# *Renal physiology*
# *Renal support*

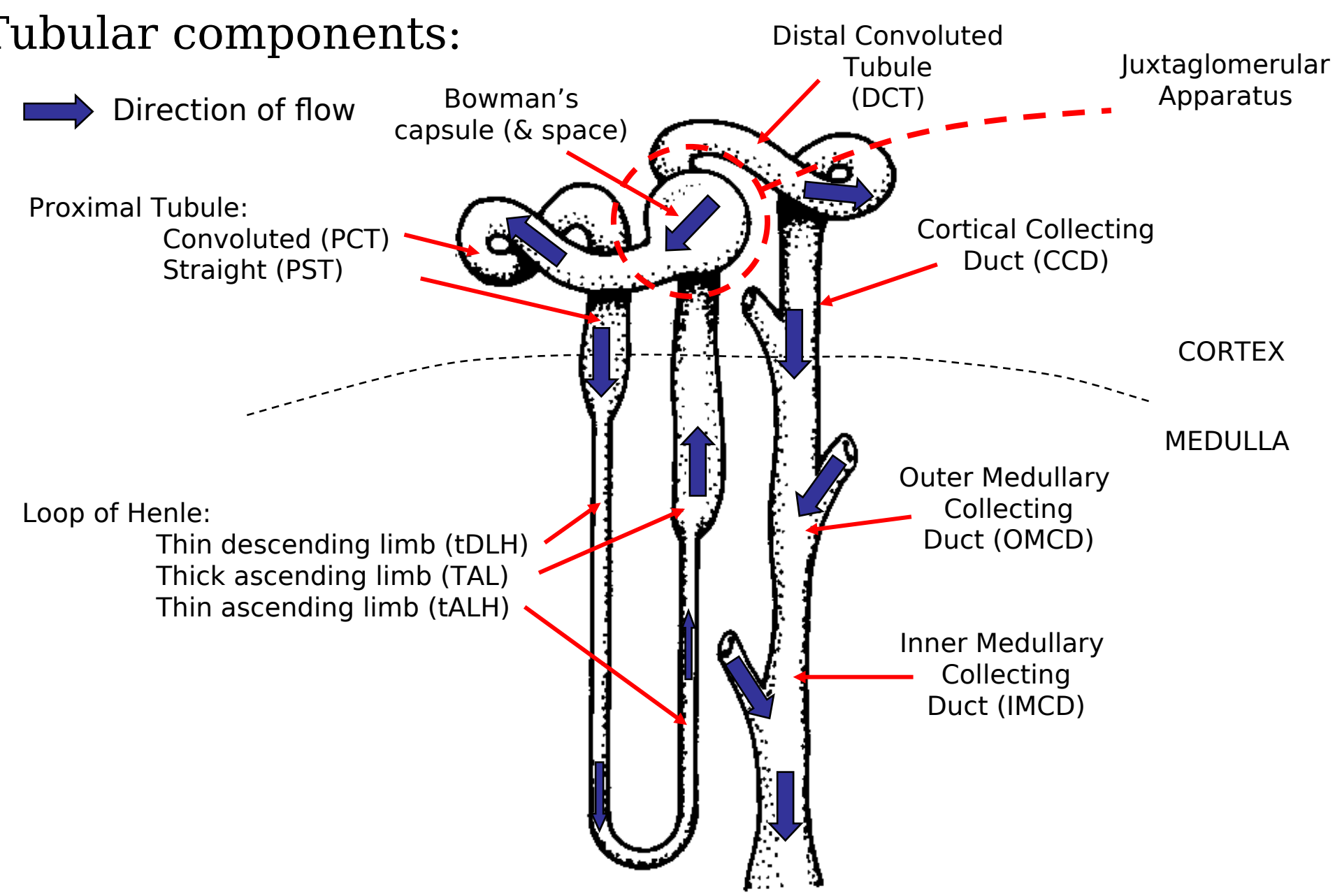
*Sotiris Papaspyros*

*April 2007*

# *Renal physiological role*

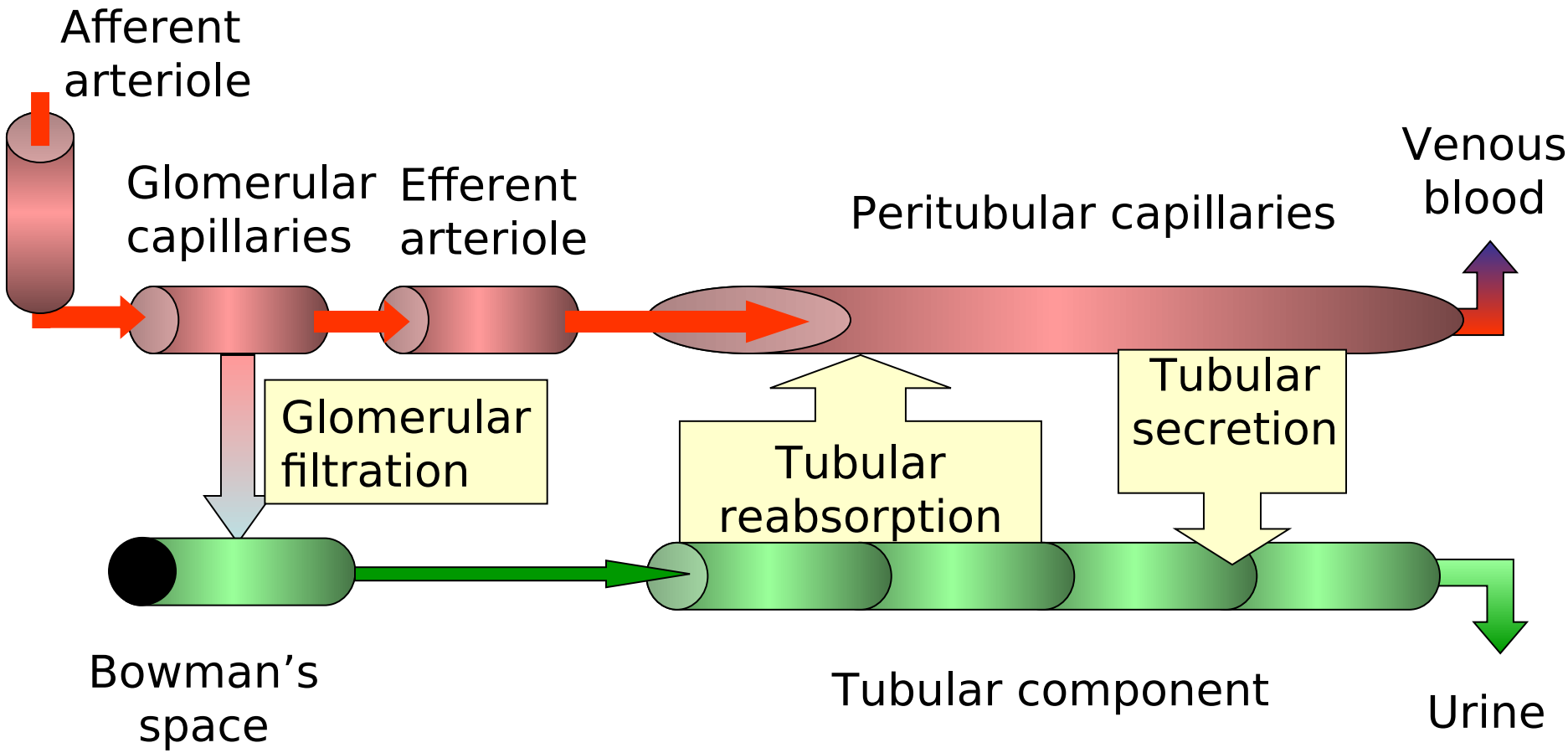
1. *Control of H2O and ion balance.*
2. *Control of acid-base status and pH homeostasis.*
3. *Endocrine role.*

# Tubular components:



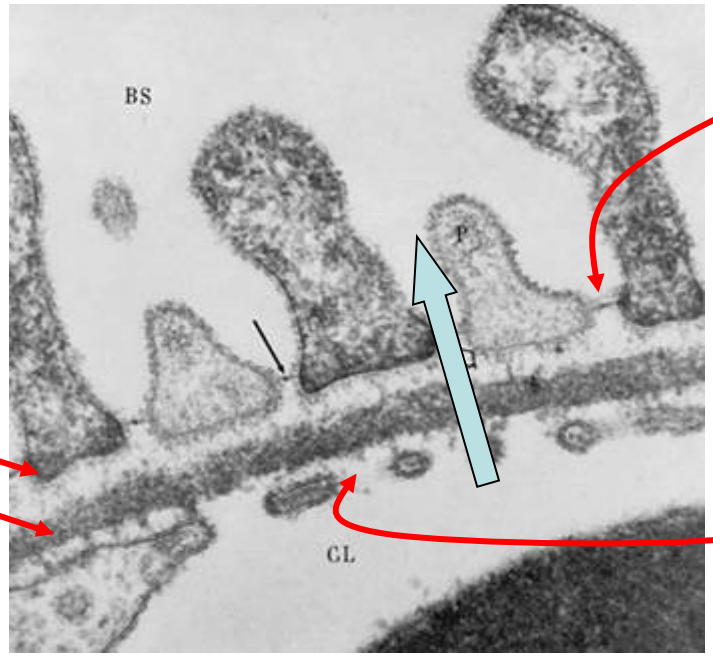

- Each segment is functionally specialised

# Three basic processes underlie the formation of urine:



# *Blood flow and filtration*

# The filter is complex:




Slit diaphragm
(pores 4-14nm)

Foot processes
are negatively
charged
(glycoproteins)

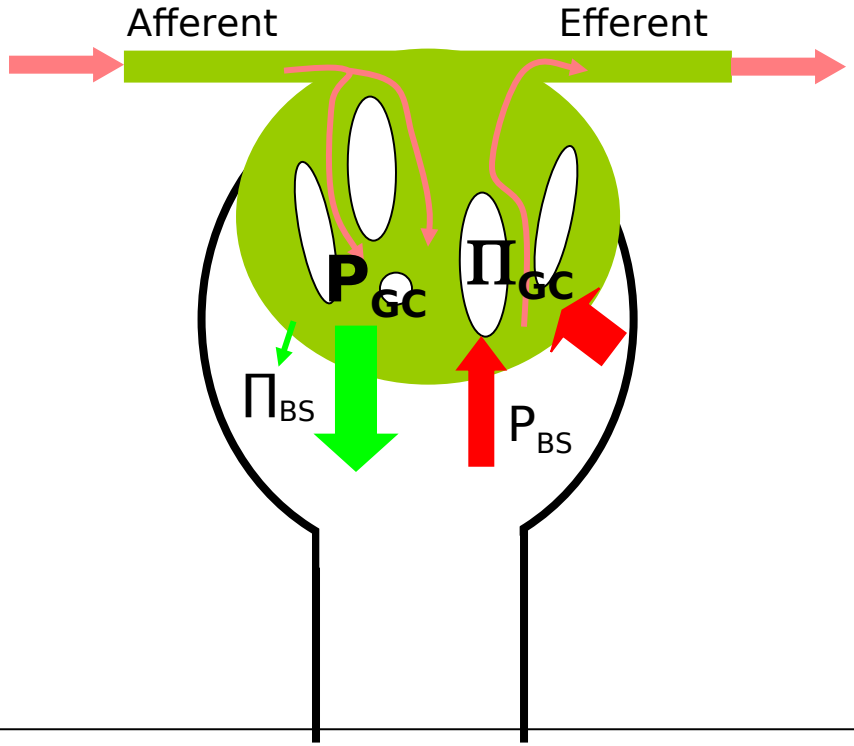
Capillary fenestrations
70 nm “holes”

Basement membrane
negatively charged
molecular sieve
(sialic acid, muco-
polysaccharides)

1. Fluid in Bowman’s space is a “protein-free” ultrafiltrate of plasma (normal electrolytes, glucose, amino acids, etc., & pH ~7.4)

2. “Filterability” of a solute depends on:
   - Molecular size
   - Electrical charge
     (anions are restricted)
   - Shape
     (rigid/globular molecules are restricted)

# Forces (Starling's) determining filtration:




**Favouring filtration:**

- Hydrostatic pressure in the glomerular capillaries ($P_{GC\sim48mmHg}$)
- Oncotic pressure in Bowman's space ($\Pi_{BS}$) ~ negligible

**Opposing filtration:**

- Oncotic pressure in the glomerular capillaries ($\Pi_{GC\sim25mmHg}$)
- Hydrostatic pressure in Bowman's space ($P_{BS\sim10mmHg}$)

# Determinants of filtration rate:

Ultra filtration pressure ($P_{UF}$)

