plasma Na^+

Assessing Kidney Function

- Plasma concentration of waste products
  (e.g. BUN, creatinine)
- Urine specific gravity, urine concentrating ability;
- Urinalysis test reagent strips (protein, glucose, etc)
- Biopsy
- Albumin excretion (microalbuminuria)
- Isotope renal scans
- Imaging methods (e.g. MRI, PET, arteriograms,
  iv pyelography, ultrasound etc)
- Clearance methods (e.g. 24-hr creatinine clearance)
- etc