

# **BMSN2603 / BMSC3104**

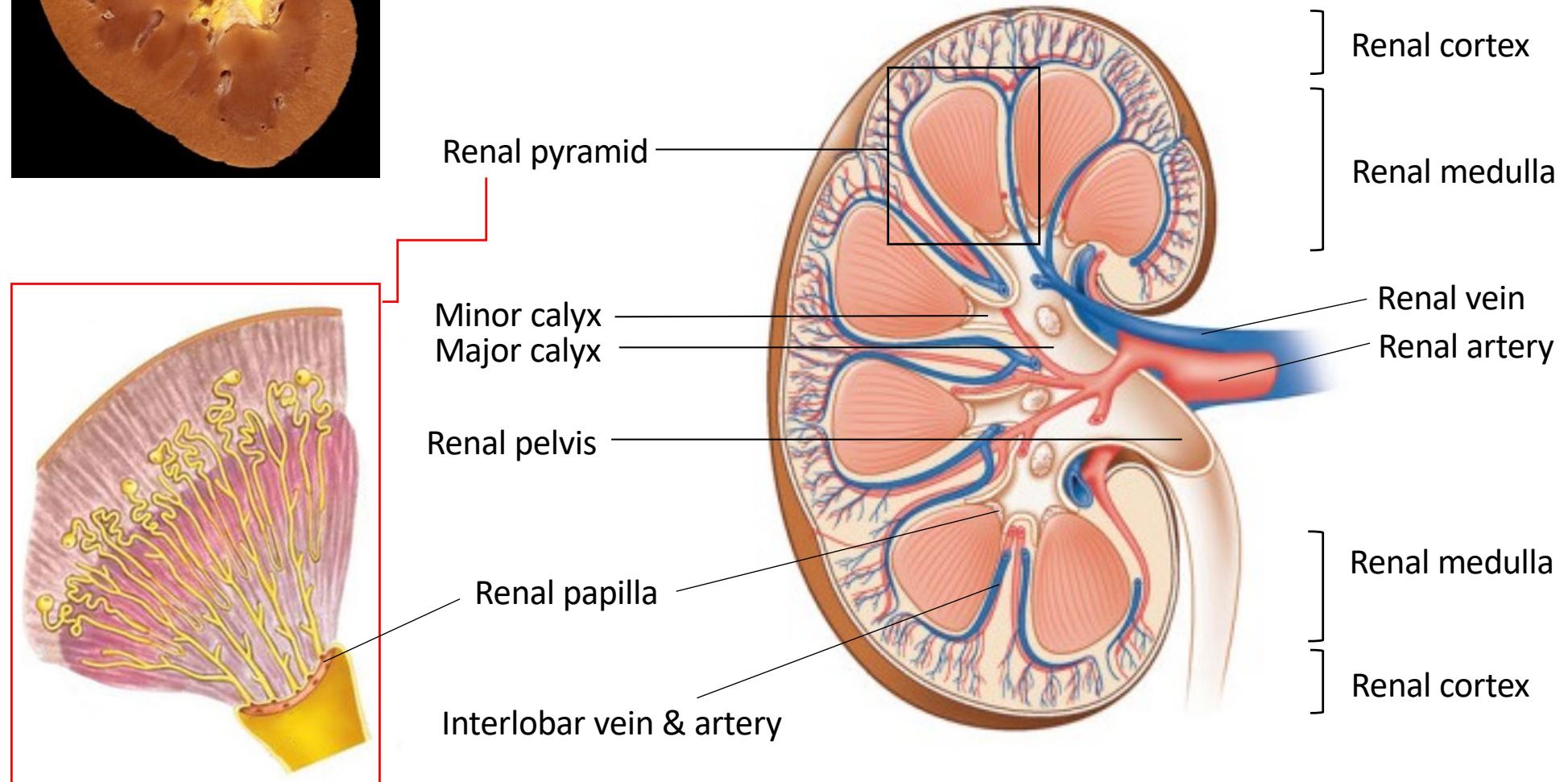
## **(Physiology)**

The Kidney, Body Fluid Homeostasis, & Related Disorders

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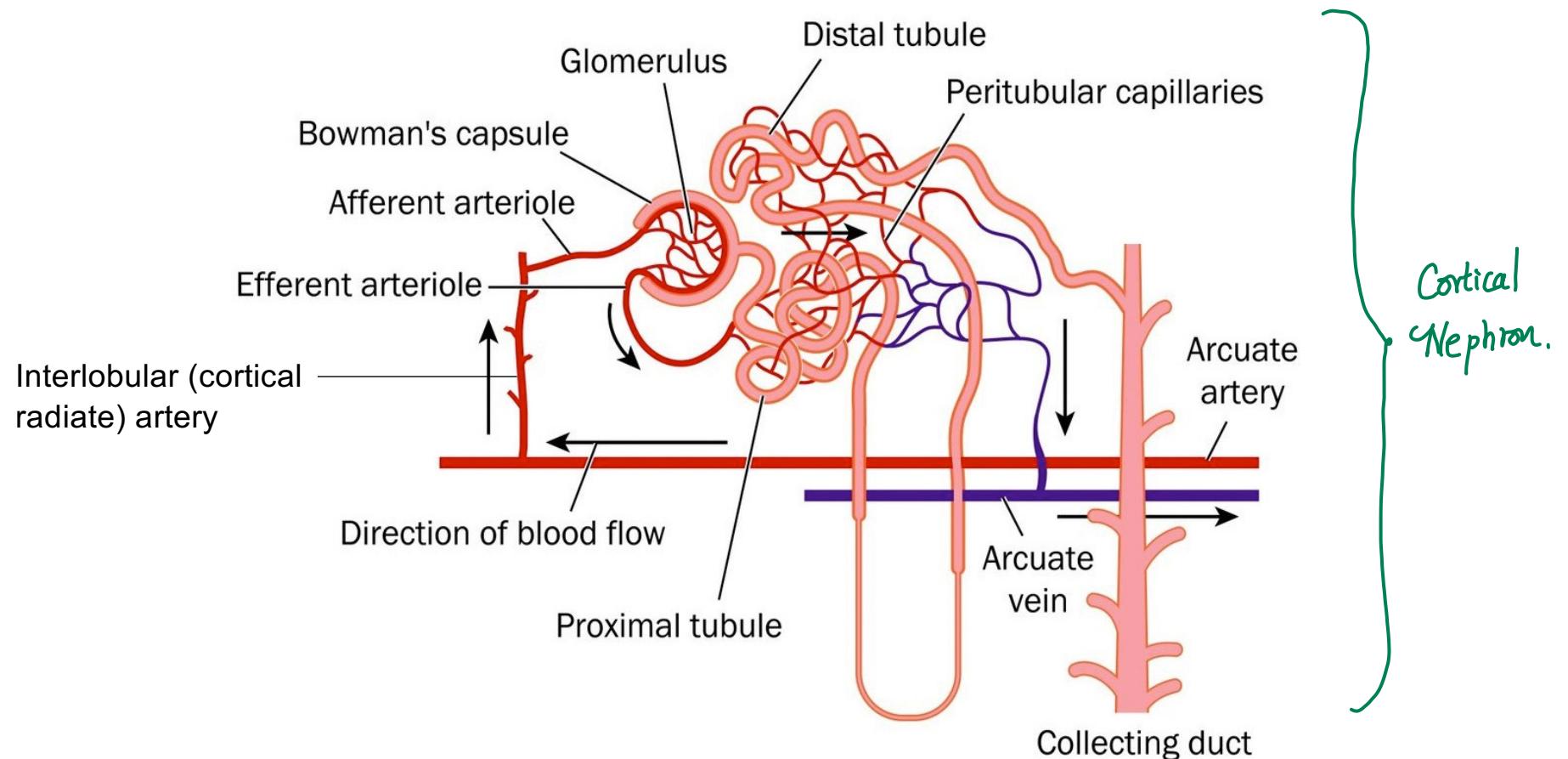


# Structure of the kidney



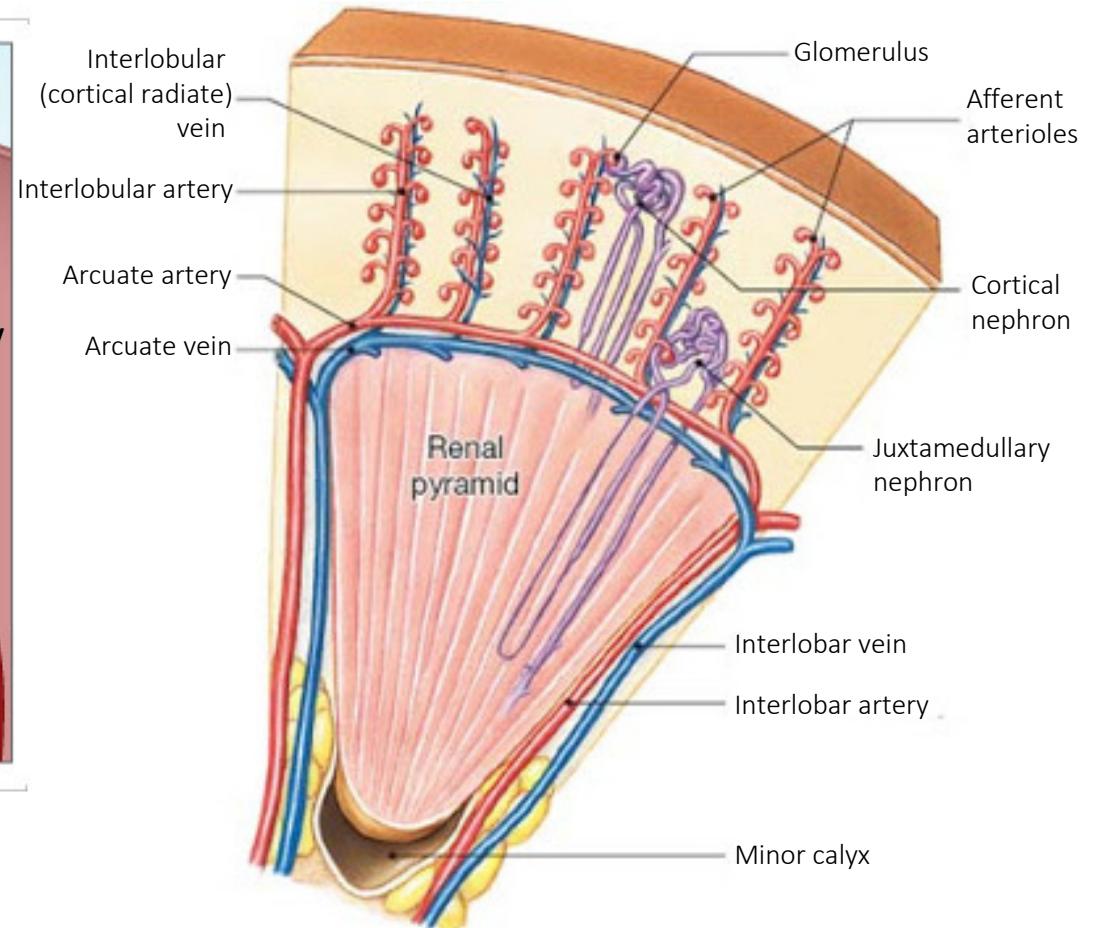
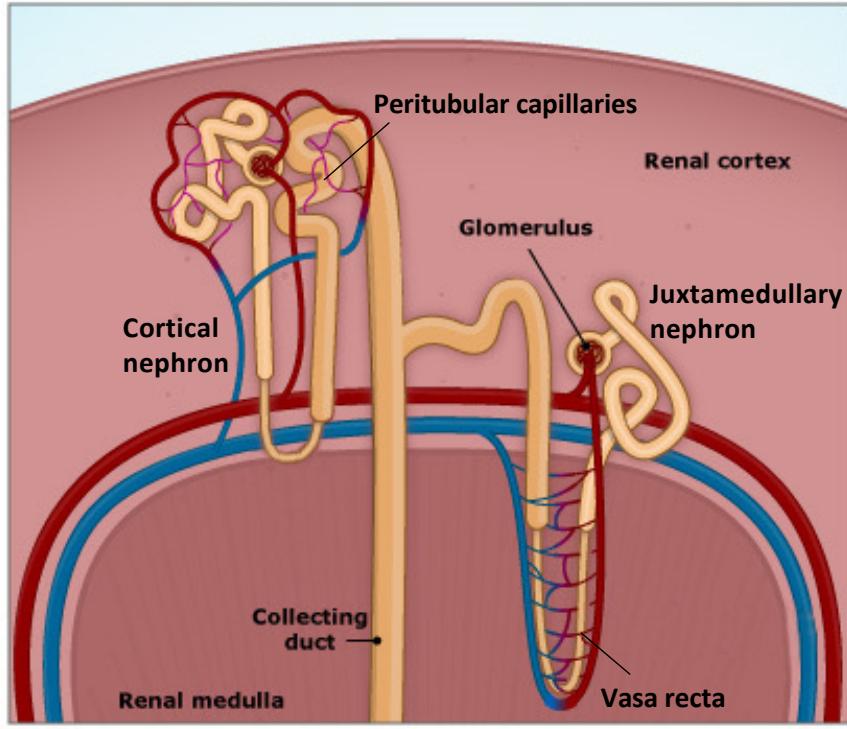
# Nephron

- Each kidney contains around a million functional units called nephrons that are bound together by connective tissue
- Nephron = renal corpuscle (glomerulus & Bowman's capsule) + renal tubule



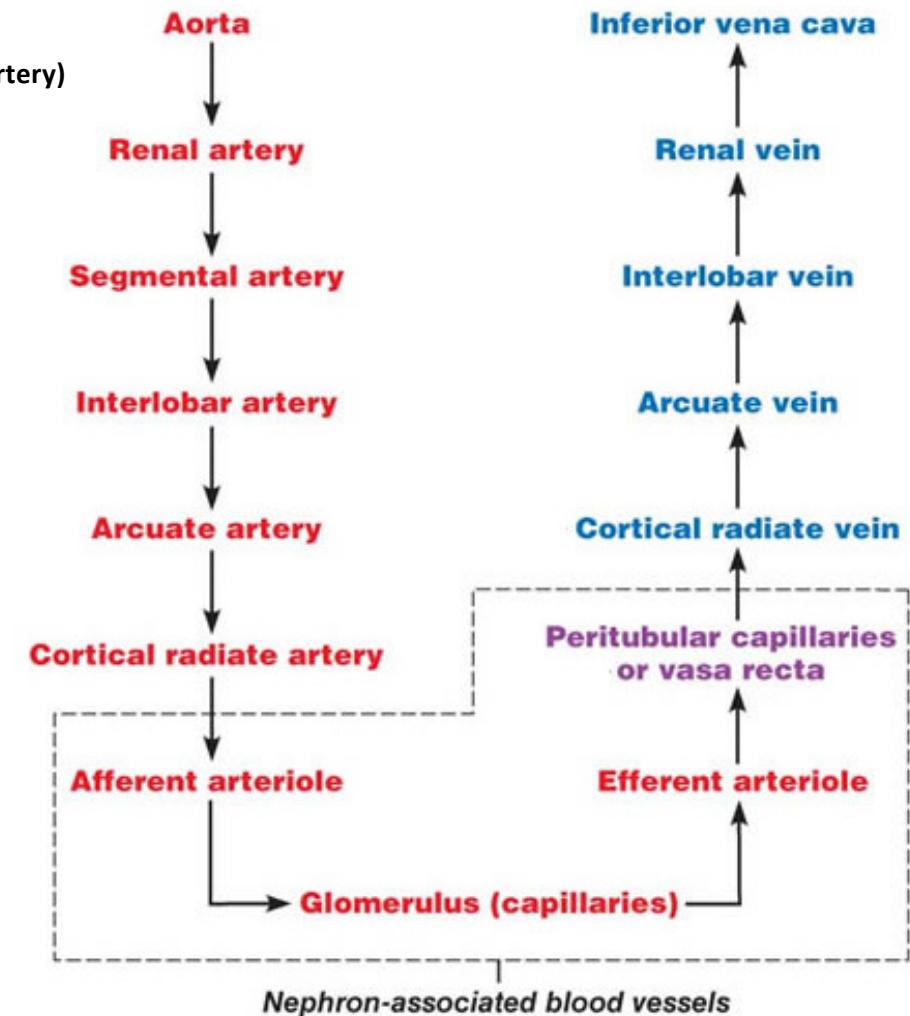
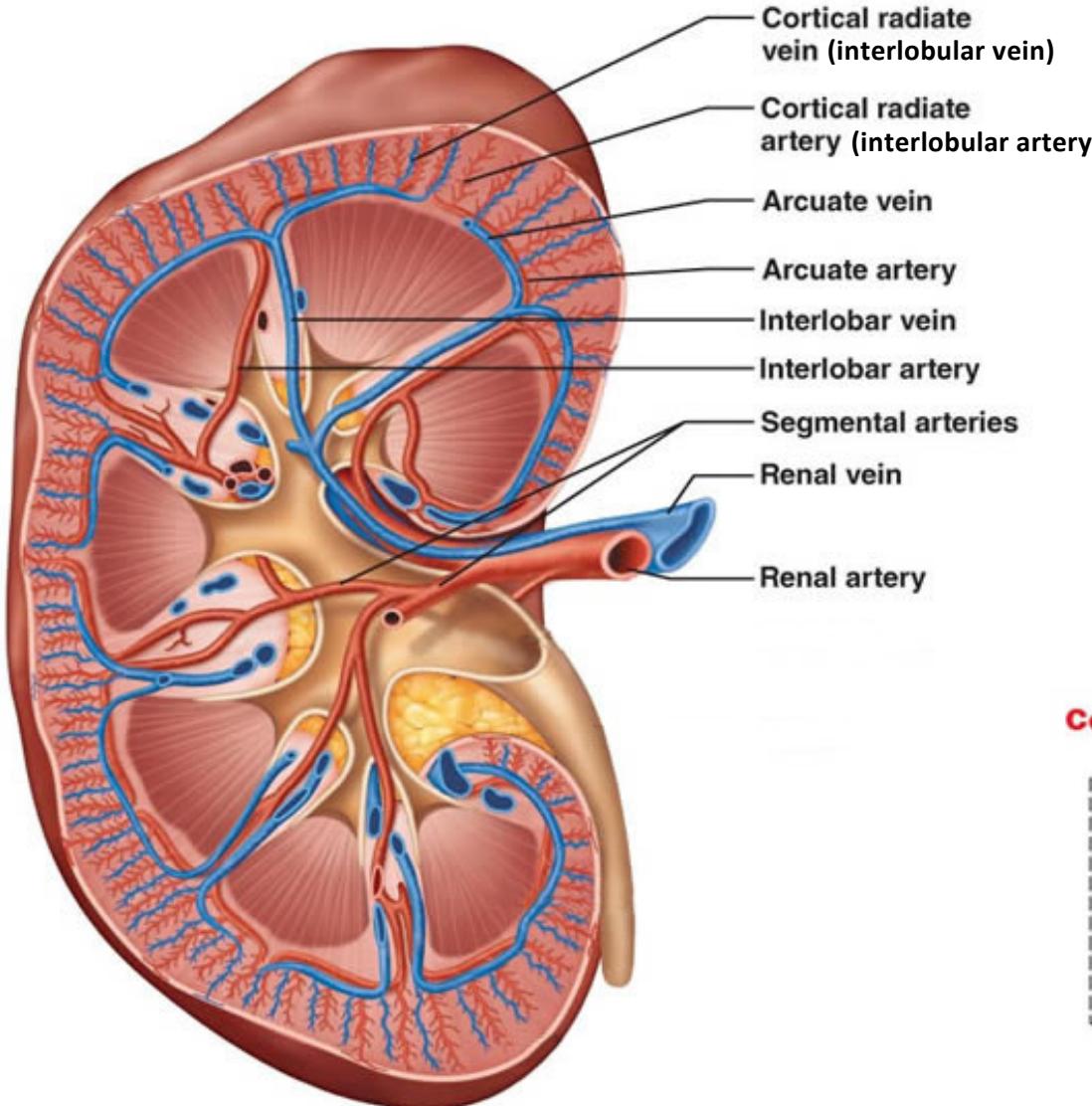
- Each nephron has 2 capillary beds: glomerulus + peritubular capillaries / vasa recta

### Types of Nephrons



- Two types of nephrons:
  - a) Cortical nephrons
    - Renal corpuscles are located in the outer portion of the renal cortex
    - Shorter loop of Henle
    - Efferent arteriole supplies peritubular capillaries
    - The most abundant type of nephrons (~85%)
  - b) Juxtamedullary nephrons
    - Renal corpuscles located deep in the cortex
    - Longer loop of Henle with vasa recta as blood supply in there
    - Efferent arteriole supplies vasa recta

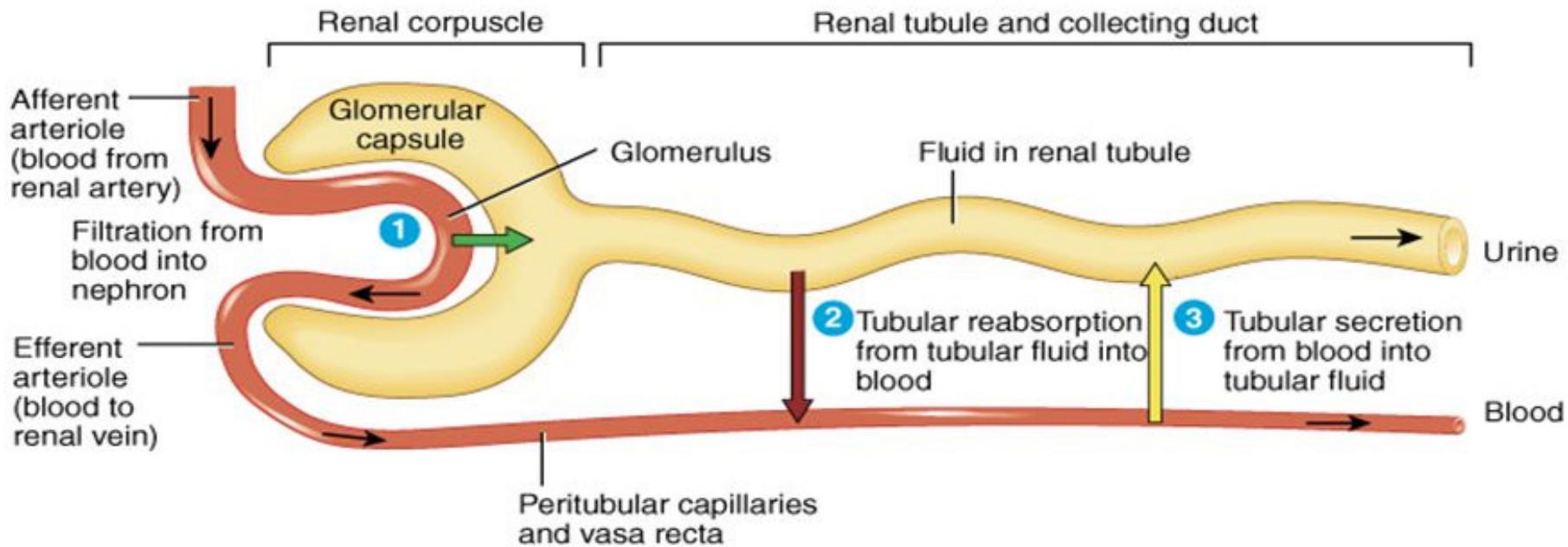
# Path of blood flow through renal blood vessels



(a) Frontal section illustrating major blood vessels

(b) Path of blood flow through renal blood vessels

# Basic Functions of a Nephron

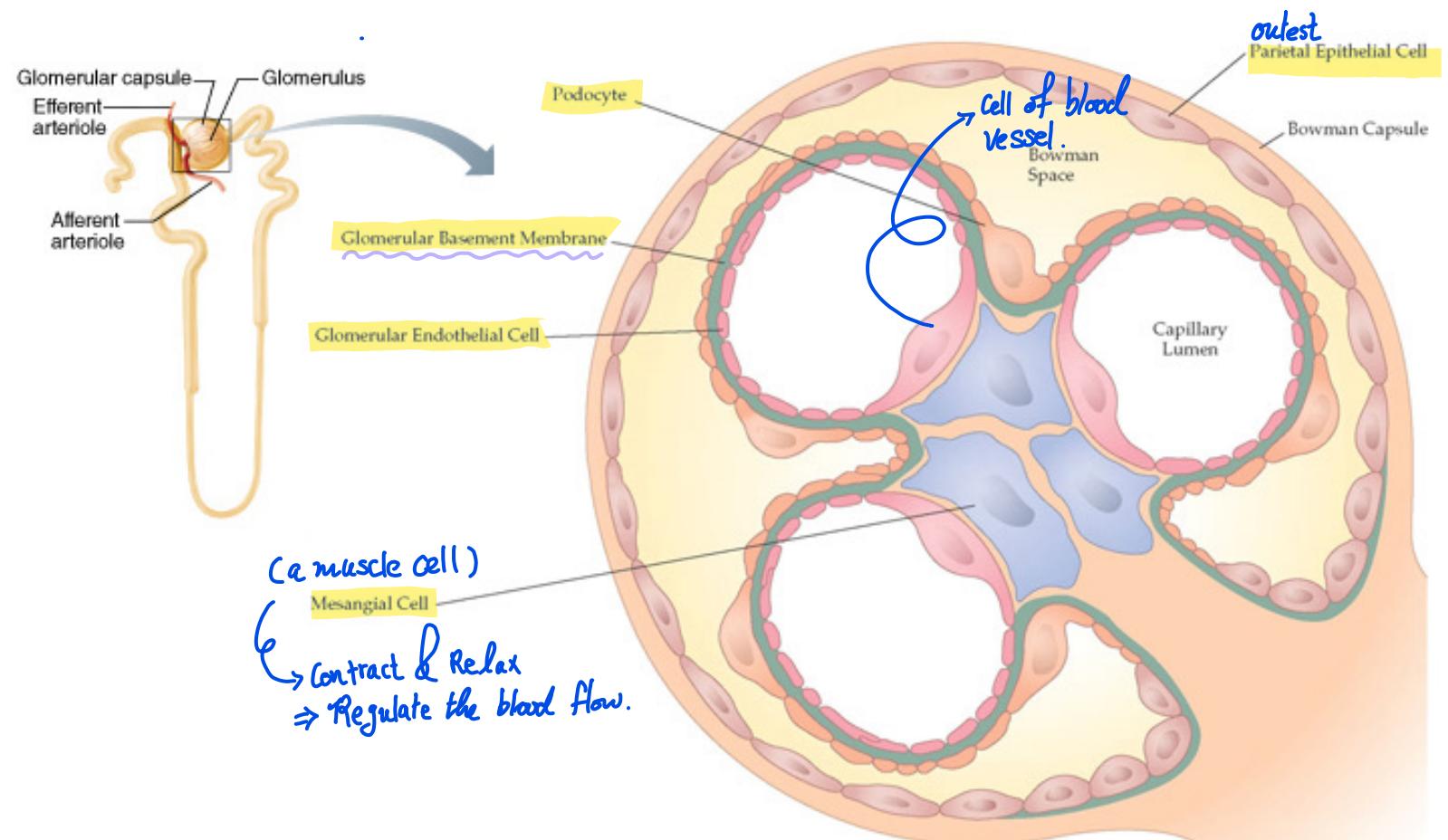


Nephrons perform 3 basic functions:

1. Glomerular filtration
2. Tubular reabsorption
3. Tubular secretion

# Renal corpuscle = Glomerulus + Bowman's capsule

- The renal corpuscle is the initial blood-filtering component of a nephron
- The glomerulus is a small tuft of capillaries (larger surface area for filtering) containing:
  - 1) endothelial cells; and 2) mesangial cells
- The Bowman's capsule has an outer parietal layer and an inner visceral layer. Cells on the visceral layer are structurally modified – known as podocytes



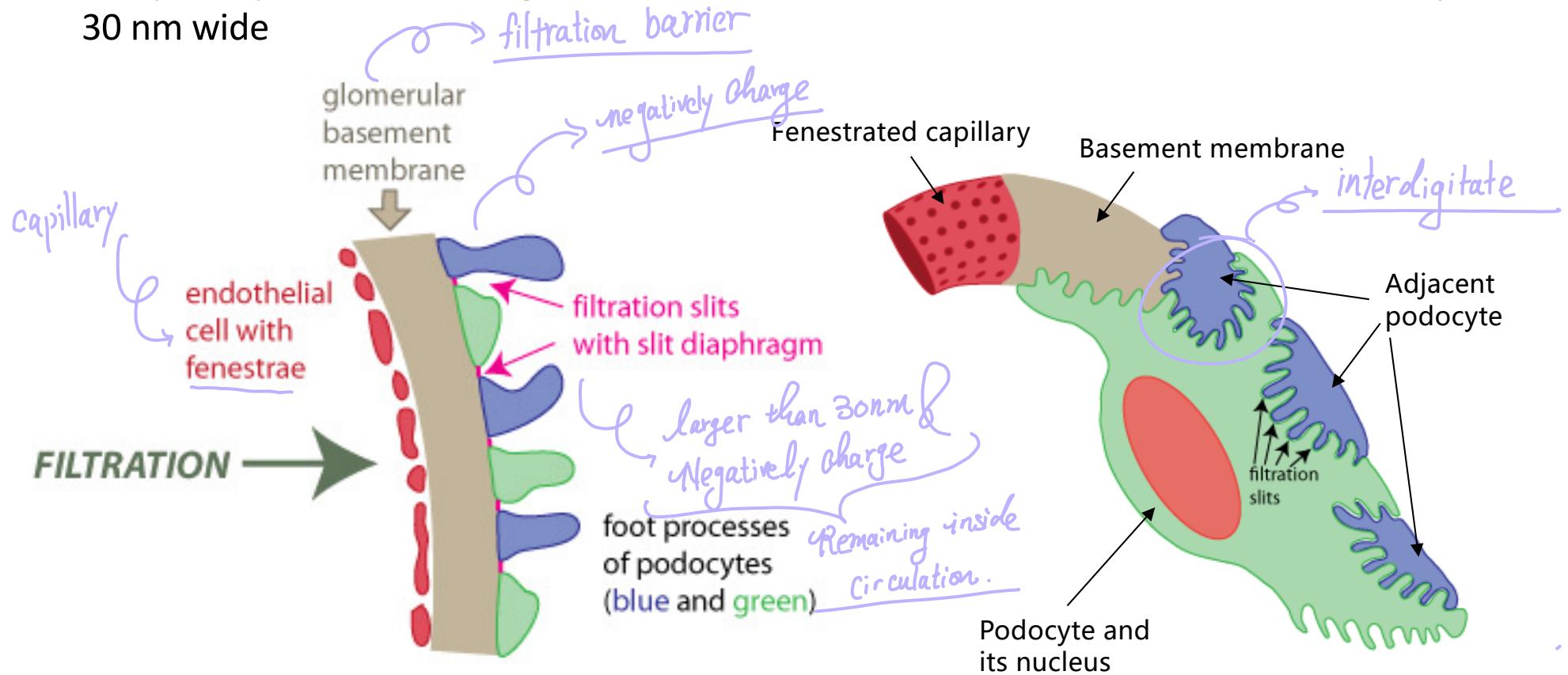
# Glomerular Filtration



# Filtration Barrier in Renal Corpuscle

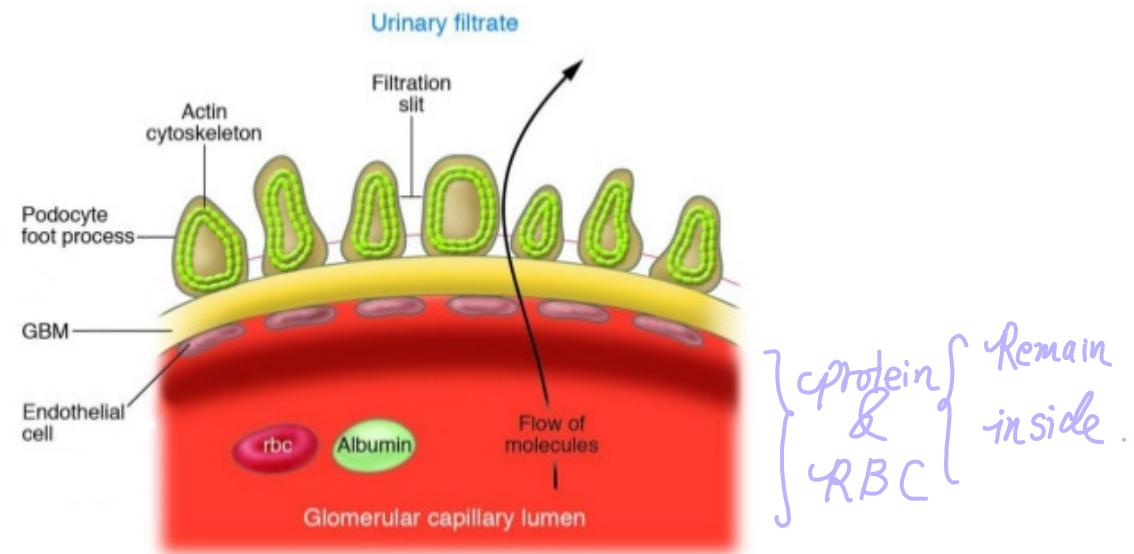
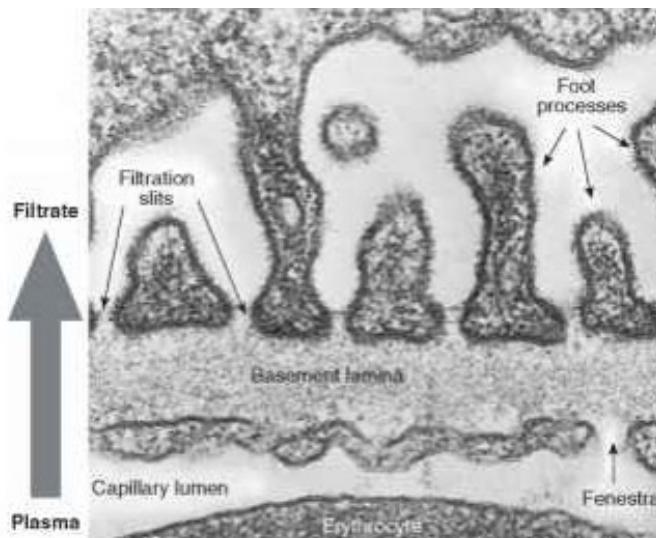
*lots of pores*

- The renal corpuscle filtration barrier is composed of:
  - the fenestrated endothelium (fenestrae at size of 50-100 nm) of glomerular capillaries
  - the fused basal lamina of endothelial cells and podocytes
  - the filtration slits of the podocytes
- The podocytes' feet interdigitate with each other to form filtration slits that are only 20-30 nm wide

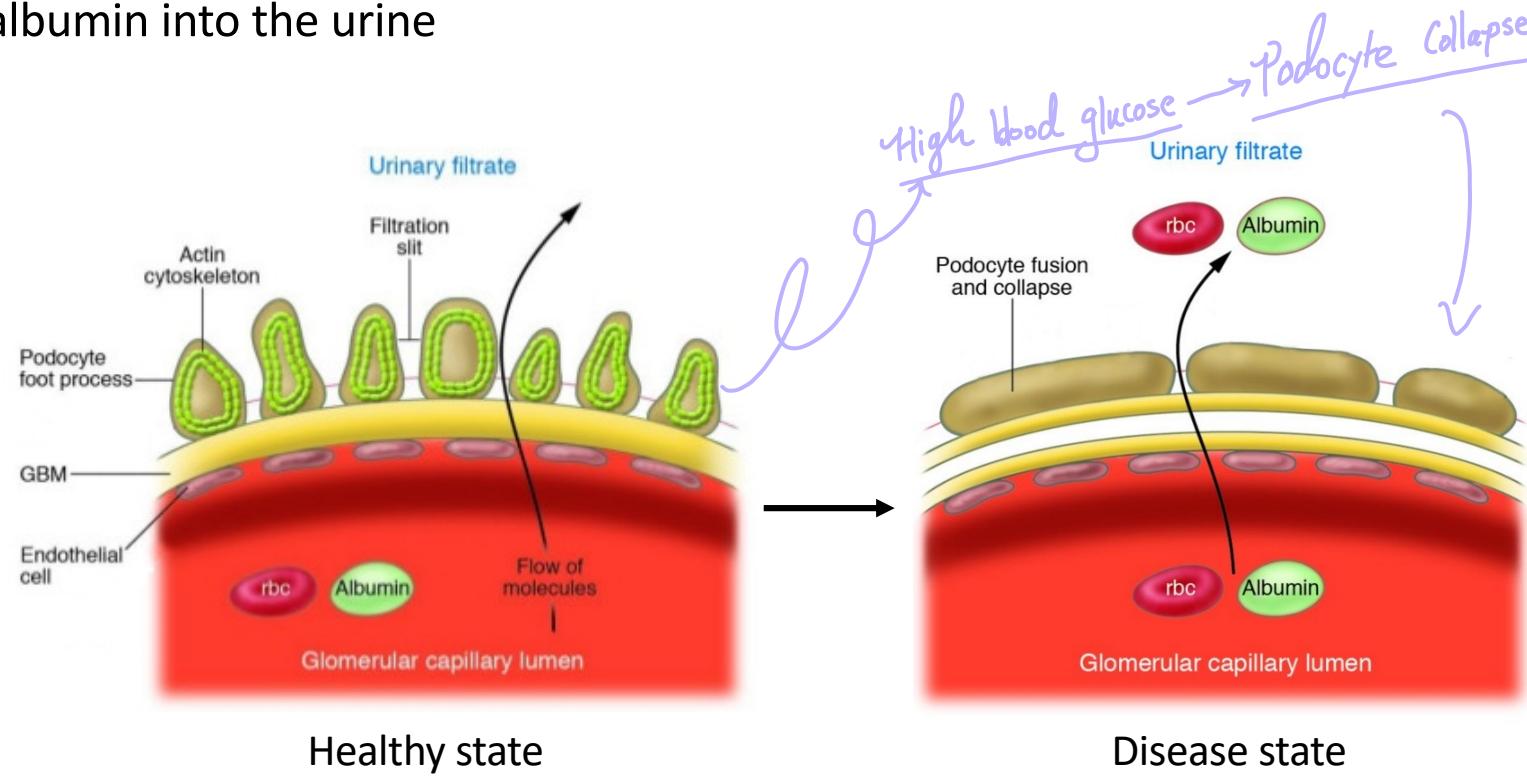


# Filtration Barrier in Renal Corpuscle

- Molecules can be sorted by this 'sieving' mechanism by size and charge (-ve charge of the basement membrane repels -ve charge proteins such as albumin)  
i.e. the filtration barrier only permits passage of water, ions, and small molecules, but not large size cells, e.g. red blood cells, from the bloodstream into the Bowman's capsule



- Proteinuria - also called albuminuria or urine albumin - is a sign of chronic kidney disease, which can result from diabetes, hypertension, and diseases that cause inflammation in the kidneys
- It can be resulted from the fusion or collapse of podocyte foot process, the splitting of the glomerular basement membrane (GBM), hence loss of proteins such as albumin into the urine



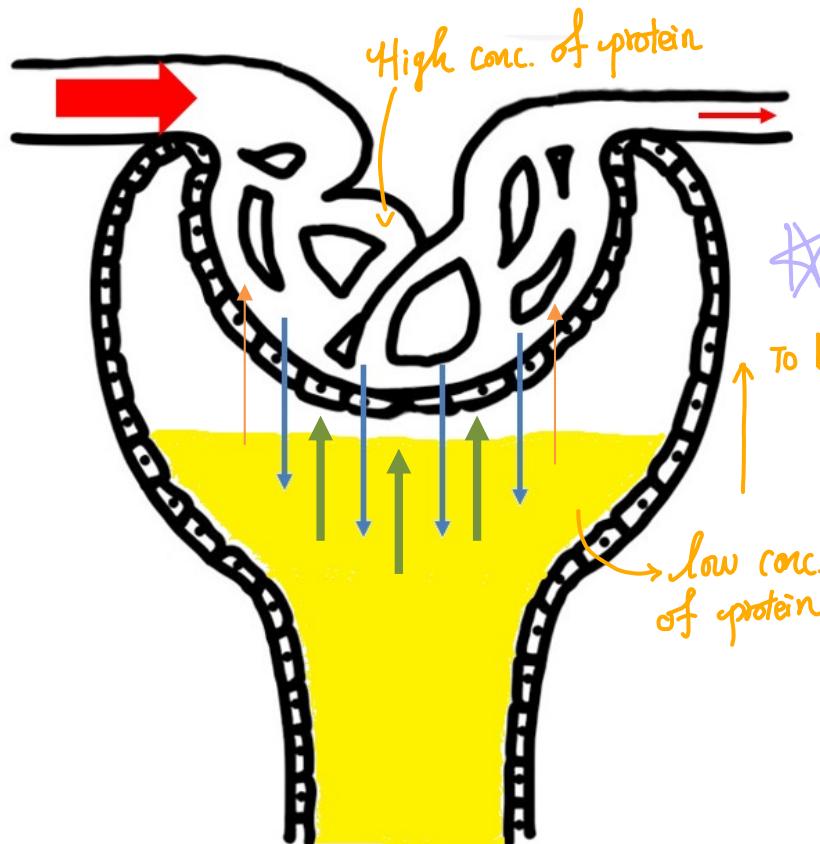
- A urine sample containing more than 150 mg/24 hours or 10 mg/100 ml is a warning that there may be a problem. Proteinuria > 3.5 g/24 hours is severe and known as nephrotic syndrome.