$$GFR = K_f.[(P_{GC} - P_{BS})-(\pi_{GC})]$$

Ultrafiltration coefficient

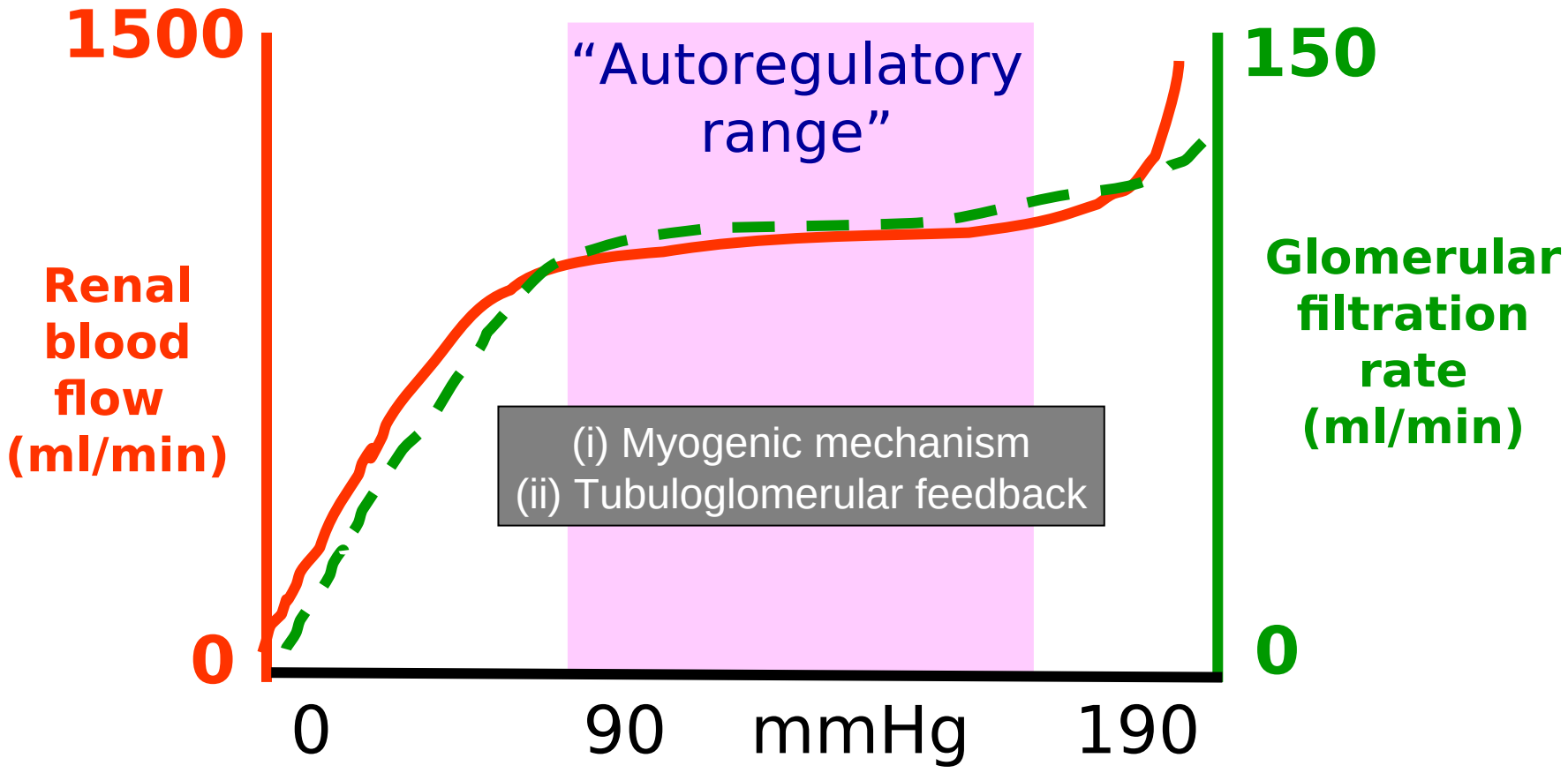
$L_p.S_f$

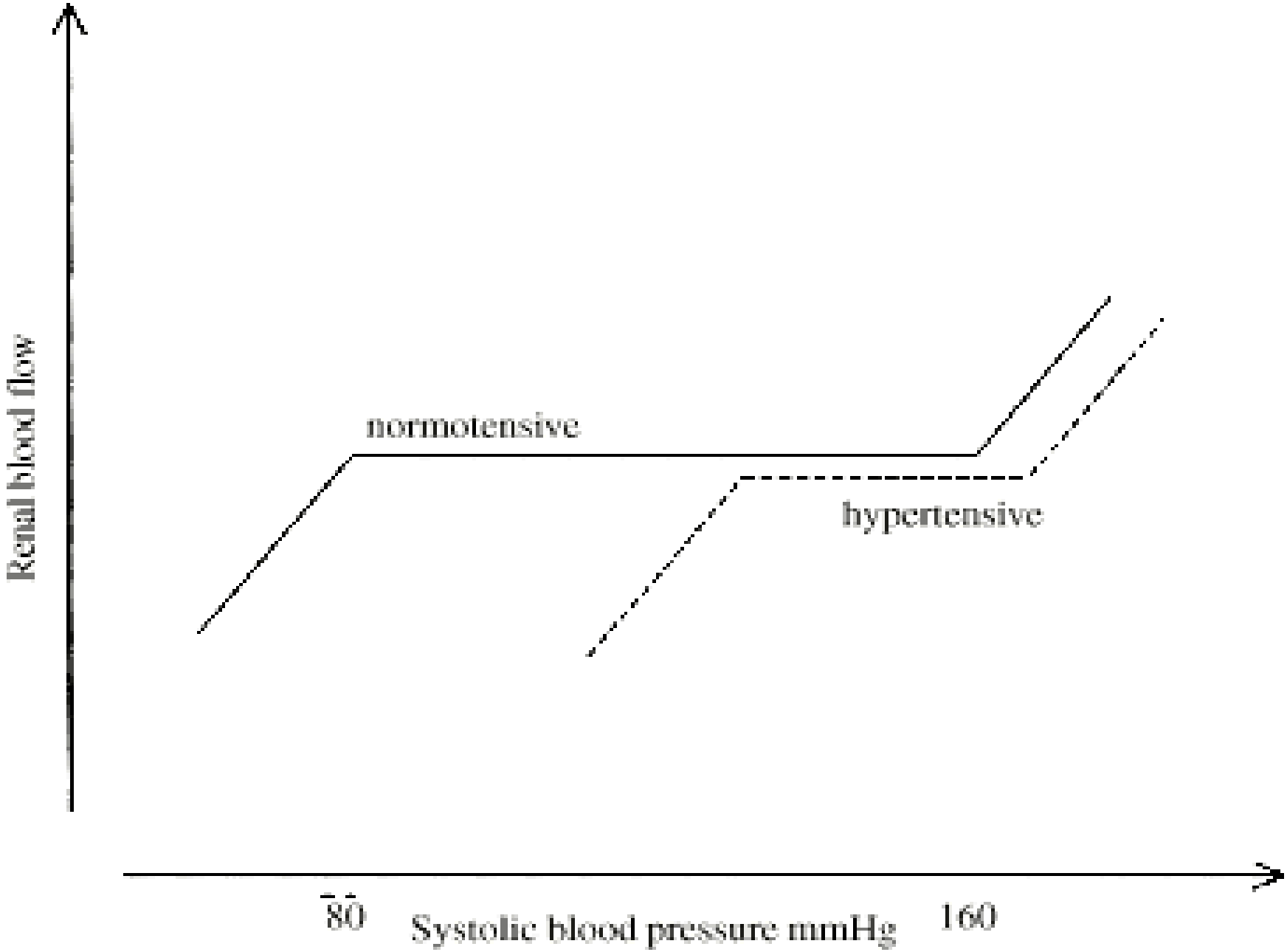
$L_p$ = hydraulic conductivity

$S_f$ = area available for filtration

- $K_f$ ~X10 that of other systemic capillary beds.

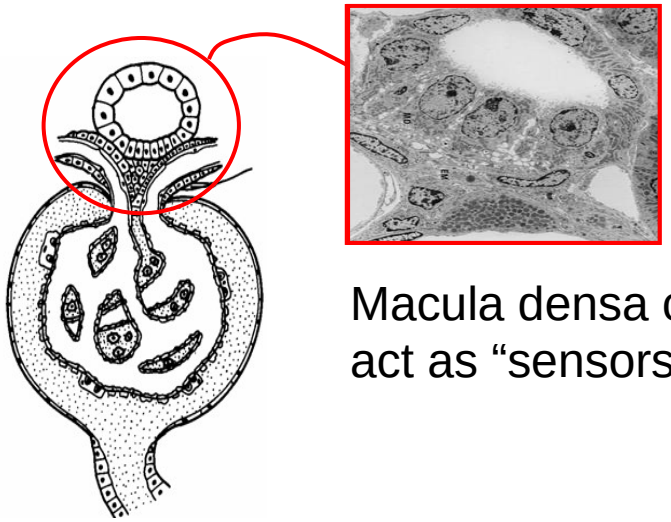
# Autoregulation of blood flow and GFR:




Renal blood flow
normotensive
hypertensive
80
Systolic blood pressure mmHg
160

# Tubuloglomerular feedback (TGF):

SNGFR regulated according to “solute flow”



Macula densa cells act as “sensors”

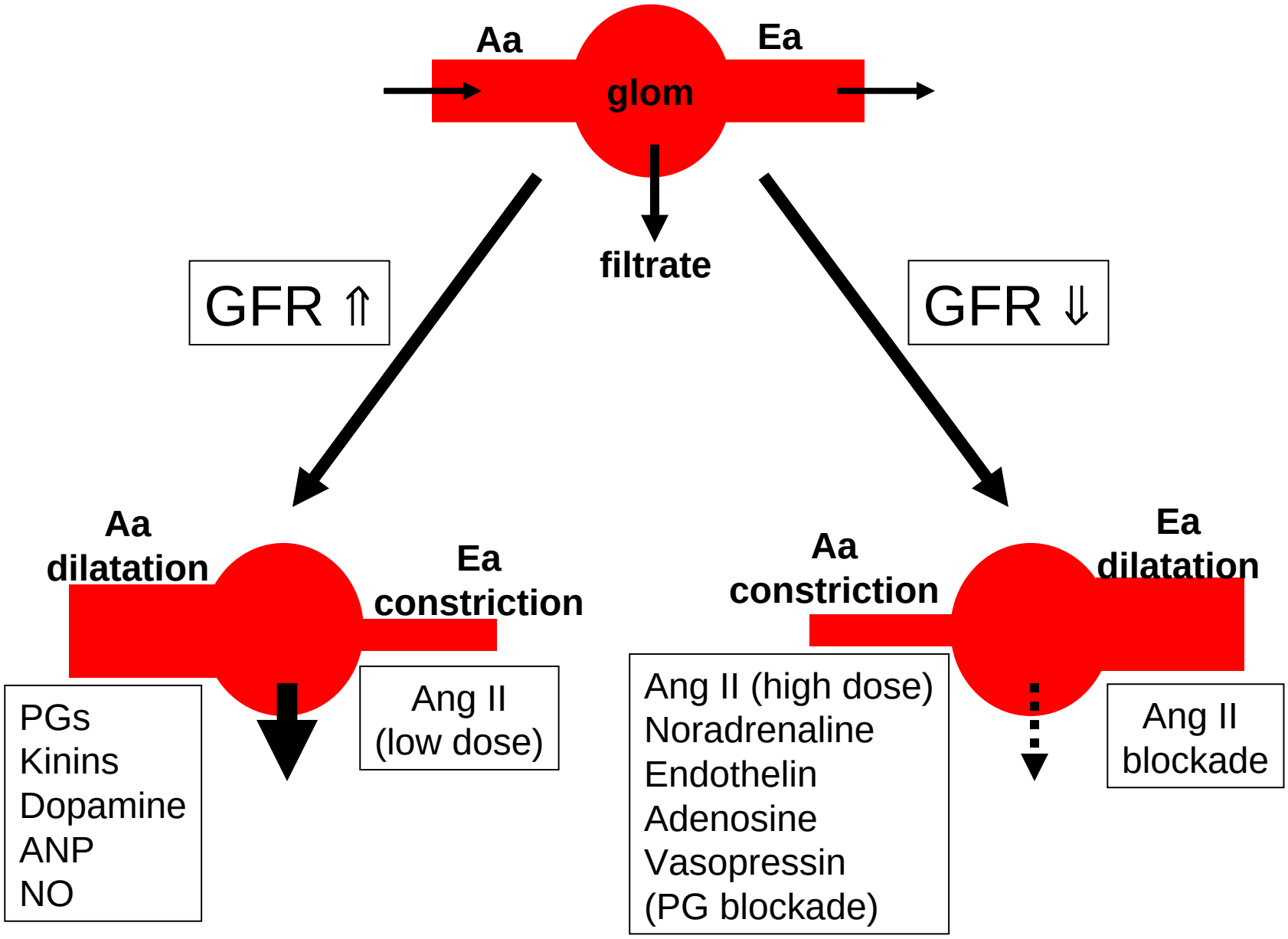
Aa dilatation

Single Nephron GFR

Aa constriction

Luminal [NaCl] at macula densa

# Alterations in arteriolar resistance affect GFR:



# Renal clearance:

"The volume of plasma that is cleared of a substance per unit time"

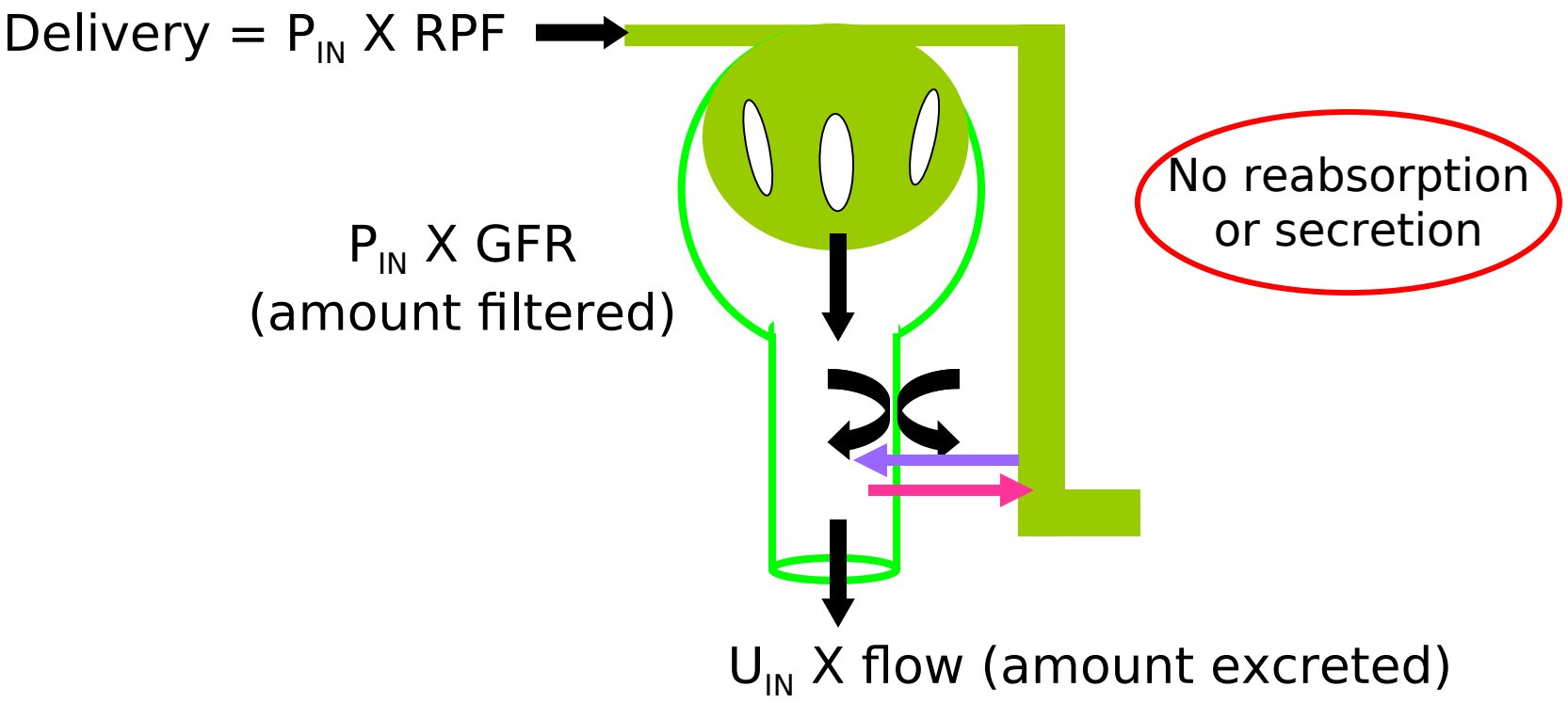
$$C_x = \frac{U_x . \dot{V}}{P_x} \text{ ml/min}$$

$U_x$ = urine concentration (mg/ml)

$P_x$ = plasma concentration (mg/ml)

$\dot{V}$ = urine flow rate (ml/min)

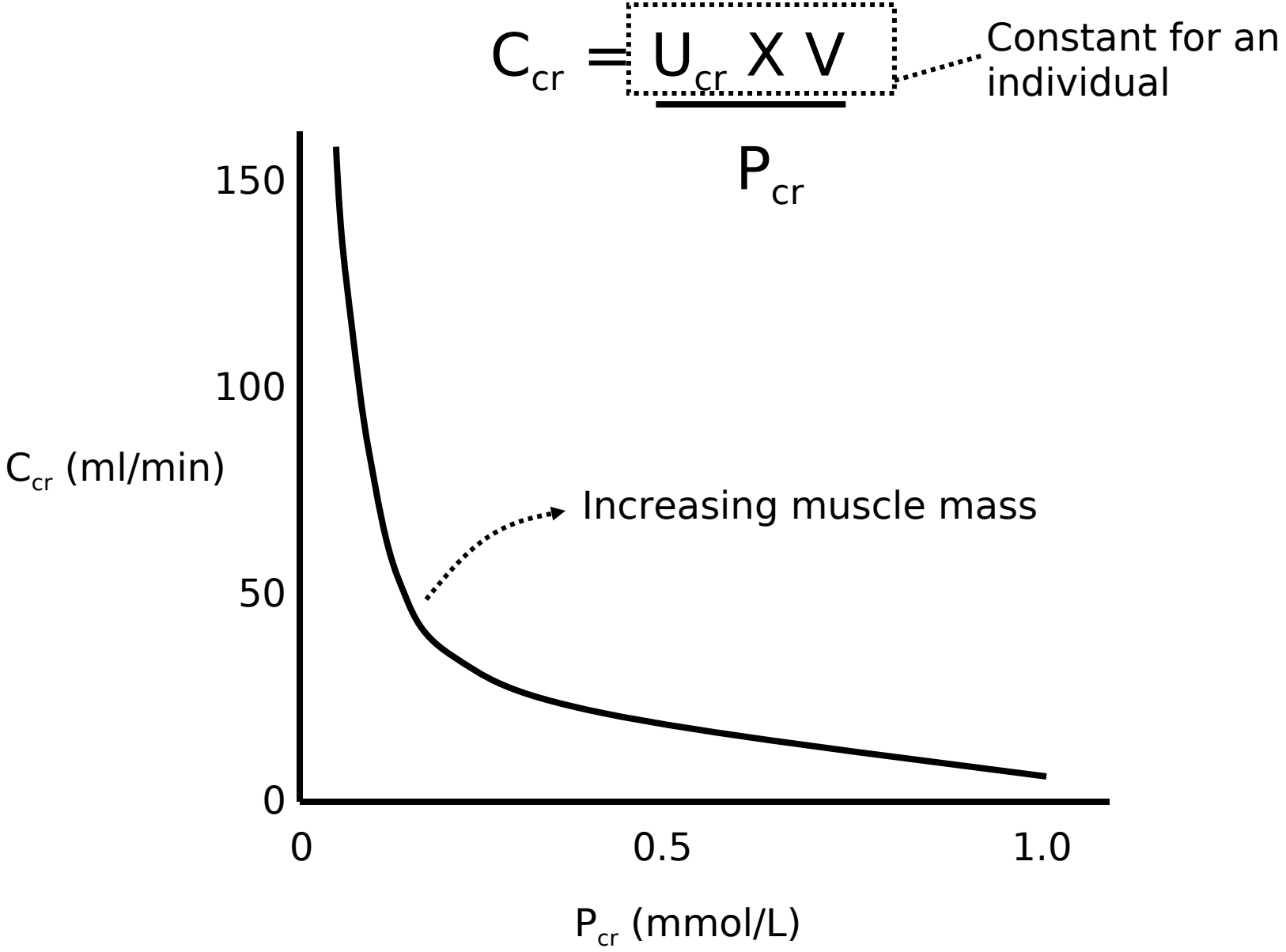
# learance of inulin / creatinine = GFR:

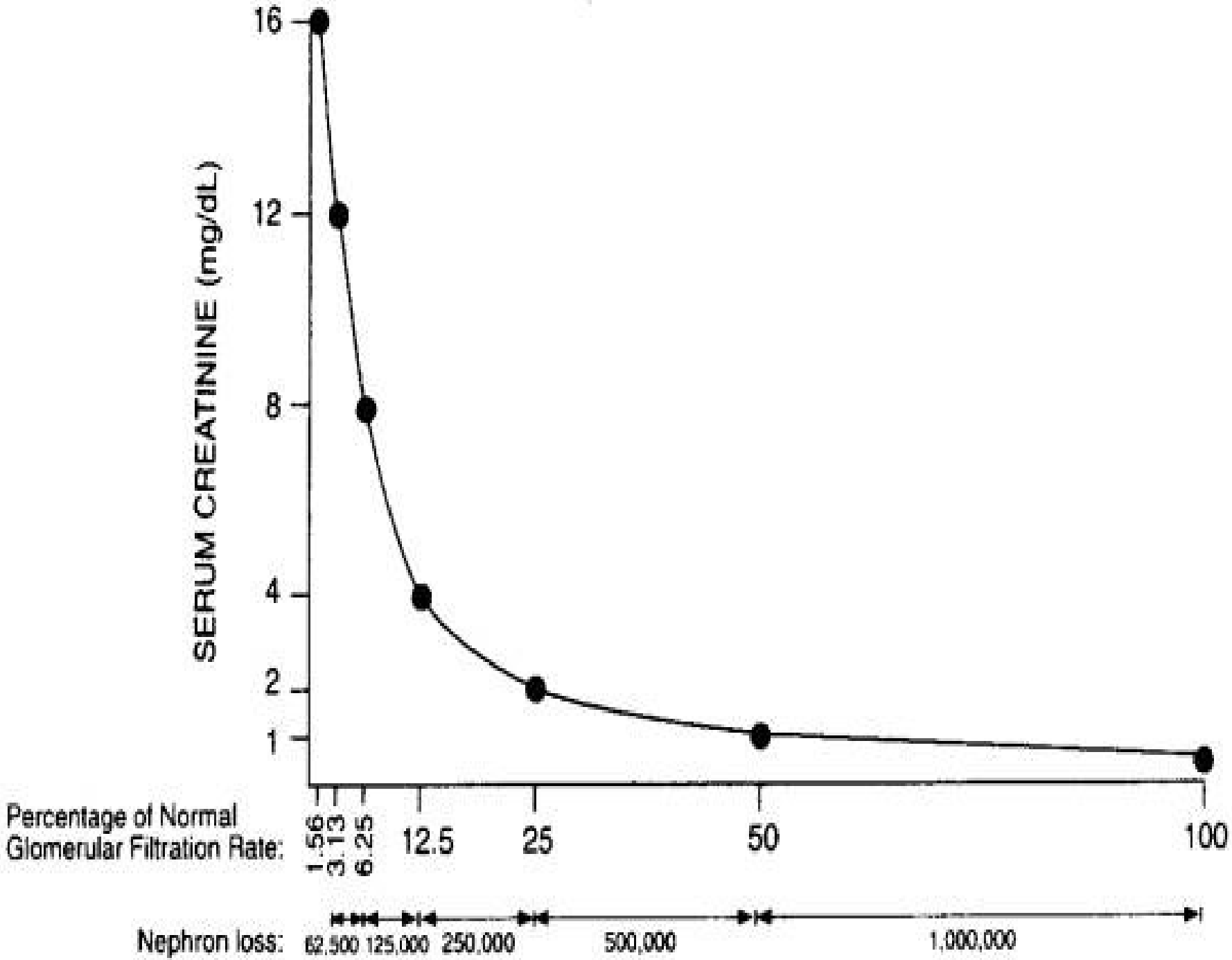



Amount filtered = Amount excreted

Therefore $C_{IN}$ = GFR ~ 125 ml/min (180 litres/day)

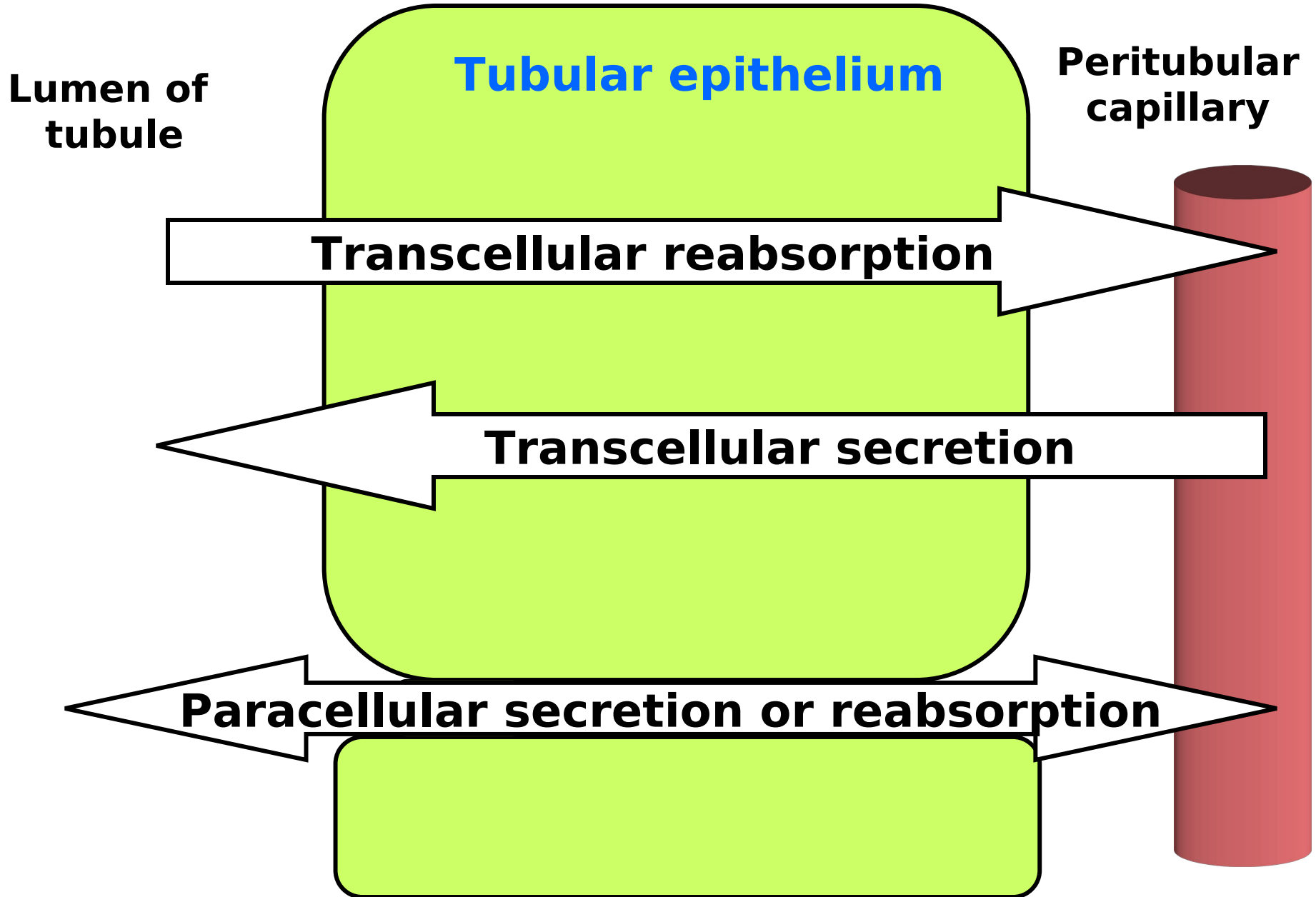
**reabsorption** $C_X < C_{IN} < C_X$ **secretion**


$C_{cr} = \frac{U_{cr} \times V}{P_{cr}}$
Constant for an individual
150
100
50
0
$C_{cr}$ (ml/min)
Increasing muscle mass
0
0.5
1.0
$P_{cr}$ (mmol/L)


SERUM CREATININE (mg/dL)
16
12
8
4
2
1
Percentage of Normal Glomerular Filtration Rate:
1.56
3.13
6.25
12.5
25
50
100
Nephron loss:
62,500
125,000
250,000
500,000
1,000,000

# *Tubular solute transport*

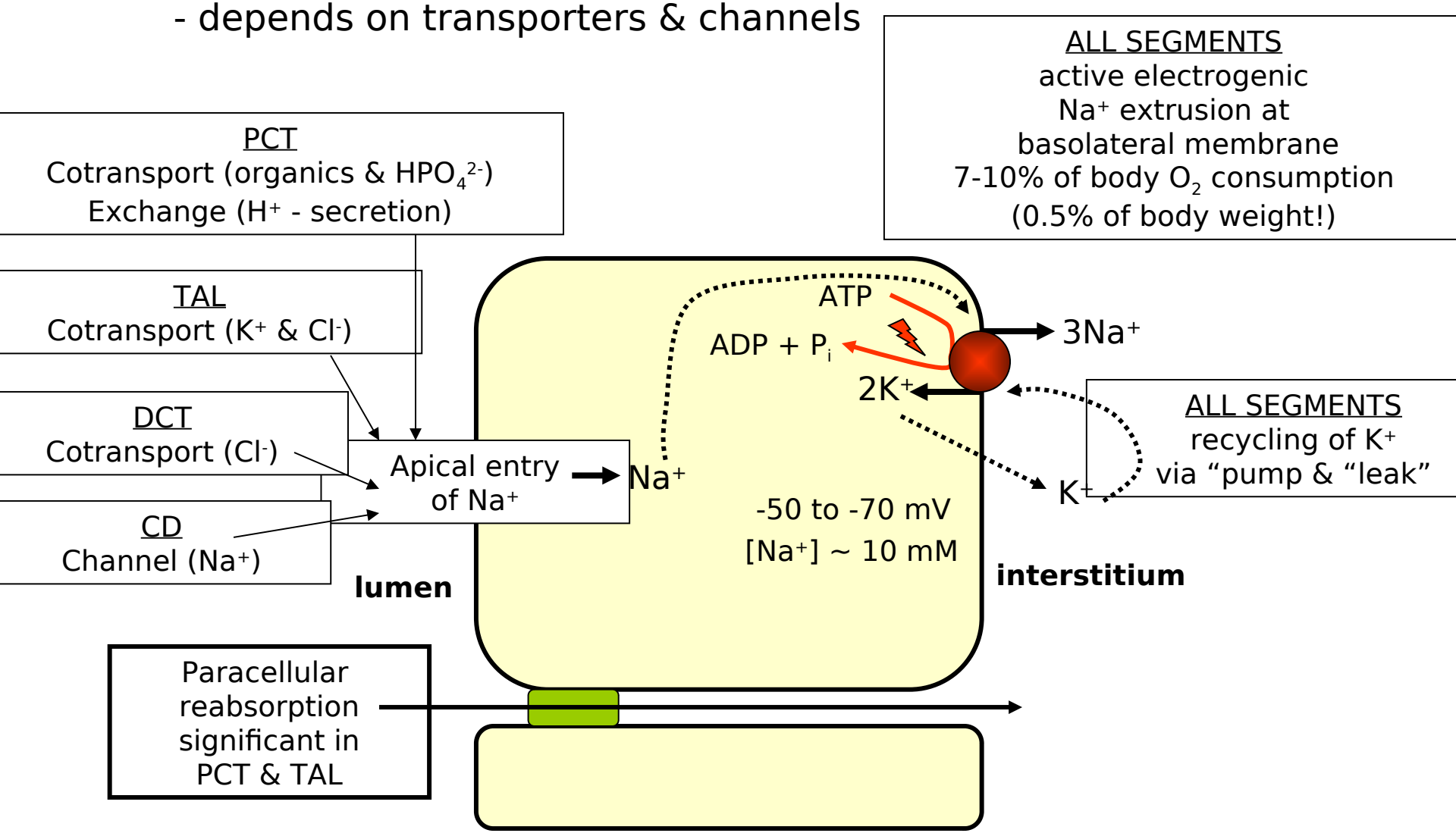
# Transepithelial pathways:



# Mechanisms of NaCl transport – general principles:

Transcellular

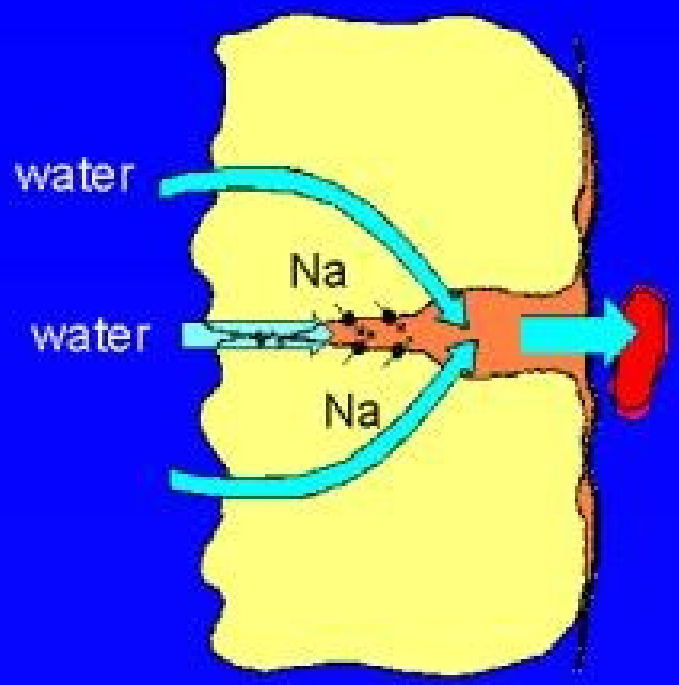
- depends on transporters & channels



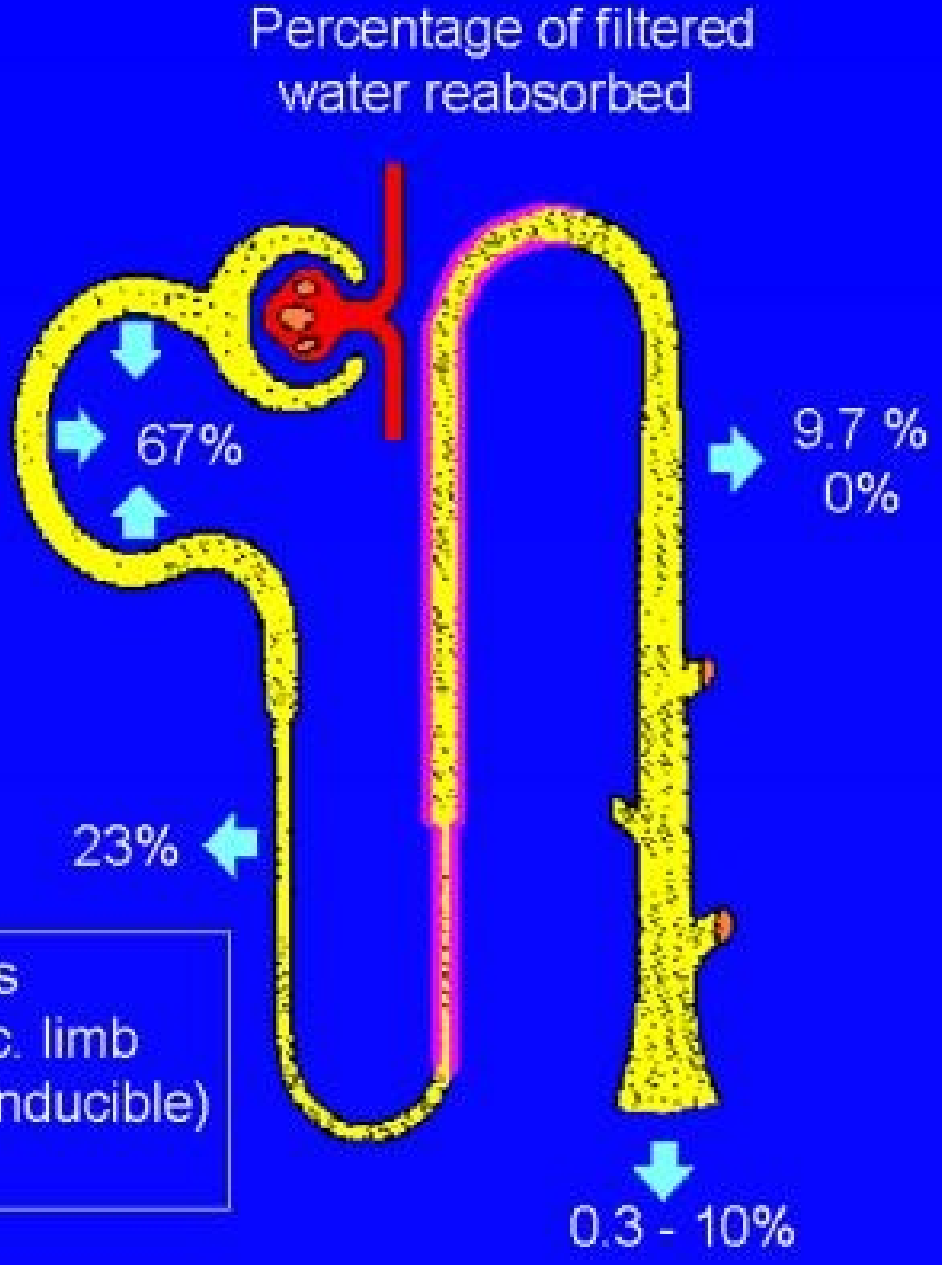

Paracellular – passive diffusion driven by +ve lumen pd

- In general $Cl^-$ & $H_2O$ follow $Na^+$ passively
- $H_2O$ can "drag" solutes

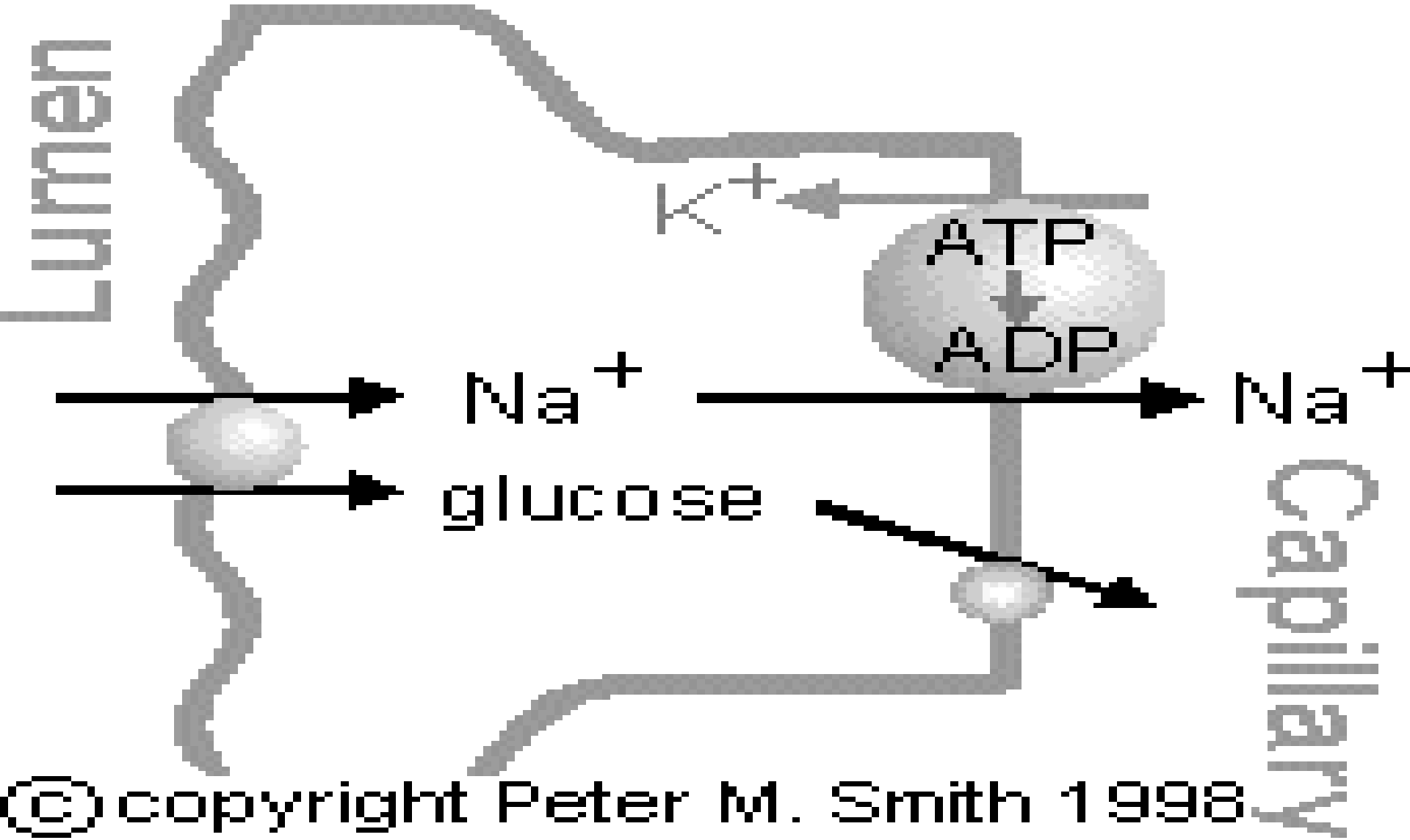
# Water Reabsorption




Isosmotic water reabsorption
at the proximal tubule

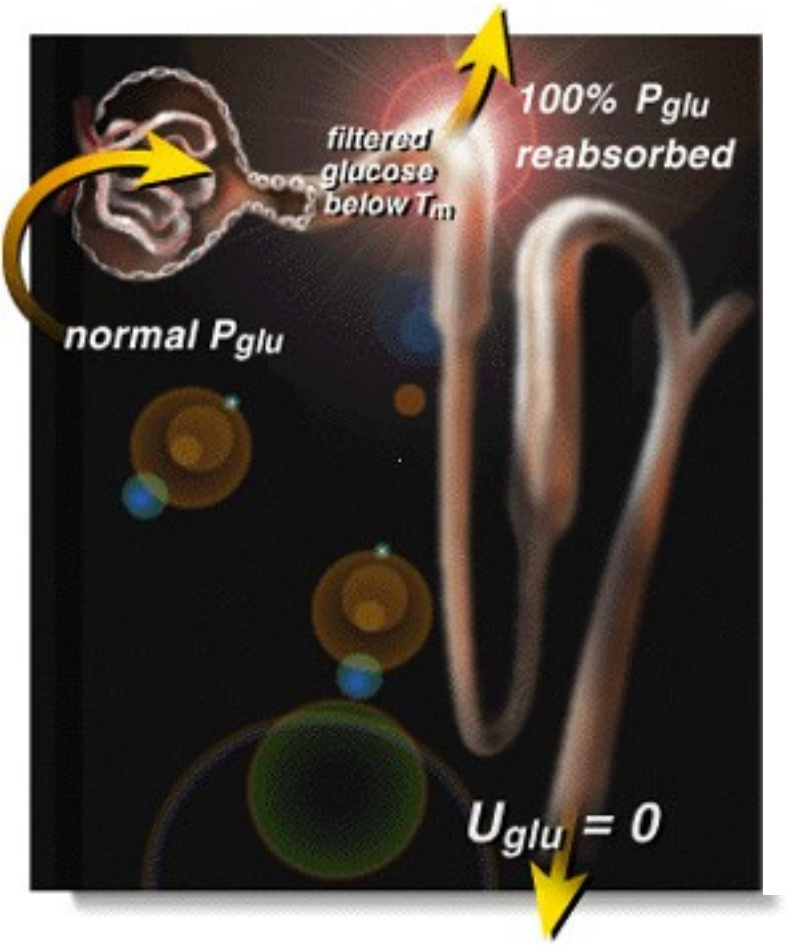


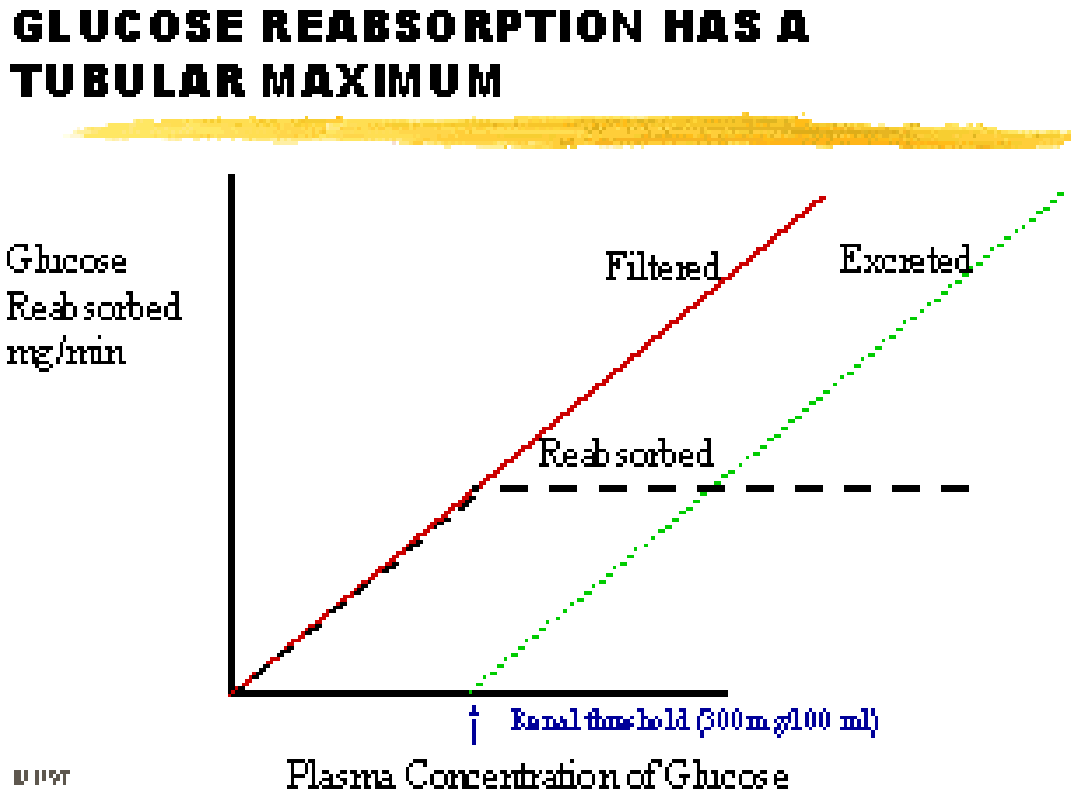

Aquaporins : 28kDa homotetramers
- AQP1 luminal, prox. tub. & desc. limb
- AQP2 luminal, coll. duct (ADH inducible)
- AQP3-4 basolateral



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# Glucose handling



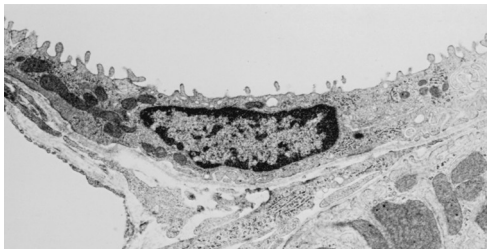



# Properties of the loop:

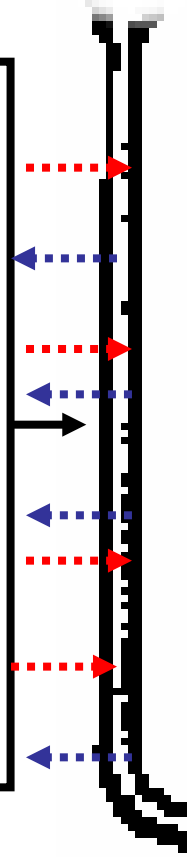
active salt movement

passive salt movement

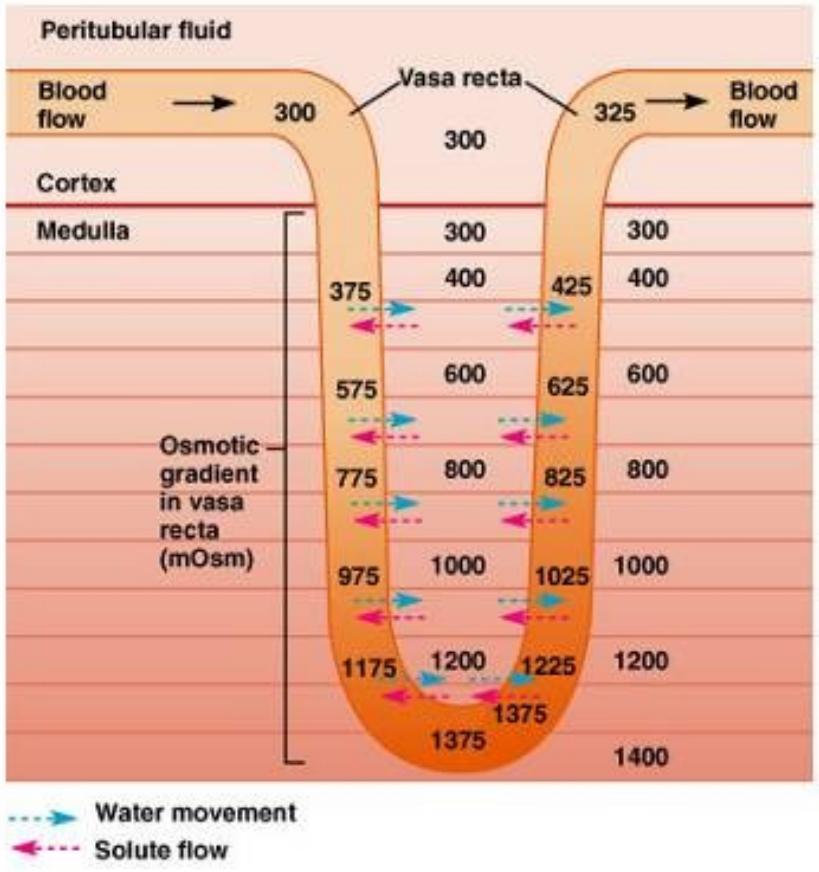
water movement



<u>Descending limb</u>
Permeable to $H_2O$
& solute:
allows passive entry
of solutes
& exit of $H_2O$