*Afferent > Efferent → High Blood pressure*

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# Ultrafiltration Forces

- Filtration occurs because of the **high pressure** in the **glomerular capillaries** -- the efferent arteriole is narrower than the afferent arteriole



Force favoring filtration:  
Glomerular capillary blood pressure (G bp)

To balance the osmolarity  
Force opposing filtration:  
Fluid (or hydrostatic) pressure in Bowman's capsule (BC hp)  
Osmotic force due to protein in the glomerulus (i.e.  
oncotic pressure /  $\pi$  osm)

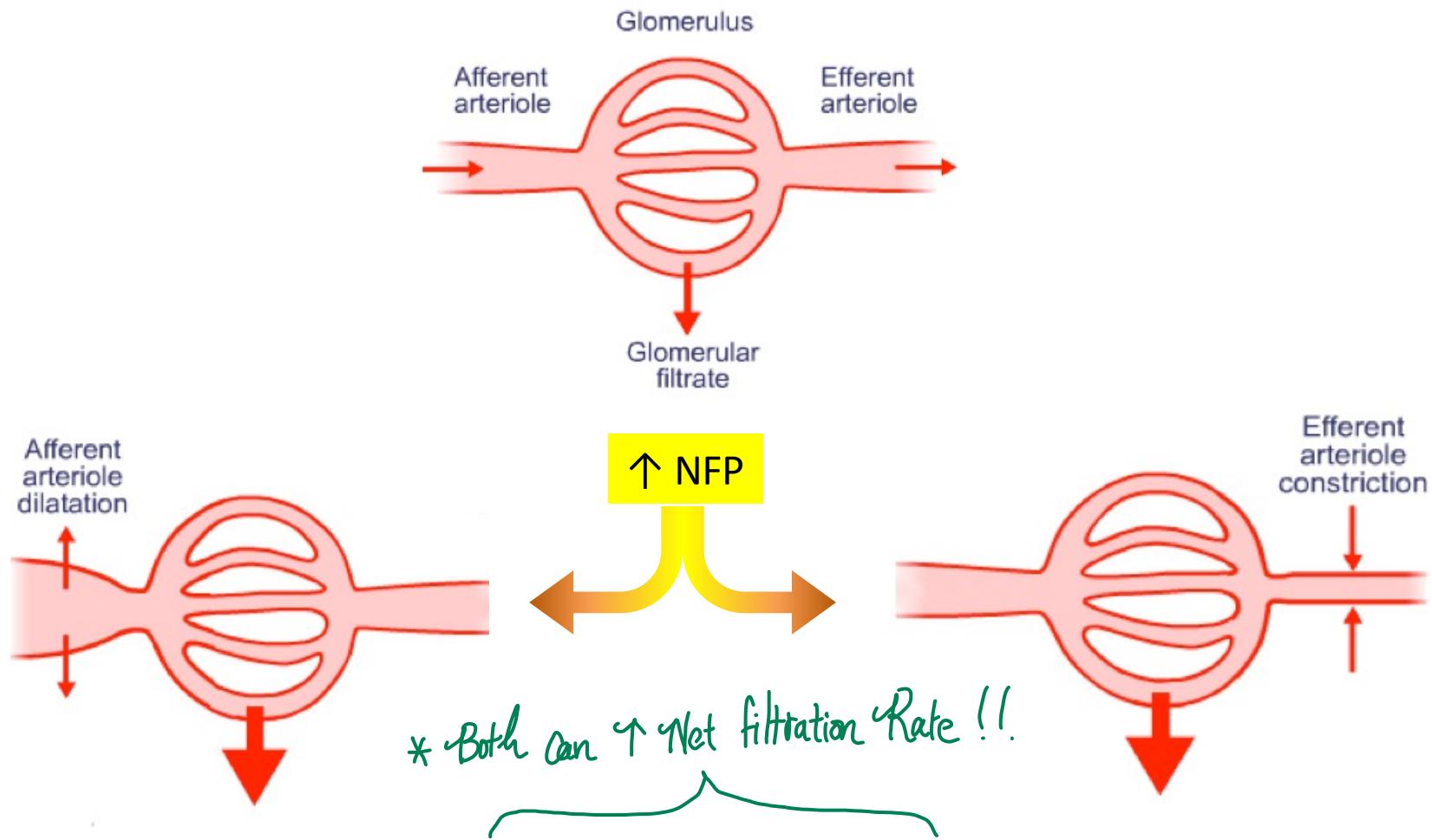
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$$\text{Net filtration pressure} = G \text{ bp} - BC \text{ hp} - \pi \text{ osm}$$

= pressure responsible for filtrate formation

- Ultrafiltration of blood to form glomerular filtrate depends on the balance of forces that favor filtration and those that oppose it

# Changes in Net Filtration Pressure



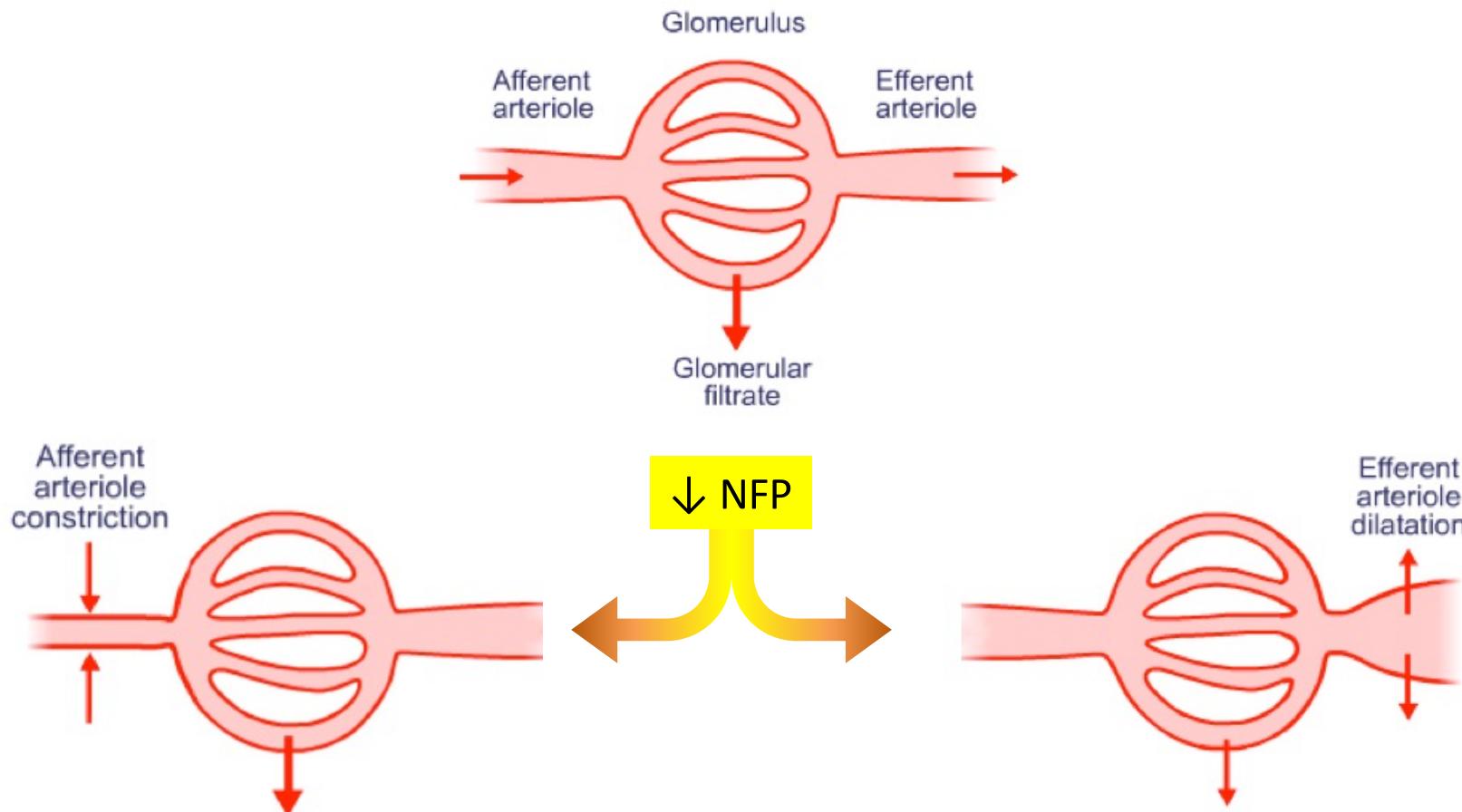
## Vasodilation of afferent arteriole:

- $\uparrow$  blood flow into the glomerulus
- $\uparrow$  capillary blood pressure
- $\uparrow$  Net filtration pressure

## Vasoconstriction of efferent arteriole:

- $\uparrow$  capillary blood pressure
- $\uparrow$  Net filtration pressure

# Changes in Net Filtration Pressure



Vasoconstriction of afferent arteriole:

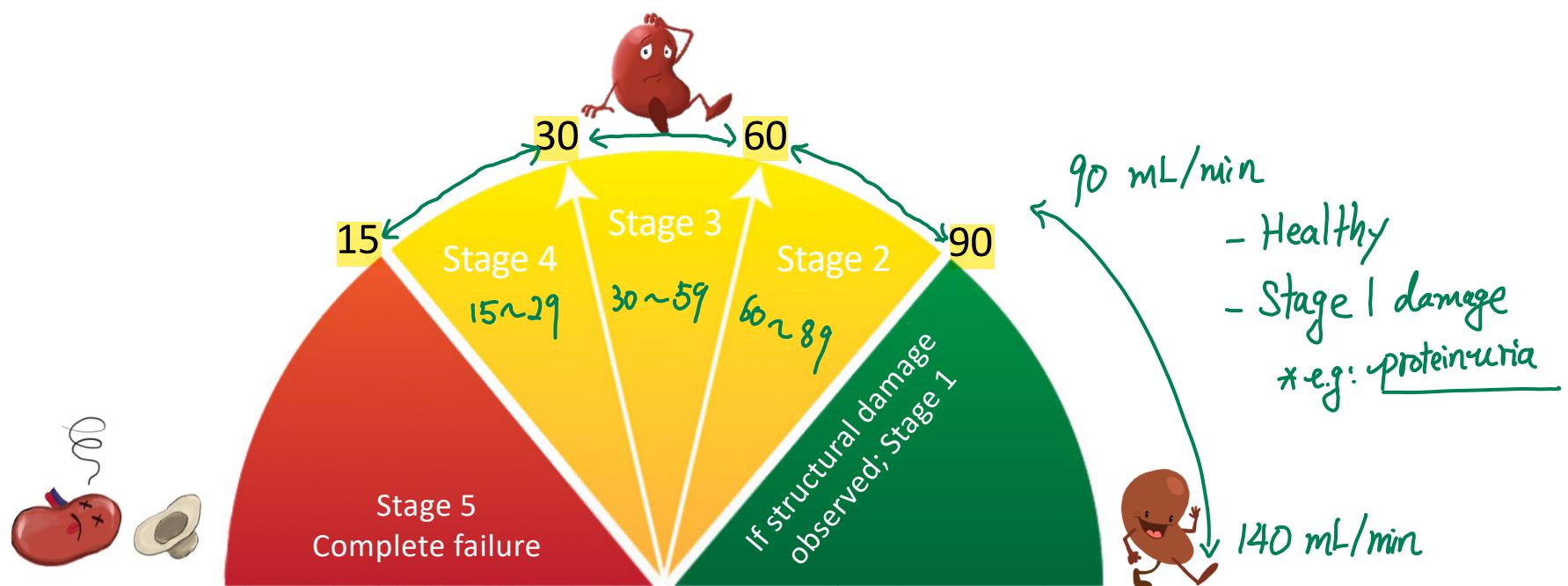
- ↓ blood flow into the glomerulus
- ↓ glomerular capillary blood pressure
- ↓ Net filtration pressure

Vasodilation of efferent arteriole:

- ↓ glomerular capillary blood pressure
- ↓ Net filtration pressure

# Glomerular Filtration Rate (GFR)

- GFR is the total amount of filtrate formed by both kidneys per min. It is a calculation that determines how well the blood is filtered by the kidneys (i.e. how well our kidneys are working).
- GFR depends on:
  - 1) Net filtration pressure
  - 2) Permeability of filtration membrane
  - 3) Surface area available for filtration
- The normal glomerular filtration rate could range anything from 90-140 mL/min



# Renal Clearance & GFR

( In one minute !! )

- Renal clearance of a substance that is neither reabsorbed nor secreted by the kidney can be used to determine GFR in our body. It refers to the volume of plasma that is cleared of a specific substance in a given amount of time.

$$\text{Clearance} = \frac{\text{Excretion amount of a substance}}{\text{Concentration of a substance in our body}}$$

No direct relation  
between  
G.F.R.

Our body



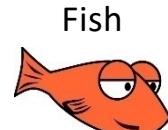
Lake



Renal tubules



River



Fish

Waste substances  
in our body

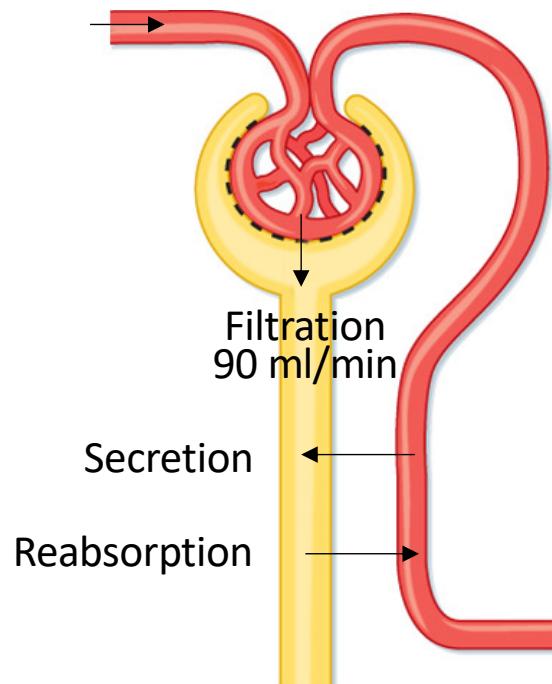


Toilet



Ocean





## Filtration - Reabsorption + Secretion = Excretion

Substance	Properties	Example of substance	Normal clearance values (ml/min)
#1	Freely filtered Fully reabsorbed	Glucose	0
#2	Freely filtered Not reabsorbed Not secreted	Inulin	90

Can be completely reabsorbed.

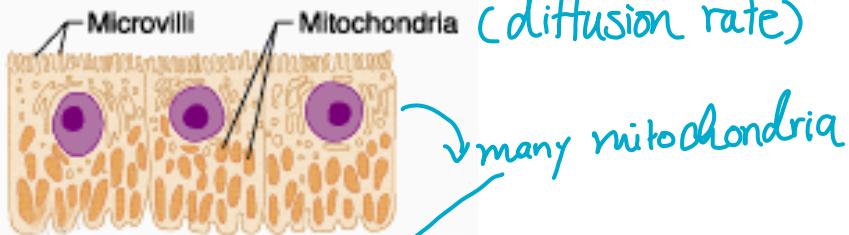
- Renal inulin clearance is a good standard for estimating GFR
- Creatinine is often used as a rough measurement of GFR, i.e. estimated GFR (eGFR)
  - Freely filtered + undergoes a small amount of secretion in kidney → slightly over-estimated GFR  
As secretion ≈ 0, no reabsorbed.
  - Levels are affected by age, gender, food intake, muscle mass, etc

# **Urine Formation: Reabsorption and Secretion in the Renal Tubules**

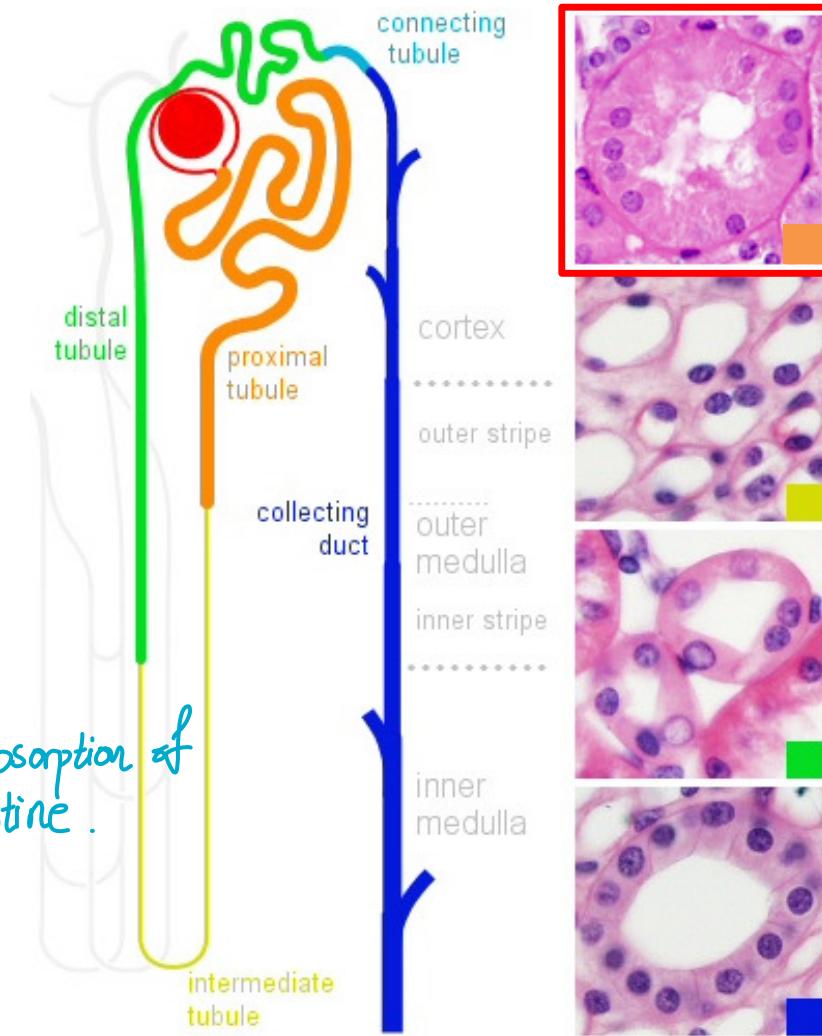
# Renal Tubules – Proximal Tubules

- Proximal tubule

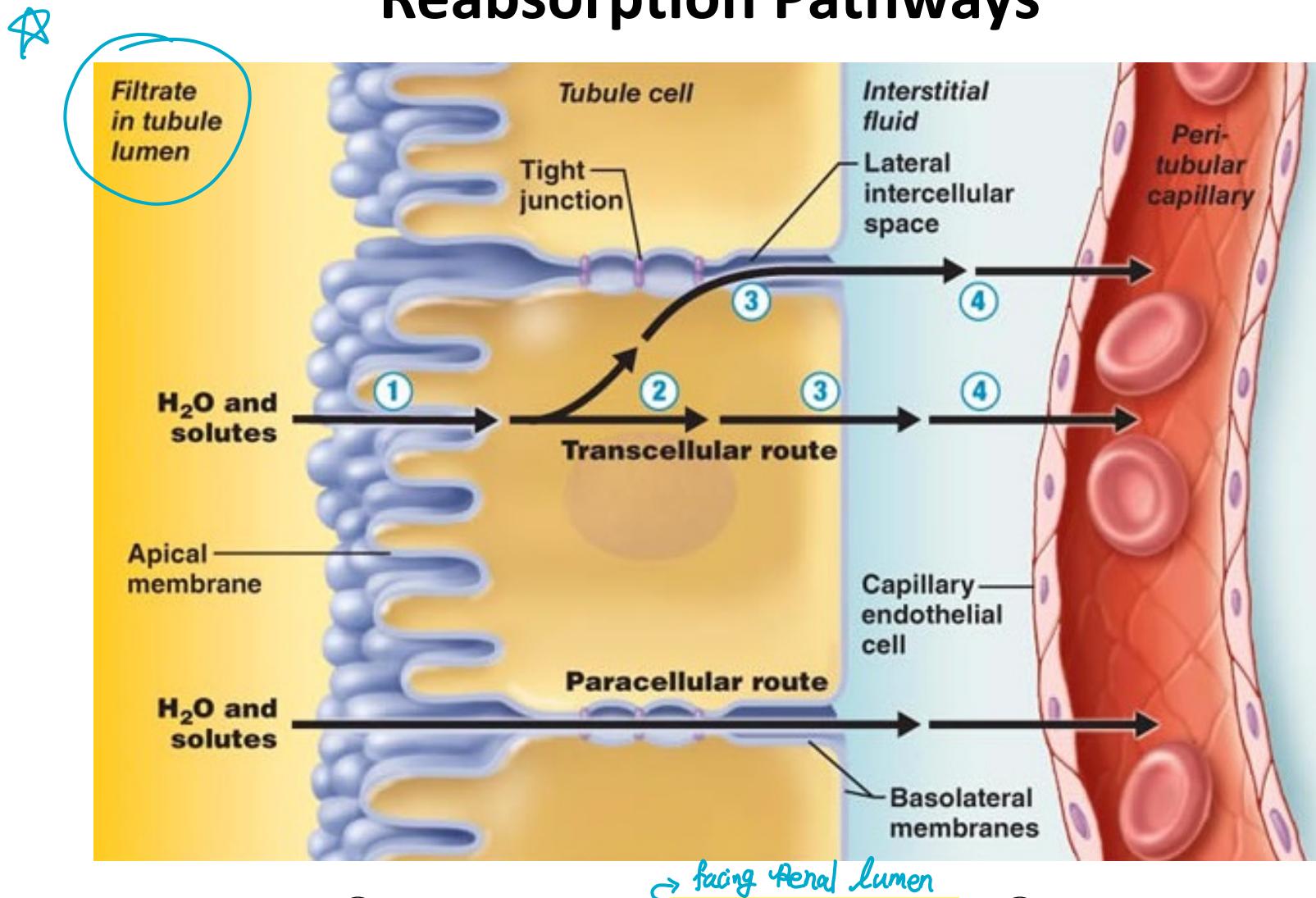
- The longest section of the nephron
- Consisted of cuboidal epithelial cells that have a wide brush border (microvilli) - maximizes the space available for reabsorption



- ~70% of the filtrate are being reabsorbed in the proximal tubules – this is the major site for reabsorption!
- Responsible for the production of calcitriol under the control of parathyroid hormone (Note: calcitriol is the active hormonal form of vitamin D, which helps  $\text{Ca}^{2+}$  absorption in intestine).



# Reabsorption Pathways



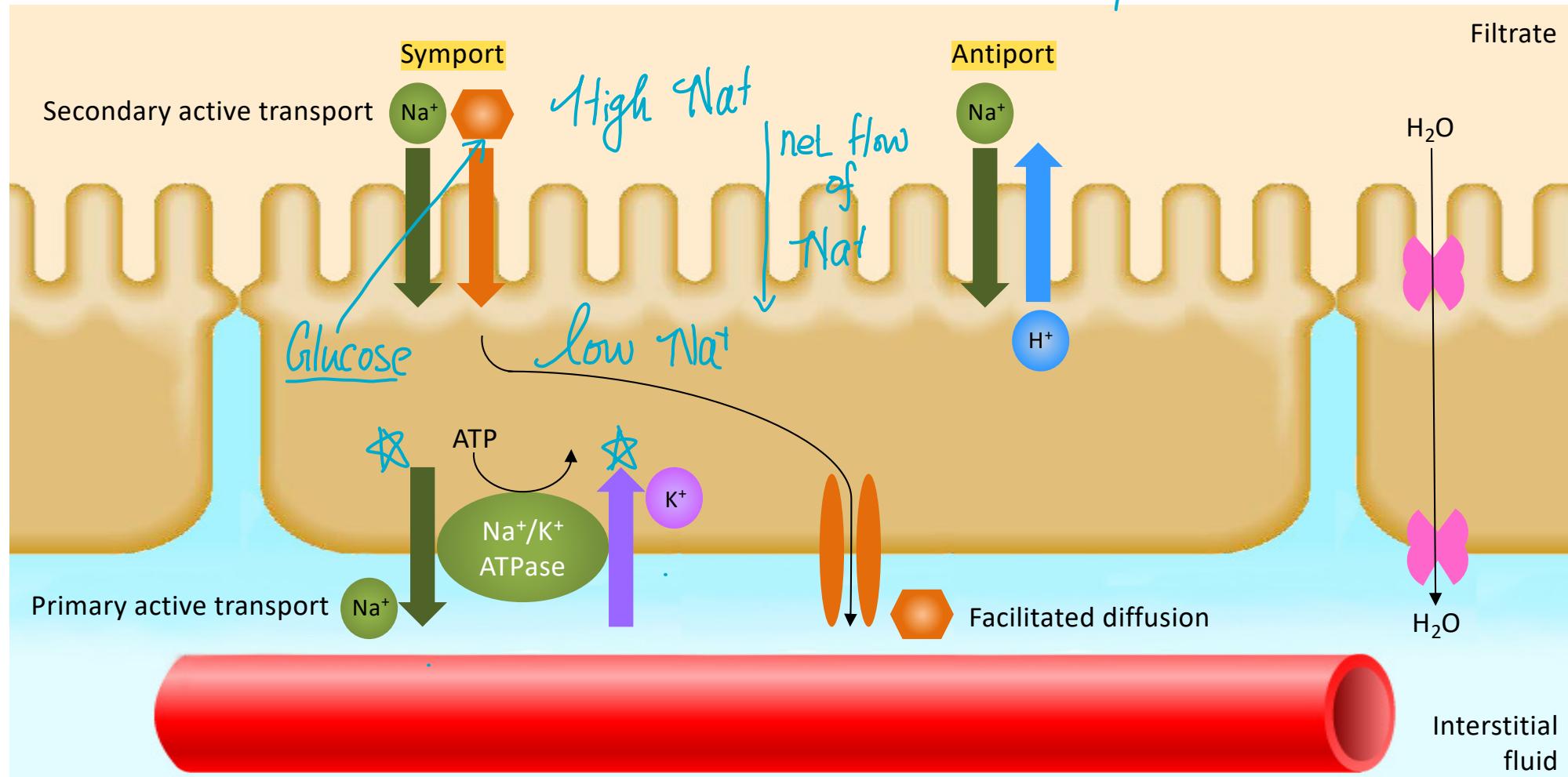
- Transcellular route = ① Transport across **apical membrane** + ② Diffuse through cytoplasm + ③ Transport across basolateral membrane + ④ Move through interstitial fluid into capillary
- Paracellular route = Movement through **leaky tight junctions**

(e.g.: Glucose )

(Some  $K^+$  &  $H^+$ )

## Reabsorption & Secretion in Proximal Tubules

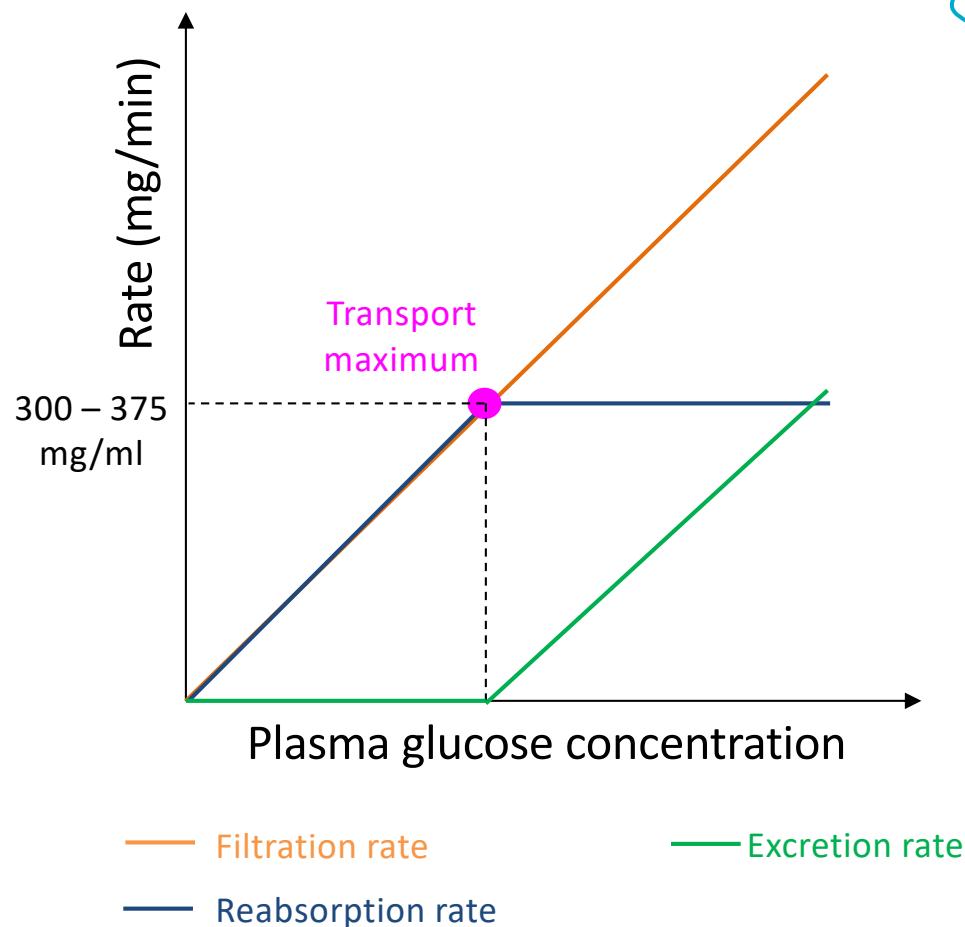
- Paracellular route = Diffusion down the concentration gradient, e.g. urea,  $Ca^{2+}$ ,  $K^+$
- Transcellular route = Primary active transport, secondary active transport, facilitated diffusion, and osmosis  
 $(Na^+/K^+ ATPase) \Rightarrow Pump$



# Transport Maximum ( $T_m$ )

- For substances reabsorbed via transporters (mainly active transport), there exists a maximum rate for their transport (transport maximum) – This is because all available carriers are occupied with the substrate

Glucose Level is too High → Transport maximum → Reabsorb. *Cannot 100% Reabsorb.*



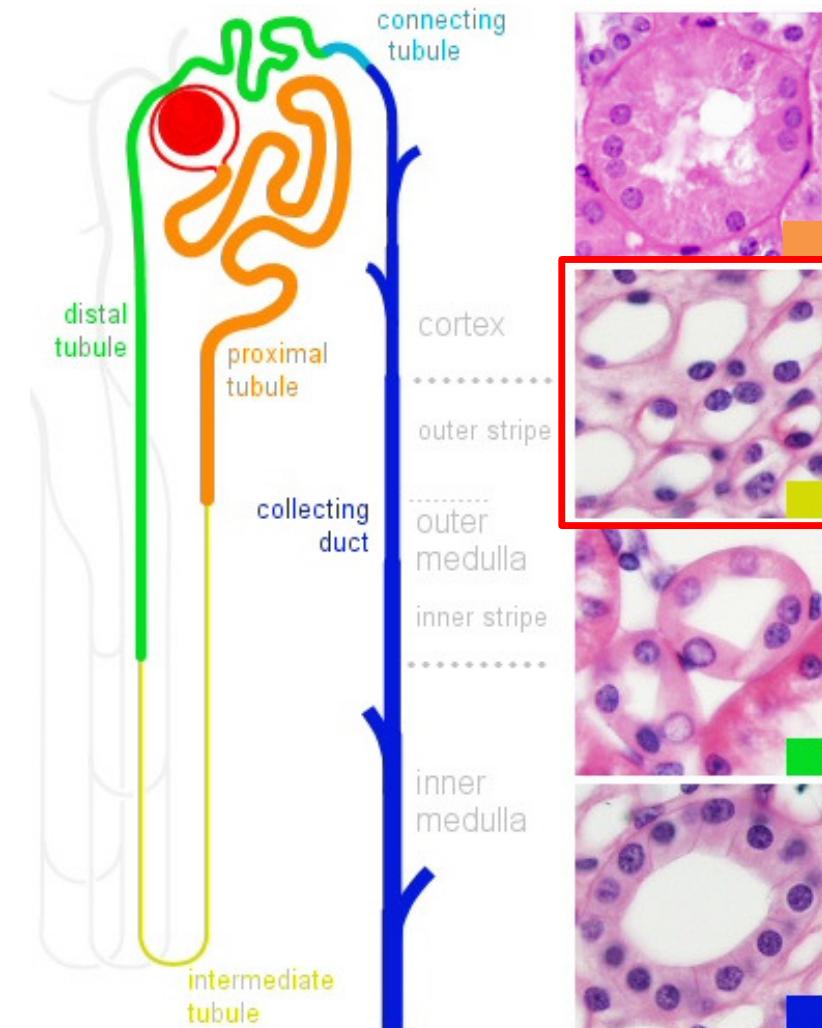
- Glycosuria in diabetes mellitus - When the amount of glucose in the filtrate exceeds the transport maximum of the proximal tubule (i.e. all glucose transporters are saturated), urine becomes more abundant and contains glucose
- In men, the maximum amount of glucose that can be recovered is about 375 mg/min, whereas in women, it is about 300 mg/min

# Renal Tubules – Loop of Henle

- Loop of Henle
  - Connecting the proximal tubules to distal tubules
  - Located exclusively in the medulla
  - It has a descendent and ascending portions and is consisted of simple squamous cells

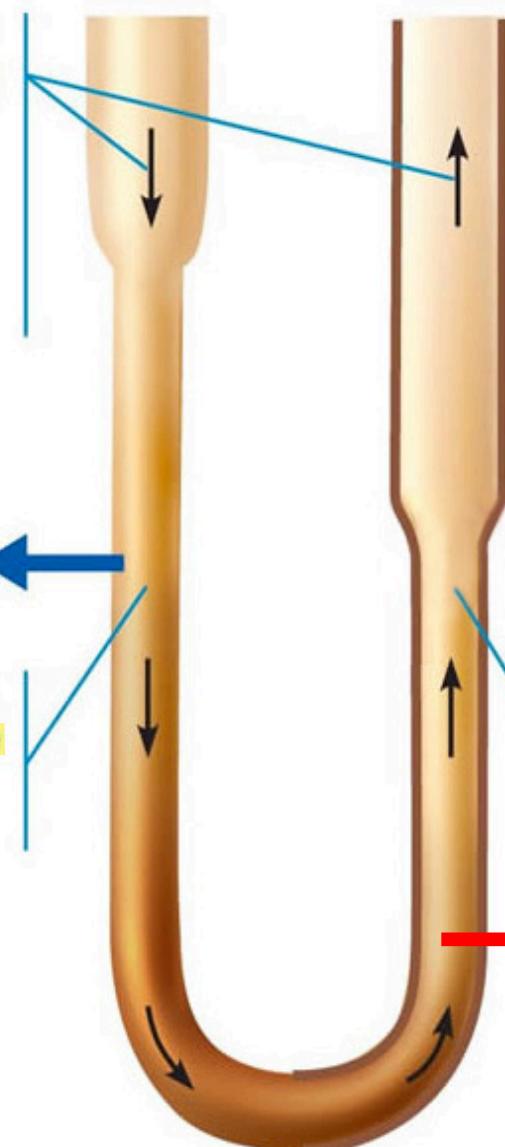


- Responsible for building up a high concentration of  $\text{Na}^+$  and  $\text{Cl}^-$  in the tissues of the medulla → this serves as driving force in the further concentration of the urine



# Salts and Water Reabsorption in Loop of Henle: The Countercurrent Multiplier System

Fluid flows in the opposite direction (countercurrent) through two adjacent parallel sections of a nephron loop.

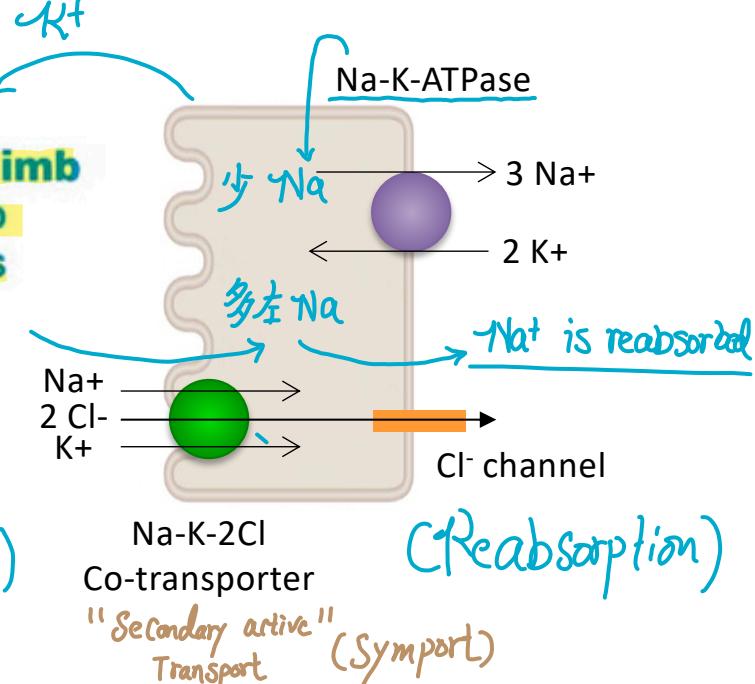


The descending limb is permeable to water, but not to salt.

The reabsorption of NaCl including passive & active transport. The Na<sup>+</sup>/K<sup>+</sup> ATPase pumps in the basal membrane create an electrochemical gradient, allowing reabsorption of Na<sup>+</sup>, Cl<sup>-</sup> and K<sup>+</sup> by bumetanide-sensitive Na-K-2Cl co-transporter (NKCC) in the apical membrane

★ No potassium ion is reabsorbed. K<sup>+</sup>

The ascending limb is impermeable to water, and pumps out salt.



(出水)

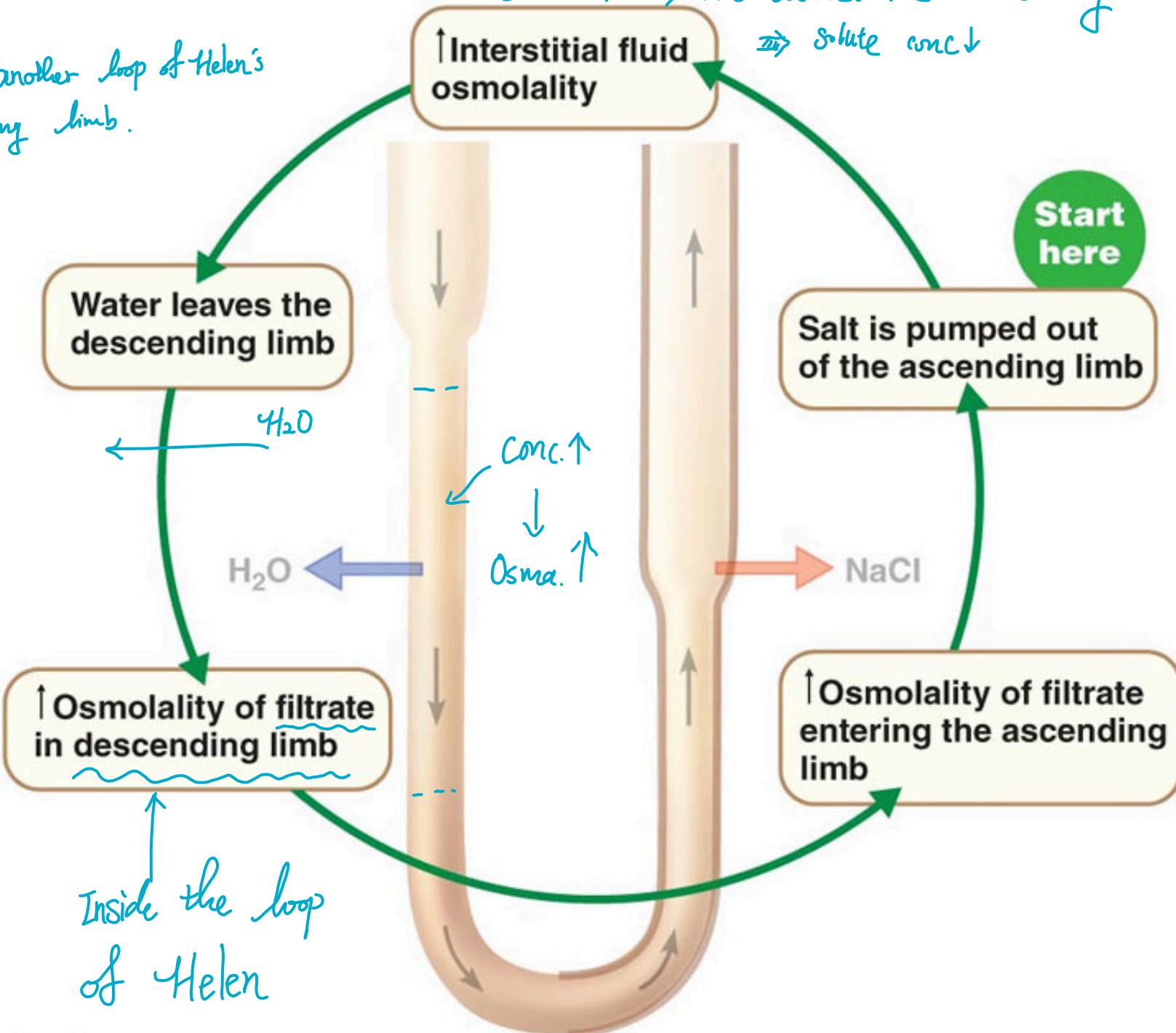
Na-K-2Cl Co-transporter

"Secondary active" Transport (Sympart)

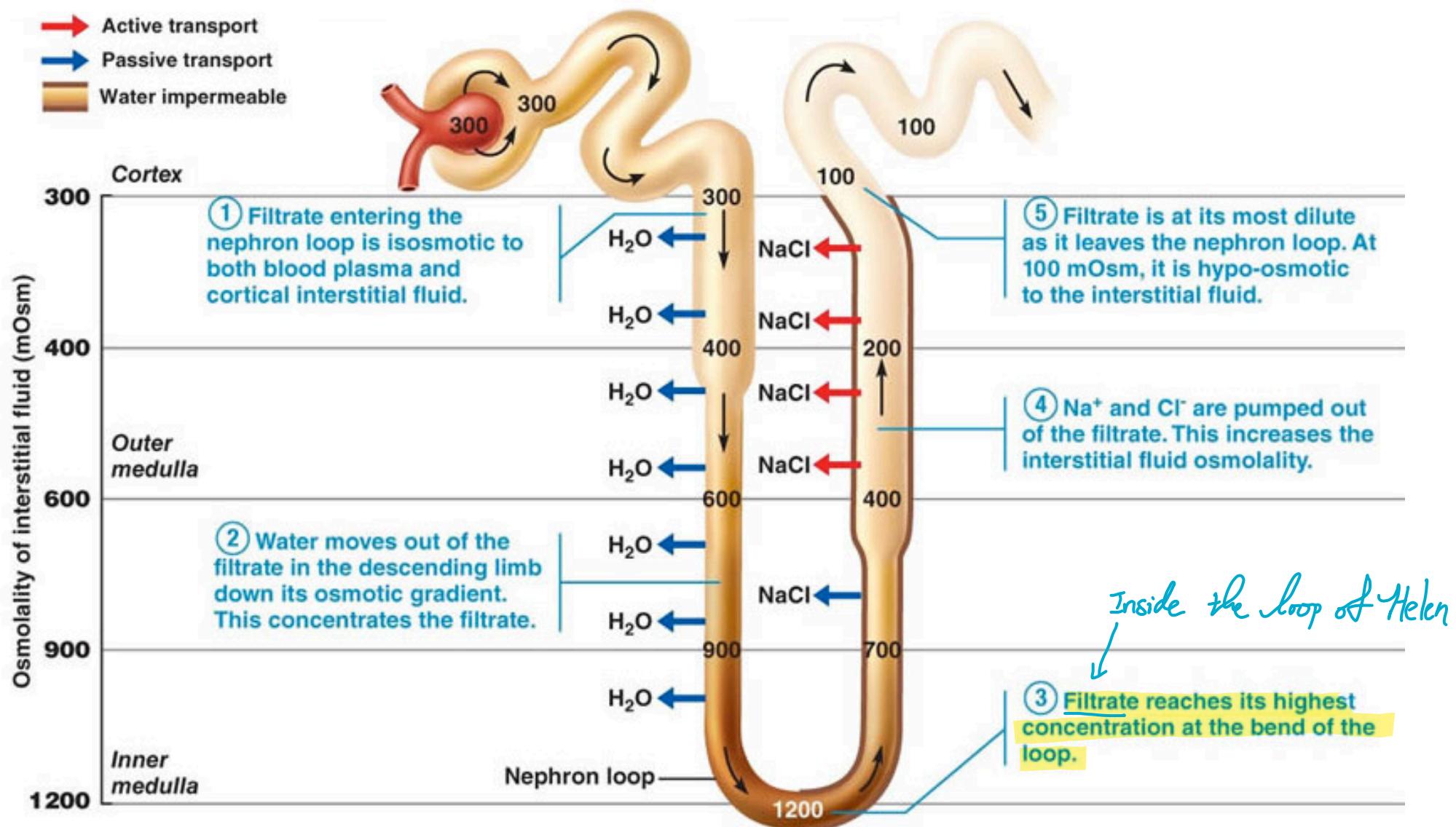
(Reabsorption)

Here is another loop of Helen's descending limb.

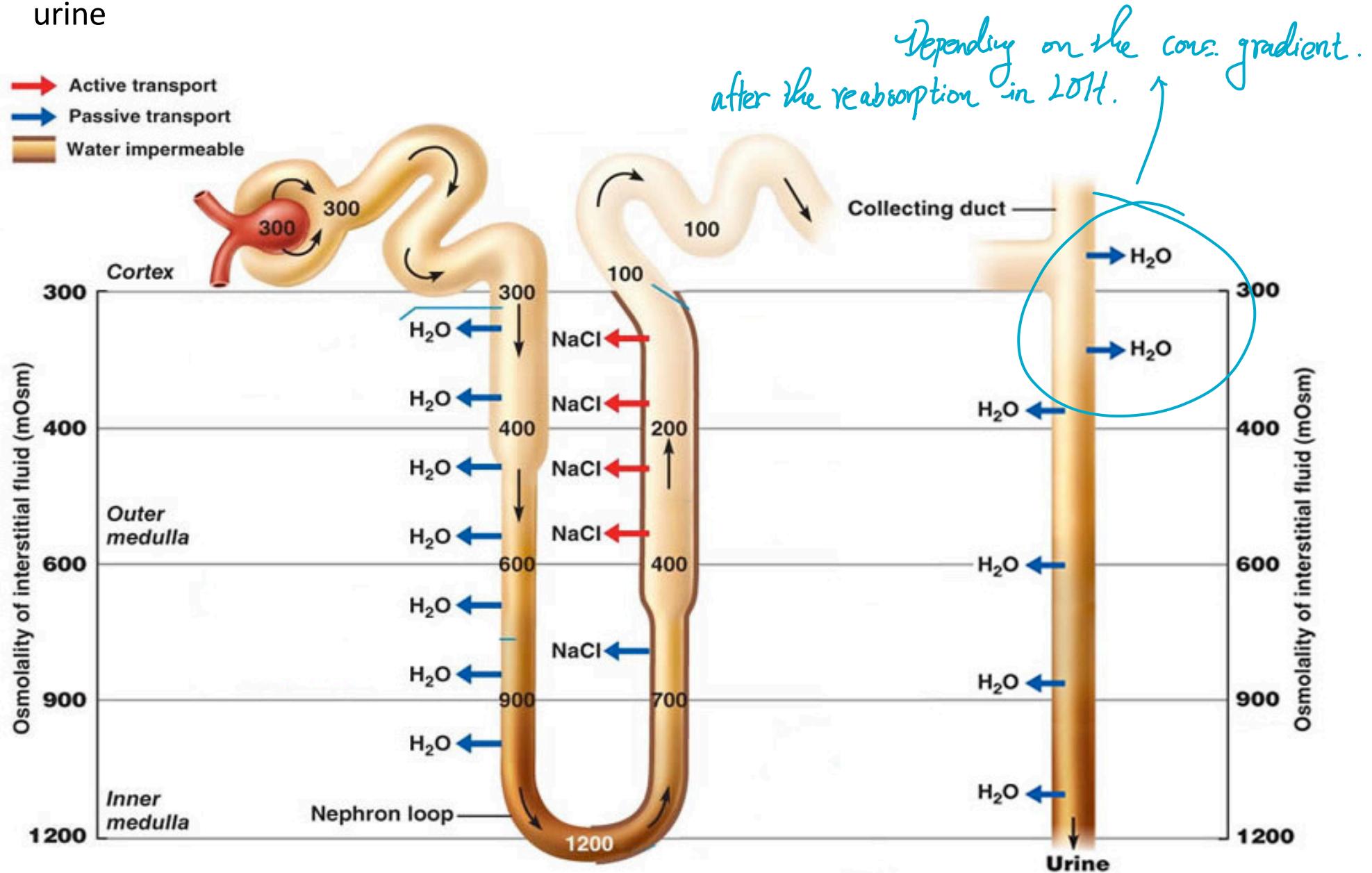
The solute conc. ↑  $\Rightarrow$  H<sub>2</sub>O leaves the descending limbs  $\Rightarrow$  solute conc. ↓



- As water and salts are reabsorbed, the loop of Henle first concentrates the filtrate, then dilute it!!!!



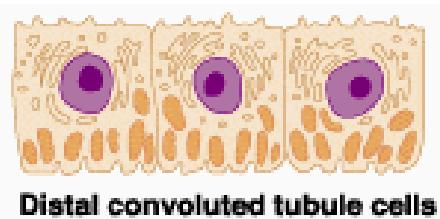
- Loop of Henle is responsible for building up a high concentration of  $\text{Na}^+$  and  $\text{Cl}^-$  in the interstitial places, so that collecting ducts can use the gradients to further concentrate the urine



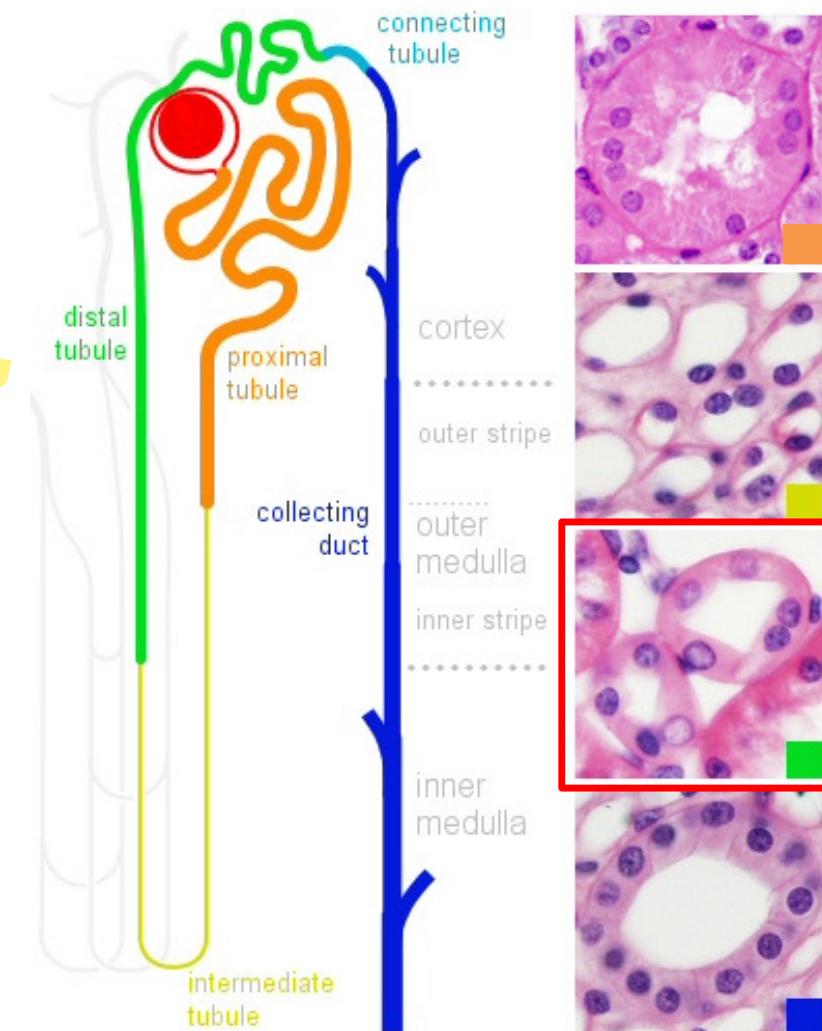
# Renal Tubules – Distal Tubules

↳ Control the blood flow.

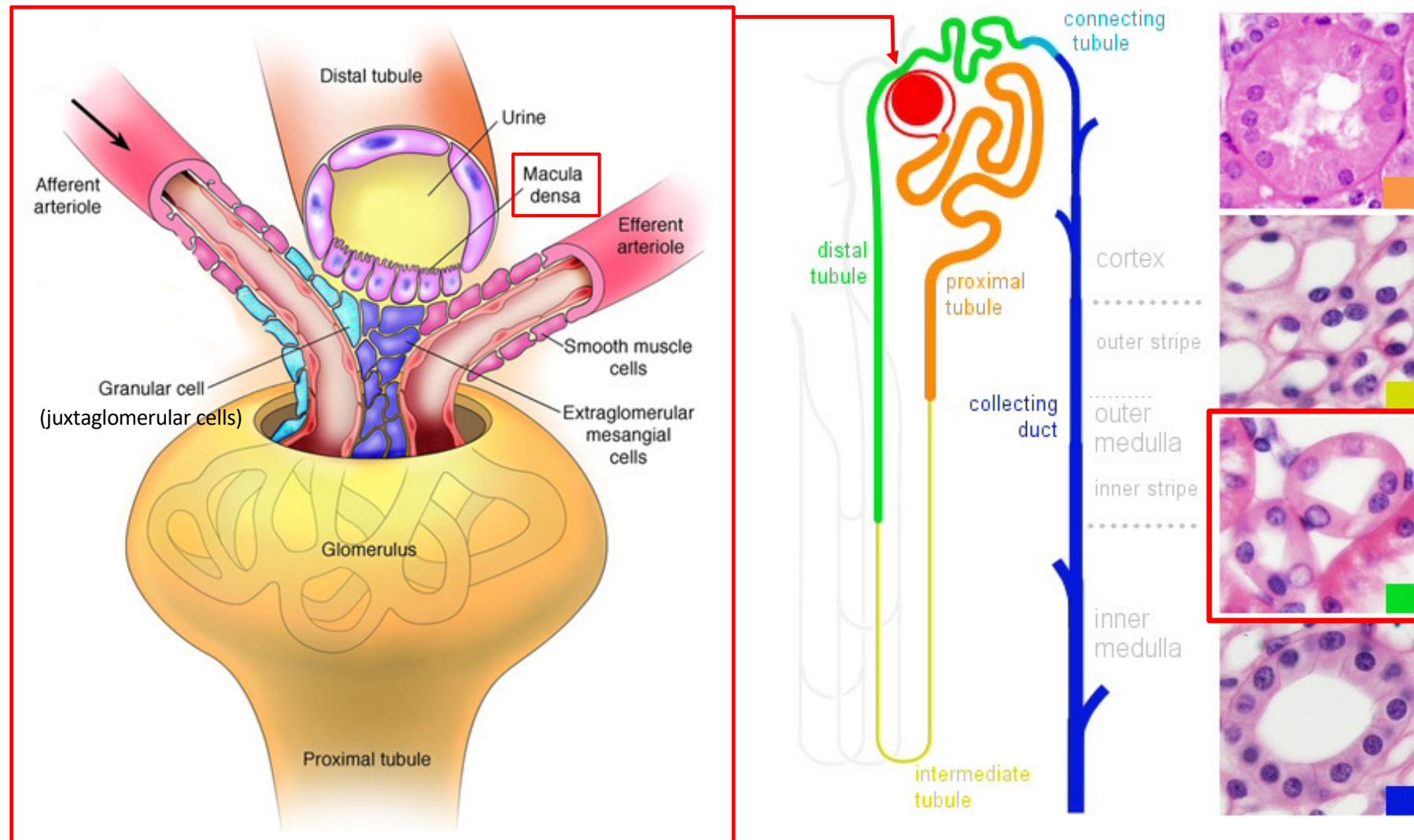
- Distal tubule
  - The shortest segment of the nephron, spanning only about 5 mm in length in humans
  - Located in the renal cortex
  - Mainly responsible for regulating flow in the glomerulus and nephrons by producing renin; also responsible for reabsorption and secretion of electrolytes
  - Consisted of cuboidal cells without a brush border



- Has unique capacity to adapt to changes in hormonal stimuli, mainly aldosterone (stimulates  $\text{Na}^+$  reabsorption) and parathyroid hormone (stimulates  $\text{Ca}^{2+}$  reabsorption)



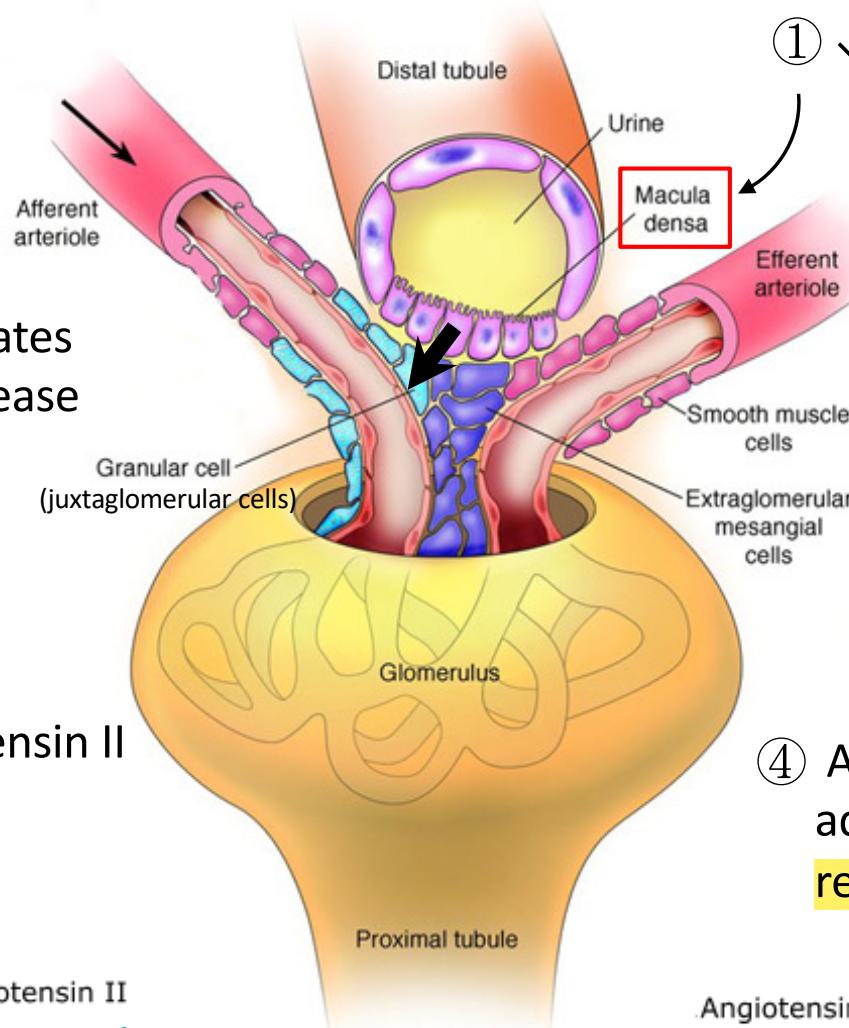
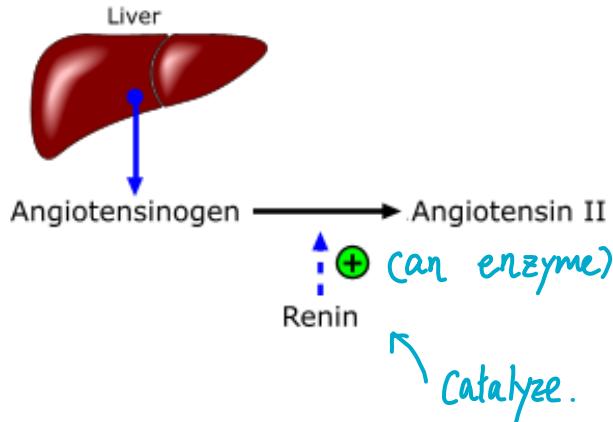
- The straight portion of the distal tubule that contacts the glomerulus = the macula densa



- The macula densa is a group of closely packed specialized cells that can sense the  $\text{Na}^+$  concentration in the filtrate

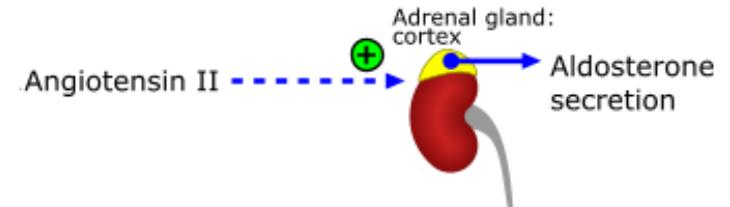
# The Macula densa, The Juxtaglomerular (JG) Cells, & the Renin-Angiotensin-Aldosterone System

- ② Macula densa stimulates nearby JG cells to release renin into the blood
- ③ Renin stimulates the production of Angiotensin II

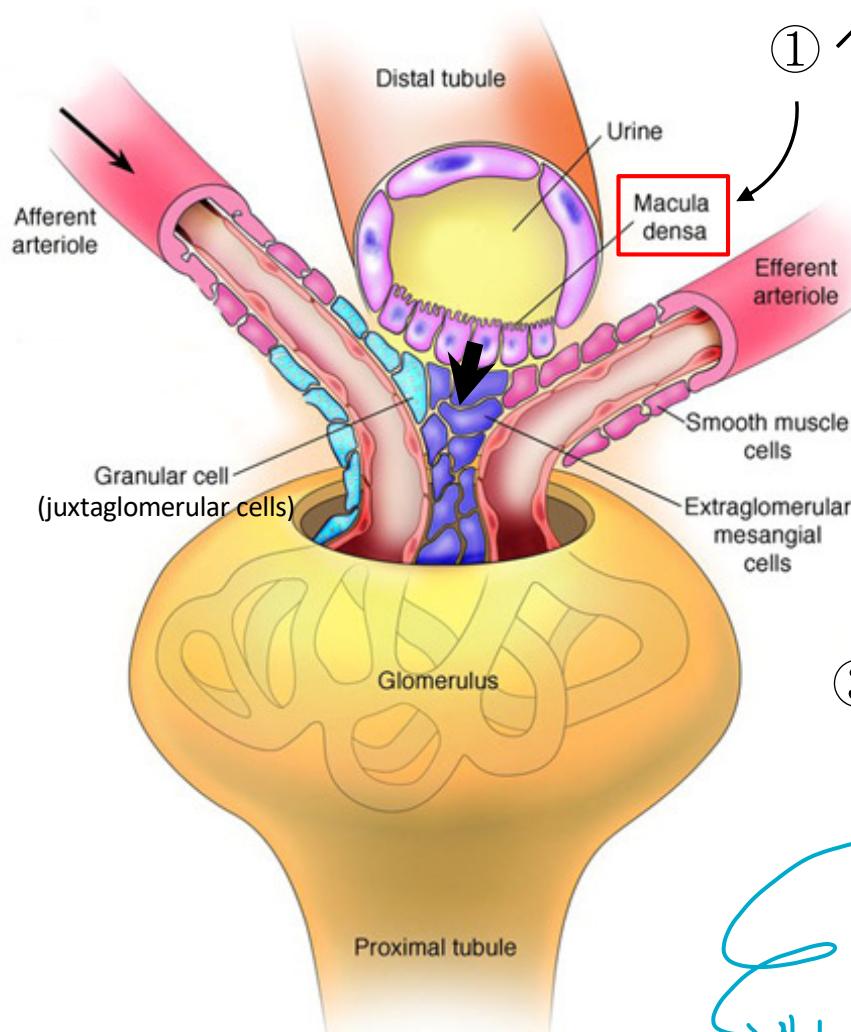


- ①  $\downarrow \text{Na}^+$  in distal tubules (indicator of  $\downarrow \text{GFR}$ )
- ② Macula densa stimulates nearby JG cells to release renin into the blood
- ③ Renin stimulates the production of Angiotensin II
- ④ Angiotensin II acts on the adrenal cortex, causing it to release aldosterone
- ⑤ Aldosterone induces reabsorption of  $\text{Na}^+$  ions and dumping of  $\text{K}^+$  ions in the distal tubules

Induce  $\text{Na}^-\text{K}^+\text{-ATPase}$  secondary transport.



# The Macula densa, The Juxtaglomerular (JG) Cells, & the Renin-Angiotensin-Aldosterone System



① ↑ Na<sup>+</sup> in distal tubules  
(indicator of ↑ GFR)

② Macula densa stimulates nearby extraglomerular mesangial cells to release Ca<sup>2+</sup>

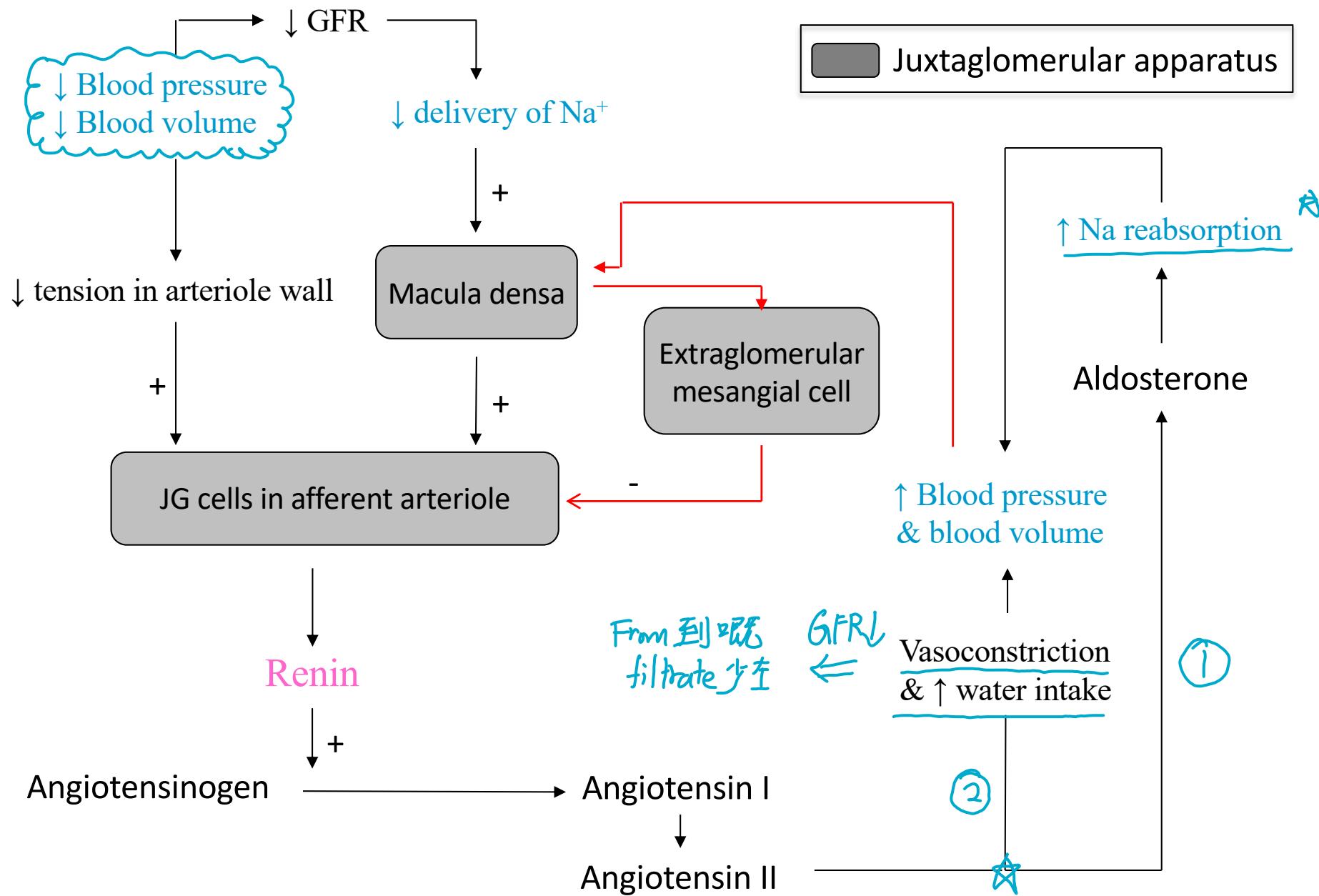
③ Ca<sup>2+</sup> spread to:

- smooth muscle cells of the afferent arteriole causing it to constrict → ↓ blood flow into glomerulus
- JG cells to inhibit renin release → No angiotensin II production

VasoConstriction.  
Net filtrate pressure → Decrease GFR

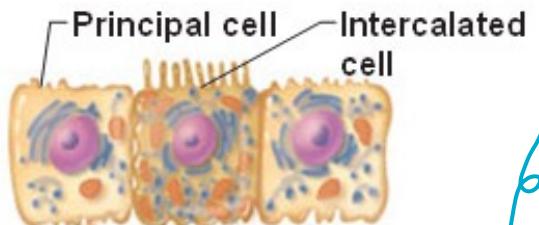
→ 水肿 → High BP

# Tubuloglomerular feedback by Juxtaglomerular Apparatus

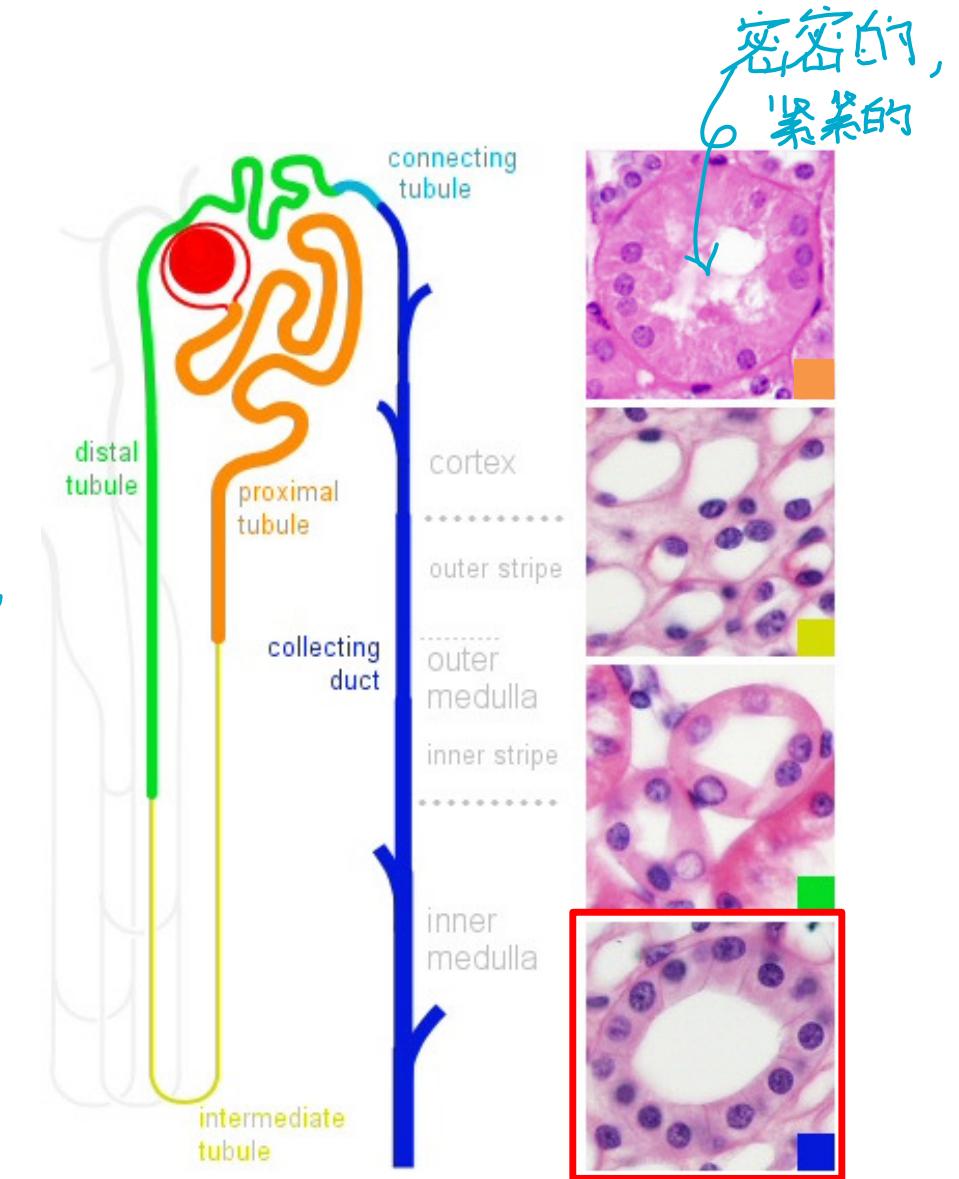


# Renal Tubules – Collecting Ducts

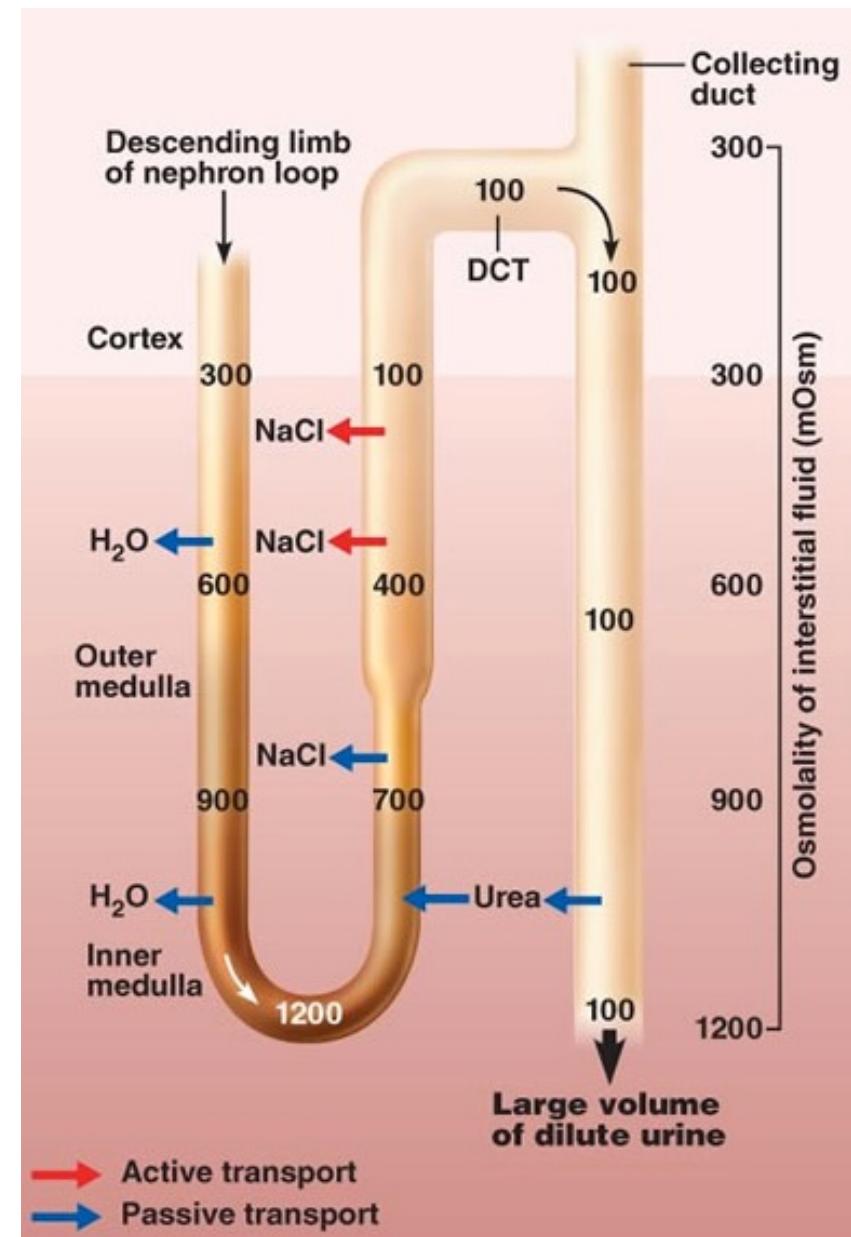
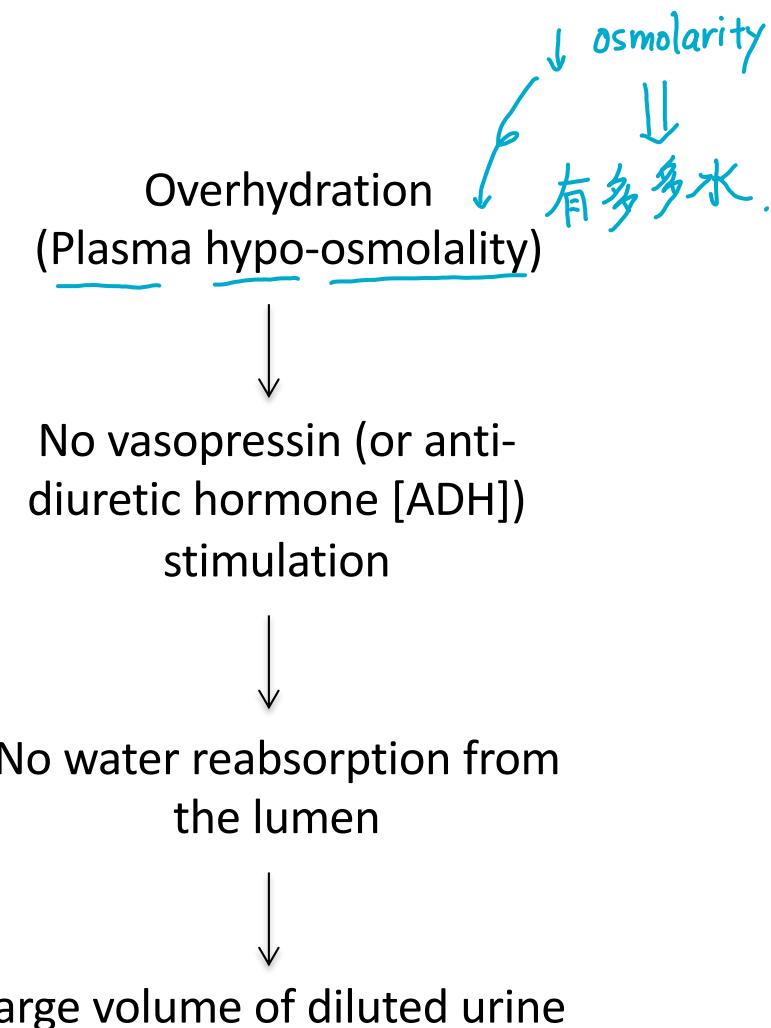
- Collecting duct
  - Has cortical and medullary portions
  - Consisted of 2 different cell types:
    1. Principal cells – responsible for water reabsorption
    2. Intercalated cells – responsible for acid-base balance
  - Cells are cuboidal shape
  - Principal cells has unique capacity to adapt to changes in hormonal stimuli, mainly vasopressin (also known as anti-diuretic hormone [ADH]), which stimulates water reabsorption from the filtrate)



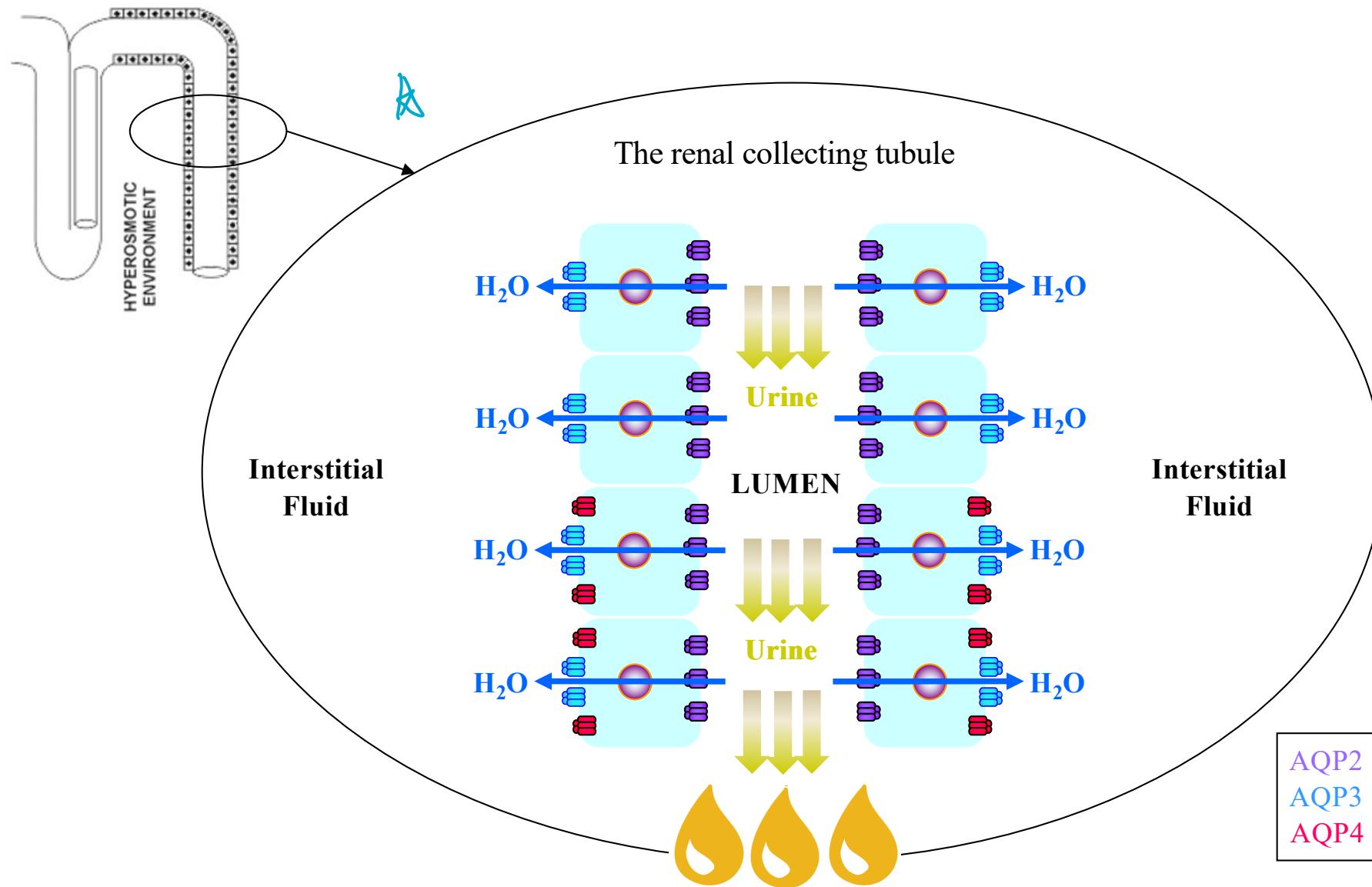
*without vasopressin,  
there is no H<sub>2</sub>O  
channel.*



- Production of a dilute urine in the collecting duct is accomplished by simply allowing filtrate from the Loop of Henle to pass on to the renal pelvis



- Formation of a concentrated urine in the collecting ducts occurs in response to the insertion of water channel, aquaporin 2 (AQP2), onto the apical membrane of collecting duct cells, hence making them permeable to water → small amount of concentrated urine 🍸