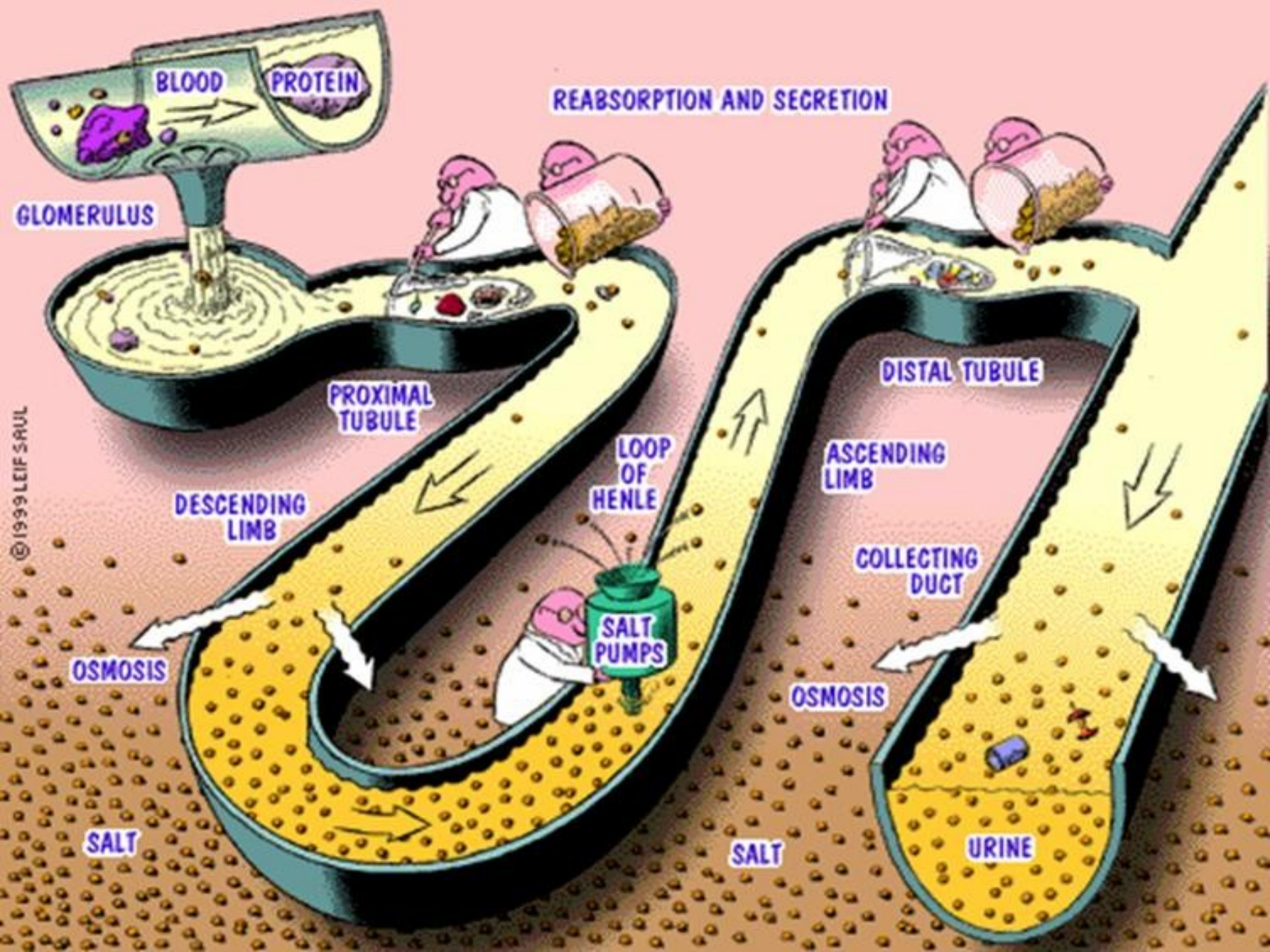


# a recta are exchangers & preserve the c-m gradient:




- Relatively low blood flow & counter current exchange mechanism minimizes wash-out of the medullary hypertonicity.

- A “compromise”: nutrients and $O_2$ are delivered to the inner medulla – corticomedullary osmotic gradient is preserved.

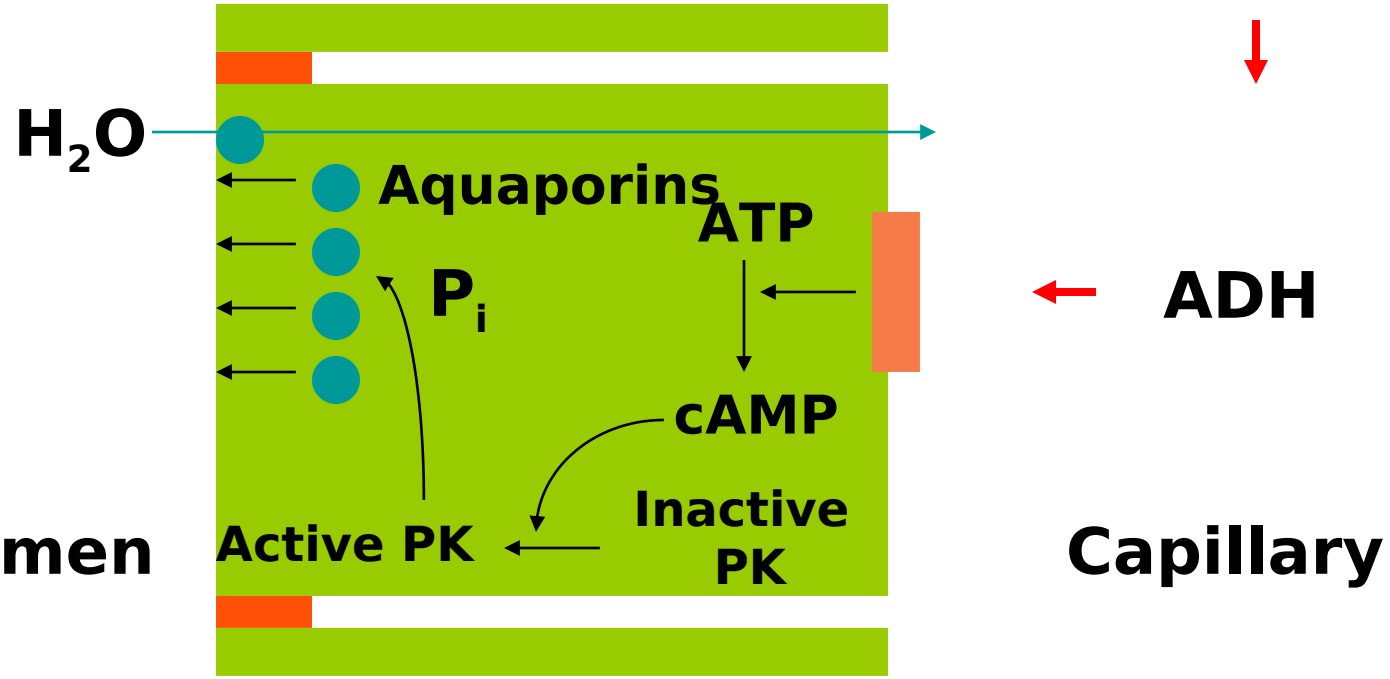

BLOOD
PROTEIN
REABSORPTION AND SECRETION
GLOMERULUS
PROXIMAL TUBULE
DISTAL TUBULE
LOOP OF HENLE
ASCENDING LIMB
DESCENDING LIMB
COLLECTING DUCT
SALT PUMPS
OSMOSIS
OSMOSIS
SALT
SALT
URINE
©1999 LEIF SAUL

# Regulation of plasma osmolality

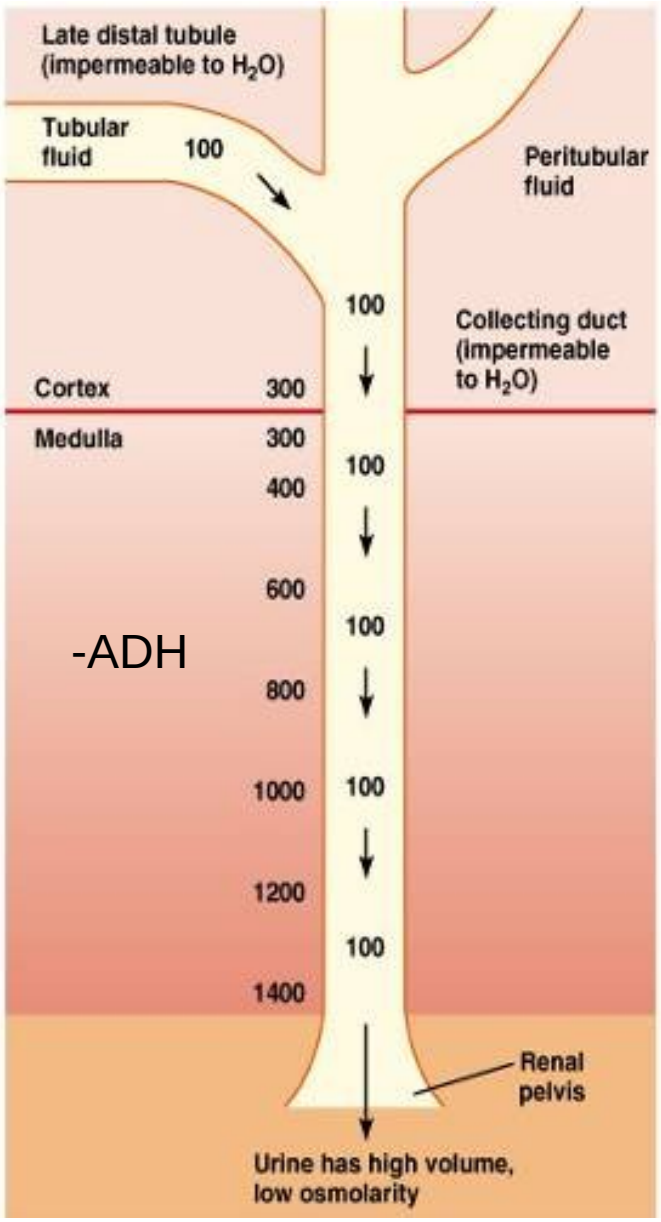
↑ osmolality

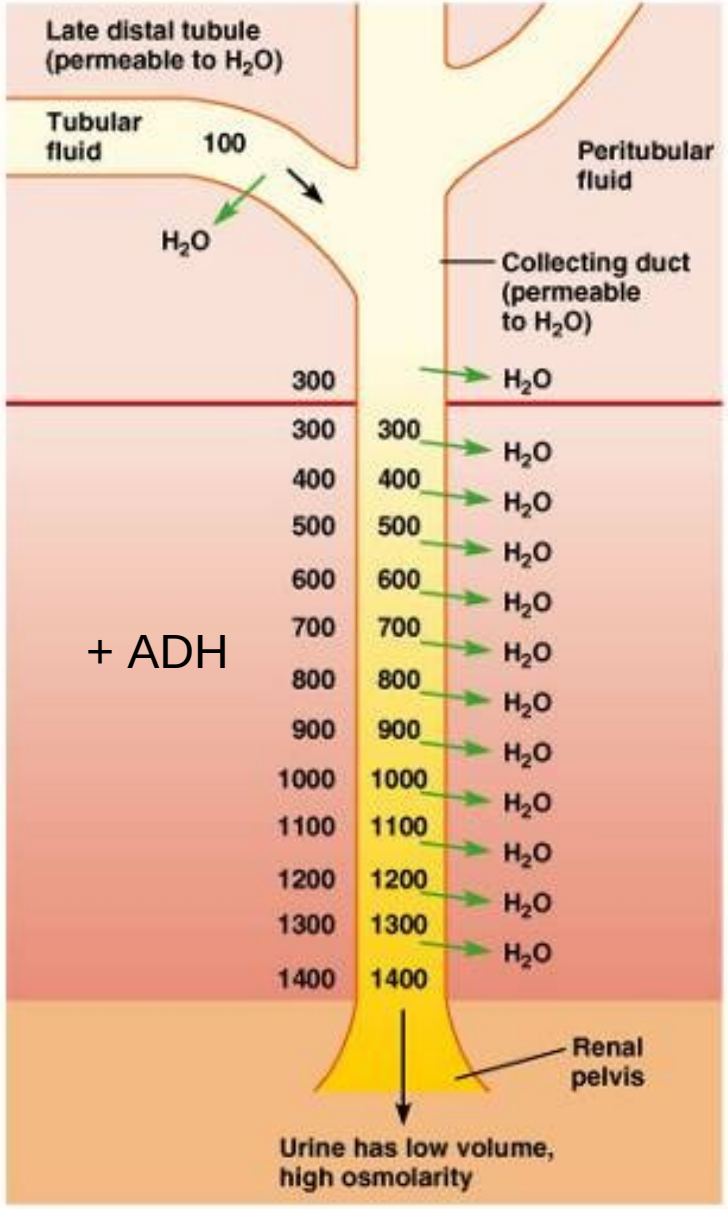
Hypothalamic osmoreceptors → Posterior pituitary → ADH secretion

↑ ADH



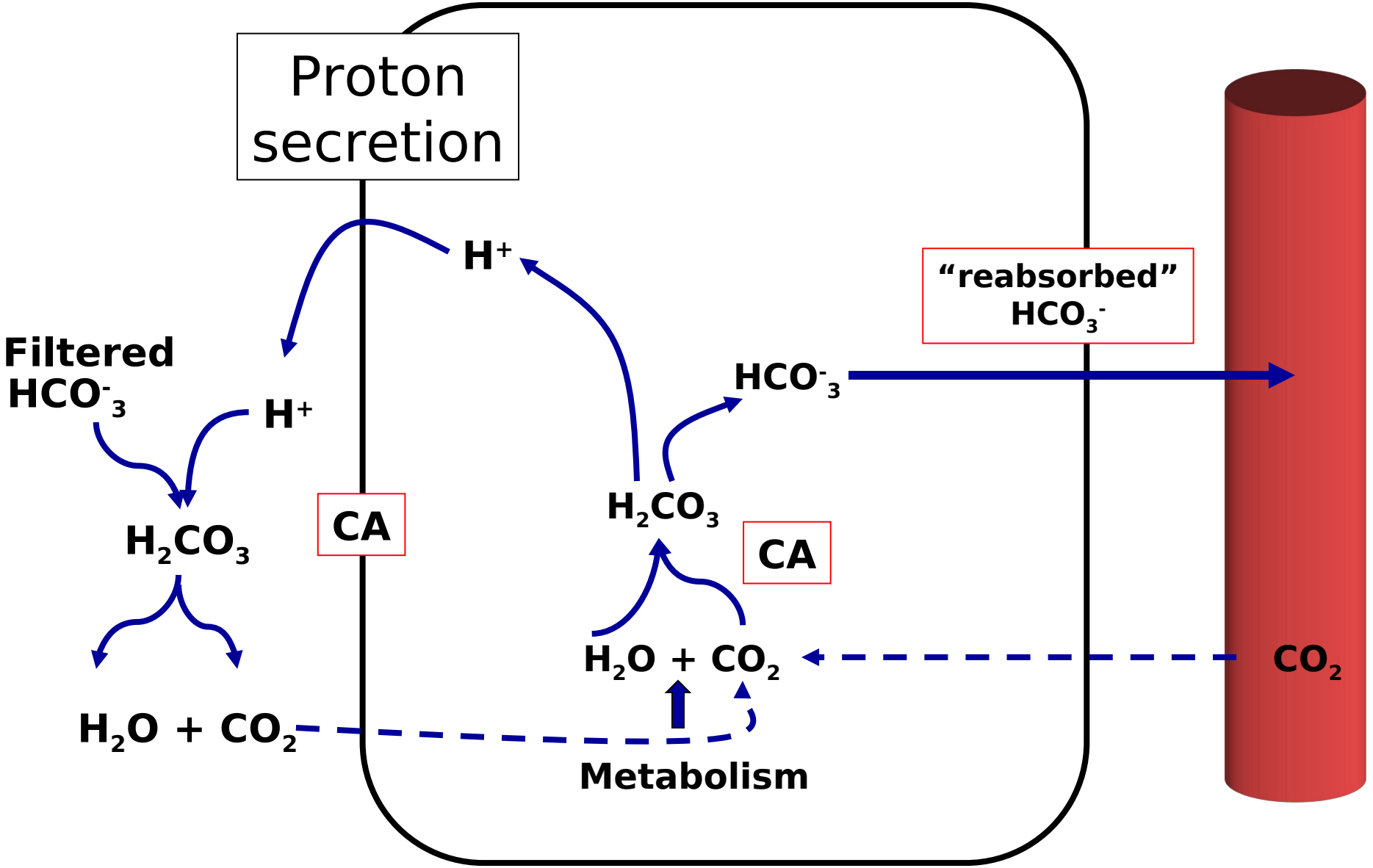
DH enables $H_2O$ equilibration across the DT & CD:



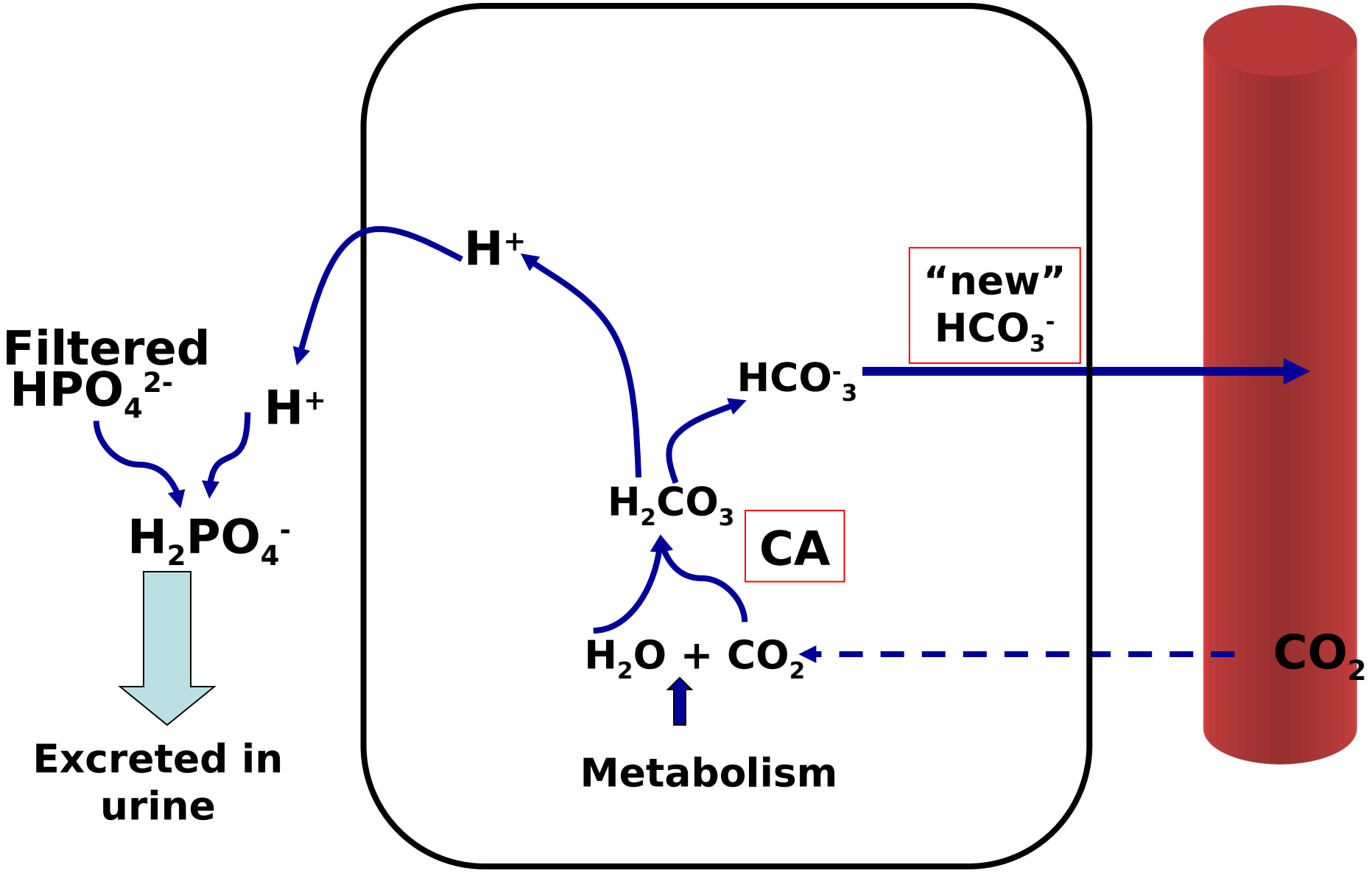



*Mechanisms of acidification and bicarbonate reabsorption*

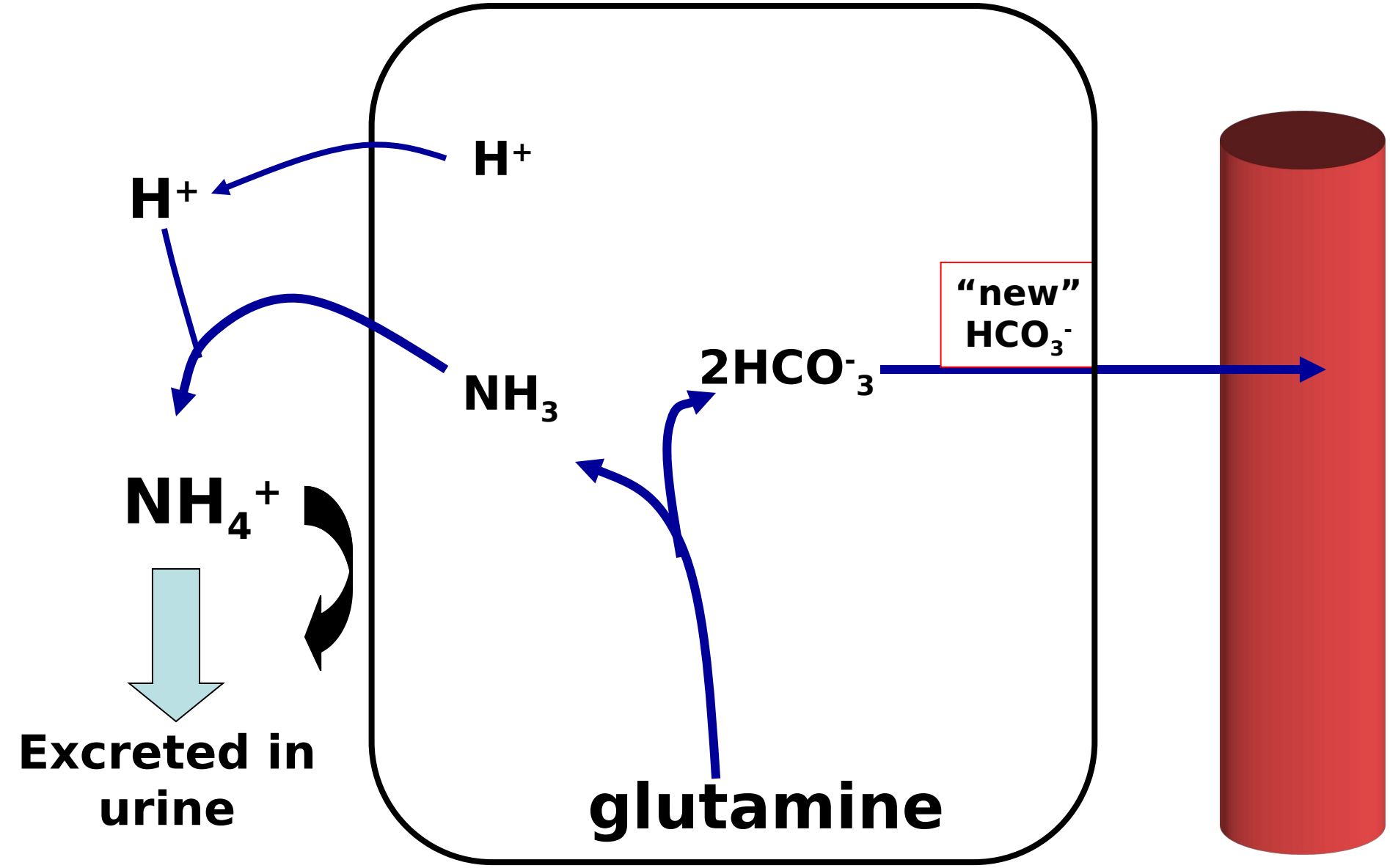
# Reabsorption of filtered $HCO_3$:



# Formation of "titratable acid" generates $HCO_3^-$:

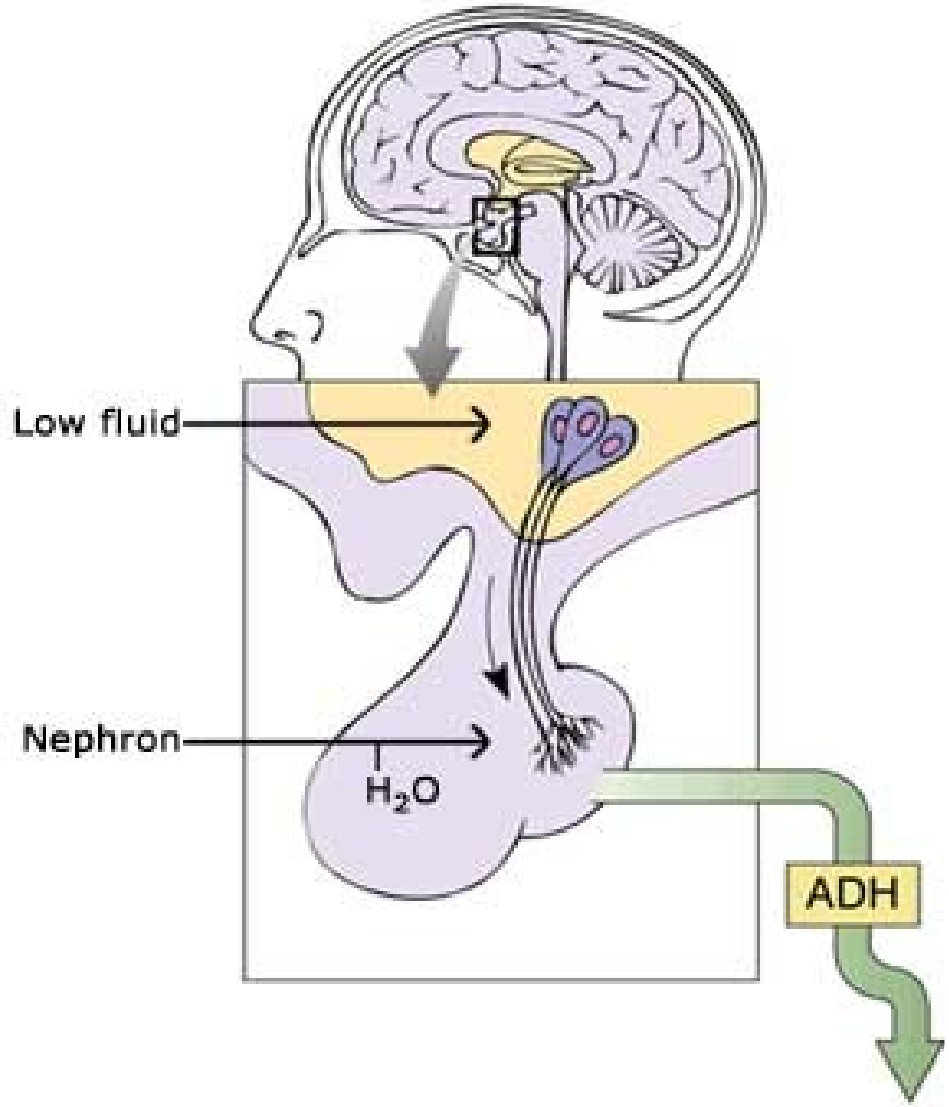


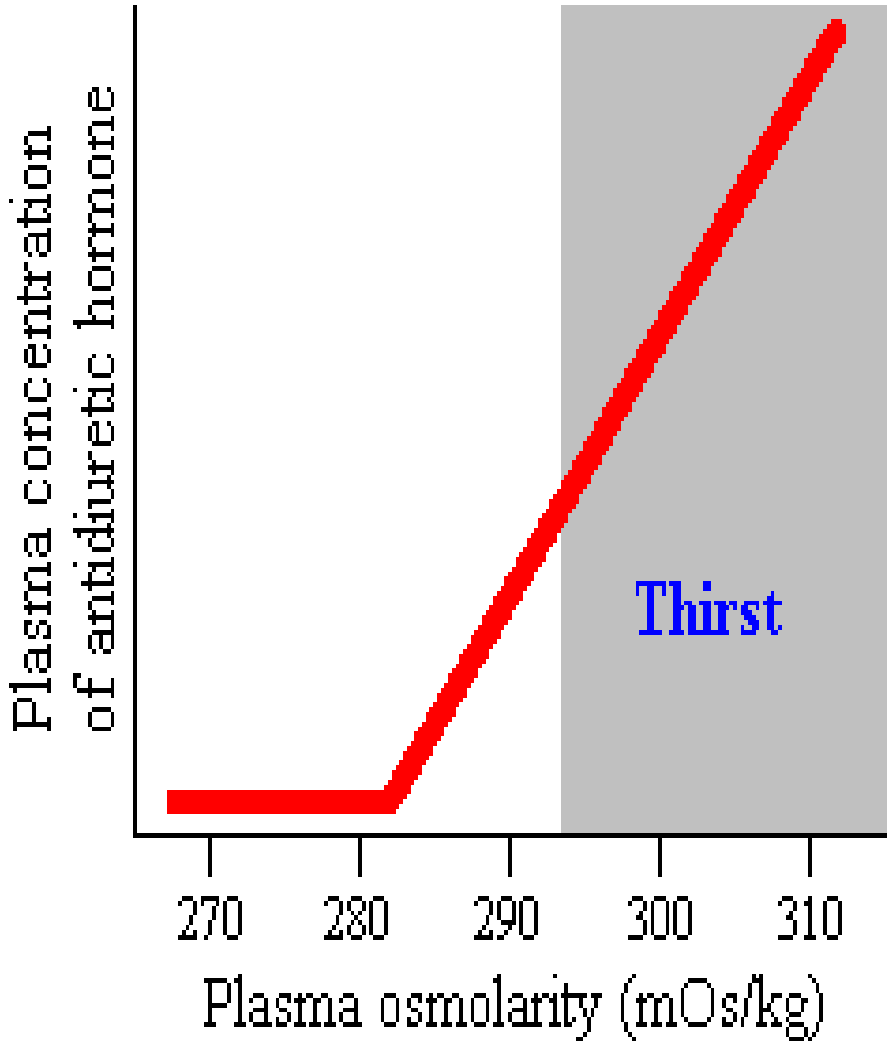
# Excretion of $NH_4^+$ generates $HCO_3^-$:



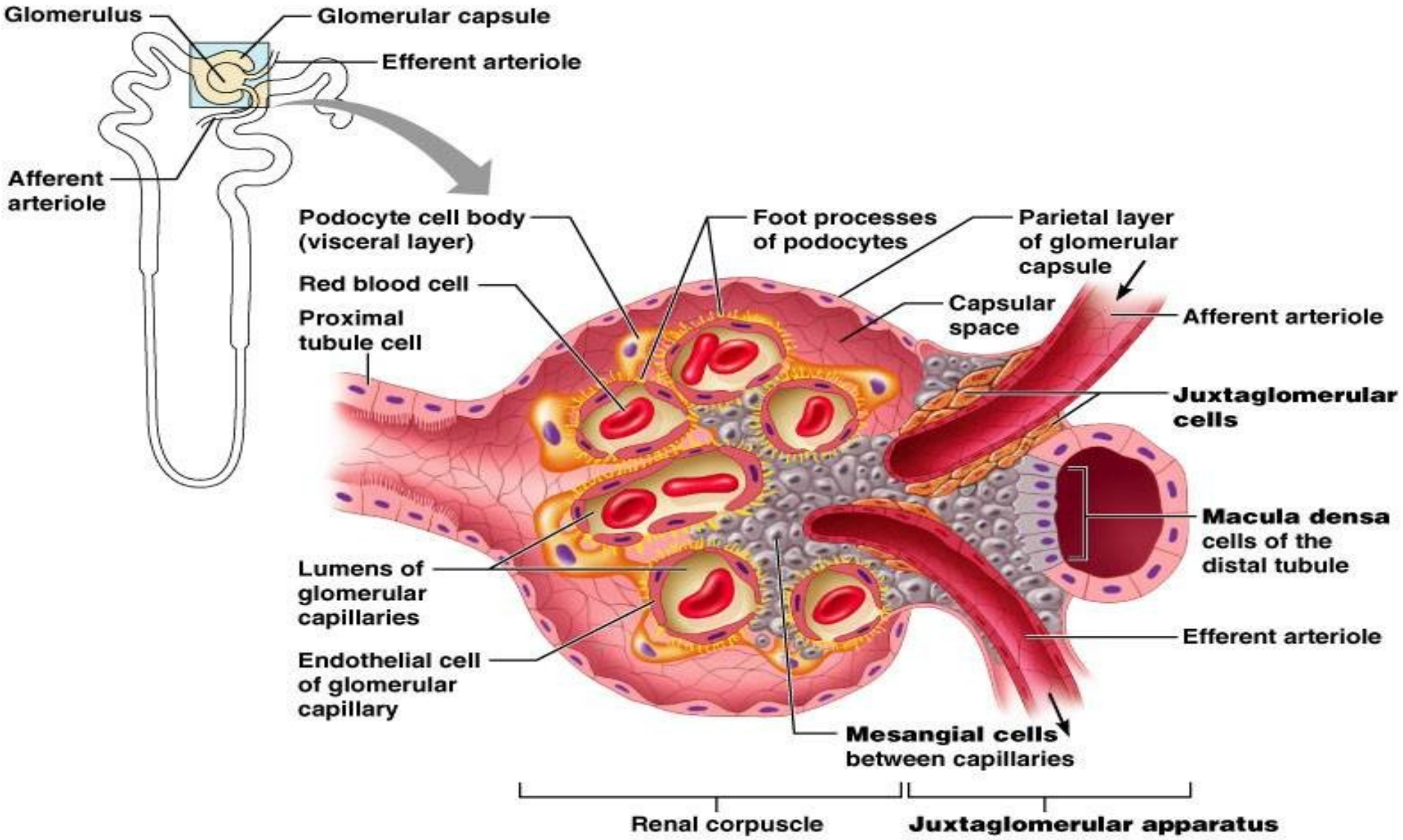
# *Endocrine function*

# ADH


Low fluid
Nephron
$H_2O$
ADH

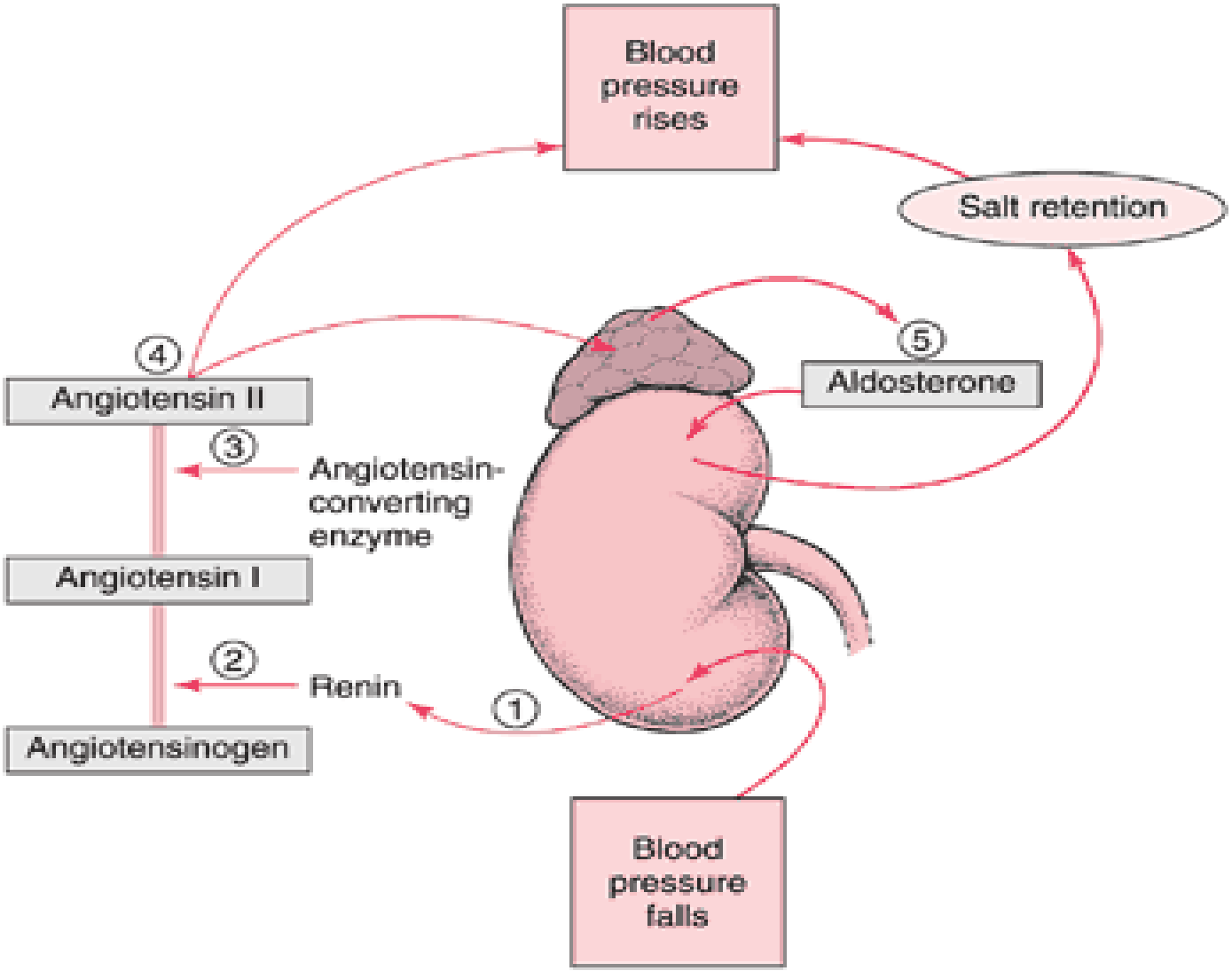

Plasma concentration of antidiuretic hormone
Thirst
270
280
290
300
310
Plasma osmolarity (mOs/kg)

# Renin

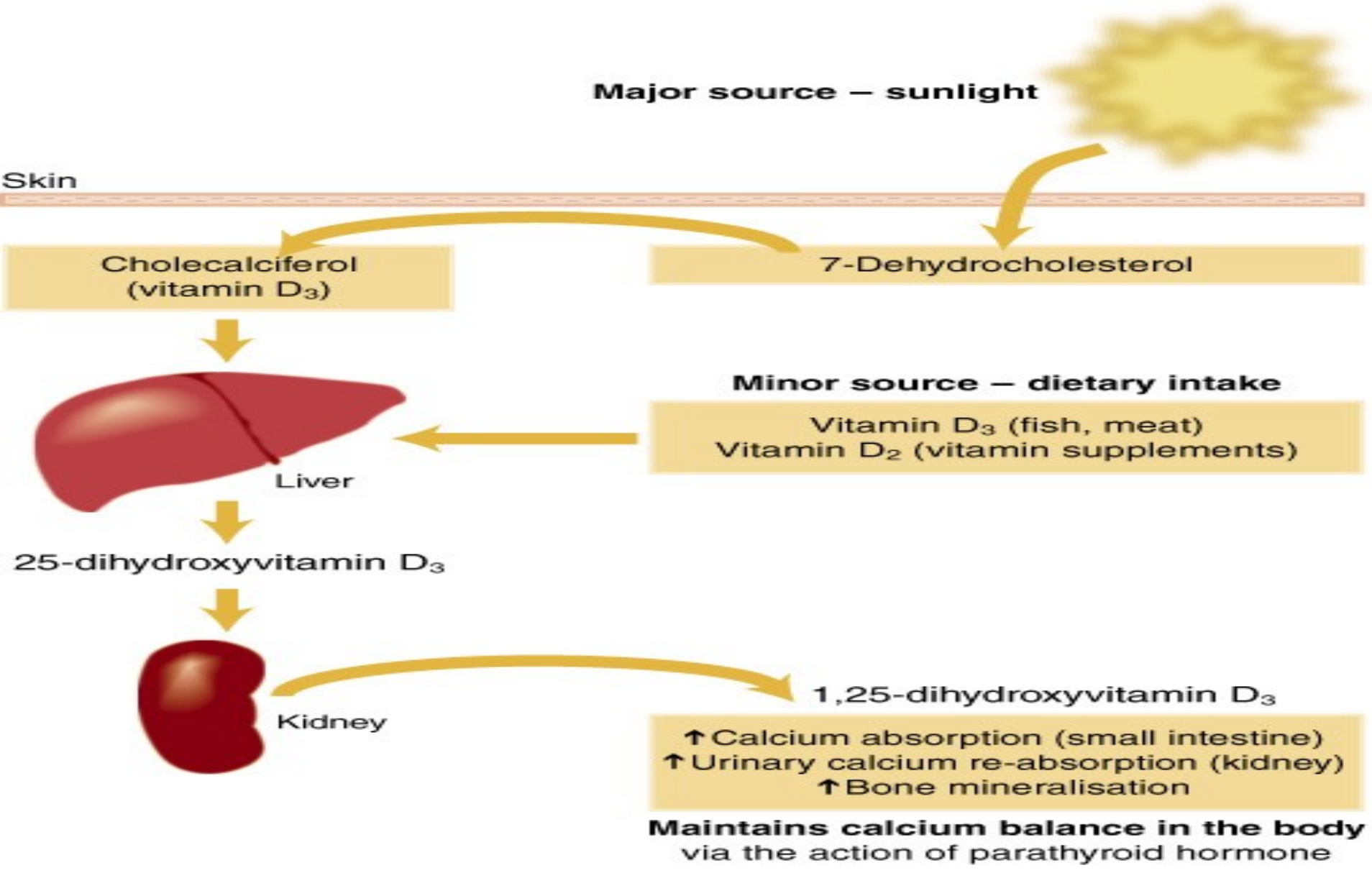



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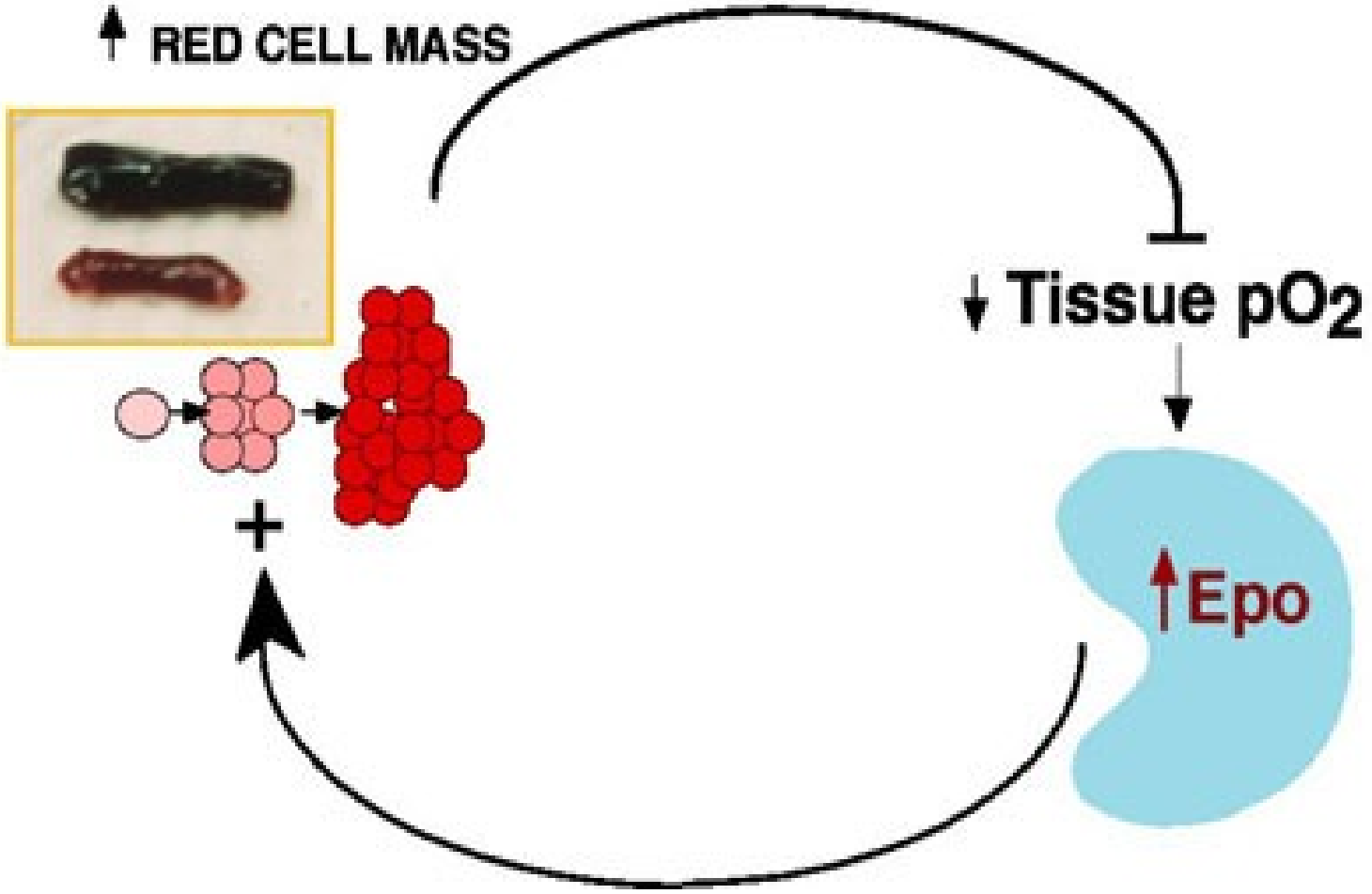
# Renin-Aldosterone



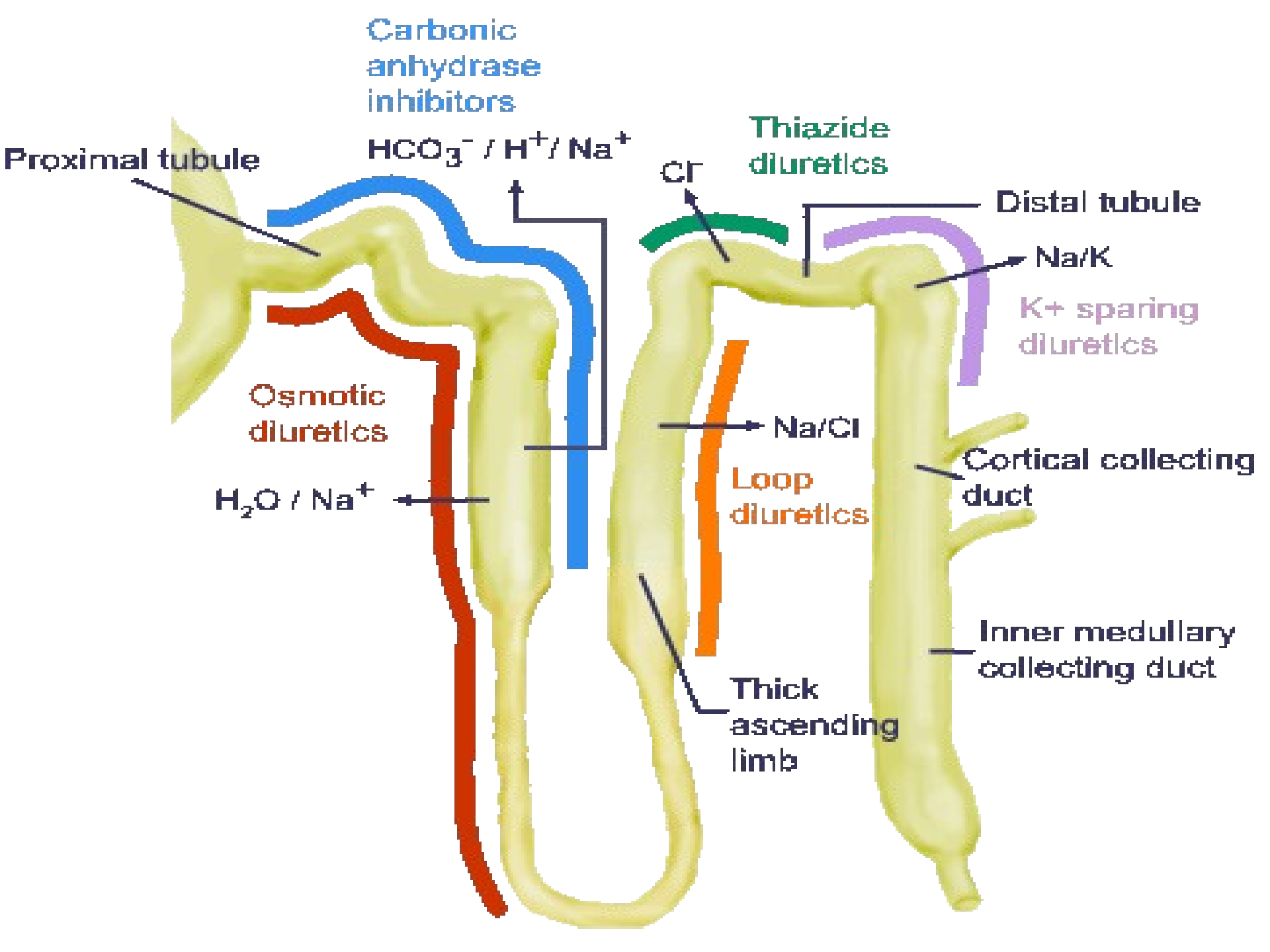
# Vitamin D


Major source – sunlight
Skin
Cholecalciferol (vitamin $D_3$)
7-Dehydrocholesterol
Minor source – dietary intake
Vitamin $D_3$ (fish, meat)
Vitamin $D_2$ (vitamin supplements)
Liver
25-dihydroxyvitamin $D_3$
Kidney
1,25-dihydroxyvitamin $D_3$
↑Calcium absorption (small intestine)
↑Urinary calcium re-absorption (kidney)
↑Bone mineralisation
Maintains calcium balance in the body
via the action of parathyroid hormone