Dehydration  
(Plasma hyperosmolality)



Vasopressin release from  
the posterior pituitary



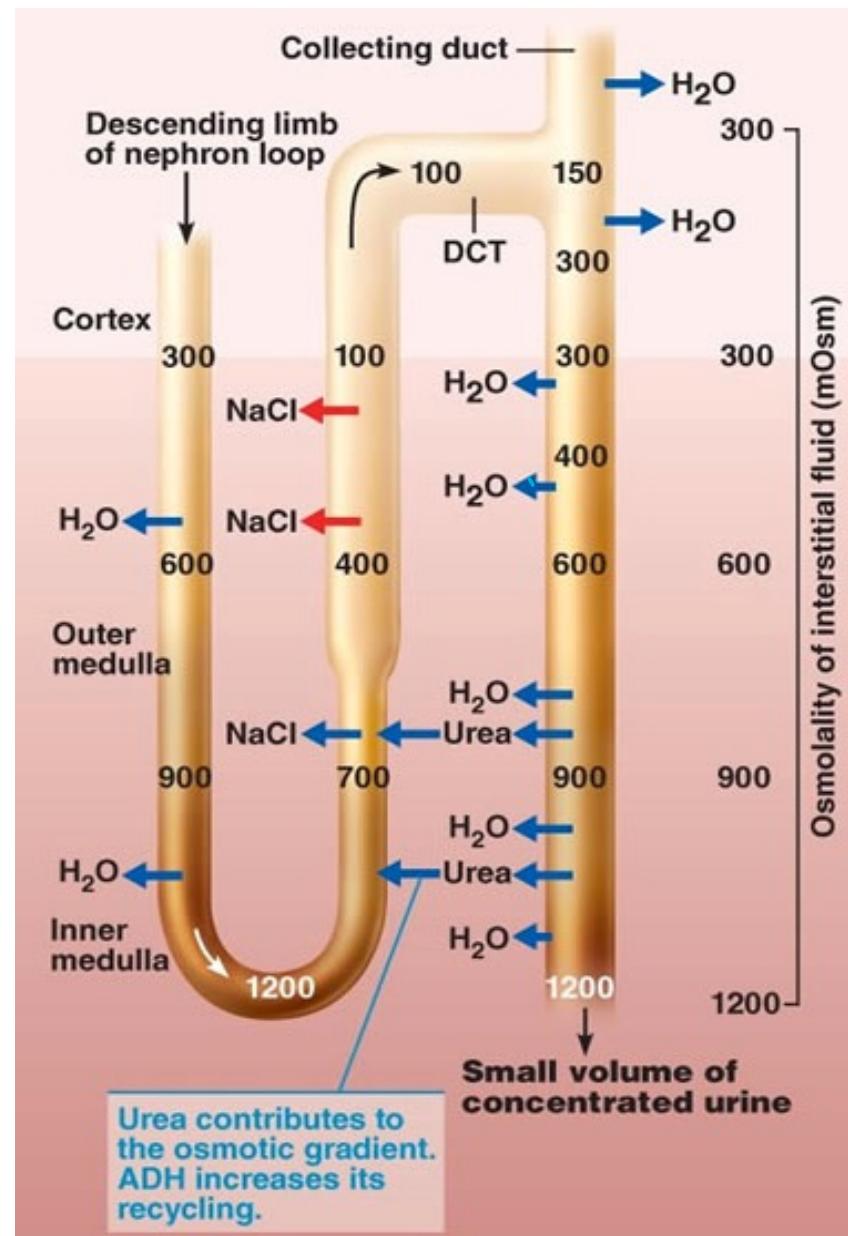
AQP2 insertion onto the  
apical membrane of  
principal cells



Water reabsorption from the  
lumen due to the hyperosmotic  
environment created by the  
loop of Henle



Small volume of  
concentrated urine

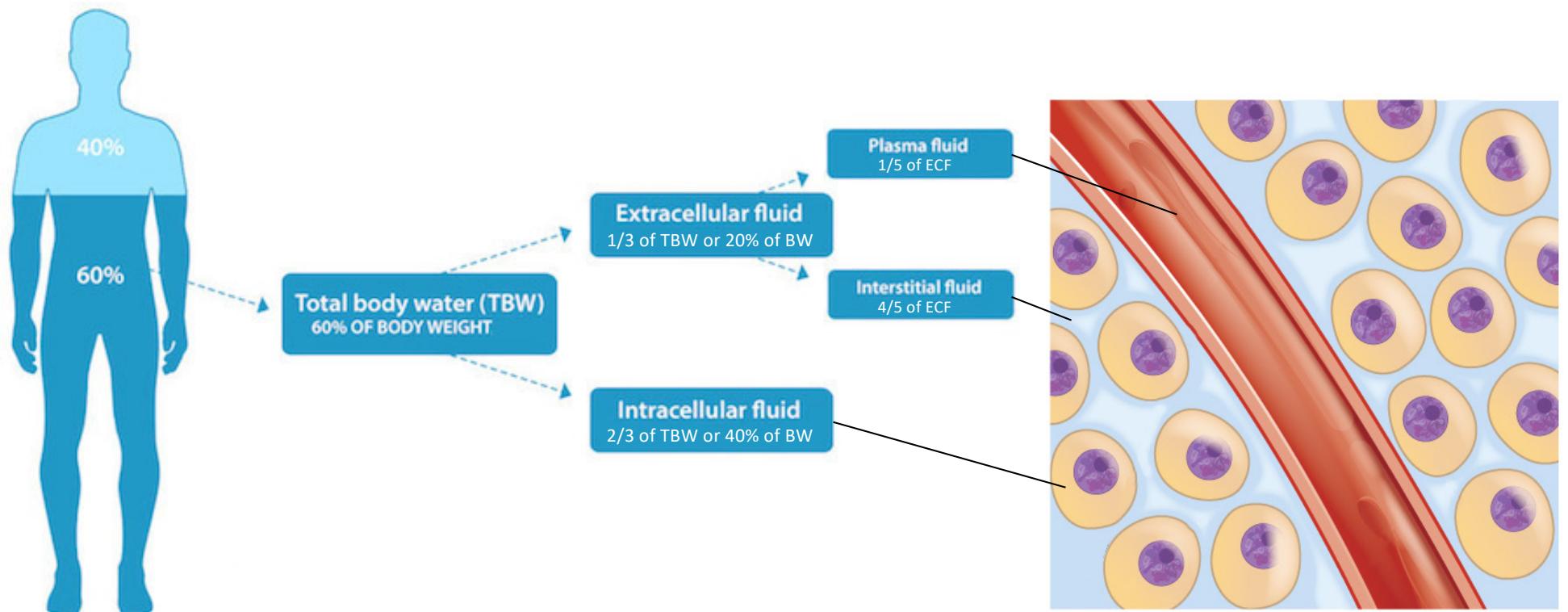


# **Body Fluid Homeostasis & Related Disorders**

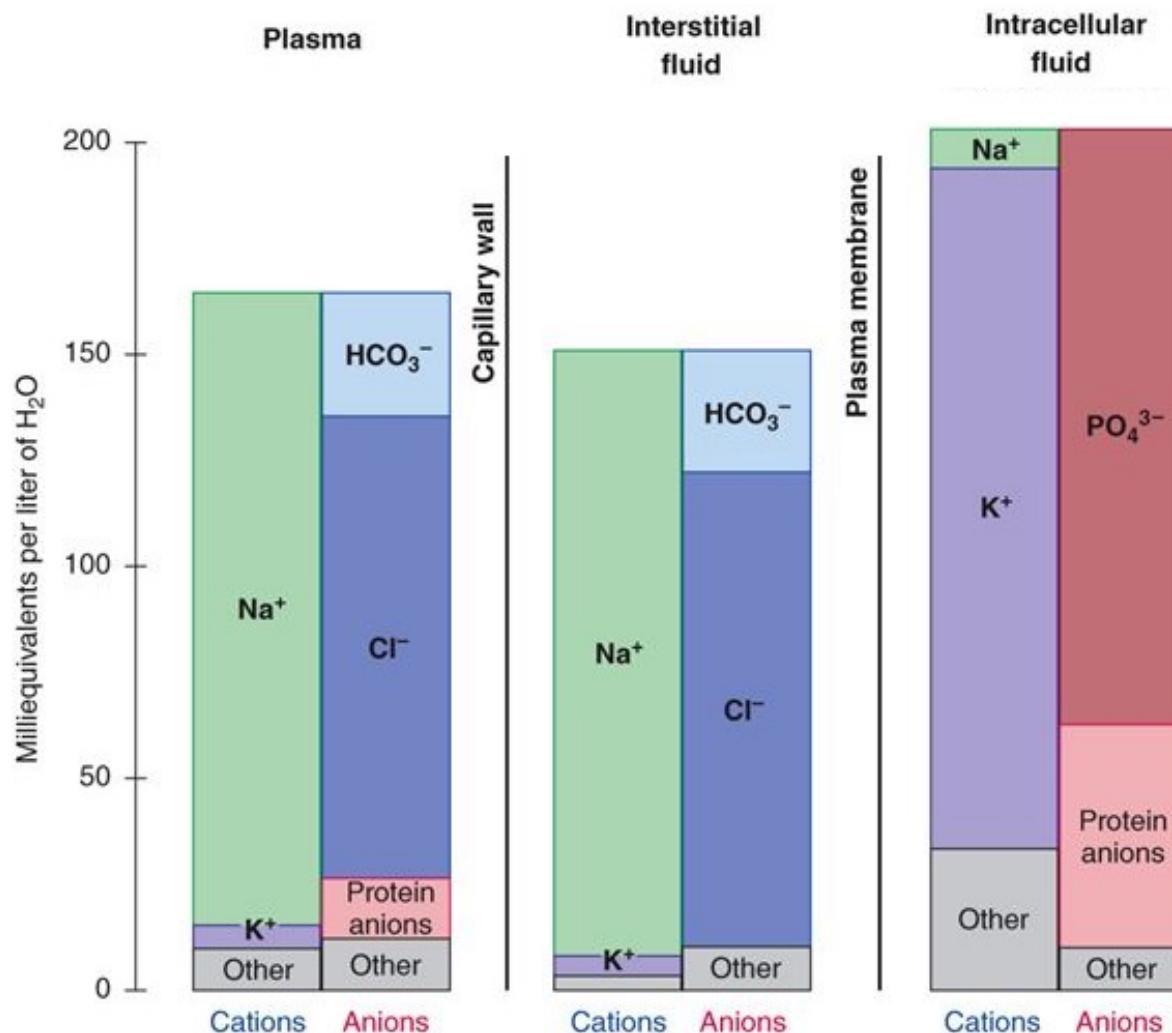
# Body Fluids

- Approximately 60% of body weight of an adult constitutes total body fluid
- A reduction in body fluids can have major effects on the body:
  - 3% reduction → thirst
  - 8% reduction → illness
  - 10% reduction → death

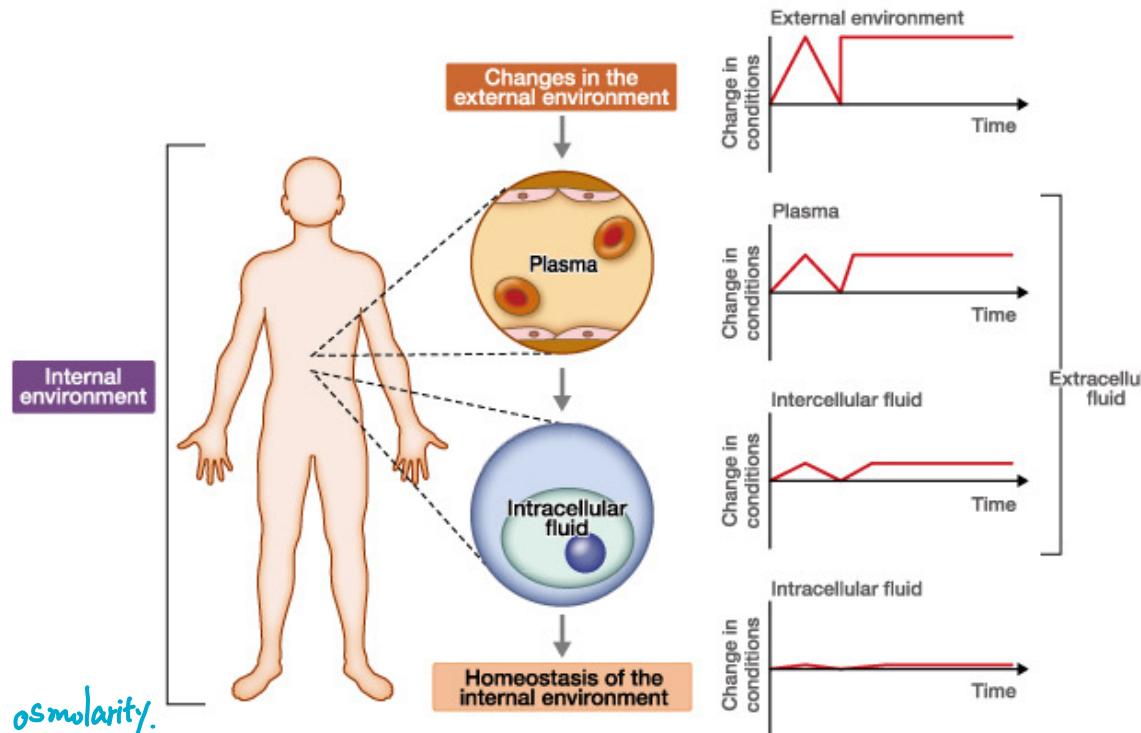
It is very essential to maintain a homeostasis of the volume and composition of bodily fluids



# Ionic Composition of the Body Fluid Compartments

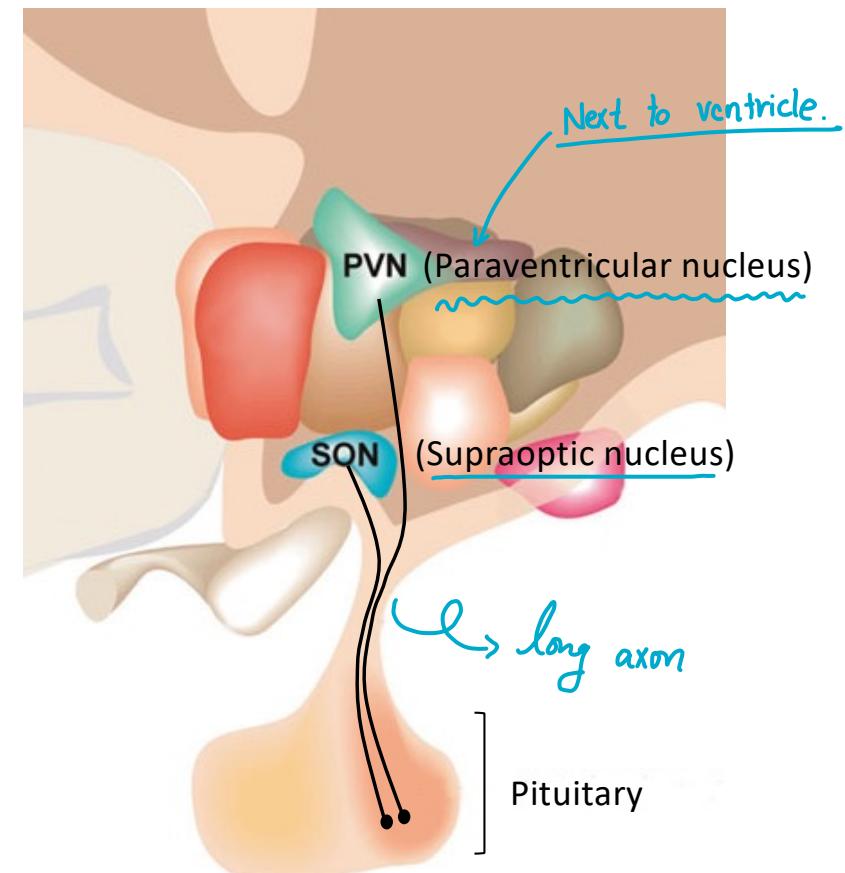
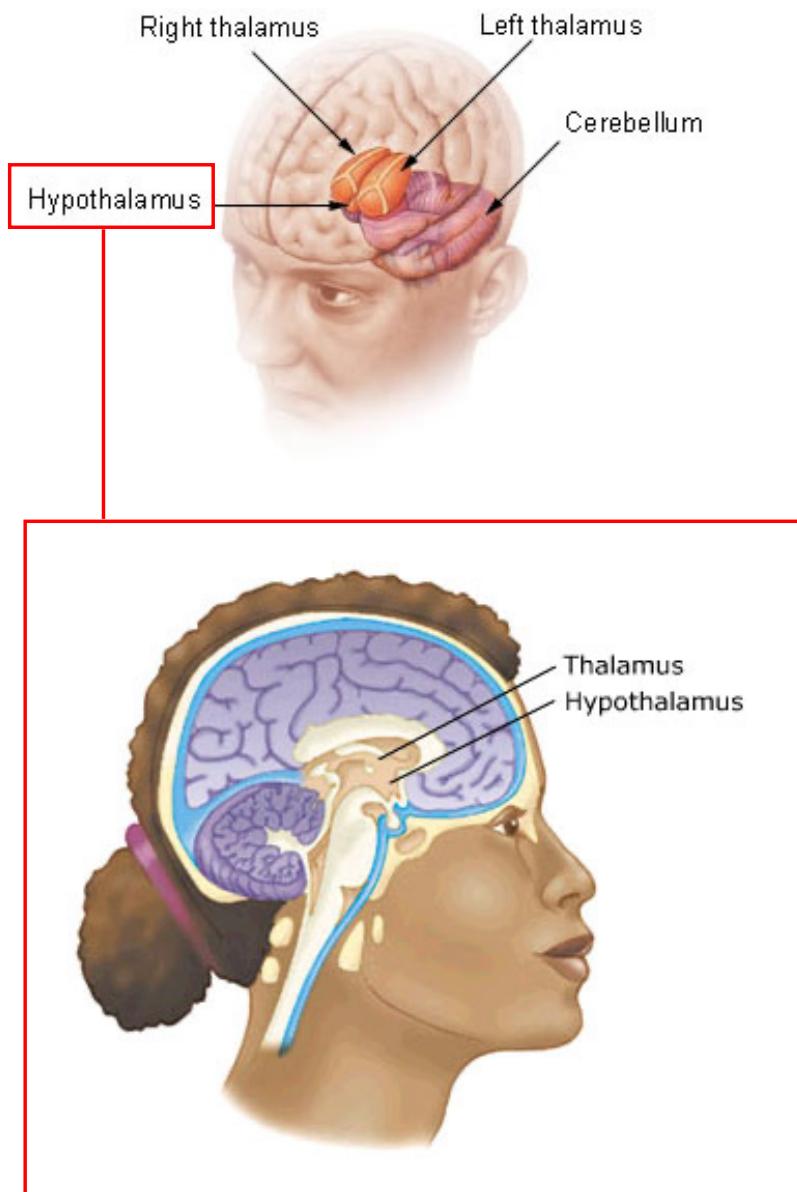


- When there is a change in the body fluid, this fluctuation is first buffered by plasma, and sequentially dampedened by the interstitial fluid, and then the intracellular fluid. Thus, the ultimate target of body fluid homeostasis is the maintenance of a stable intracellular environment.



- Responses toward a change in the body fluid:
    - detect the osmolarity.
    - detect RAA System.
    - Release Vp.
  - Brainstem, lamina terminalis, and the hypothalamic-pituitary axis
  - Vasopressin (Vp; also known as antidiuretic hormone/ADH)
  - Renin-angiotensin-aldosterone system
  - Circumventricular organs
  - Renin-angiotensin system
  - detect 至 osmolarity.
  - at ventricle 1/3 neurons.
- } Physiological response
- } Behavioral response

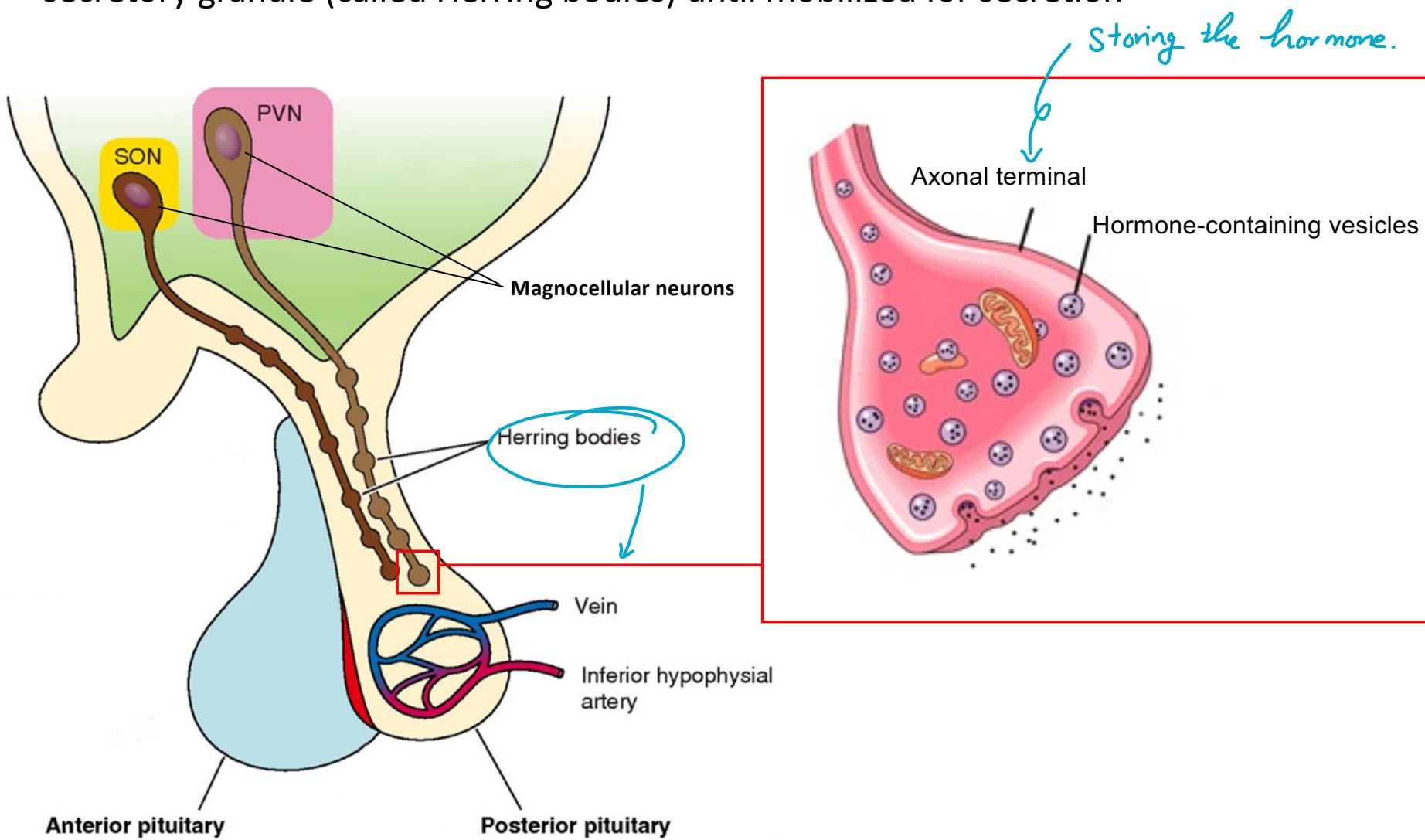
# The Hypothalamo-Pituitary Axis



- Vasopressin (Vp), synthesized in the magnocellular neurons of PVN and SON, is transported through the long axon to the axon terminals in the posterior pituitary gland

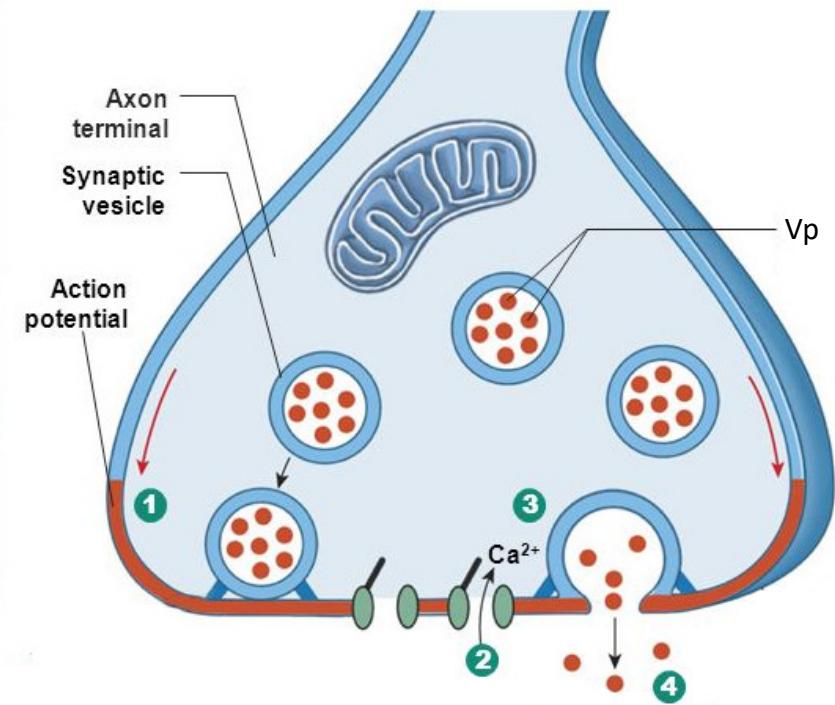
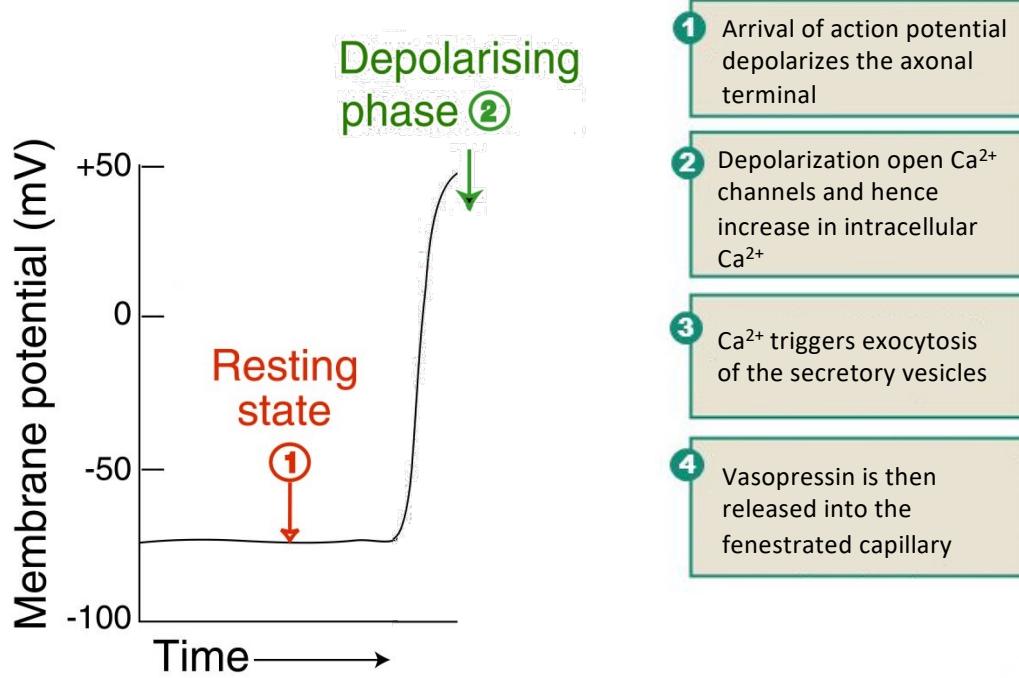
# Storage of Vp in the posterior pituitary

- Within the axon and axon terminals of magnocellular neurons, Vp is stored in the secretory granule (called Herring bodies) until mobilized for secretion



# The stimuli-induced Vp secretion into the circulation

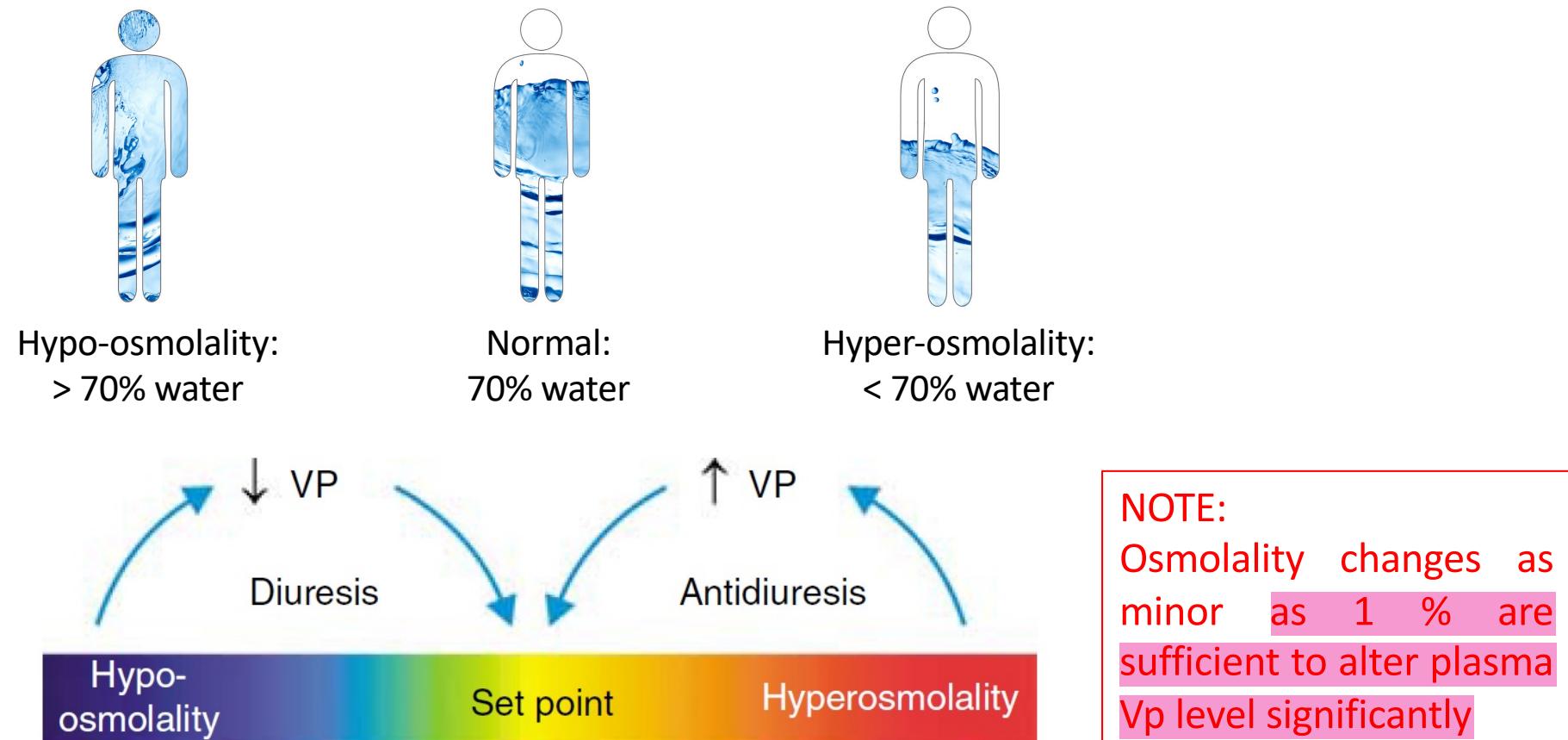
- Vasopressin is released from the posterior pituitary in response to stimuli that are primarily detected at the cell body in the SON and PVN of the hypothalamus
- With the right stimulus, the magnocellular neurons will depolarize and propagate an action potential down their axon. At the axonal termini, arrival of action potential increases intracellular  $\text{Ca}^{2+}$ , leading to exocytosis of vasopressin-containing vesicles



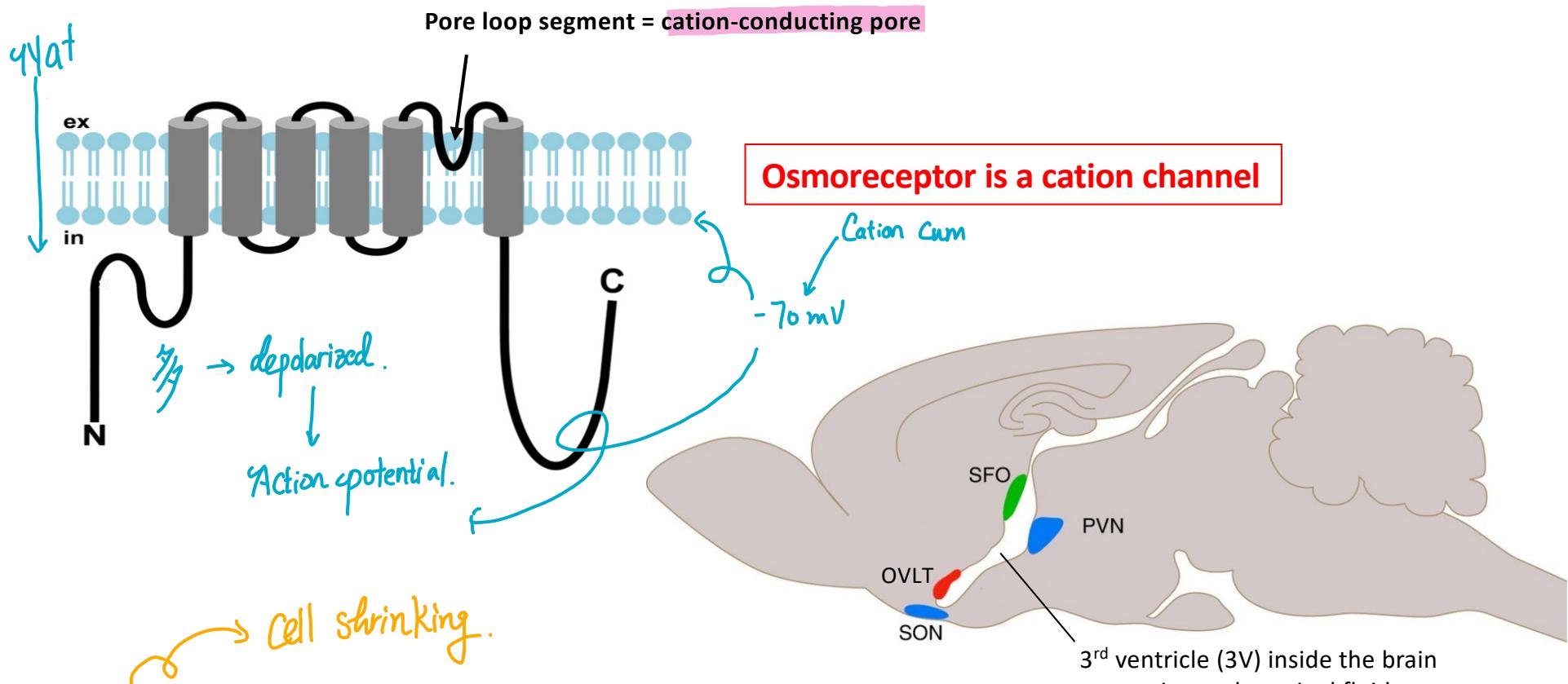
# Factors that affect Vp release from the posterior pituitary:

## 1) Osmolality of the body fluid

- Osmolality (osmotic factor; osmoreceptor-mediated) – a measure of the total amount of solutes in our body. It is controlled purely by modulating the amount of free water in our body, hence diluting or concentrating the already-present solutes



- The osmoreceptor is responsible for sensing small changes in plasma osmolality. It is a specialized mechanosensitive receptor, known as Transient Receptor Potential Vanilloid (TRPV), that converts changes in plasma osmolality into electrical signals.



- Osmoreceptor is located in several brain areas:

*2 Brain Region.*

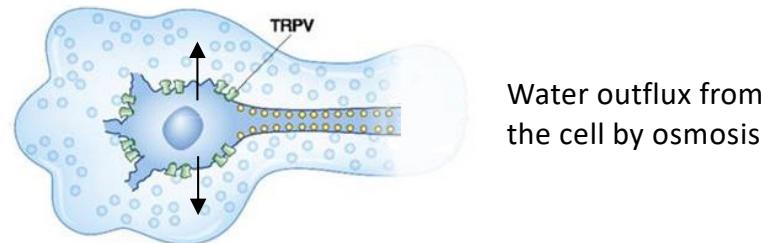
{ 1) The Organum Vasculosum of the Lamina Terminalis (OVLT)  
2) The Subfornical Organ (SFO)  
3) The Hypothalamic PVN & SON }

{ Neurons. } Circumventricular organs (CVOs) that lack blood-brain barrier, hence exposed to the ionic and hormonal environment of the systemic circulation

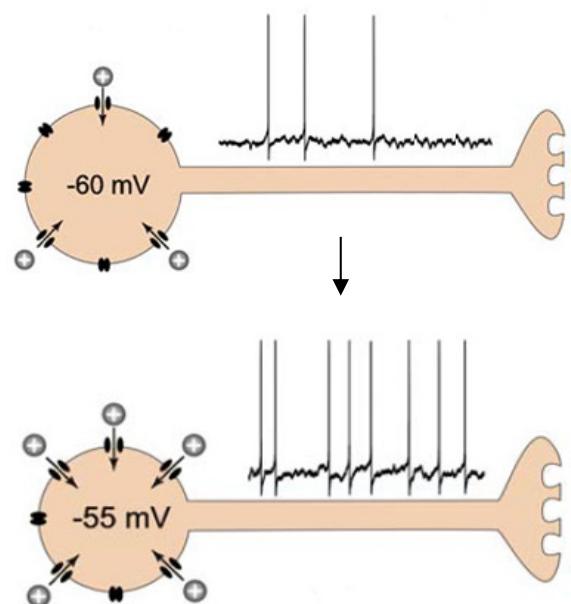
↳ Release of Hormone / V<sub>p</sub>.

## Hyper-osmolality

1. Dehydration/ plasma hyperosmotically induce cell shrinkage

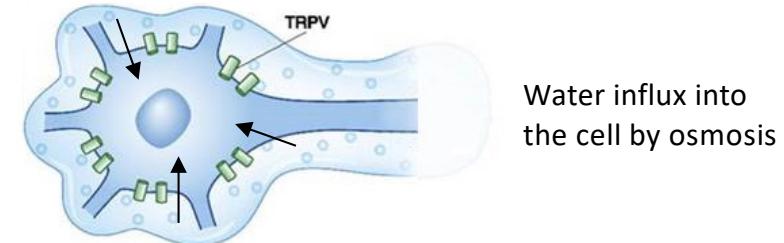


2. Cell shrinkage causes a conformational change of osmoreceptor (mechano-sensitive cation channel), leading to opening of the pore loop and hence +ve ions influx → depolarization and firing of action potential along the axon to the axonal terminal

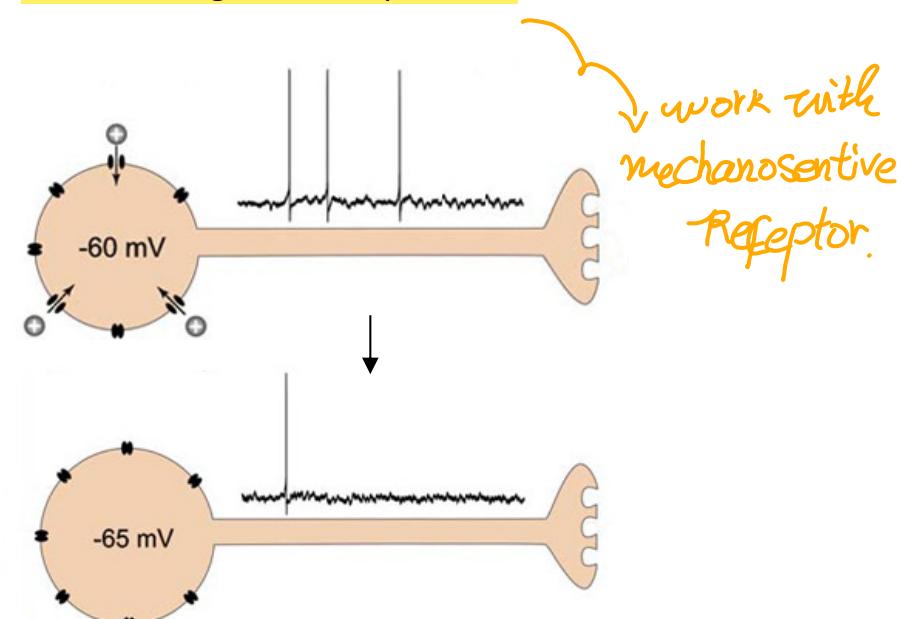


## Hypo-osmolality

1. Systemic hypotonicity causes entry of water into the cells



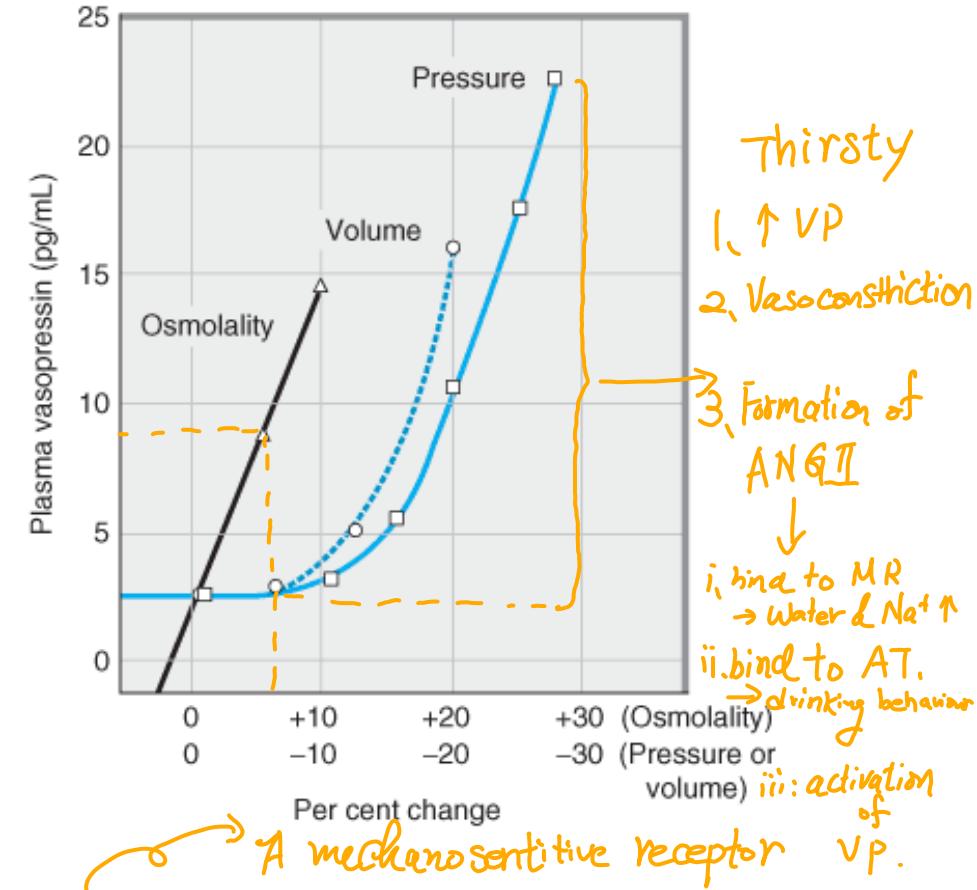
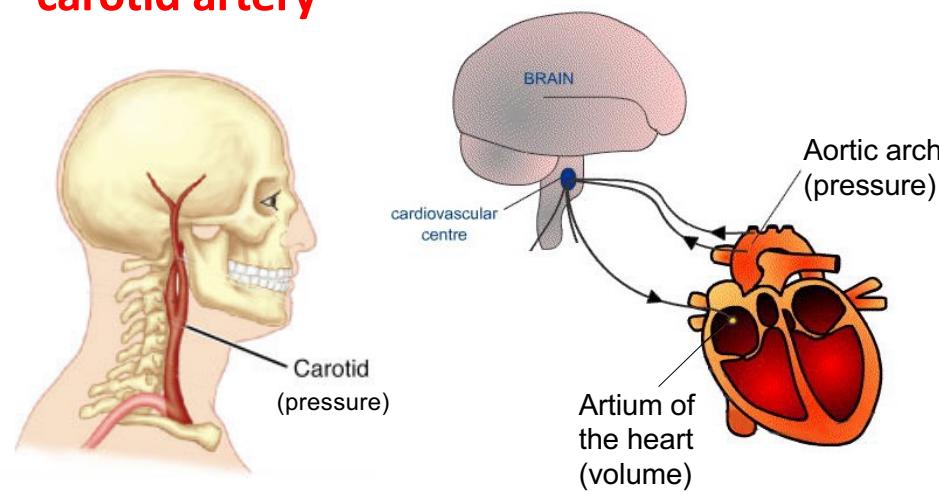
2. Stretching of cell membrane suppresses osmoreceptor, reducing whole-cell cation conductance → membrane hyper-polarization and inhibits firing of action potential



# Factors that affect Vp release from the posterior pituitary:

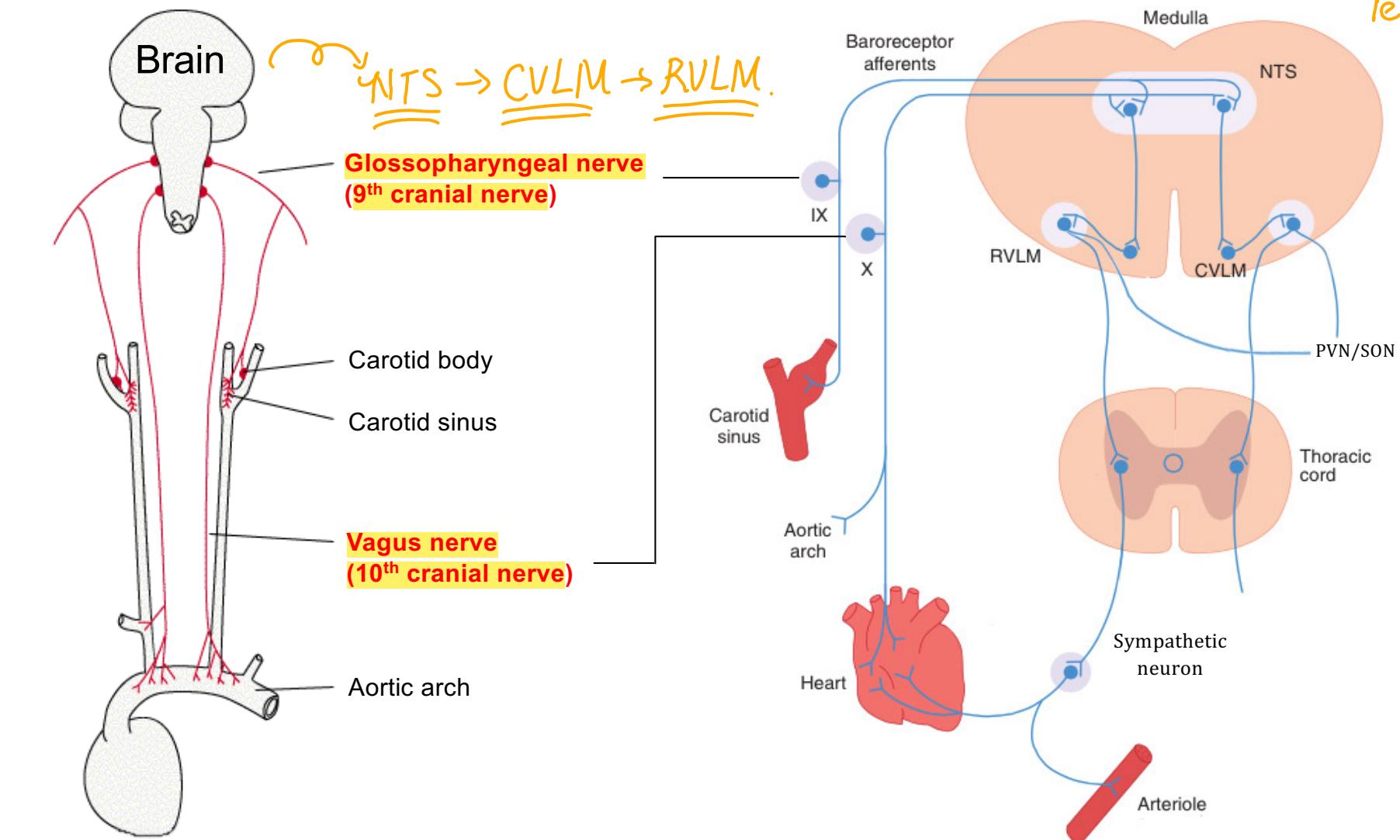
## 2) Volume and pressure of the vascular system

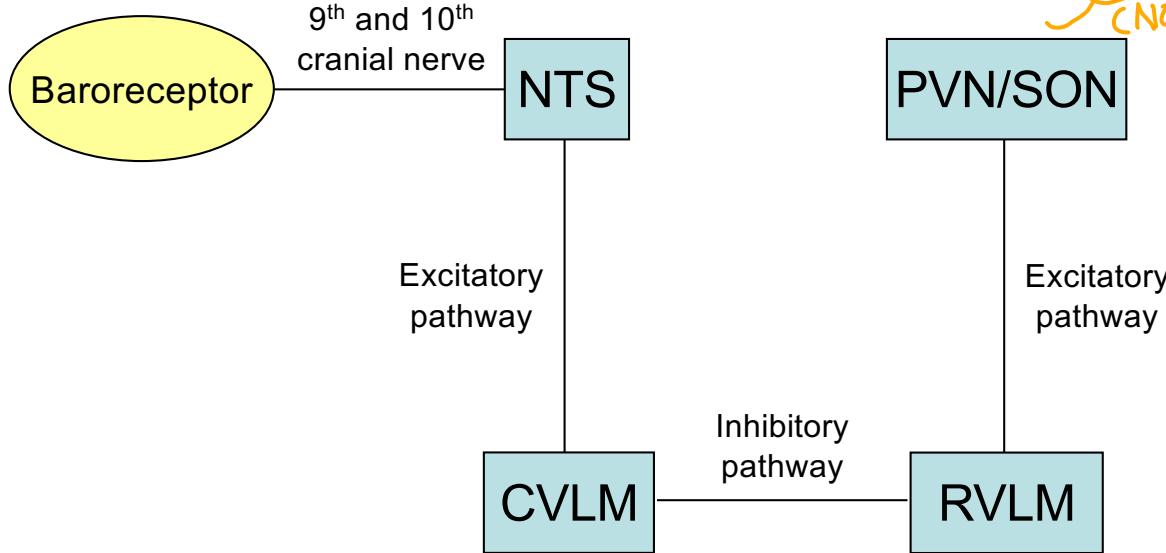
- The relationship between Vp secretion and hemodynamic factors follows an exponential pattern  
i.e. the response is imperceptibly small until blood volume or pressure declines more than 8%
- Hemodynamic influences on Vp secretion are originating from baroreceptors in the **atrium of the heart, aortic arch, and the carotid artery**



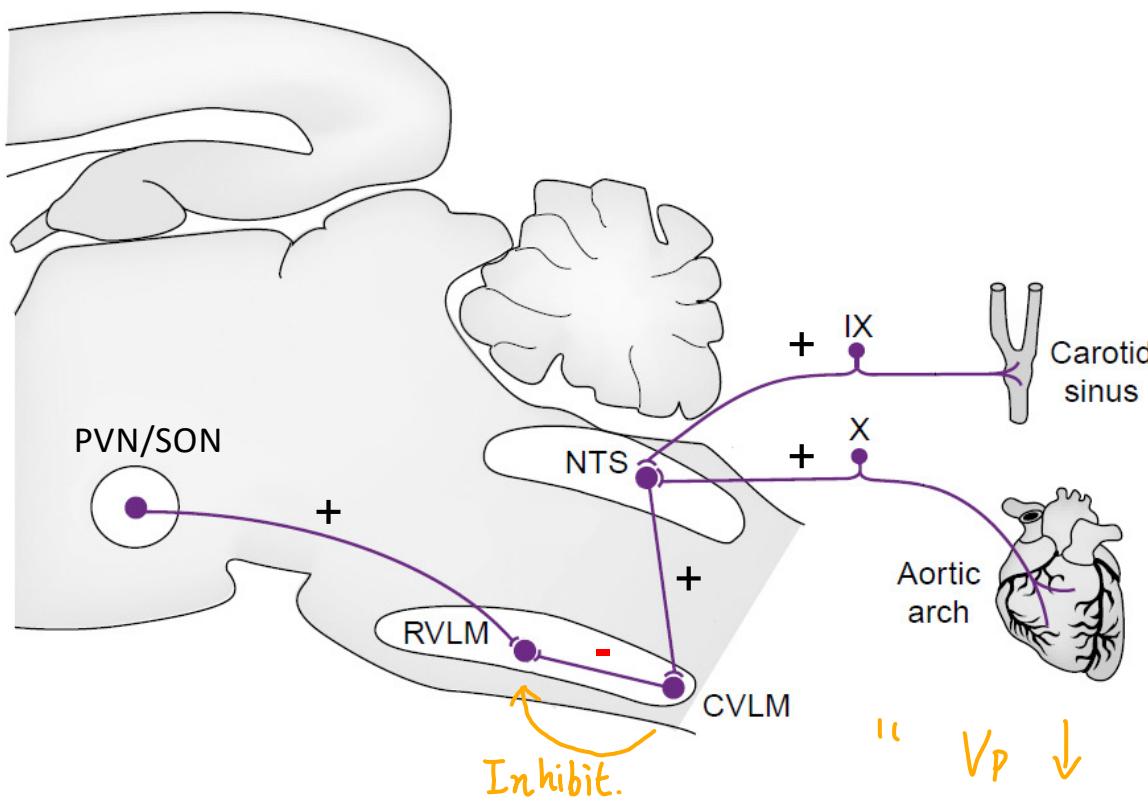
- Baroreceptors are a type of mechanoreceptor sensory neuron that is excited by stretch of the blood vessel
- Cell Stretching! (detection by mechanosensitive r.)

- The signals from **baroreceptor** ascend via axons of the glossopharyngeal (IX cranial nerve) and vagus nerves (X cranial nerve) to the **Nucleus of the Solitary Tract (NTS)** in the medulla of brainstem, which then relay via **Caudal Ventrolateral Medulla (CVLM)** and **Rostral Ventrolateral Medulla (RVLM)**
- RVLM can directly regulate blood pressure via sympathetic neurons or indirectly via **PVN/SON**





- Depressed Up  
- Regulate blood pressure.
- ① The primary baroreceptor afferents terminate in depressor sites of the NTS
- ② The NTS neurons send excitatory projections to the CVLM
- ③ CVLM neurons excitation lead to a reduction in vasomotor tone, because CVLM send inhibitory signal to the RVLM to inhibit its excitatory activity
- ④ The excitatory neurons of the RVLM project directly to the hypothalamic PVN/SON



NOTE:

Activation of baroreceptors lead to inhibition of Vp secretion from the hypothalamic PVN/SON "ECF"  $\xrightarrow{H_2O}$  ICF "

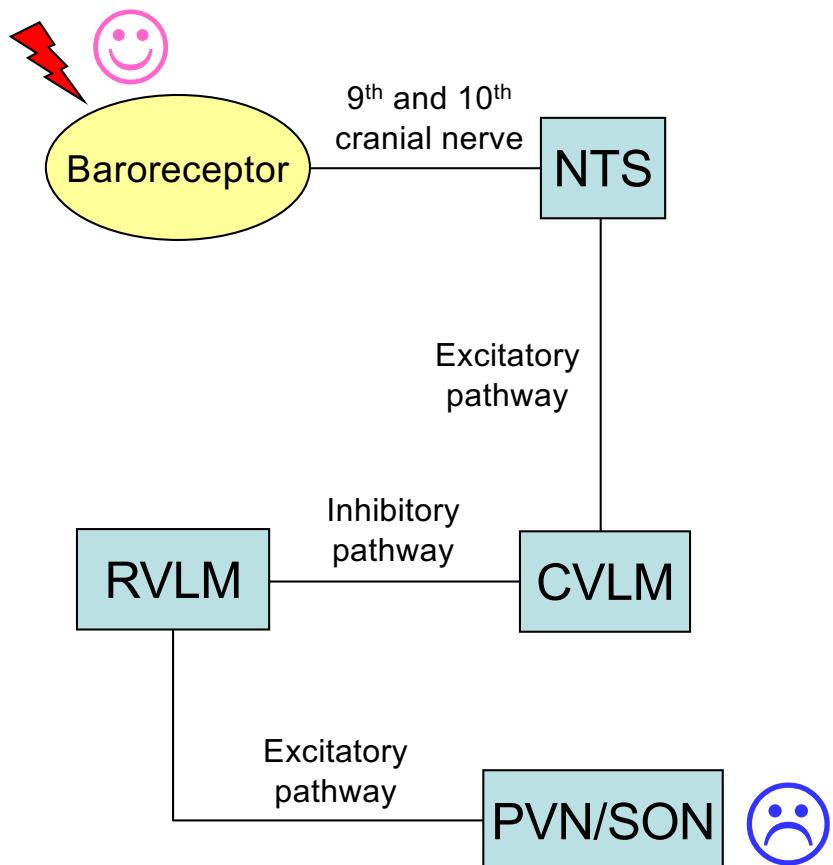
Cell is stretching  
 $\Downarrow$   
 $H_2O \rightarrow ICF$   
"Ke " Wanna  $\downarrow H_2O$  in ECF"

Release Vp.

## Normal condition/Hypertension

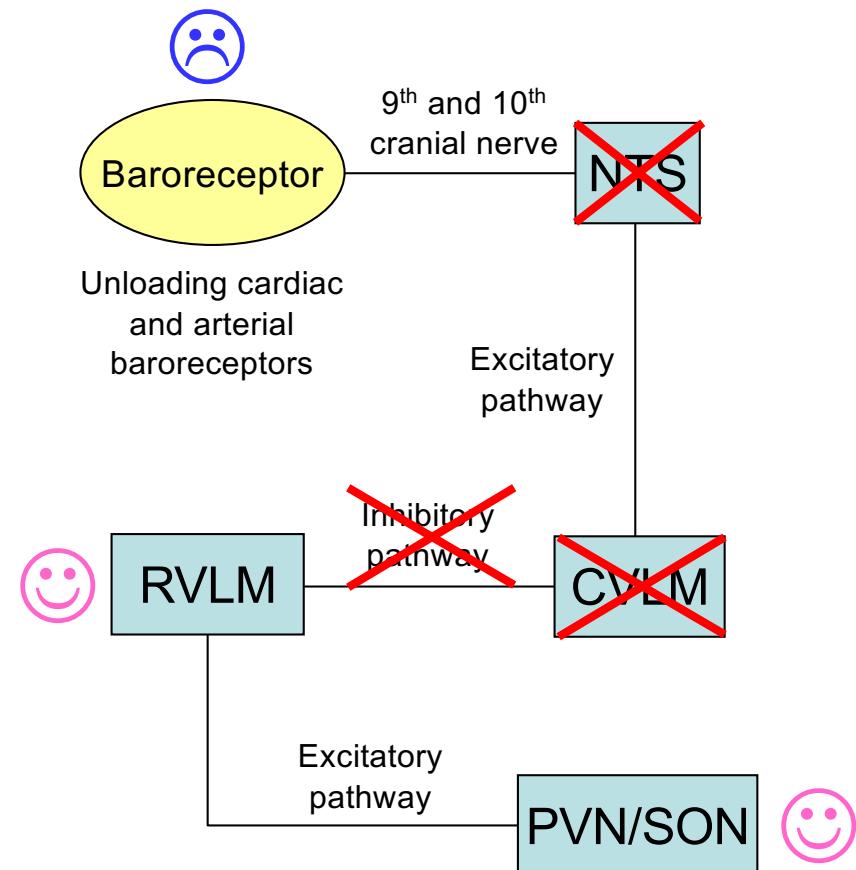
- On-going baroreceptor activity tonically inhibits the excitatory signals from RVLM neurons to the hypothalamic PVN and SON → no Vp secretion from the posterior pituitary

Inhibit Vp.

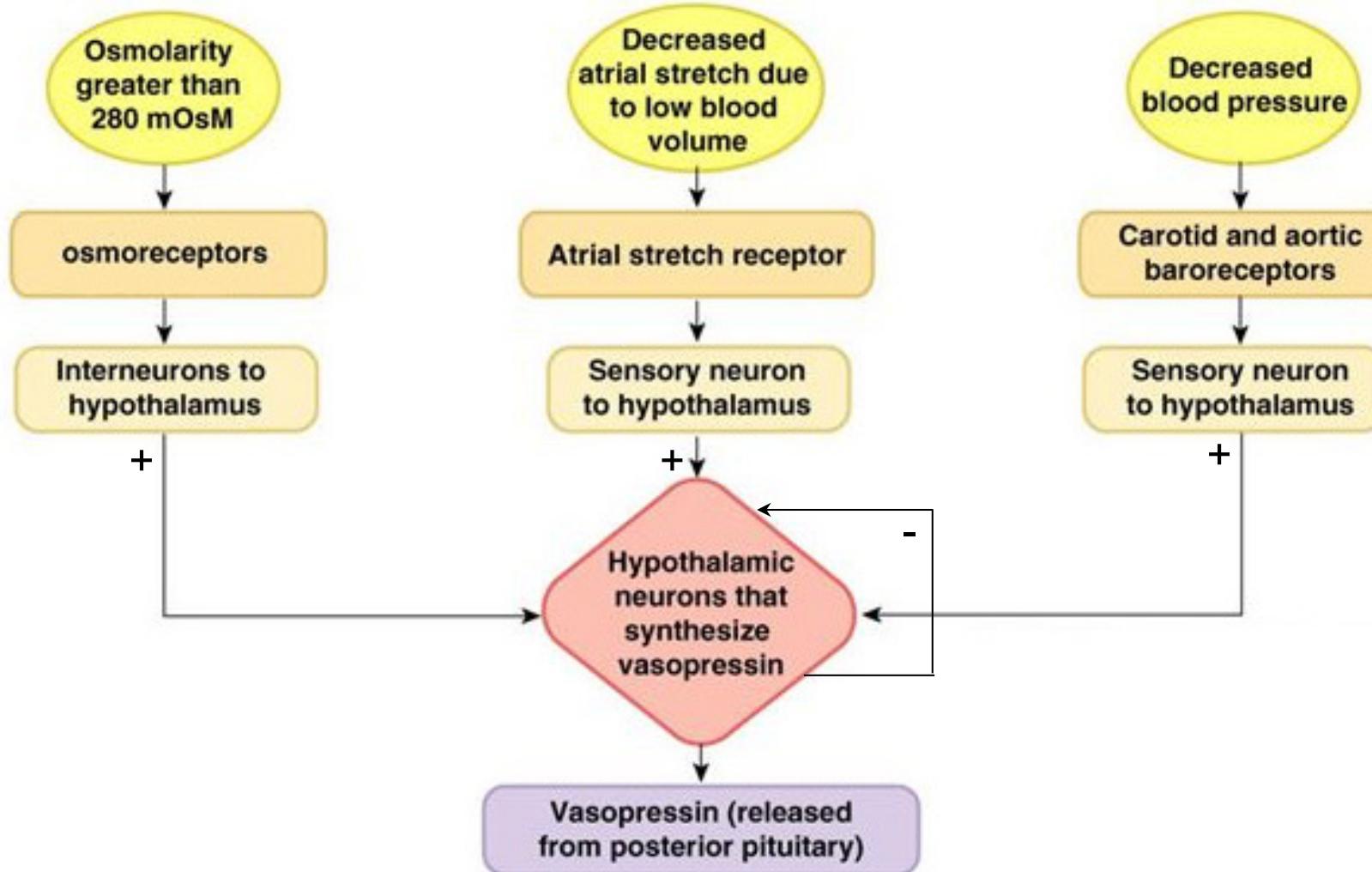


## Hypotension

- Unloading of baroreceptor activity results in decrease firing of action potential to NTS, hence CVLM
- Removal of the inhibitory signal from CVLM to RVLM causes a tonic excitatory input into PVN/SON, hence VP secretion



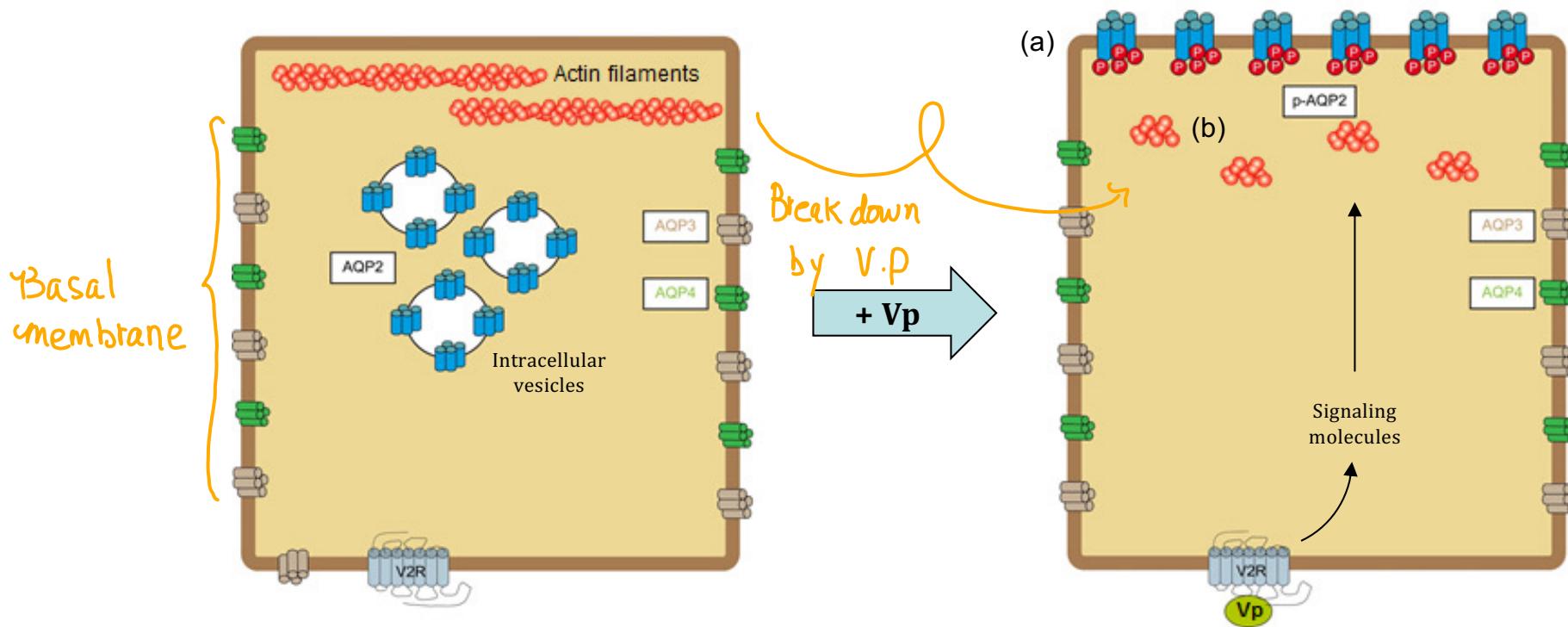
# Summary of the stimuli that trigger Vp release from the posterior pituitary

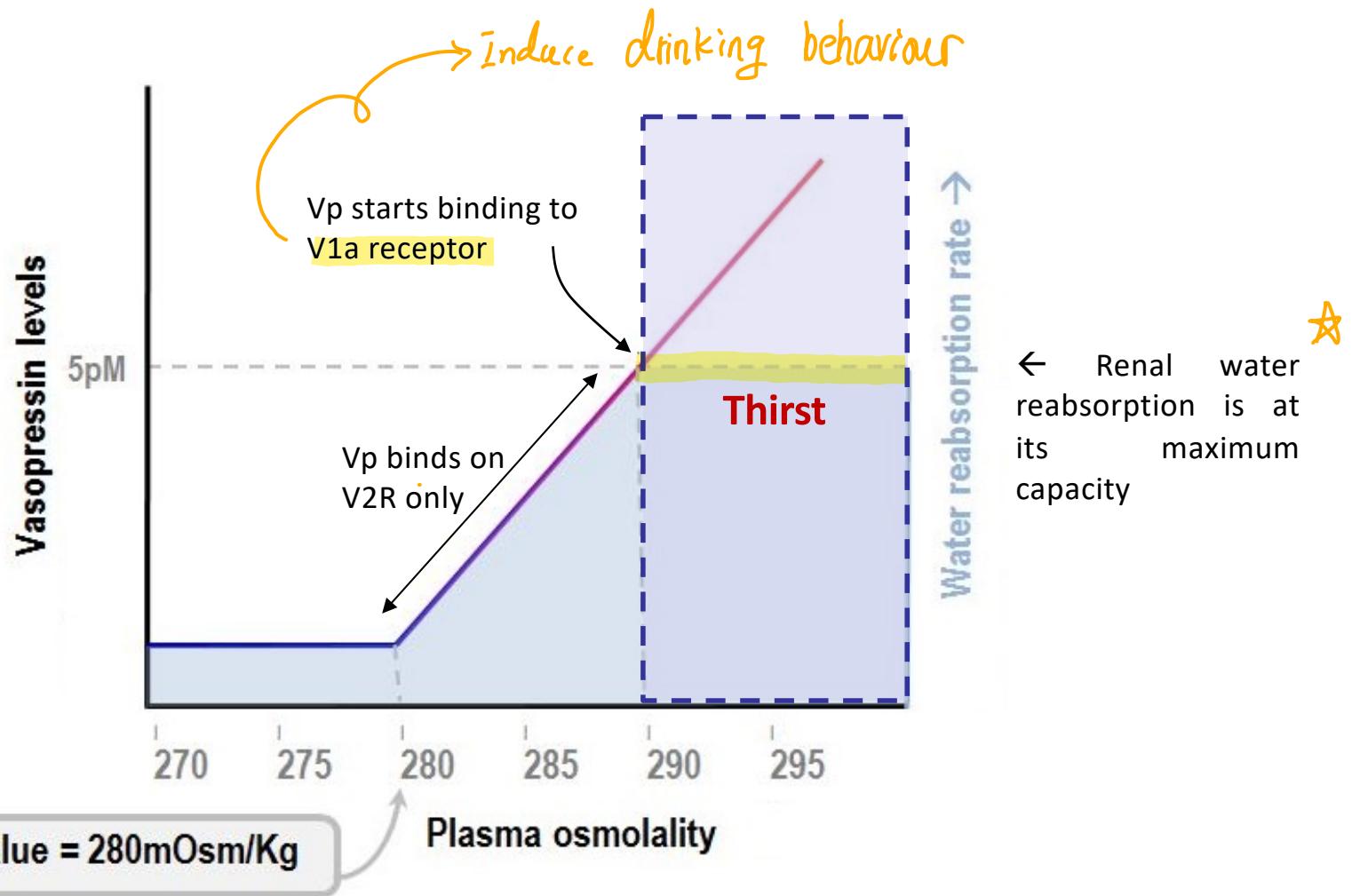


# Physiological Effects of Vasopressin

1. At low level of plasma vasopressin, it binds to its receptor V2R and...
    - a. Causes phosphorylation of the water channel, aquaporin-2 (AQP2), at Ser<sup>256</sup>, hence trafficking of AQP2-bearing intracellular vesicles to the apical membrane
    - b. Causes depolymerize the apical actin network, hence facilitating AQP2 sorting
- 

Net effect: Insertion of AQP2 onto the apical membrane of principal cells in the collecting ducts → Anti-diuretic effect





- Thirst is the response to osmolality over 290 mOsm/kg. It increases water intake once maximal renal vasopressin effect is achieved (at 5 pM), thereby restoring the tonicity of the body fluid, restoring the blood volume and pressure, and diluting the body fluid.

2. At high level of plasma vasopressin, it binds to V1a receptor (V1aR) and...

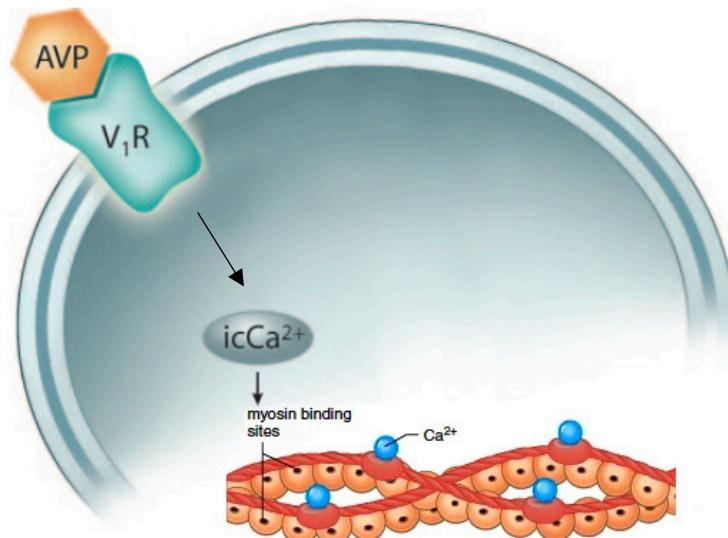
(Vp. type 1a receptor)

at blood vessel.

### A) Direct effect on vasoconstriction

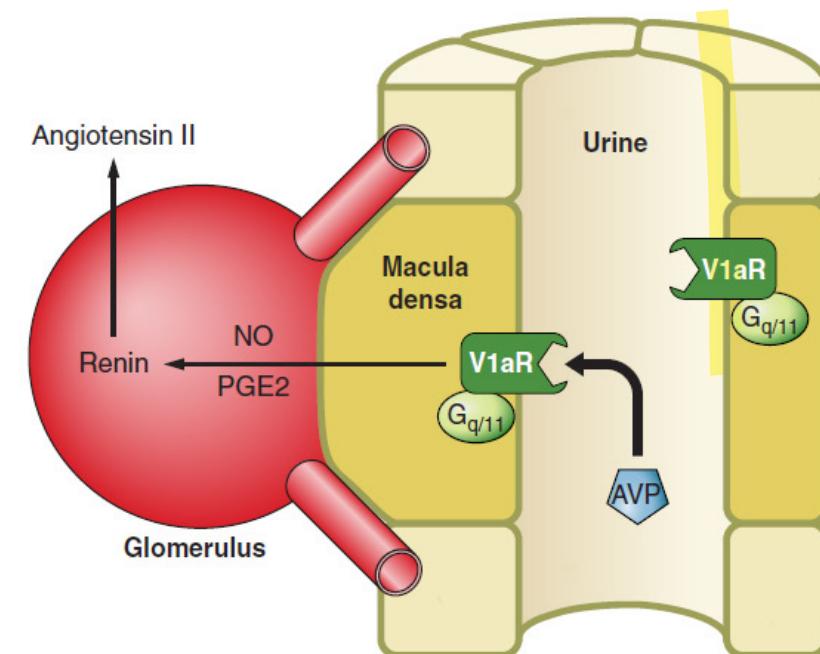
- V1aR is expressed on vascular smooth muscle cells of the systemic and coronary circulations
- Activation of V1aR leads to increase in intracellular  $\text{Ca}^{2+}$ , hence activating myosin light chain kinase → smooth muscle contraction and therefore vasoconstriction

→ Reduce filtrate rate.

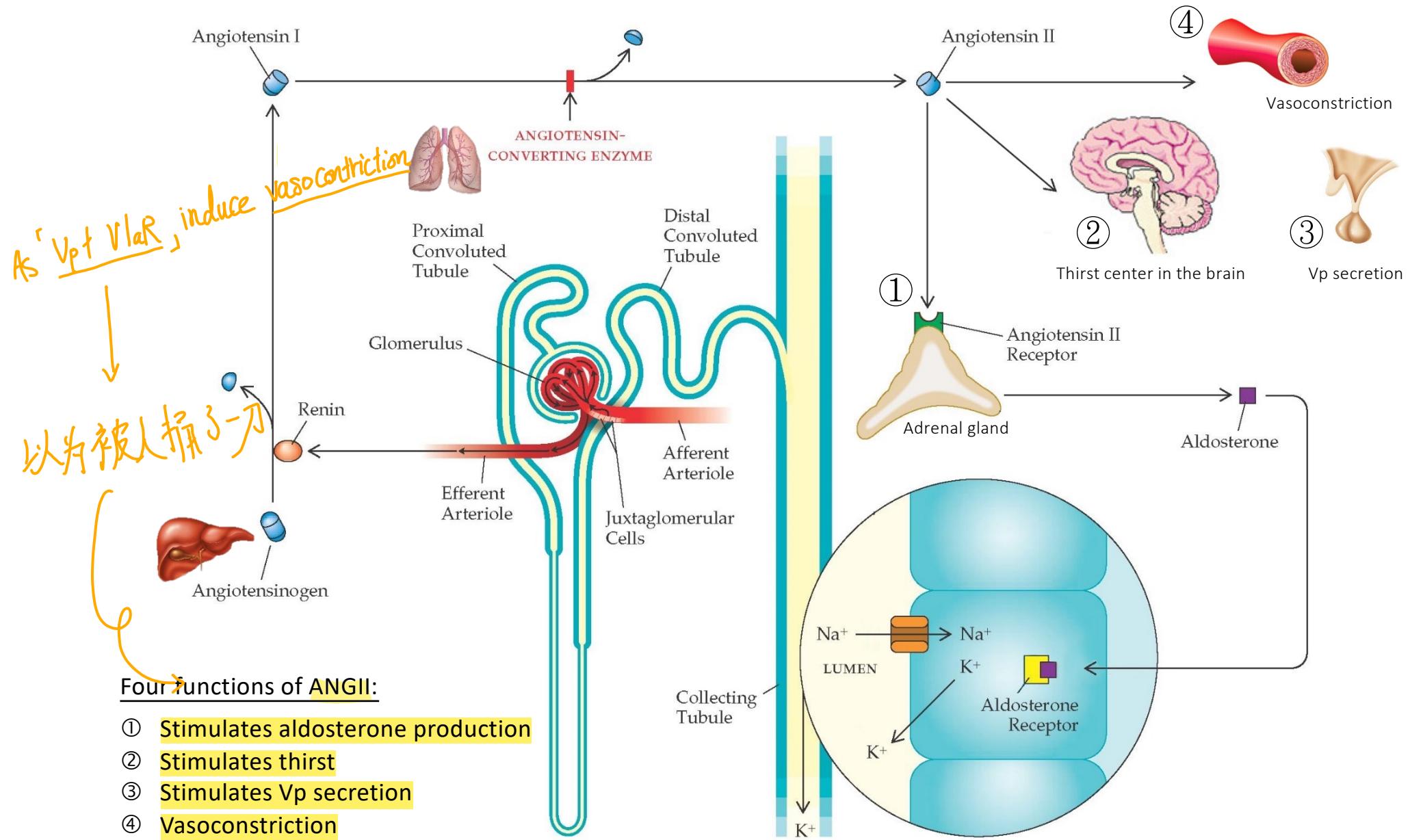


### B) Indirect effect via renin-angiotensin-system

- V1aR is expressed on Macula Densa cells
- Activation of V1aR leads to the production of nitric oxide (NO) and prostaglandin E2 (PGE2) by macula densa cells, which subsequently stimulate renin production by the adjacent juxtaglomerular cells

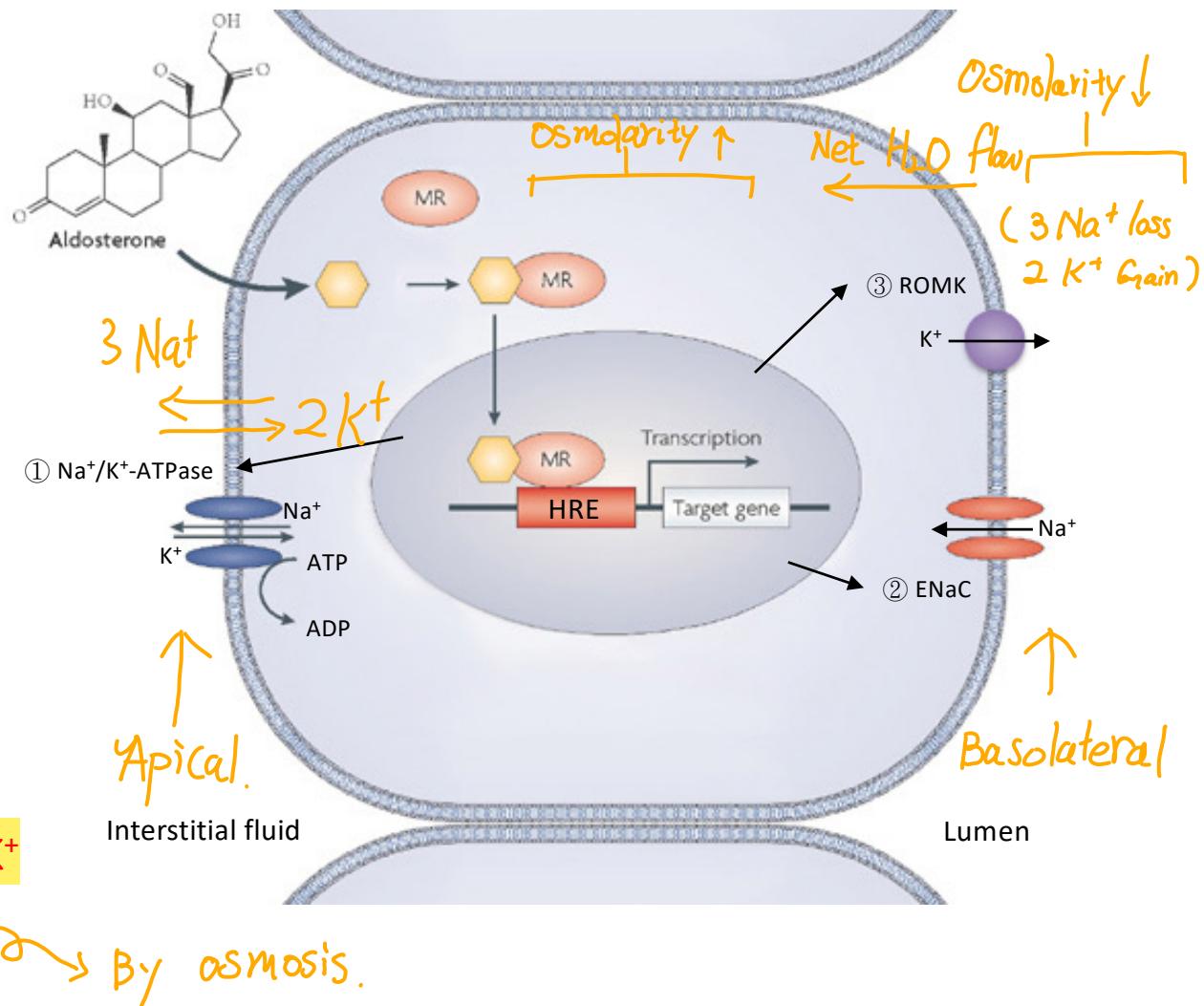


- Renin catalyzes the conversion of a plasma protein called angiotensinogen into angiotensin I, which is then further converted by angiotensin-converting enzyme (ACE) into angiotensin II (ANGII)



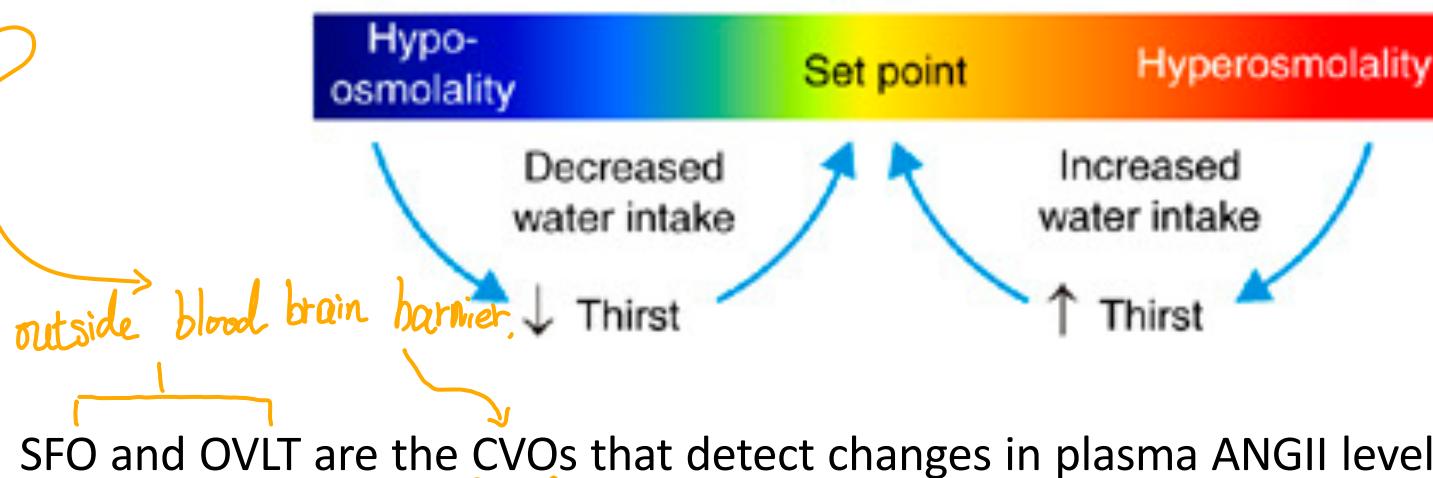
## 1) The effect of ANGII-induced aldosterone secretion from the adrenal gland:

- Angiotensin type 1 receptor (AT1) is expressed in the adrenal cortex → binding of ANGII to AT1 leads to increase production of aldosterone in the adrenal cortex
- Aldosterone, upon secreted into the bloodstream, will bind to its receptor, the mineralocorticoid receptor (MR), expressed in the distal nephron
- Activation of MR results target gene expression:
  - ① Induction of  $\text{Na}^+/\text{K}^+$ -ATPase expression on the basolateral membrane
  - ② Induction of  $\text{Na}^+$  channel (ENaC) expression on the apical membrane
  - ③ Induction of renal outer medullary  $\text{K}^+$  channel (ROMK) expression on the apical membrane

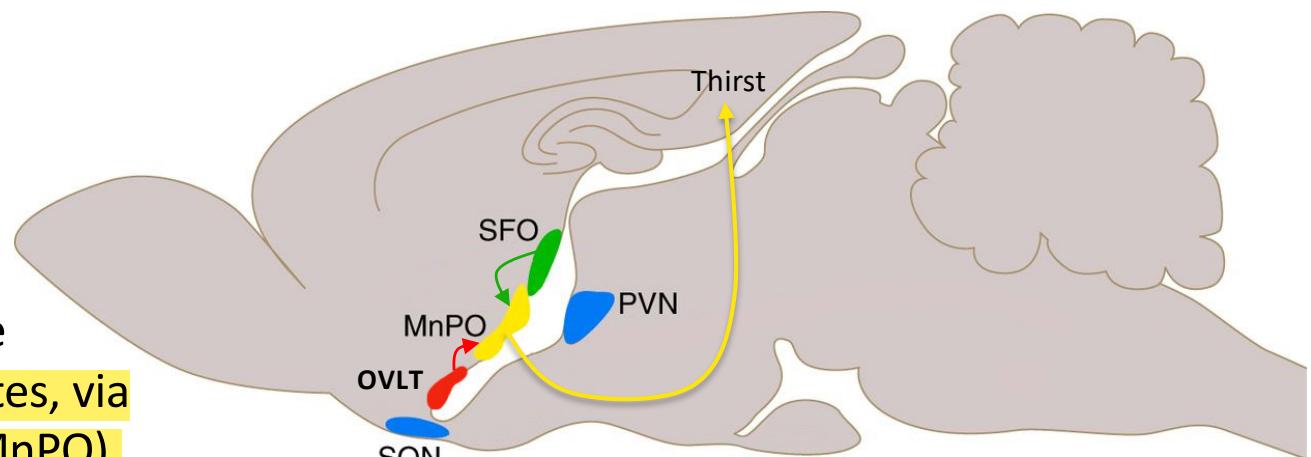


## 2) ANGII-induced drinking behavior/thirst:

- Thirst is a subjective perception that provides the urge to drink fluids. It is a component of the regulatory mechanisms that maintain body fluid homeostasis and ultimately is essential for survival.