# Erythropoietin



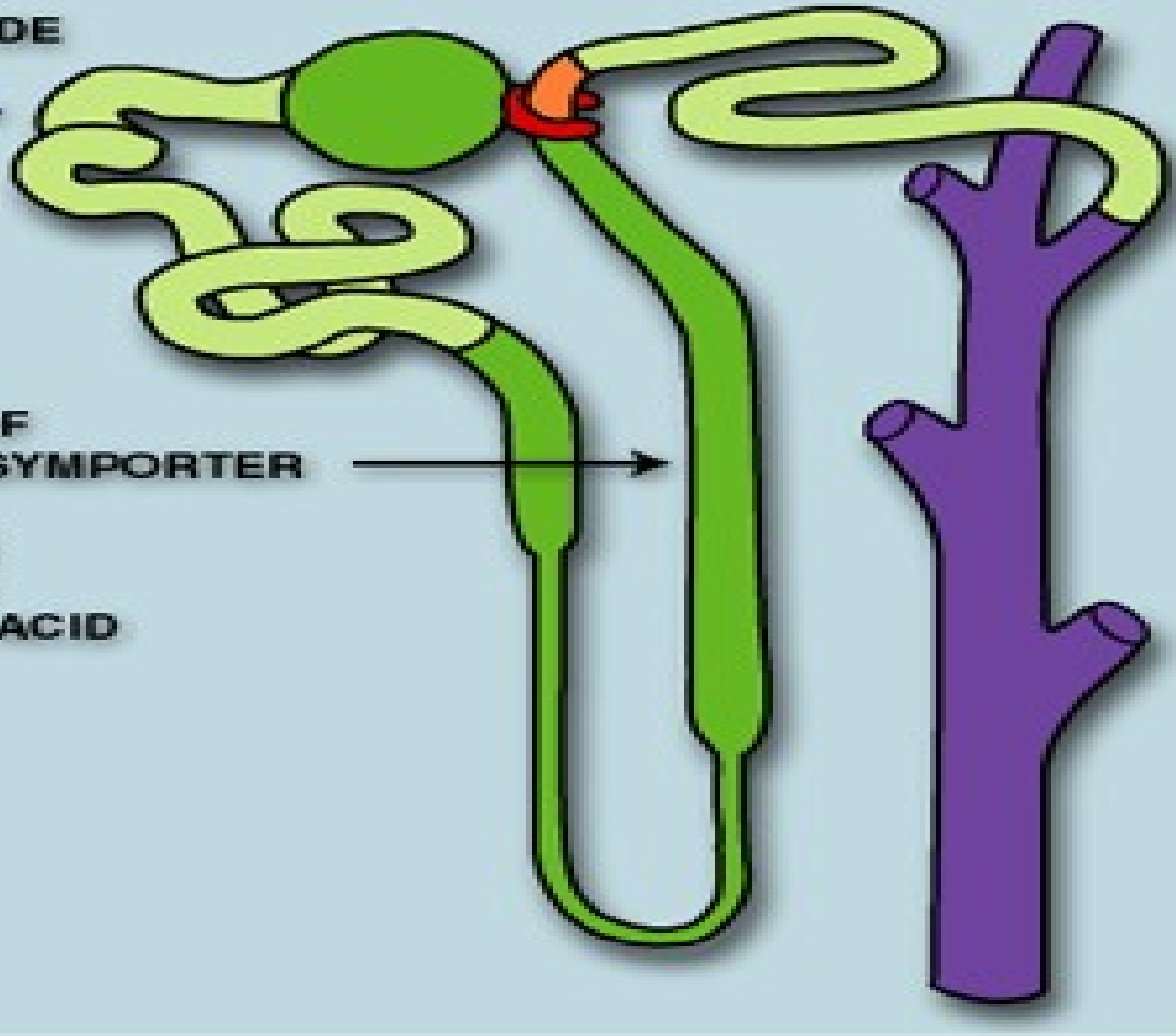
# *Diuretics*


Carbonic anhydrase inhibitors
$HCO_3^- / H^+ / Na^+$
Proximal tubule
Thiazide diuretics
$Cl^-$
Distal tubule
Na/K
K+ sparing diuretics
Osmotic diuretics
$H_2O / Na^+$
Na/Cl
Loop diuretics
Cortical collecting duct
Inner medullary collecting duct
Thick ascending limb

# DIURETICS

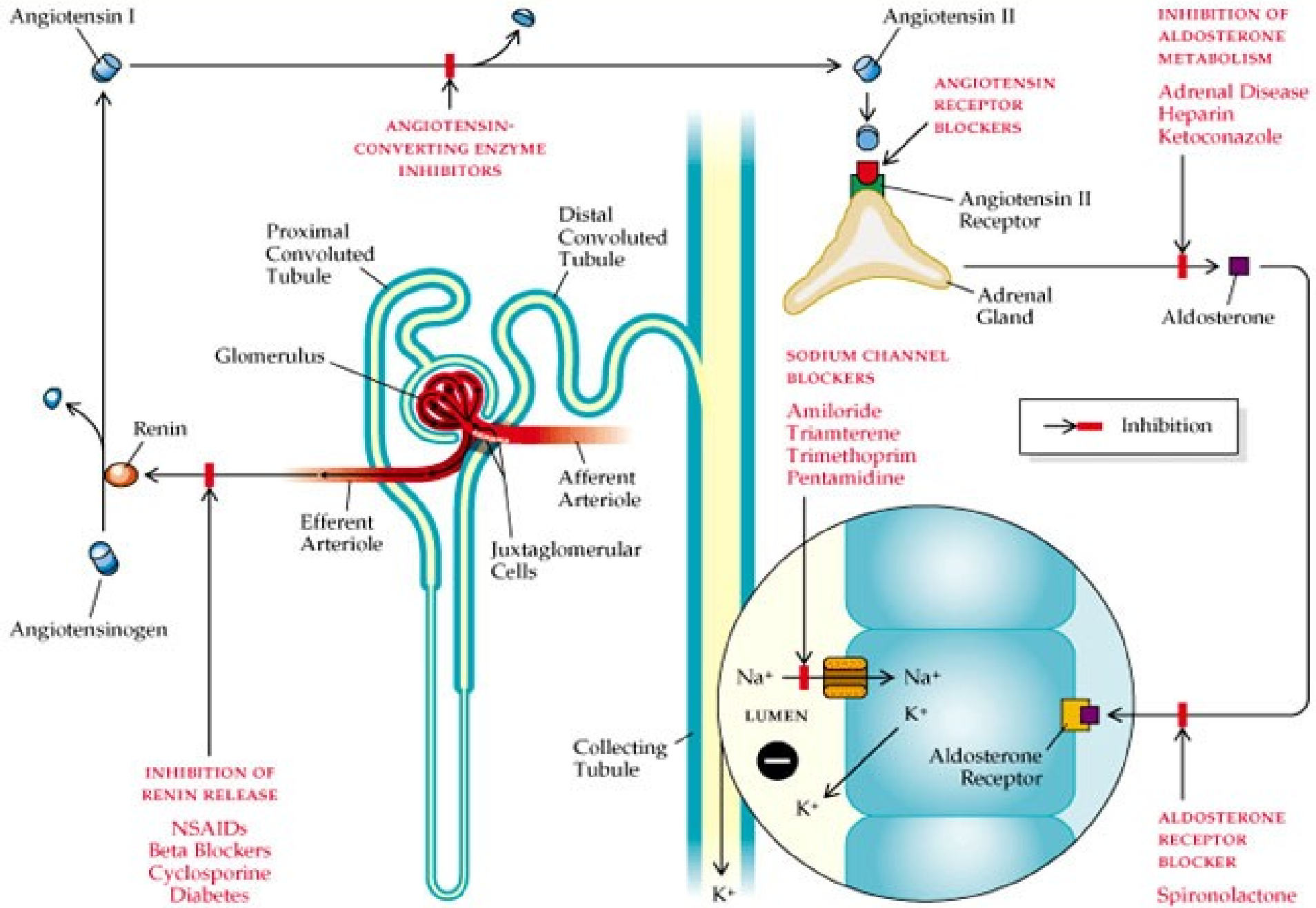
## INHIBITORS OF CARBONIC ANHYDRASE

ACETAZOLAMIDE



## INHIBITORS OF $Na^+$, $K^+$, $2Cl^-$ SYMPORTER

FUROSEMIDE
BUMETANIDE
ETHACRYNIC ACID




Source: ACP Medicine © 2004 WebMD Inc.

# *Acute Renal Failure*

- *ARF: acute oliguria (<400ml/day) or a rapid (hours to weeks) decline in GFR as manifested by a rise in Ur and Cr.*
- *It is generally believed that a urine output of <0.5ml/kg/hr for greater than two hours is an important marker of renal hypoperfusion and should trigger remedial action.*

# *Causes of ARF*

***Prerenal: 21%***

- *↓ CO (dysfunction or hypovolaemia).*
- *Redistribution of blood (sepsis, liver fail.).*

***Renal: 45%(ATN)***

- *ATN(from any prolonged prerenal cause)*
- *ATN from toxins (drugs, contrast media)*
- *Vasculitis, emboli, glomerulonephritis.*

***Postrenal: 10%***

- *Obstruction (stones, prostate, tumours etc.)*

# *Management of ARF*

***Principles:***

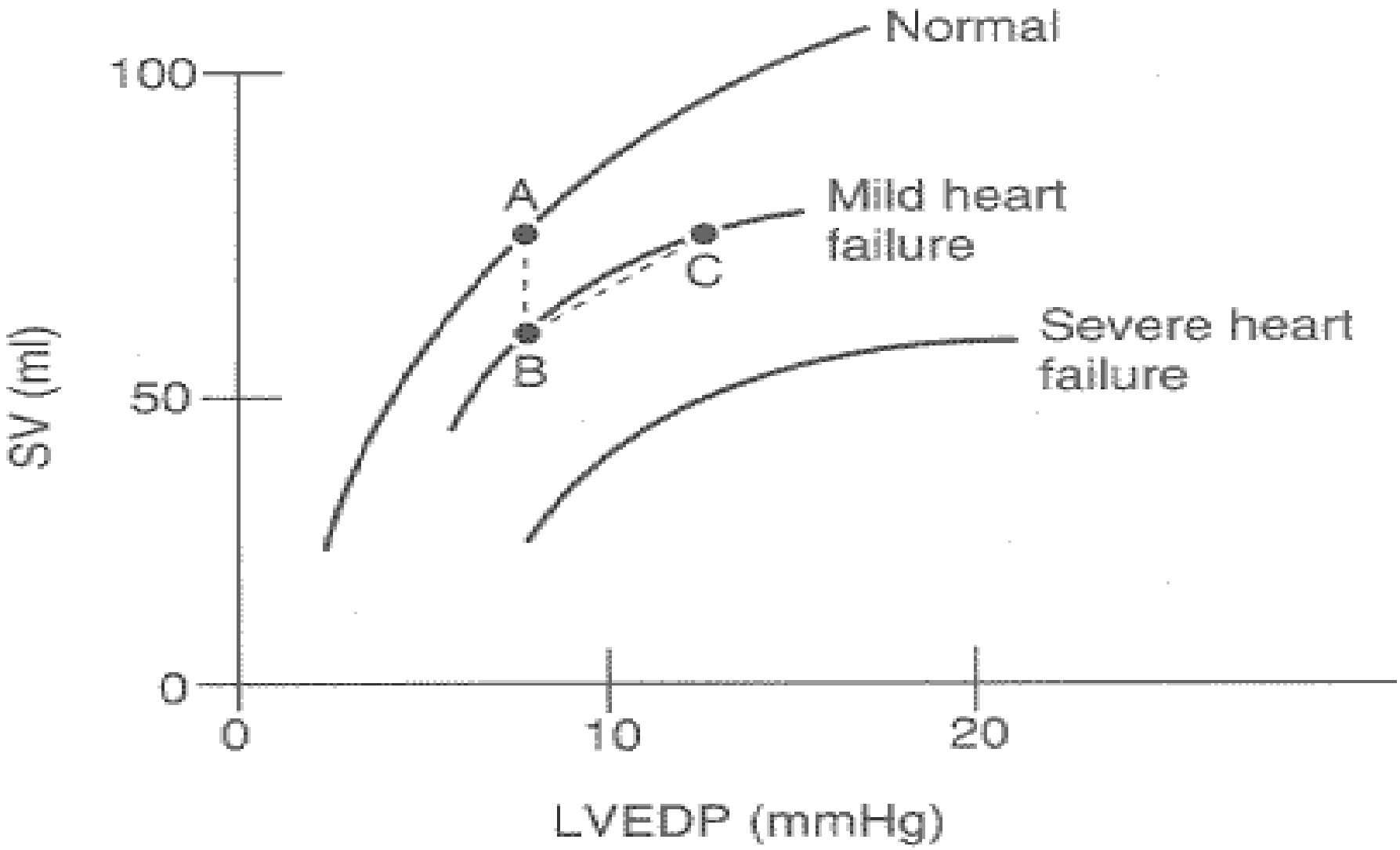
1. *Treat **hyper-Kalaemia** first.*
2. *Correct **hypovolaemia**, establish effective circulating volume.*
3. *Treat **hypoperfusion**.*
4. *Exclude **obstruction** as soon as possible.*
5. *Treat the underlying **cause**.*

# *Renal Replacement Therapy*

***Indications:***

1. ***HyperKalaemia*** *especially if ECG changes.*
2. ***Volume*** *overload.*
3. ***Metabolic Acidosis*** *severe and worsening.*
4. ***Uraemic*** *complications (encephalopathy, pericarditis and seizures).*

# *Renal support in cardiac failure*



# *Step 1*

1. ***Posture and oxygen.***
2. ***Nitr****ates.*
3. ***Loop diuretics****. Indicated for all patients with acute pulmonary oedema. (Frusemide). Generally the initial iv dose should be 2x the usual daily dose and at a rate of <4mg/min.*
4. ***Opioids.*** *(venodilation, ↓ preload).*

# *Step 2*

1. ***Escalate diuretic dosage****. Urinary catheter for urine output, double initial diuretic dose. The dose escalation to overcome the substantial diuretic resistance of renal impairment is frequently underestimated. (250mg-500mg are not uncommon).*
2. ***Sequential nephron blockade.*** *Compensatory increase in ion transport by the remaining tubular symporters →response to frusemide declines. To minimise this effect bendrofluazide is added po, cautiously followed by amiloride or spironolactone in refractory cases.(to maintain not to initiate diuresis).*
3. ***Dopamine.*** *(Needs central venous access)*
4. ***Dobutamine.*** *↑ contractility.*
5. ***CPAP.***