- SFO and OVLT are the CVOs that detect changes in plasma ANGII level by expressing AT1 receptor.
- By responding to ANGII and integrating plasma osmolality information, these regions then relay the signals to various cortical sites, via median preoptic nucleus (MnPO), to drive thirst and fluid intake.



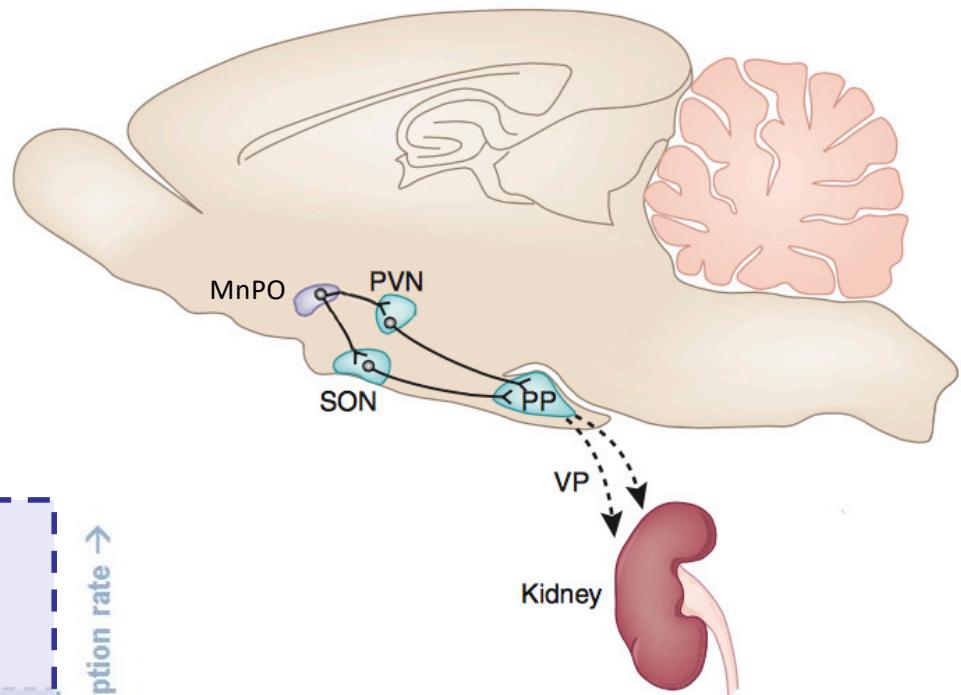
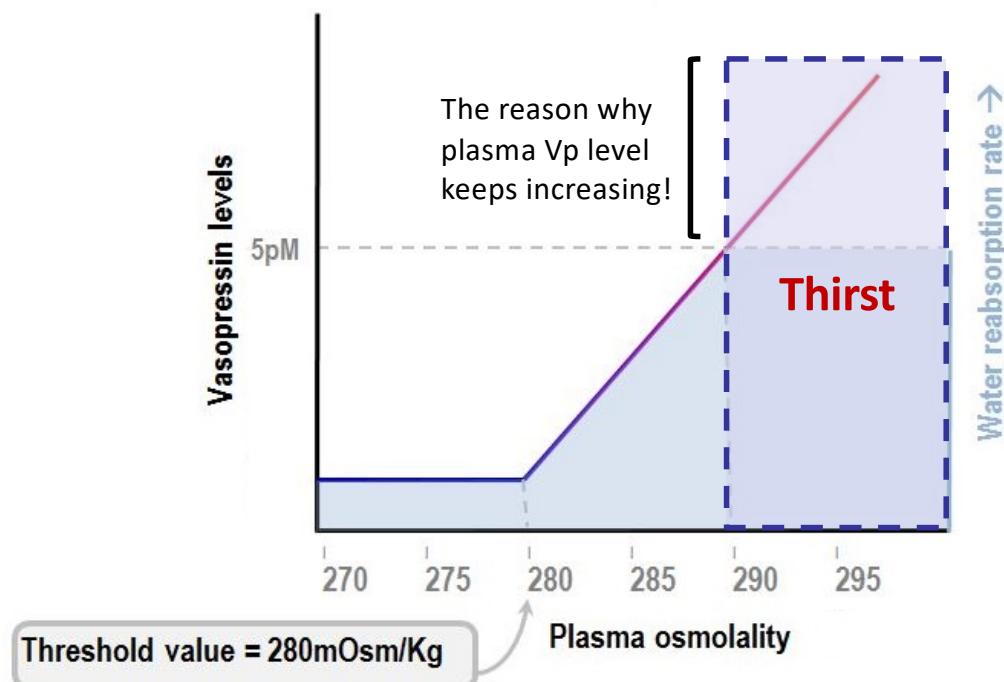
The lamina terminalis = SFO + MnPO + OVLT

### 3) ANGII-induced Vp secretion:

→ ANG-II induce

1. Drinking behaviour 2. Stimulate SFO & OVLT → More V. p.

- SFO and OVLT are the CVOs that detect changes in plasma ANGII level by expressing AT1 receptor
- Once the SFO and OVLT neurons are electrophysiologically activated, signals will be sent via MnPO to the magnocellular neurons of the hypothalamic PVN & SON



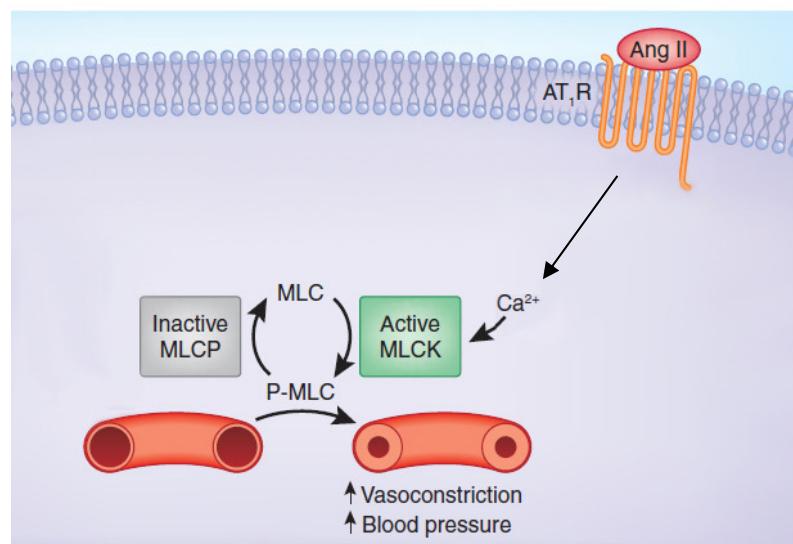
#### 4) ANGII-induced vasoconstriction:

- The effects of Ang II to increase blood pressure are mediated by AT1 receptors that are expressed in the blood vessels and cardiovascular control center in the brain.

##### Vascular smooth muscle

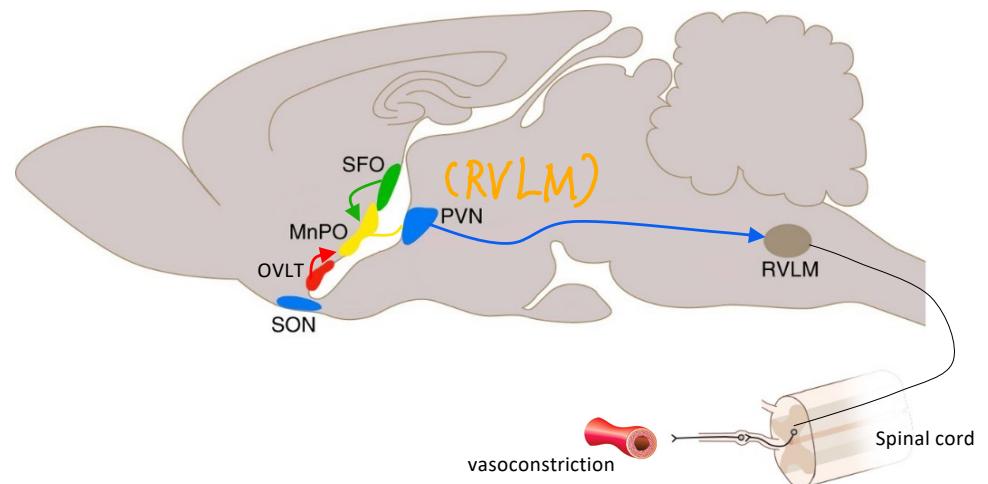
##### Further vasoconstriction

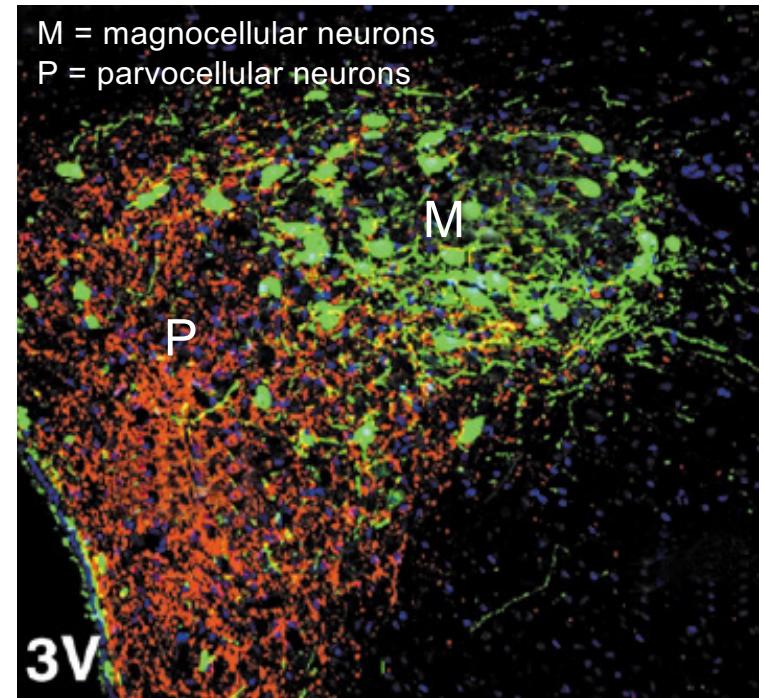
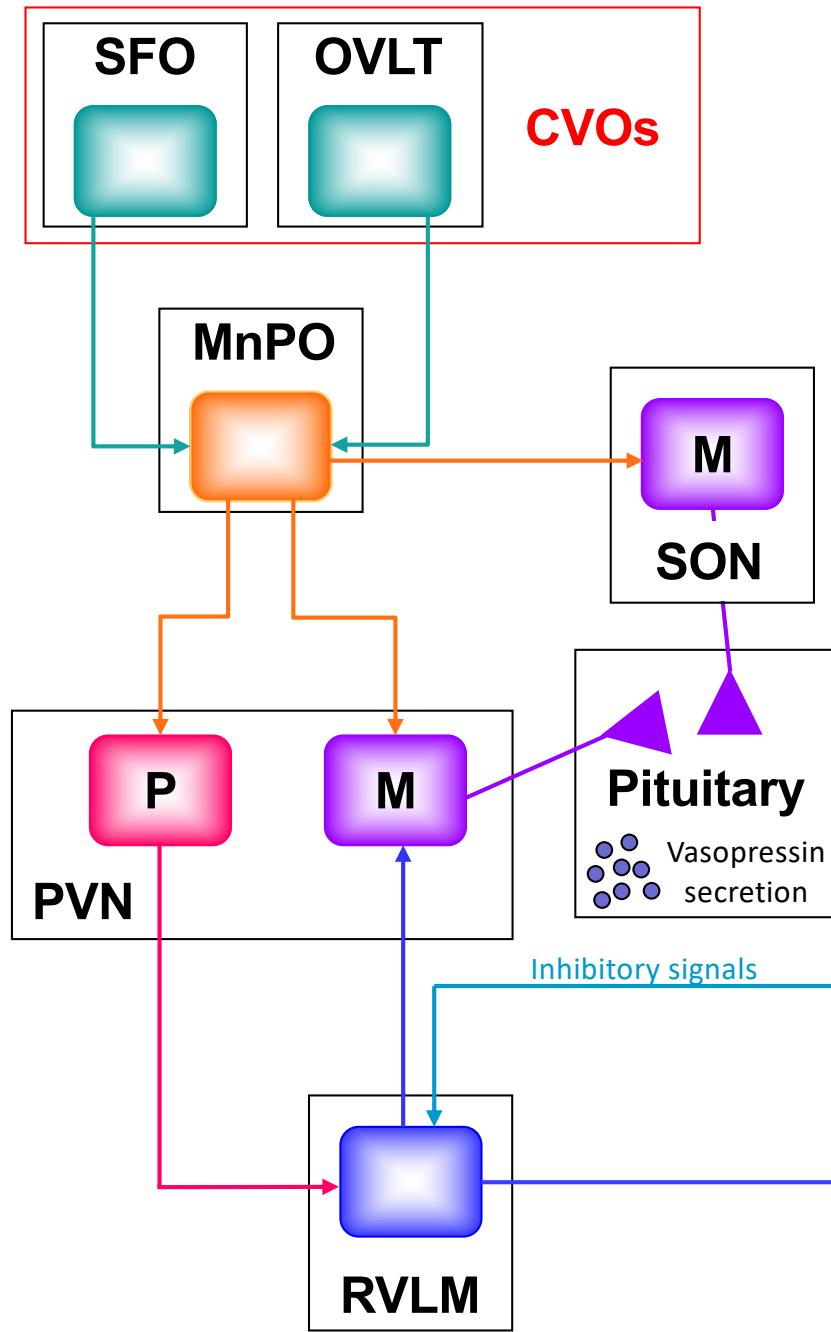
- Binding of ANGII to AT1 receptor increases intracellular  $\text{Ca}^{2+}$ , which, activates myosin light chain kinase (MLCK) → blood vessel smooth muscle contraction and elevation of blood pressure

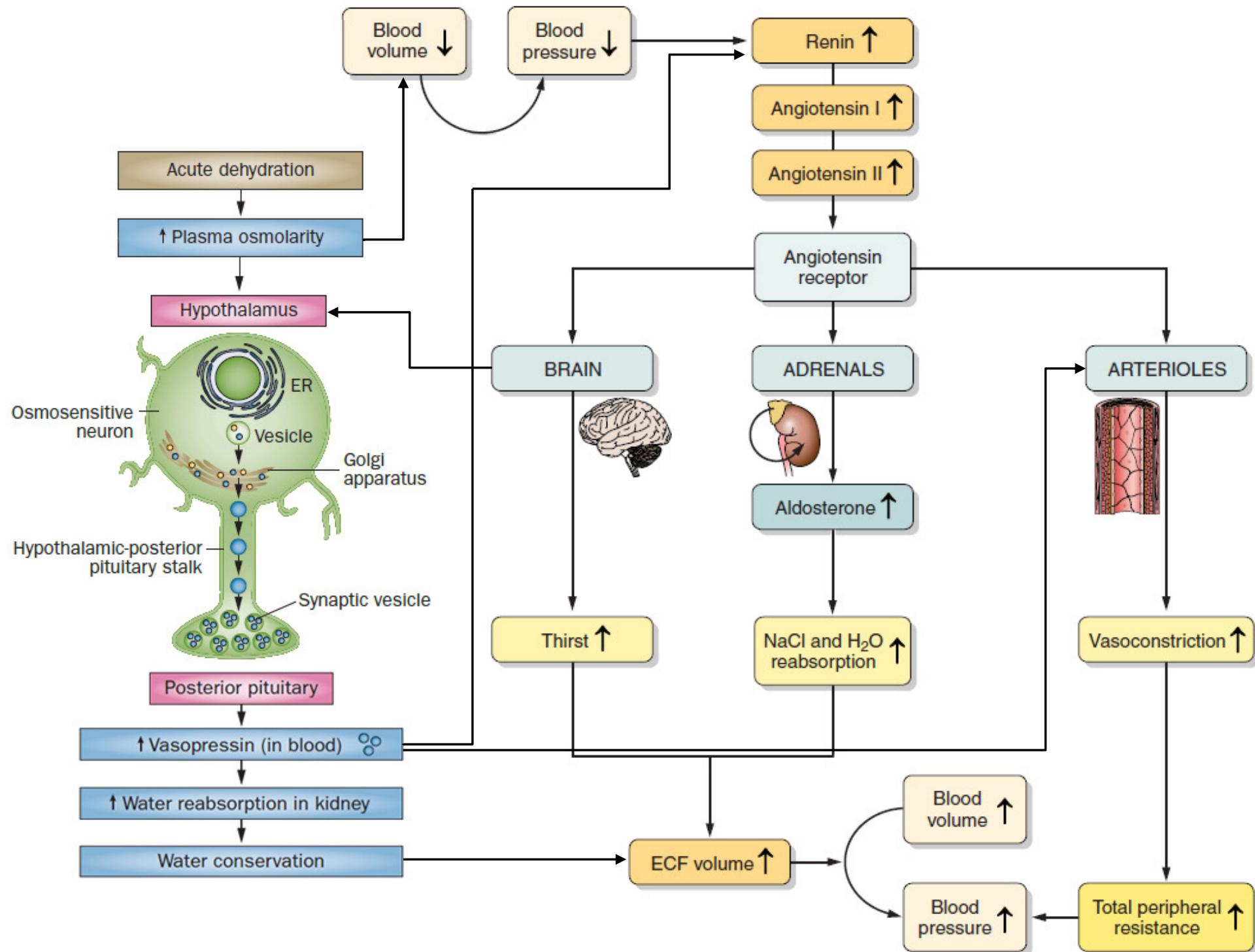


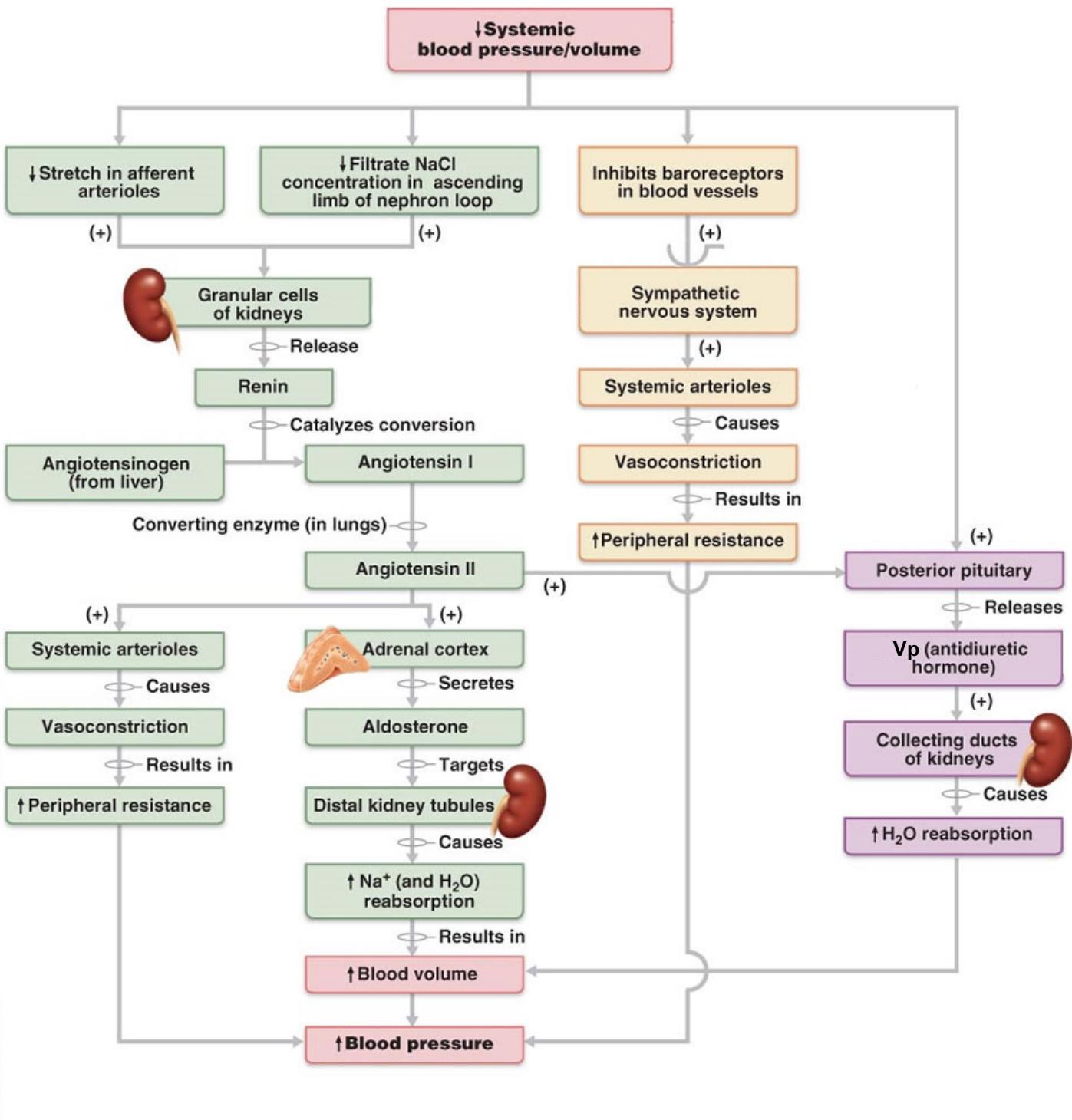
##### Cardiovascular control center in the brain

- Neurons within MnPO are connected to RVLM, the “pressor area” in the brainstem, via the parvocellular neurons of the hypothalamic PVN
- Once SFO and OVLT are activated by circulating ANGII, RVLM will send sympathoexcitatory signals to cause vasoconstriction









# Disorders related to Vasopressin

1. Vasopressin deficiency – known as **diabetes insipidus** -- the **inability** of kidney under physiologic conditions to **concentrate urine adequately**
  - ① Central diabetes insipidus (CDI) – The term given to conditions where there is a defect of vasopressin production or release
  - ② Nephrogenic diabetes insipidus (NDI) – The term given to conditions where kidney is unable to respond to vasopressin by producing a concentrated urine
    - a. Mutation in V2R
    - b. Genetic defect in the AQP2 gene → result in impaired trafficking to the plasma membrane

more male  
♂  
Same gender:

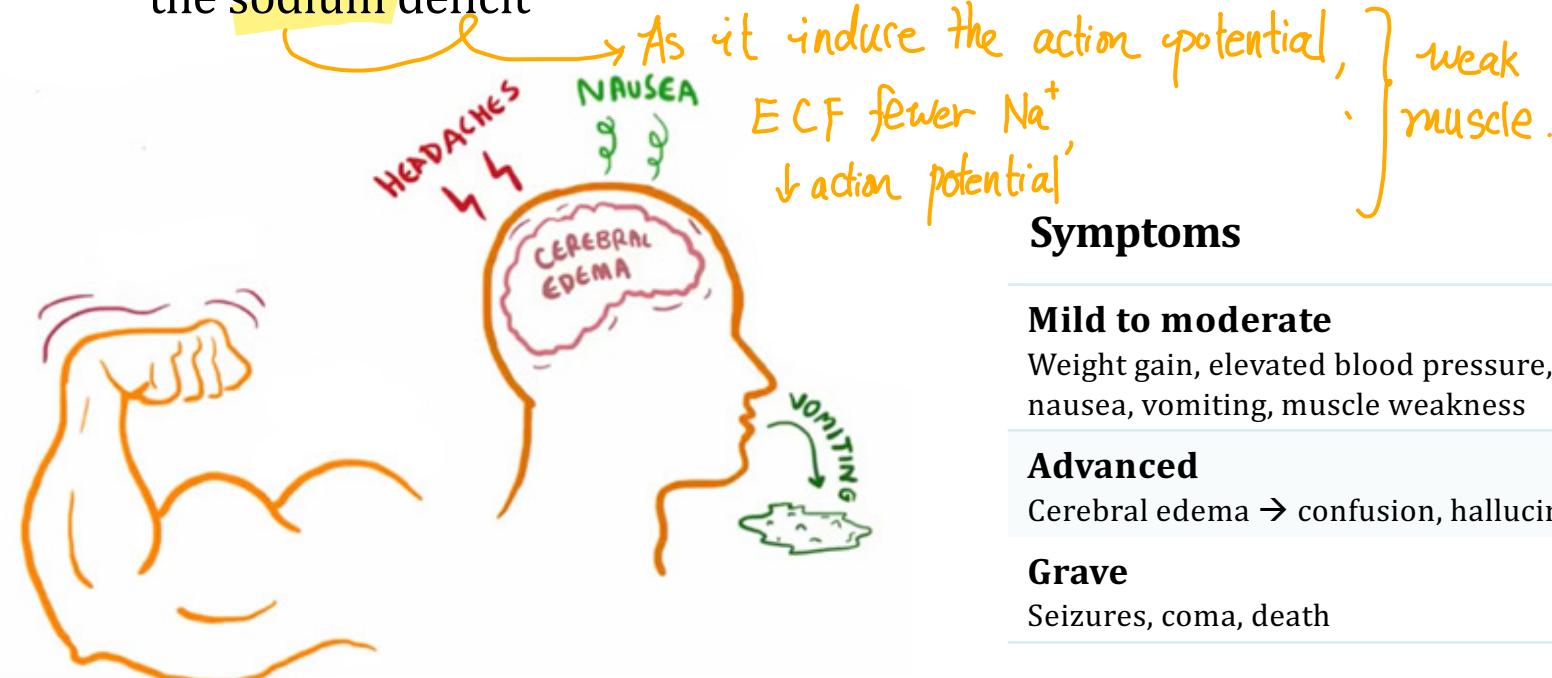
Mode of Transmission	Gene	Protein involved
X-linked	Xq28	Vasopressin type 2 receptor (V2R)
Autosomal	12q13	AQP2

NOTE: Diabetes insipidus generally does not cause hypernatremia because thirst prompts replacement of urinary losses of water

2. Excess vasopressin -- Syndrome of “inappropriate” secretion of ADH (SIADH) – when kidney conserving too much water

Release Sth.  
Similar to  
V.P.

- Occurs in people with:
  - a. Diseased posterior pituitary, hence a slow and constant leak of Vp
  - b. Small cell lung carcinoma, which is a tumor characterized by differentiation into the neuroendocrine system and the secretion of Vp
  - c. Impaired hypothalamus-pituitary-adrenal (HPA) axis function & anti-depressant medication history ↗ 情开心 !! → release ADH → More Vp
- Signs and symptoms are associated with water retention and lowered levels of sodium (dilutional hyponatremia), and may vary depending on the degree of the sodium deficit



# Disorders related to Aldosterone

## 1. Hyperaldosteronism

- When there is an excessive secretion of aldosterone
- Due to:
  - a. An aldosterone-producing adenoma
  - b. Abnormal activation of the renin-angiotensin system (renovascular disease)
- Symptoms:

- a. Hypertension (due to hypernatremia)
  - b. Hypokalemia

A – Alkalosis      *→ cell loss K<sup>+</sup>*

*→ lower action potential.*

S – Shallow respiration

I – Irritability

C – Constipation ( $\downarrow$  gut motility)

W – Weakness (especially muscle)

A – Arrhythmia (irregular heart rate)

L – Lethargy (fatigue)

T – Thready (weak) pulse



## 2. Hypoaldosteronism

- When there is a deficient in aldosterone secretion
- Due to:
  - a. Adrenal insufficiency
  - b. Renal insufficiency due to chronic renal failure → hence low renin level
  - c. Intake of anti-hypertensive drugs, e.g. ACE blockers, angiotensin II receptor blockers, renin inhibitors etc.

➤ The major clinical manifestations in patients are hyponatremia and hyperkalemia

Hypotension (due to hyponatremia)

Arrhythmia

Muscle cramps

Abdominal cramping

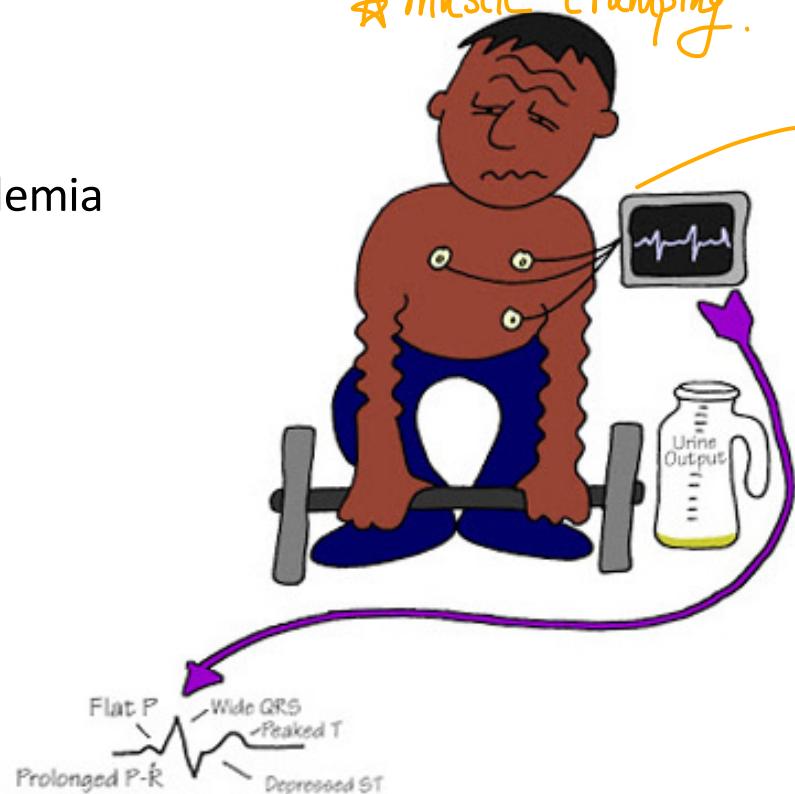
Diarrhea

Metabolic acidosis

} Due to hyperkalemia

\* K<sup>+</sup> influx to the cell

\* muscle cramping.



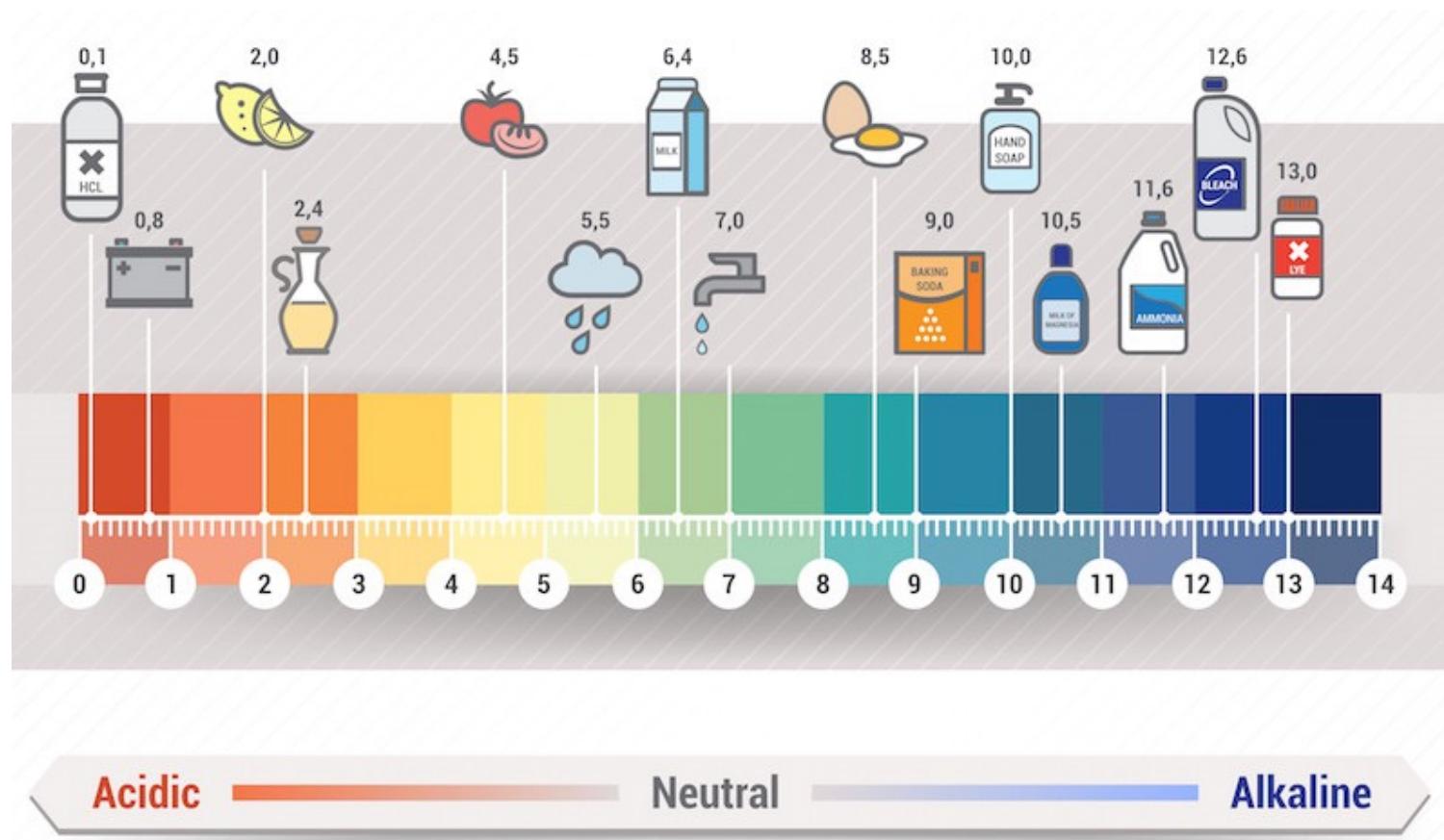
# Summary of Key Learning Objectives

- State how water is distributed throughout our body.
- List the body's major electrolytes and differentiate their distribution in intracellular and extracellular fluid.
- Explain how our body detects the changes in osmotic factor and hemodynamic factors. Elaborate how changes in these factors lead to appropriate physiological and behavioral responses.
- Explain how loop of Henle, collecting ducts, and Vp coordinate to regulate urine concentration.
- List the FOUR functions of angiotensin II.
- Understand the disorders related to Vp and aldosterone, and describe how it affects the electrolyte balance in our body
- Describe the clinical manifestations of the following imbalances:
  - Hypernatremia
  - Hyponatremia
  - Hyperkalemia
  - Hypokalemia

# **Acid-Base Balance & Related Disorders**

# pH scale

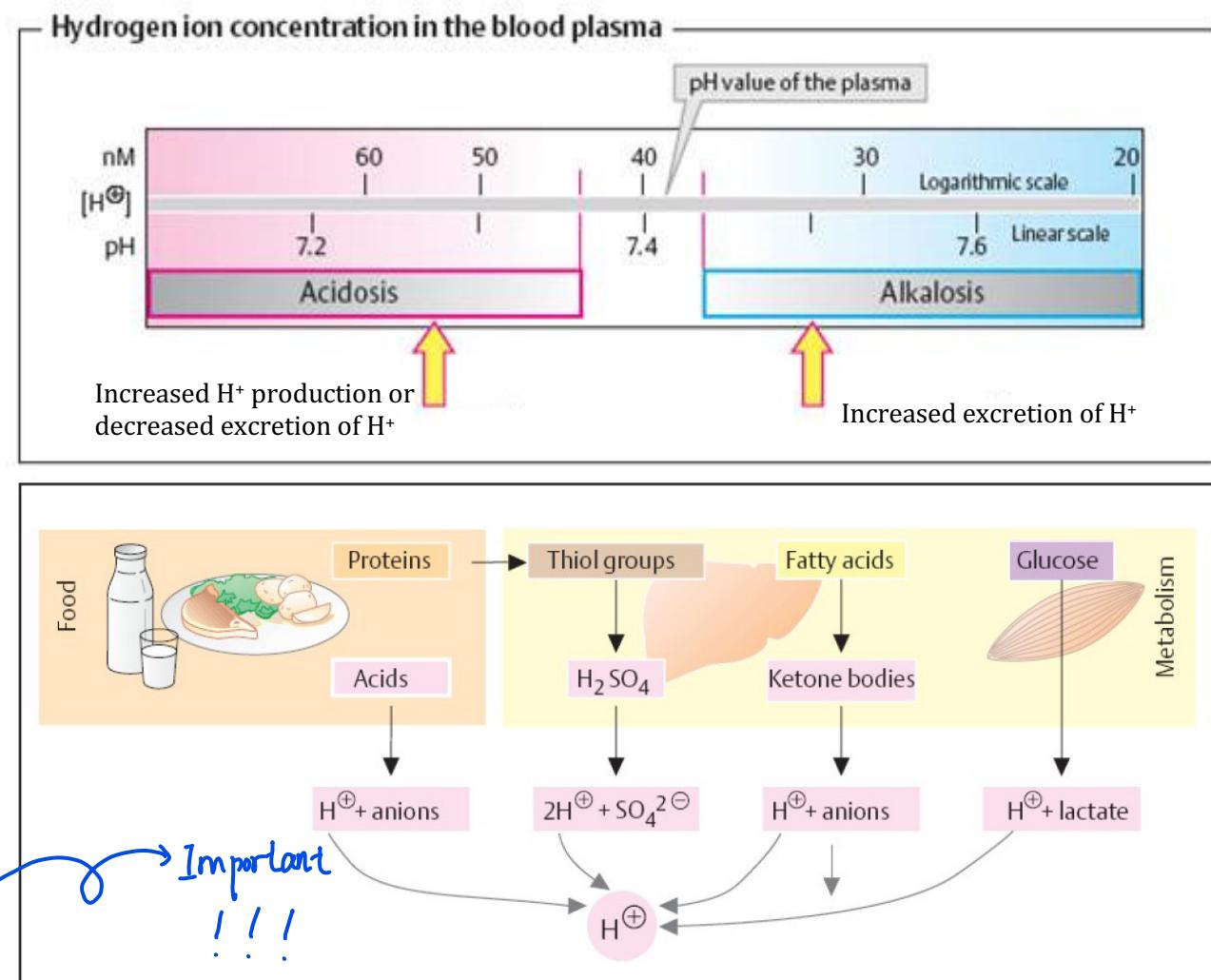
- Acidity and alkalinity are expressed on the pH scale, which stands for potential of hydrogen.
- pH scale ranges from 0 (strongly acidic) to 14 (strongly basic or alkaline). A pH of 7.0, in the middle of this scale, is neutral.



# Acid-Base Balance

- Systemic acid-base chemistry is very tightly controlled, in spite of the fact that there is always a net addition of acid to the body after consuming typical diets

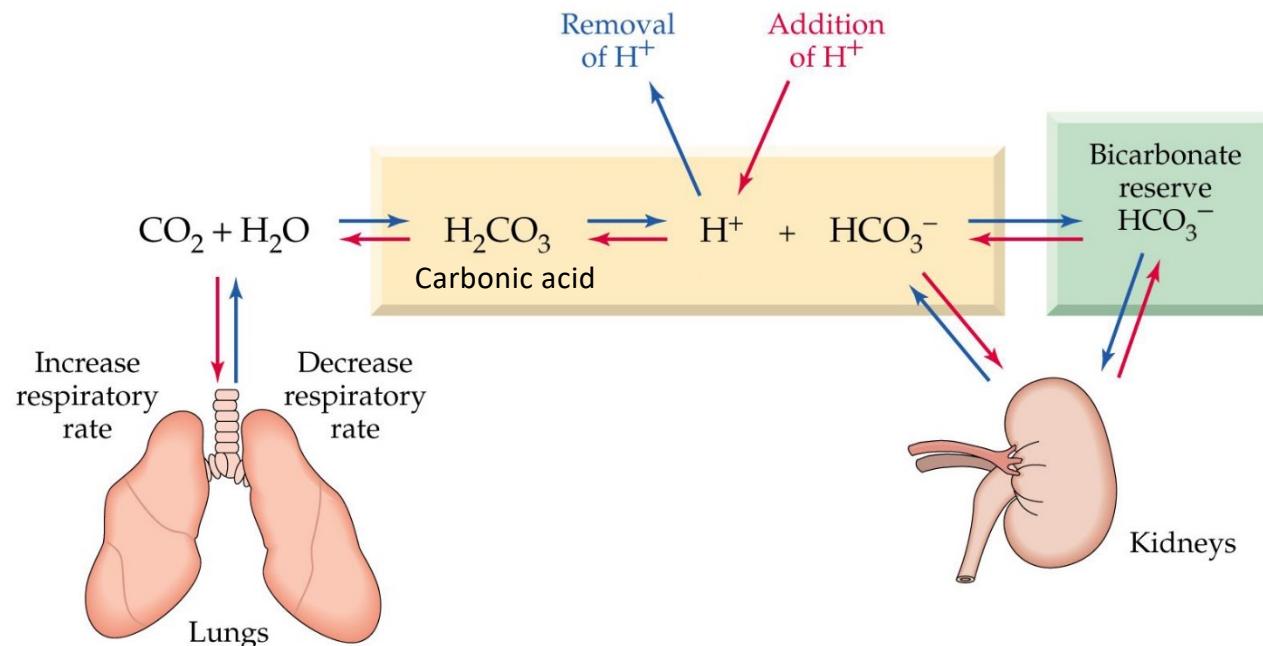
- Proper organ and cellular function depends on enzymes activity that are sensitive to pH, it is therefore essential to control pH within a narrow range of 7.38 to 7.42



- For acid-base balance, the amount of acid excreted per day must equal to the amount produced per day

# Chemical Buffer System

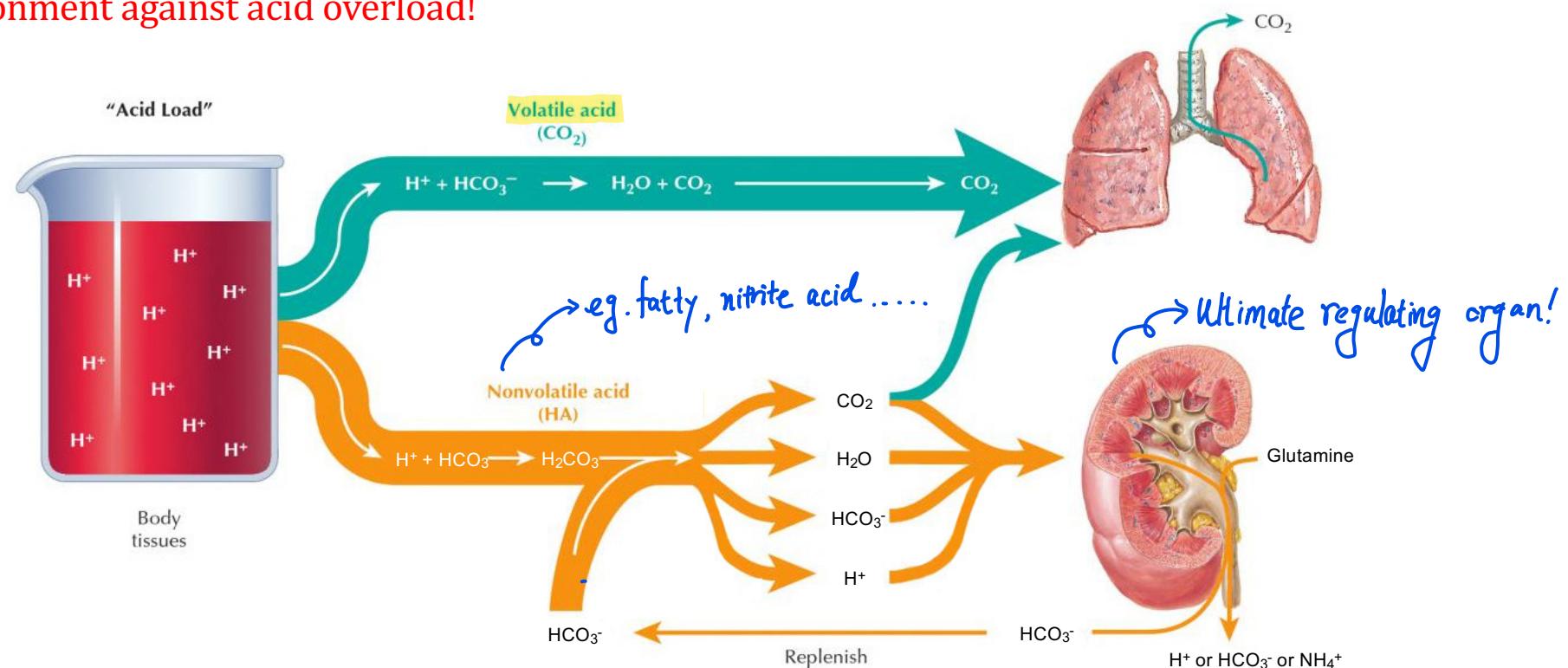
- The body's acid-base balance is tightly regulated by chemical buffering agents, in which one or two molecules binds H<sup>+</sup> when the pH drops, or releases H<sup>+</sup> when the pH rises
- The carbonic acid-bicarbonate buffer system is the main buffer of the extracellular fluid. It consists of carbonic acid and its salt, sodium bicarbonate (HCO<sub>3</sub><sup>-</sup>).
- Even though the chemical buffer system can inactivate excess acids and bases momentarily, they are unable to eliminate them from the body --> Lungs and Kidneys have critical role in eliminating acid in the body



# Renal Mechanism in Acid-Base Balance

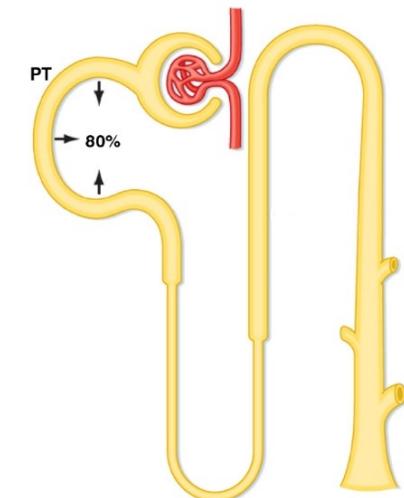
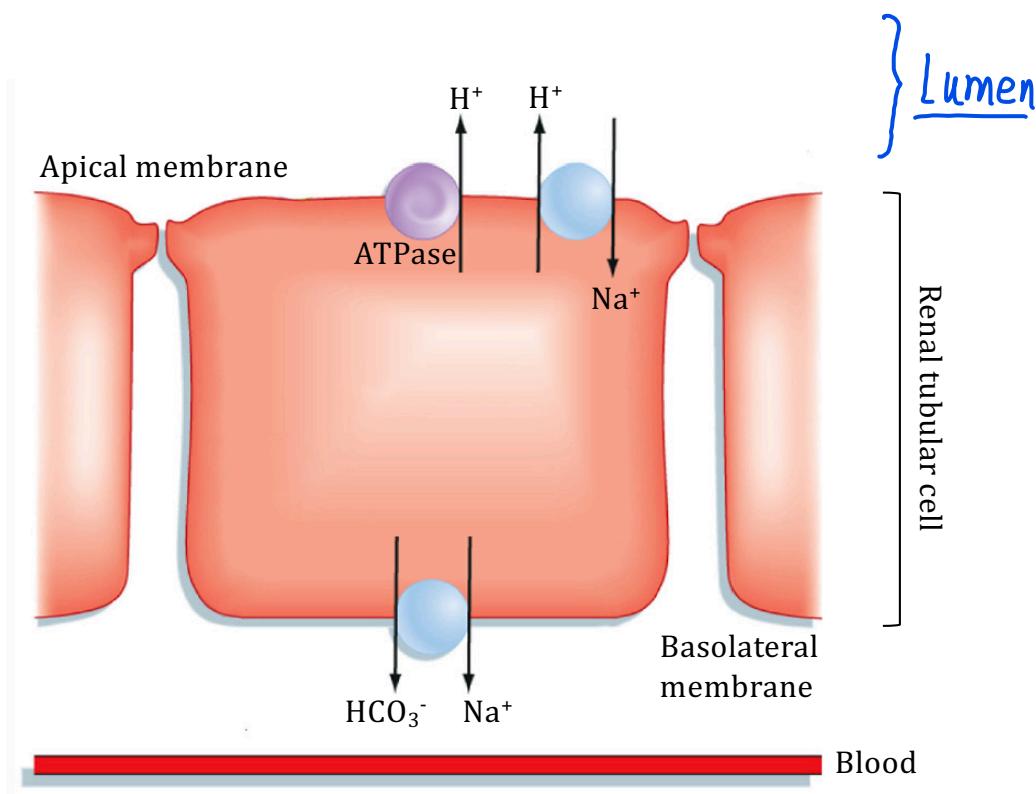
- The renal system vs The respiratory system:
  - Only the renal system can rid the body of non-volatile acids such as uric acids, lactic acids, and ketone bodies (excretion of H<sup>+</sup>)
  - Only the renal system can regulate alkaline substances in the blood (excretion of HCO<sub>3</sub><sup>-</sup>)
  - Only the renal system can restore chemical buffers that are used in managing H<sup>+</sup> levels in extracellular fluids (reabsorption of HCO<sub>3</sub><sup>-</sup> from filtrate, and generation of new HCO<sub>3</sub><sup>-</sup> from glutamine)

Conclusion: Kidney is the ultimate acid-base regulatory organ to protect the internal environment against acid overload!



# Acid-Base Balance in Proximal Tubules

- Approximately 80 % of the filtered  $\text{HCO}_3^-$  is reabsorbed by the proximal tubules, the rest is reabsorbed by the distal nephrons  
$$-\ddot{\text{A}}\ddot{\text{C}} \text{ HCO}_3^- \Leftrightarrow -\ddot{\text{A}}\ddot{\text{C}} \text{ H}^+$$
- The reabsorption of filtered  $\text{HCO}_3^-$  is always accompanied by the secretion of  $\text{H}^+$  and vice versa



- $\text{HCO}_3^-$  reabsorption in proximal tubules is achieved by  **$\text{Na}^+/\text{HCO}_3^-$  cotransporter** on the basolateral membrane.
- $\text{H}^+$  secretion into the lumen of proximal tubules is achieved by two transporters expressed on the apical membrane:
  1.  **$\text{Na}^+/\text{H}^+$  exchanger (NHE)**
  2.  **$\text{H}^+$ -ATPase**

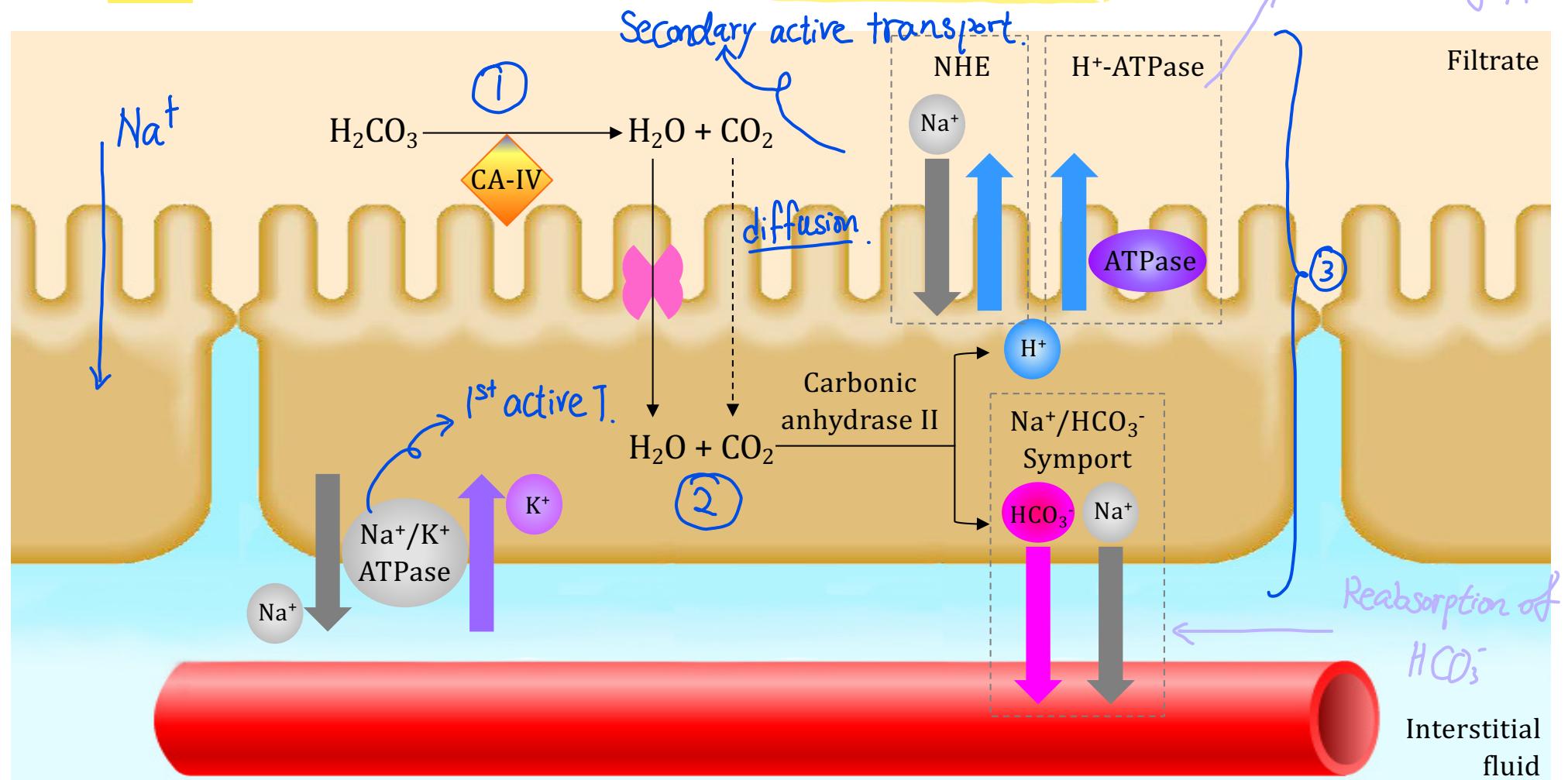
「身体过酸!!!」

## H<sup>+</sup> Secretion & HCO<sub>3</sub><sup>-</sup> Reabsorption in Proximal Tubules

- Carbonic anhydrase (CA) plays an important role in H<sup>+</sup> secretion and HCO<sub>3</sub><sup>-</sup> reabsorption in the proximal tubules. It is a family of enzymes that catalyze the rapid interconversion of carbon dioxide and water to bicarbonate and protons (or vice versa)



- Intracellular CA (CA-II) facilitates the generation of H<sup>+</sup> and HCO<sub>3</sub><sup>-</sup>, whereas membrane-bound CA (CA-IV) facilitates the production of H<sub>2</sub>O and CO<sub>2</sub> from carbonic acid



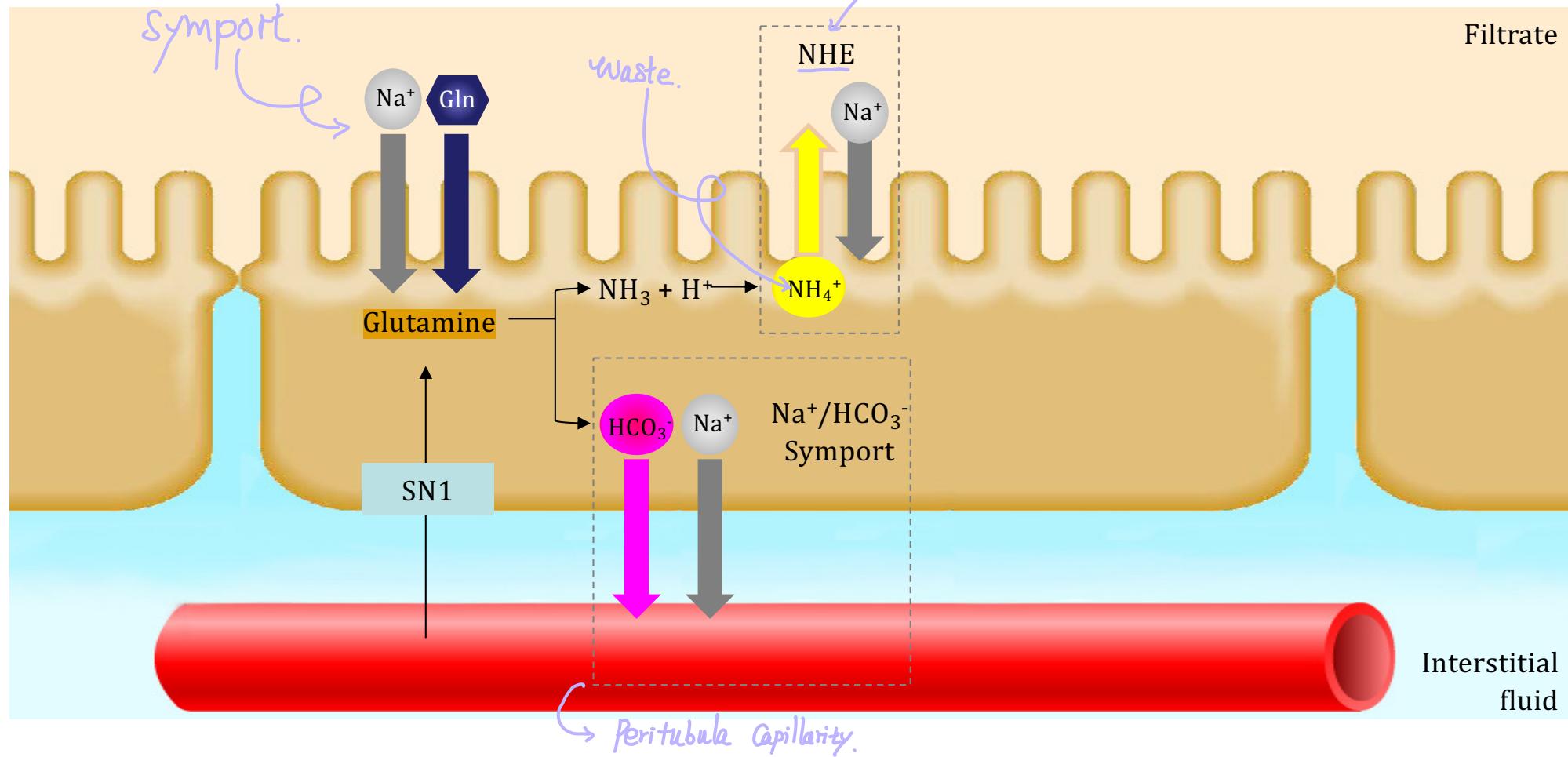
→ 身体过酸!!

## Generation of new $\text{HCO}_3^-$ in Proximal Tubules

- In the proximal tubules, generation of a novel bicarbonate molecule is achieved by the process of ammonium ( $\text{NH}_4^+$ ) synthesis (ammoniagenesis):

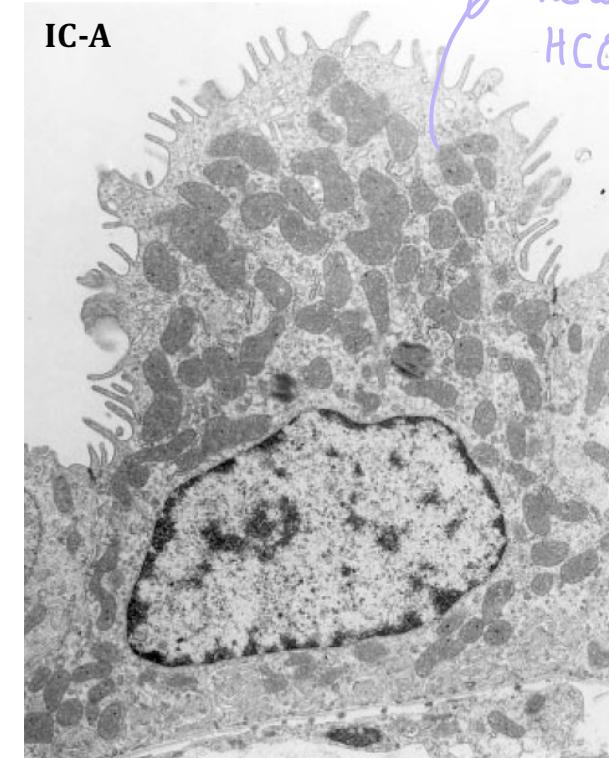
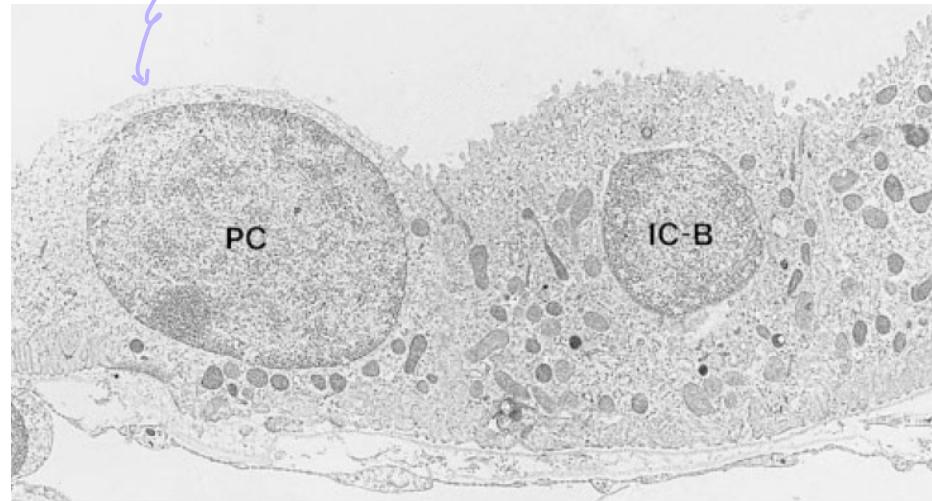


- Glutamine is 100% reabsorbed from the filtrate by the apical amino acid transporter. It can also be uptaked from the circulation via the basolateral glutamine transporter, SN1 (also known as SNAT3), during acidosis



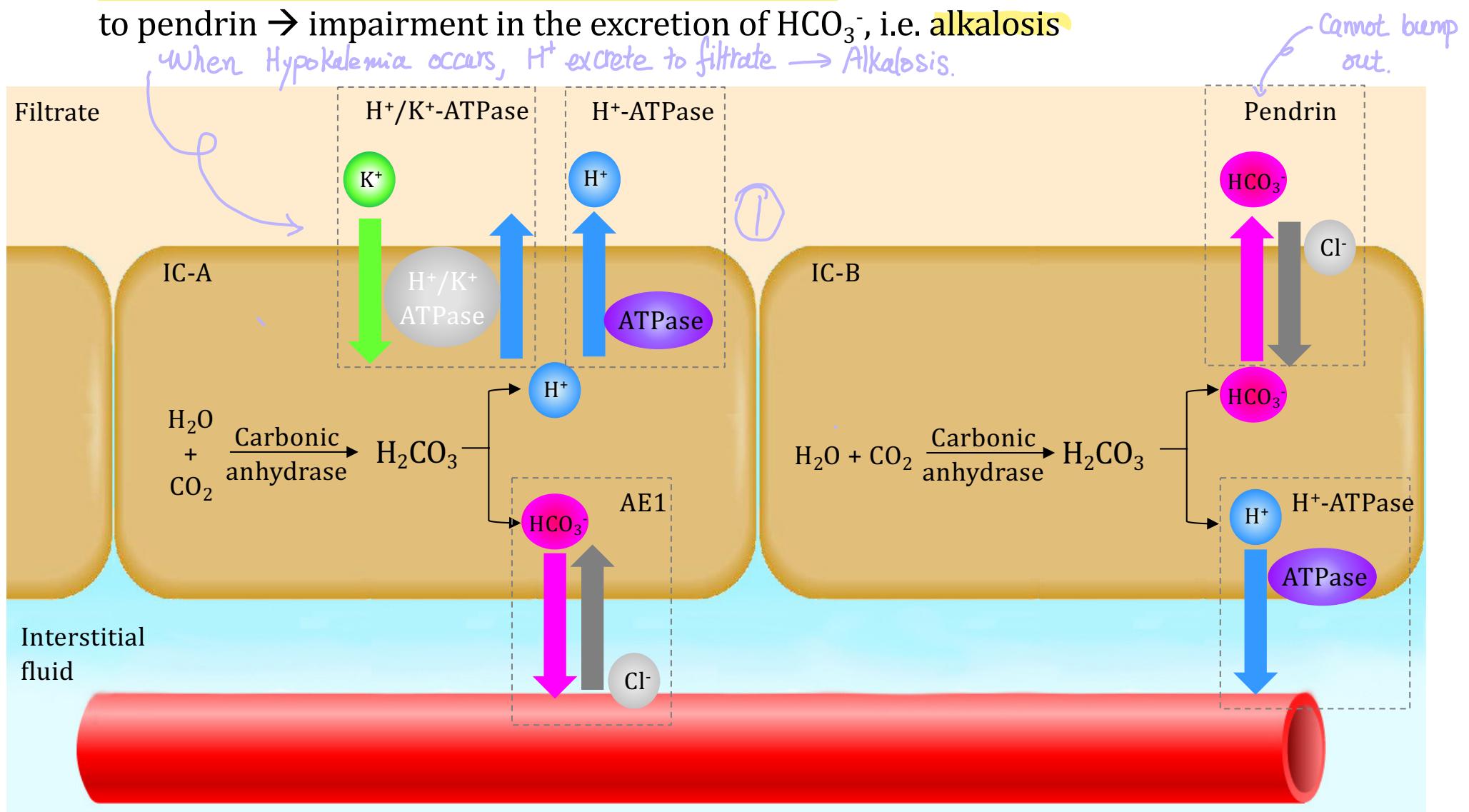
# Acid-Base Balance in Collecting Ducts

- Collecting duct has a heterogenous cell population:
  - Principal cells (PC) – response to Vp
  - Intercalated cells (IC) – for acid-base transport

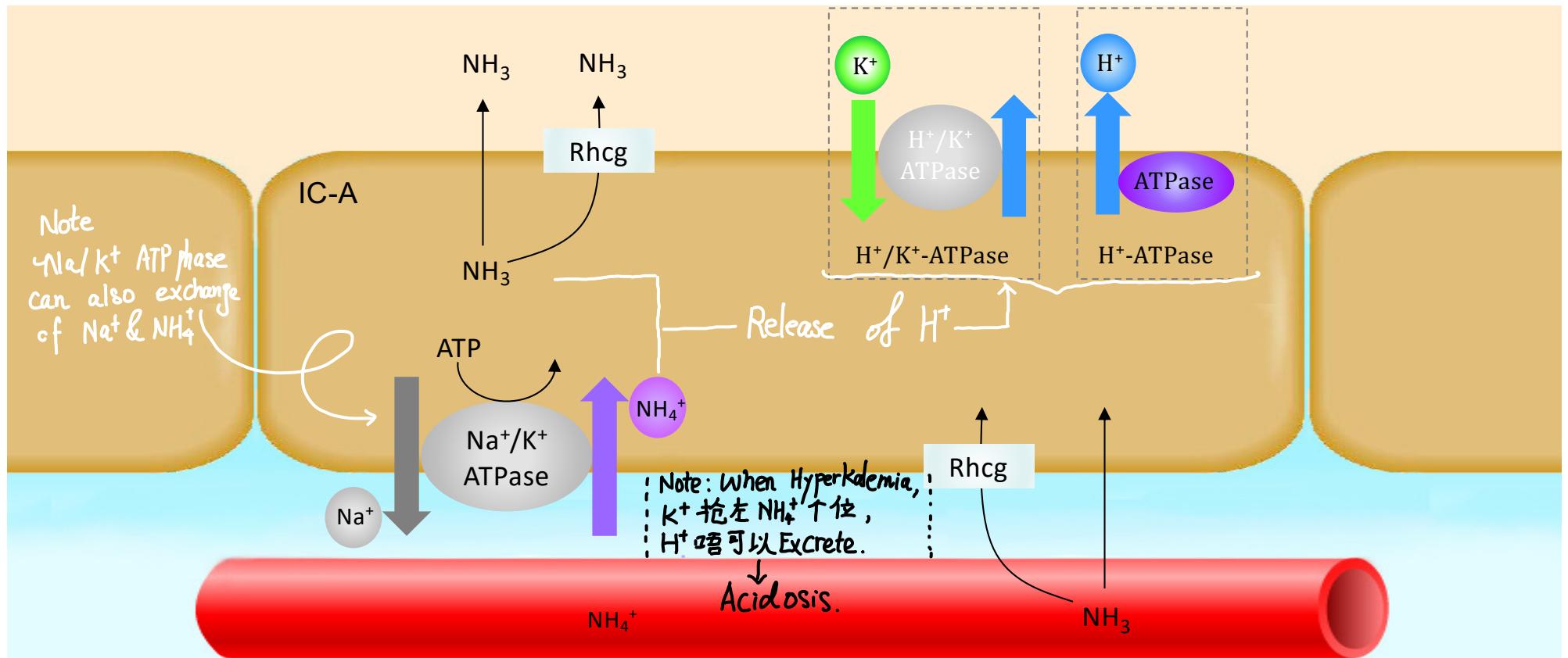


- Two subtypes of intercalated cells can be distinguished based on the substances being secreted:
  - Type A (IC-A) → Excrete acid.
    - Secretes  $H^+$  and  $NH_3$  – Due to luminal expression of both  $H^+$ -ATPase and  $H^+/K^+$ -ATPase @ luminal m.
    - Expresses anion-exchanger AE1 on the basolateral membrane
  - Type B (IC-B)
    - Secretes  $HCO_3^-$  – Due to luminal expression of  $Cl^-/HCO_3^-$  exchanger, called pendrin
    - Expresses only  $H^+$ -ATPase on the basolateral membrane

- Bicarbonate secretion into the lumen occurs in Type B intercalated cells and is mediated via pendrin (SLC26A4), which exchanges luminal chloride for cellular bicarbonate.
- Chloride ion depletion results in hypochloremia hence decreasing chloride delivery to pendrin → impairment in the excretion of  $\text{HCO}_3^-$ , i.e. alkalosis  
*When Hypokalemia occurs,  $\text{H}^+$  excrete to filtrate → Alkalosis.*

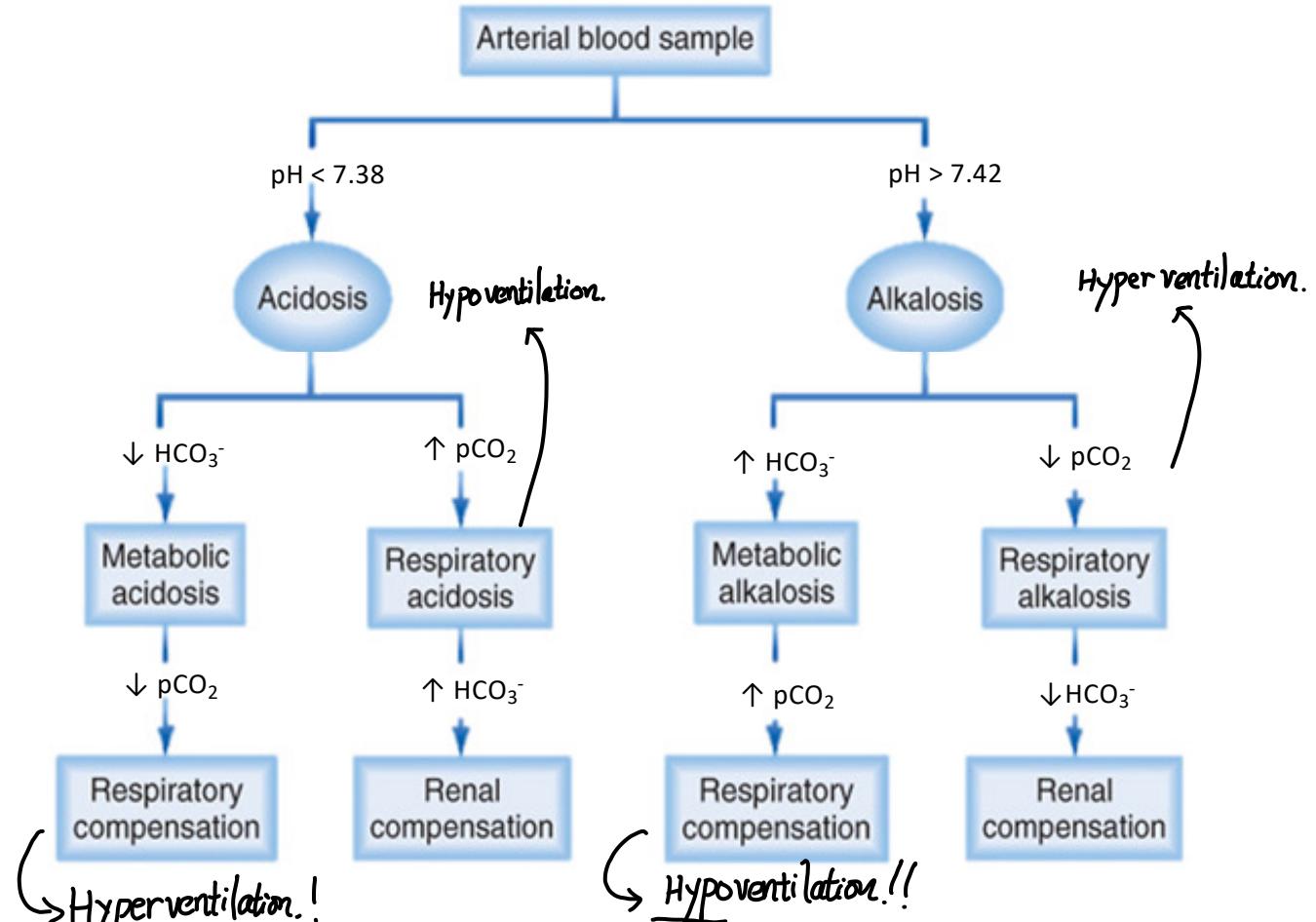


- Efficient  $\text{H}^+$  secretion depends on the concomitant secretion of ammonia ( $\text{NH}_3$ ) from type A intercalated cells, which is subsequently protonated in the lumen to ammonium ( $\text{NH}_4^+$ )
- Luminal  $\text{NH}_3$  titrates luminal  $\text{H}^+$ , forming  $\text{NH}_4^+$  ( $\text{NH}_3 + \text{H}^+ \rightarrow \text{NH}_4^+$ ), and hence maintaining a low luminal  $\text{H}^+$  concentration necessary for further  $\text{H}^+$  secretion
- $\text{NH}_3$  can freely diffuse across the membrane, or via the **Rhesus glycoprotein**, Rhcg, ammonia-specific transporters.



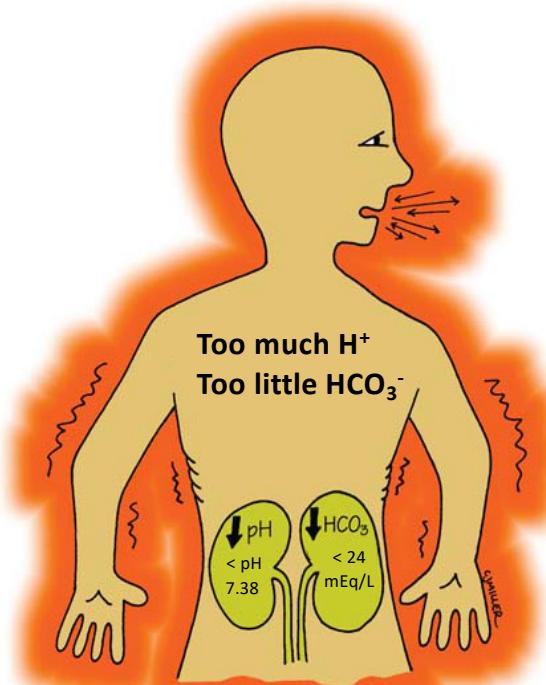
# Dysregulation of Acid-Base Equilibrium

- Acidosis and alkalosis are the general terms referring to low pH and high pH, respectively, in body fluids
- Alterations in pH caused by **respiratory abnormality** are referred to as respiratory acidosis (caused by hypoventilation, e.g. airway obstruction) or respiratory alkalosis (caused by hyperventilation)
- Alterations in pH caused by **metabolic disease or abnormal renal function** are described as metabolic acidosis or metabolic alkalosis
- Any primary disturbance will immediately trigger a compensatory response, e.g. respiratory disorder will be compensated for by the kidneys, whereas metabolic disorder will be compensated for by the lungs

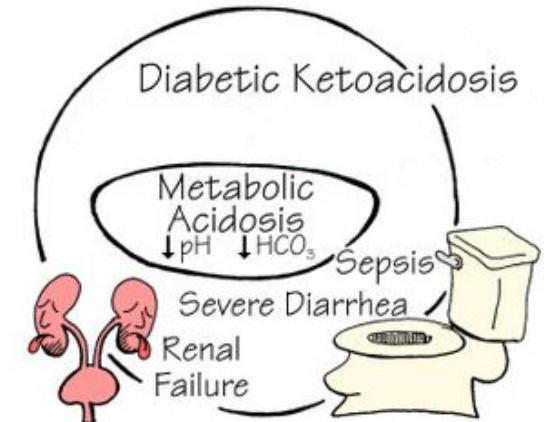


## Metabolic Acidosis

- Defined as an excessive accumulation of non-volatile acid manifested as a primary reduction in serum bicarbonate concentration in the body associated with low plasma pH
- Often due to:
  - Diabetes mellitus-induced ketoacidosis
  - Hypoxia- or sepsis-induced lactic acidosis
  - Severe diarrhea, hence loss of  $\text{HCO}_3^-$  from the GI tract
  - Renal failure
  - Hyperkalemia

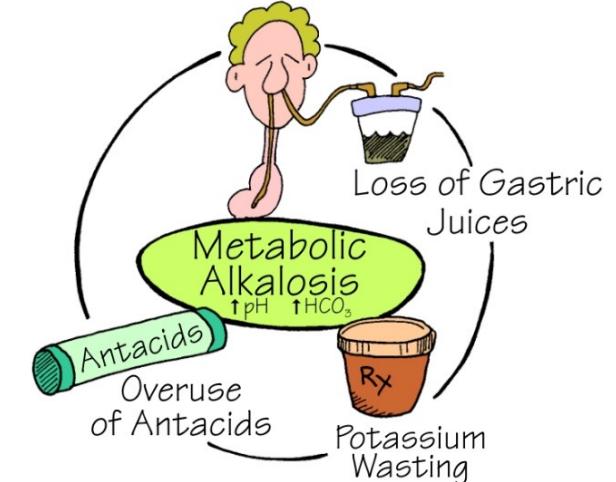


- Symptoms:
  - Headache
  - Rapid and shallow breathing (compensatory hyperventilation)
  - Fatigue
  - ↑ heart rate
  - Breath that smells fruity (only a sign for diabetes-induced ketoacidosis)
  - Weakness of bone (osteoporosis)
- If unchecked, metabolic acidosis would lead to acidemia, hence coma, death

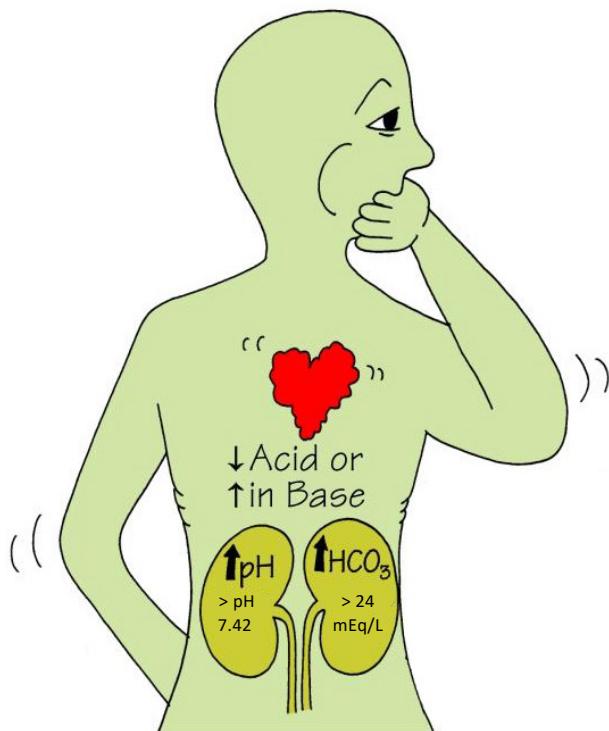


## Metabolic Alkalosis

- A metabolic alkalosis is an acid-base disorder in which the plasma  $\text{HCO}_3^-$  rise to a level higher than expected
- The pathogenesis of metabolic alkalosis involves 2 processes, the generation of metabolic alkalosis and the maintenance of metabolic alkalosis



- Most often due to:
  - a) Kidney failure
  - b) Prolonged vomiting, hence loss of  $\text{H}^+$  from the stomach
  - c) Hyperaldosteronism (Hypokalemia)
  - d) Hypochloremia
- Symptoms of metabolic alkalosis are not specific, because hypokalemia is usually present:
  - Headache
  - Compensatory hypoventilation
  - Arrhythmias
  - Muscle weakness



# **Overall Summary of Renal Functions**

**Water.** Ensures that there's not too much or too little of water in the body.

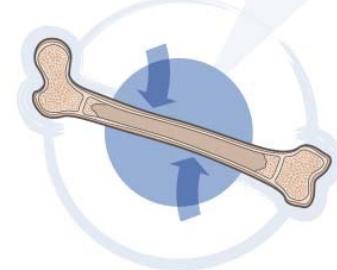


## Homeostasis.

Maintains a balance of electrolytes and plasma pH level.



**Bone.** Produces active vitamin D (calcitriol) in the proximal tubules. This helps body absorb calcium and maintain healthy bone status.



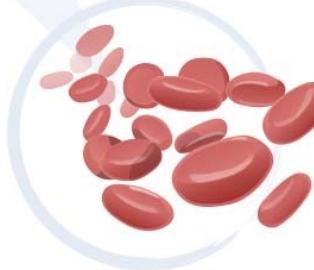
## Blood pressure.

Make sure that pressure isn't too high or too low by regulating the renin-angiotensin-aldosterone axis.



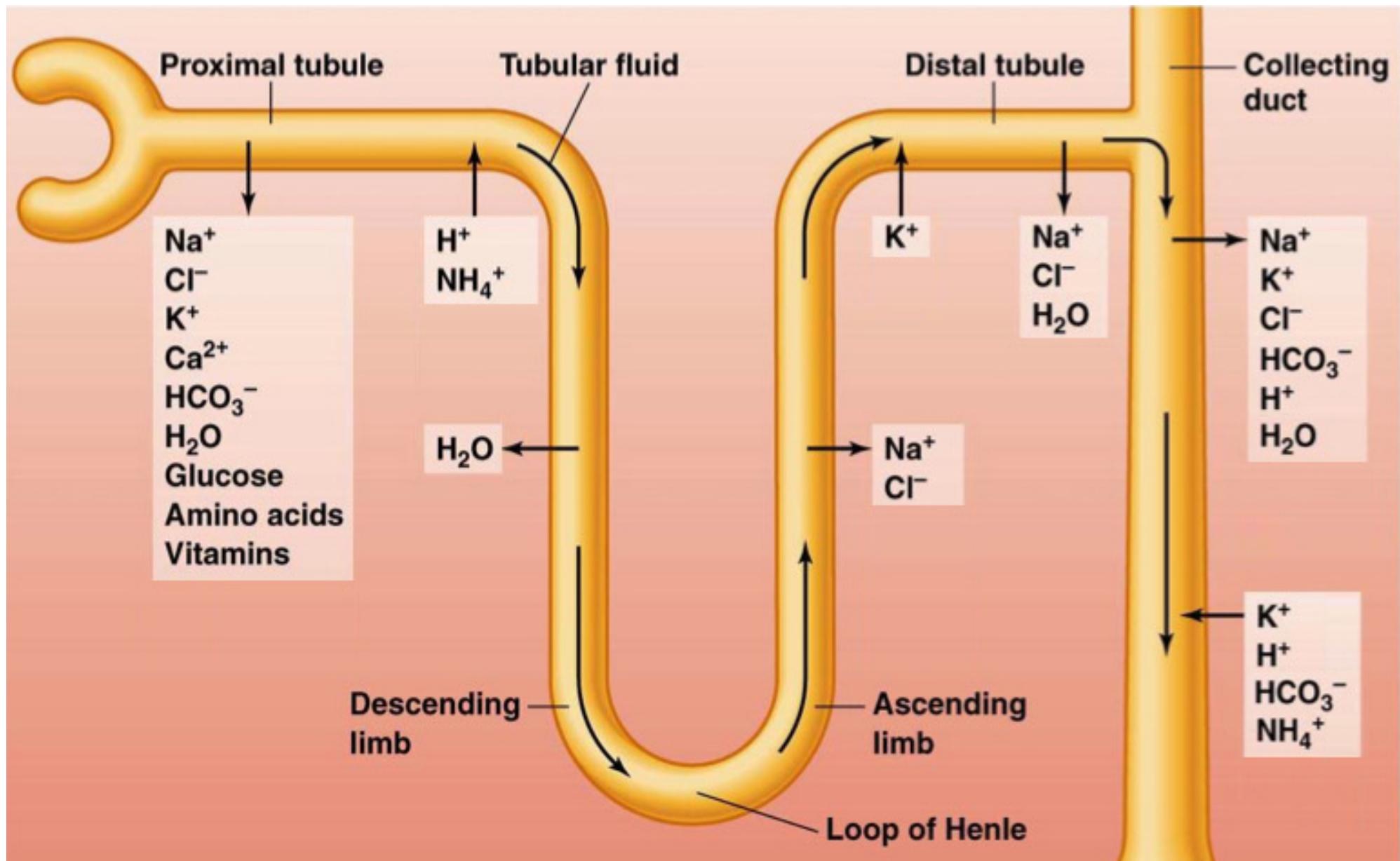
## Filtering

**waste.** Get rid of unwanted substances and wastes via urine.



**Blood.** Releases erythropoietin, which tells bone marrow to make red blood cells.

# Solutes & Substances Handling within the Nephron



# Proximal Tubules

Region	Substance	Transport mechanism
Proximal tubules	Sodium ions	
	Chloride ions	
	Potassium ions	
	Calcium ions	
	Bicarbonate ions	
	Water	
	Glucose	
	Glutamine	
	Other amino acids / vitamins	
	Hydrogen ions	
	Ammonium ions	

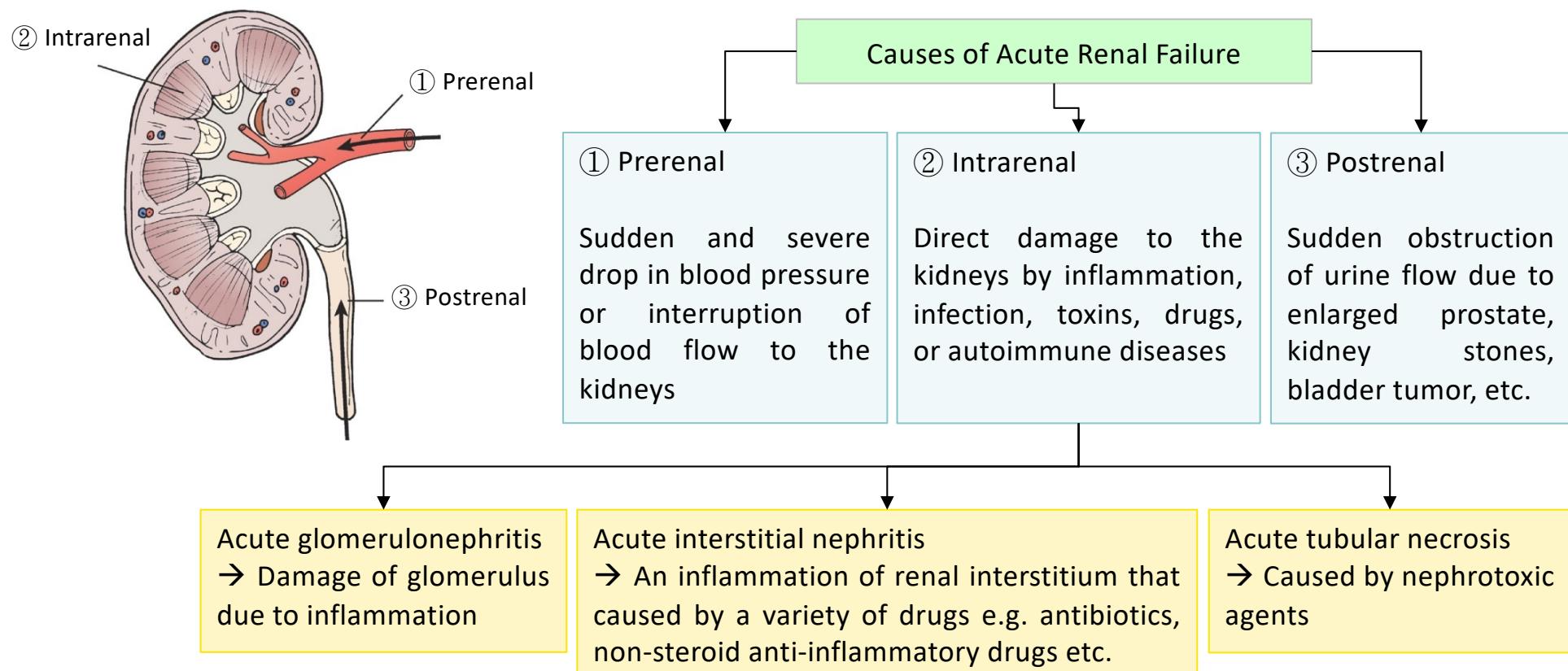
# Distal Tubules & Collecting Ducts

Region	Substance	Transport mechanism
Distal tubules	Sodium ions	
	Chloride ions	
	Potassium ions	
	Water	
Collecting ducts	Sodium ions	
	Chloride ions	
	Potassium ions	
	Bicarbonate ions	
	Hydrogen ions	
	Ammonium ions	
	Water	

# **Renal Failure & Treatment Options**

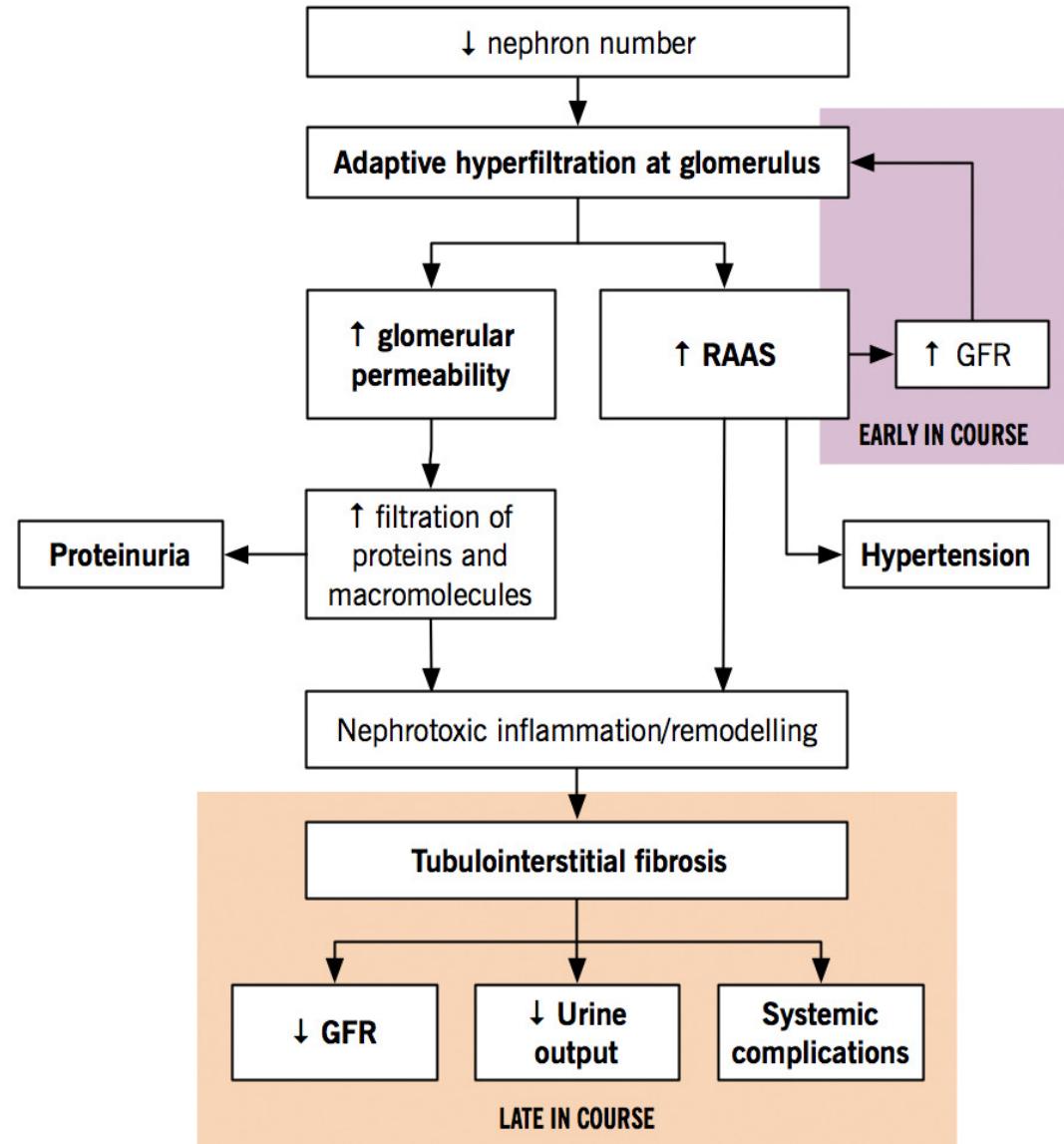
# Acute Renal Failure

- Acute renal failure develops rapidly over a few hours or a few days. It occurs when the kidneys suddenly lose the ability to eliminate excess salts, fluids, and waste products from the blood, leading to accumulation of excess electrolytes and waste materials to dangerous levels that can be life-threatening.

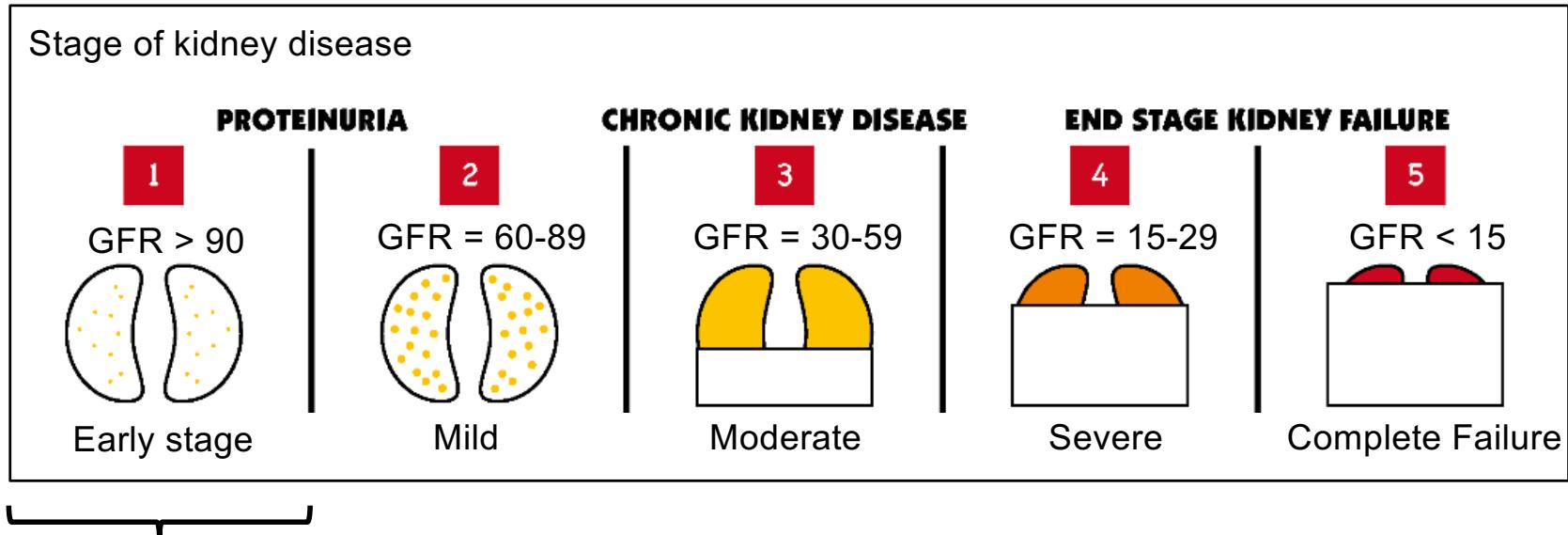


# Chronic Kidney Disease

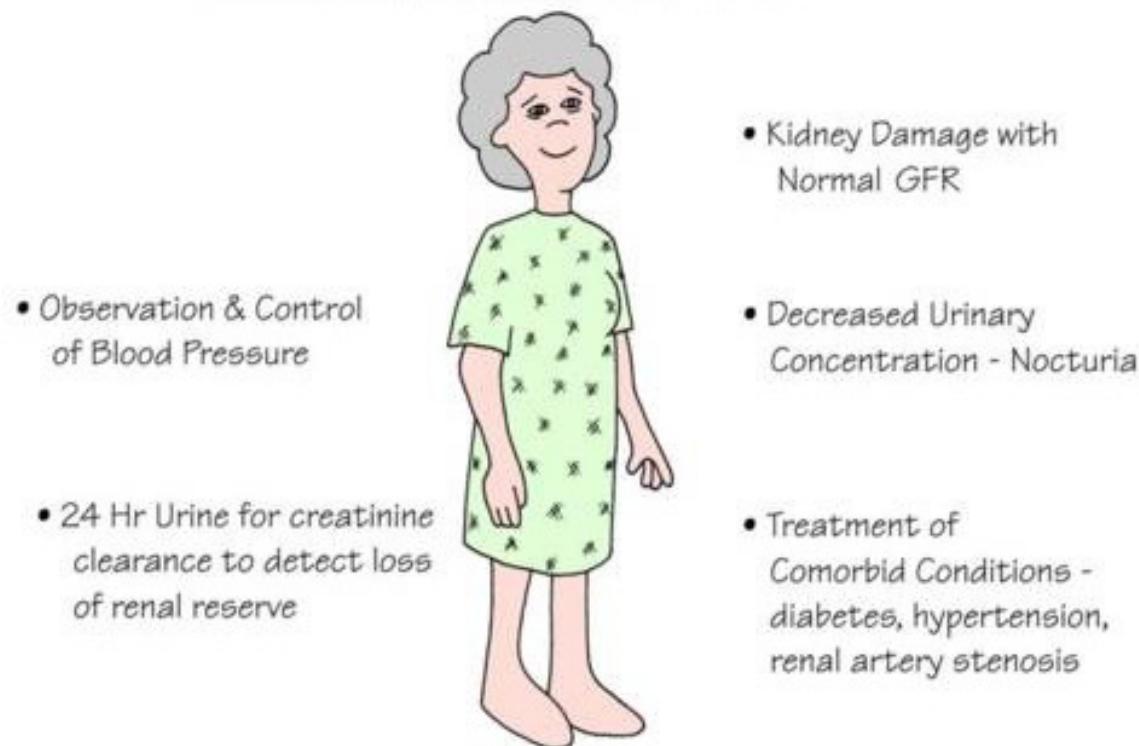
- Chronic kidney disease is a condition characterized by a gradual loss of kidney function over a period of months or years, resulting in permanent compromise of renal function
- Causes of chronic kidney disease:
  - a. Type 1 or Type 2 diabetes
  - b. Hypertension
  - c. Autoimmune diseases, e.g. lupus nephritis
  - d. Inherited diseases, e.g. polycystic kidney disease
- Chronic kidney disease may not become apparent until the function of kidneys is significantly impaired
- Classification of chronic kidney disease is based on estimated GFR, and recognizes 5 stages of kidney diseases



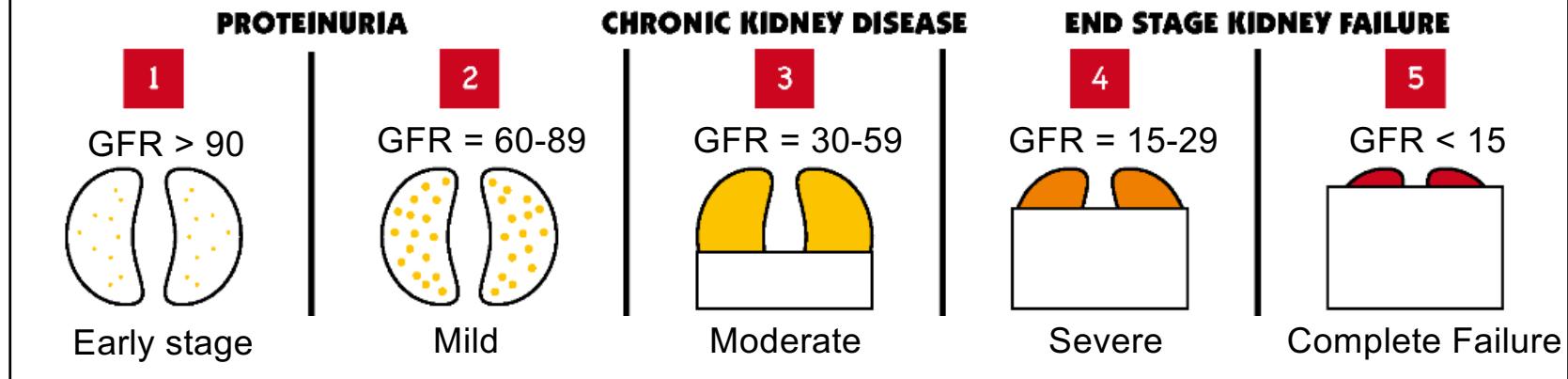
### Stage of kidney disease



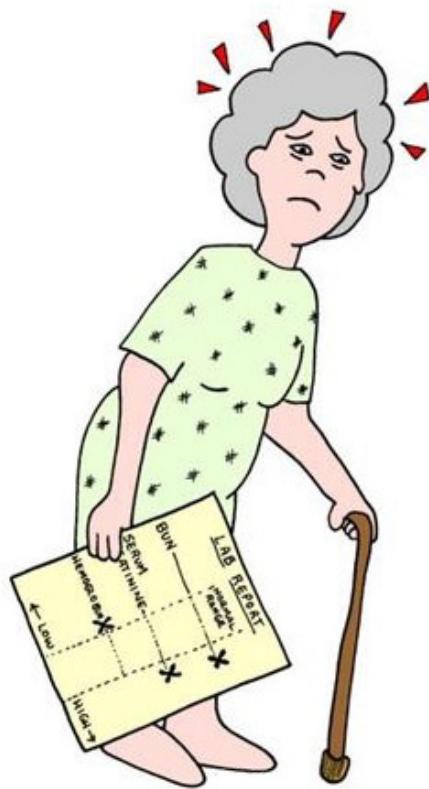
Diminished renal reserve – GFR is still normal, but with reduced renal function



### Stage of kidney disease



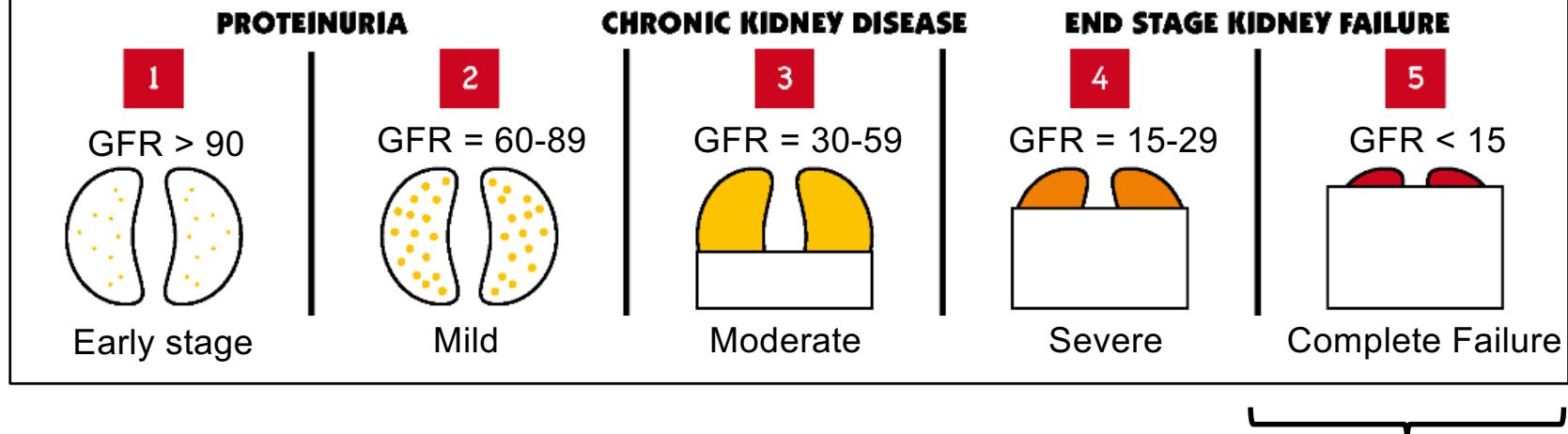
### Renal Insufficiency



#### Symptoms:

- Headaches
- Fatigue
- Decreased ability to concentrate urine
- Low urine output (oliguria)
- Rise in serum creatinine concentration and blood urea nitrogen [BUN] concentration
- Edema
- Mild anemia
- Hyperkalemia
- Hypertension
- Metabolic acidosis

### Stage of kidney disease

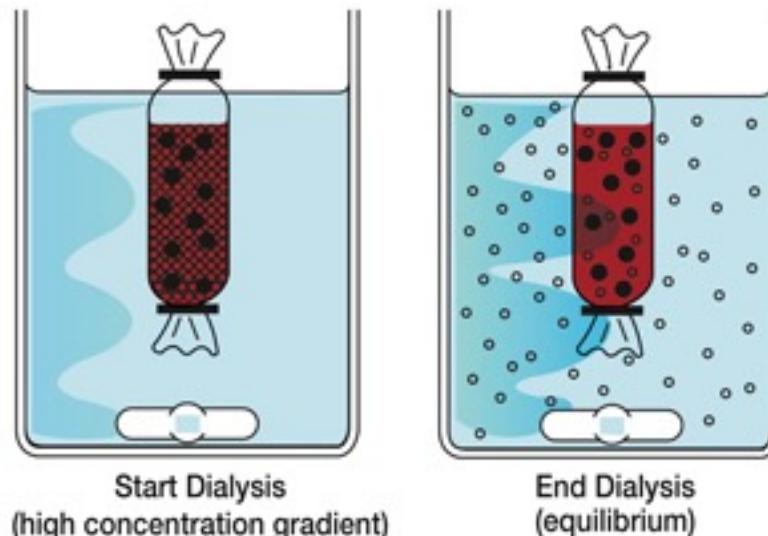


#### Symptoms:

- Neurological problems, e.g. confusion and fatigue
- Cardiovascular problems, e.g. hypertension, arrhythmias
- Respiratory problems, e.g. pulmonary edema
- Gastrointestinal problems, e.g. nausea/vomiting
- Hematological problems, e.g. anemia and hyperkalemia
- Dermatological problems, e.g. dry roughened skin with yellowish discoloration
- Musculoskeletal problems, e.g. muscle cramps, osteoporosis (caused by low calcitriol and high parathyroid hormone level in the blood)

# Treatments for End Stage Renal Failure

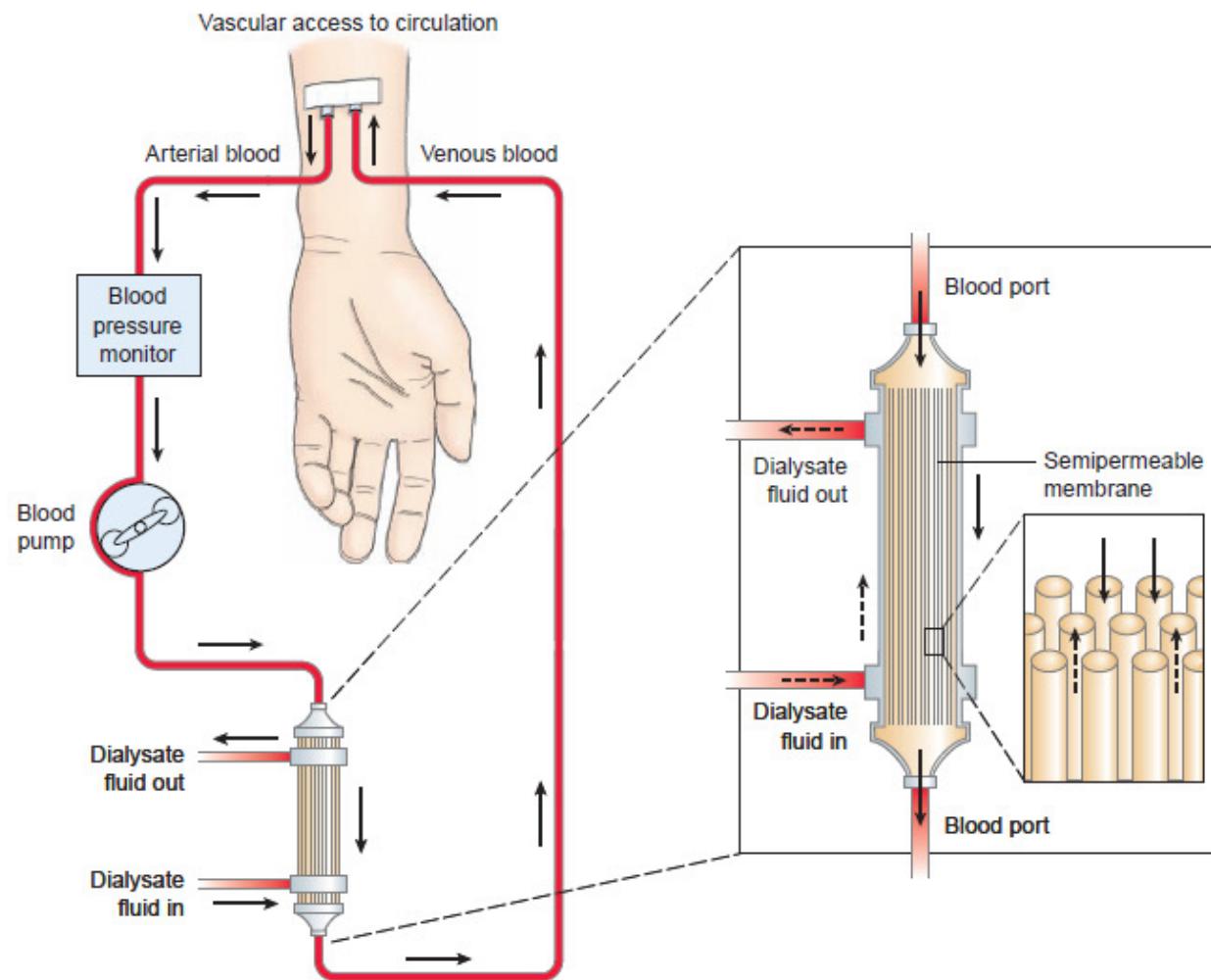
- There is no cure for end stage renal failure, but there are few treatment options:
  1. Dialysis
    - Works on the principles of the diffusion of solutes and ultrafiltration of fluid across a semi-permeable membrane
    - It is a process for removing waste and excess water from the blood which is used primarily as an artificial replacement for lost kidney function in people with end-stage kidney failure



➤ There are two types of dialysis that may be performed:

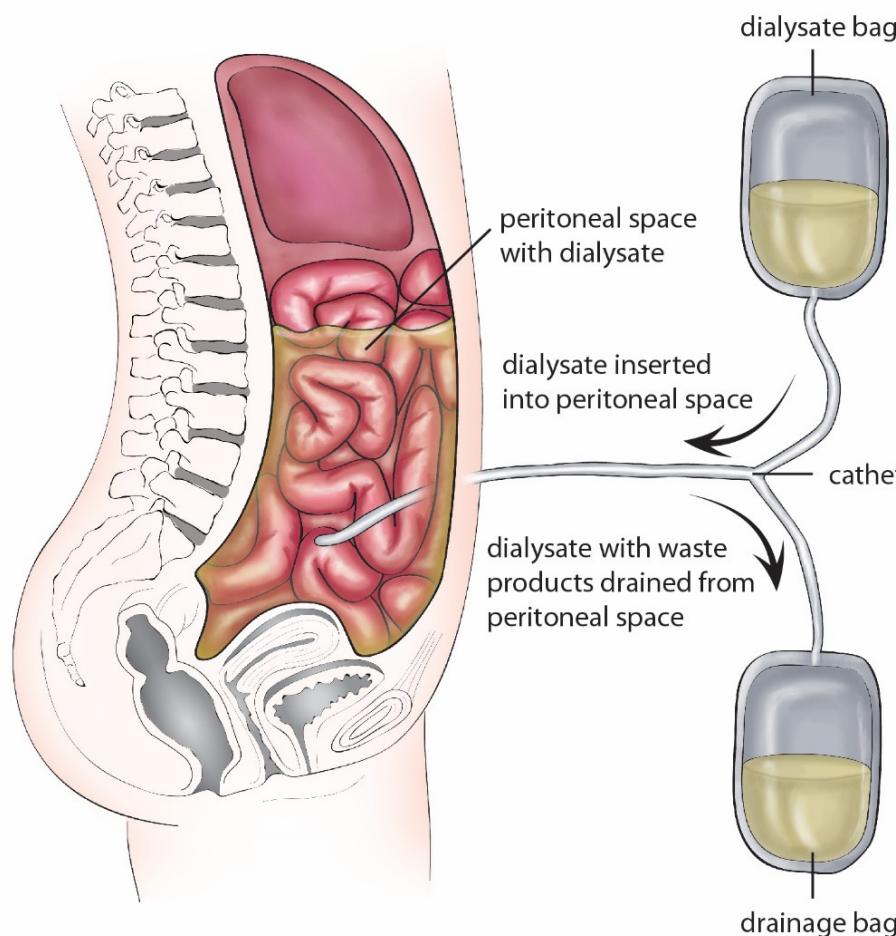
a. Hemodialysis

- ◆ Utilizes a hemodialysis machine that drains the blood, bathes it in a special dialysate solution which removes waste substances and fluid, then returns it to your bloodstream

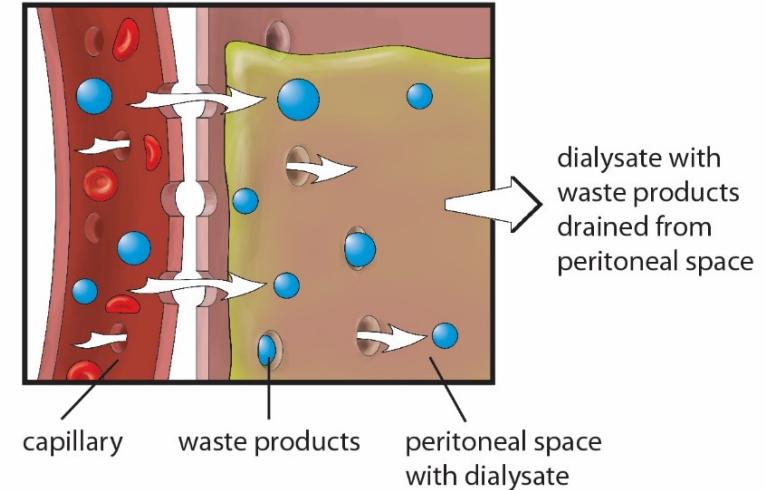


## b. Peritoneal dialysis (PD)

- ◆ Utilizes patient's peritoneum as a semipermeable dialysis membrane
- ◆ The dialysate is left in the abdomen for a designated period of time to allow sufficient time for ultrafiltration and diffusion to occur



waste products cross the semipermeable membranes into the peritoneal space



## HOSPITAL/CLINIC



### HEMODIALYSIS (HD)



4 HRS  
3 X/WEEK  
• MAKE DIETARY CHANGES

## at HOME



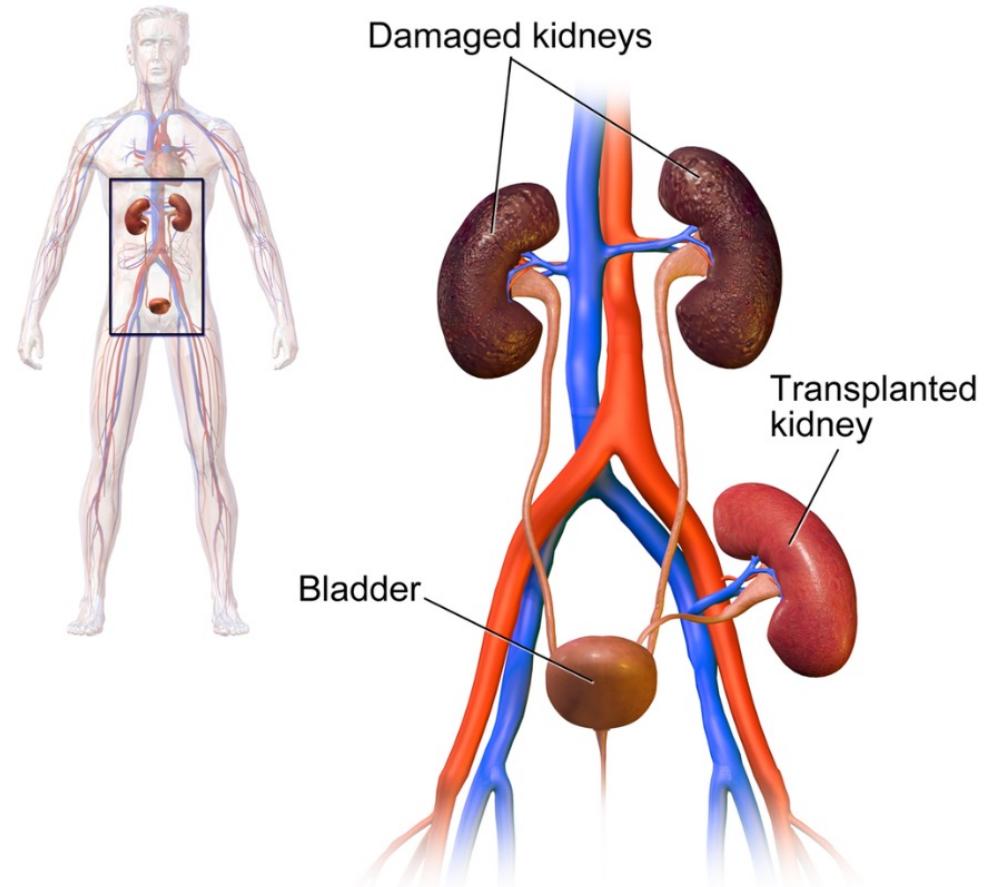
### PERITONEAL (PD)



30 MINUTES  
4 X/day

## 2. Kidney transplantation

- A surgery to place a healthy kidney into a person with kidney failure
- In most cases the non-functioning kidneys of the patients are not removed, and the new kidney is usually placed in a location different from the original kidney
- The new kidney can either come from a living donor or an unrelated donor who have died (deceased donor)

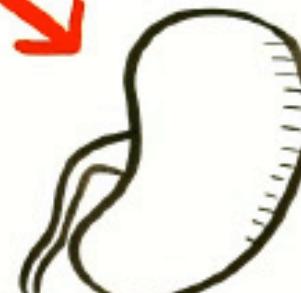


# Donated Kidney

LIVING  
DONOR



DECEASED  
DONOR



THIS IS  
THE BEST  
TREATMENT  
OPTION

LIVE  
LONGER,  
& BETTER

- FAMILY  
MEMBERS &  
FRIENDS
- HAPPEN EARLIER
- LAST LONGER

• ONLY 40-70 CASES PER  
YEAR IN HONG KONG

• 1300 DIALYSIS PATIENTS  
ON WAITING LIST

• NEED TO WAIT FOR 18  
YEARS ?!!

Talk to  
your  
FAMILY &  
FRIENDS