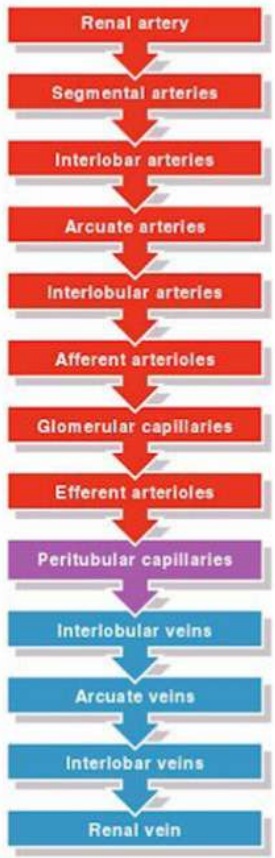
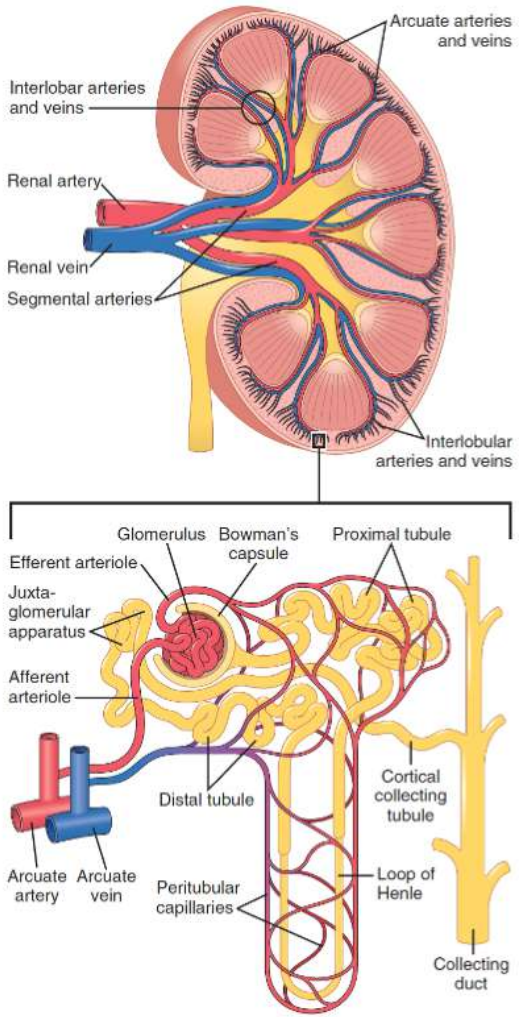
Major functions of the Kidney

Homeostasis	Excretion	Biosynthesis
➢ Regulation of water and electrolyte balances ➢ Regulation of arterial pressure ➢ Regulation of acid-base balance	➢ Metabolic waste products (urea, uric acid, creatinine & bilirubin) ➢ Foreign chemicals and drugs ➢ Hormones (e.g insulin)	➢ Erythropoietin ➢ Thrombopoietin ➢ 1,25 dihydroxycholecalciferol (Vitamin D) ➢ Renin ➢ Prostaglandins ➢ Adenosine ➢ Endothelin, NO, bradykinin ➢ Glucose

Renal Blood Supply

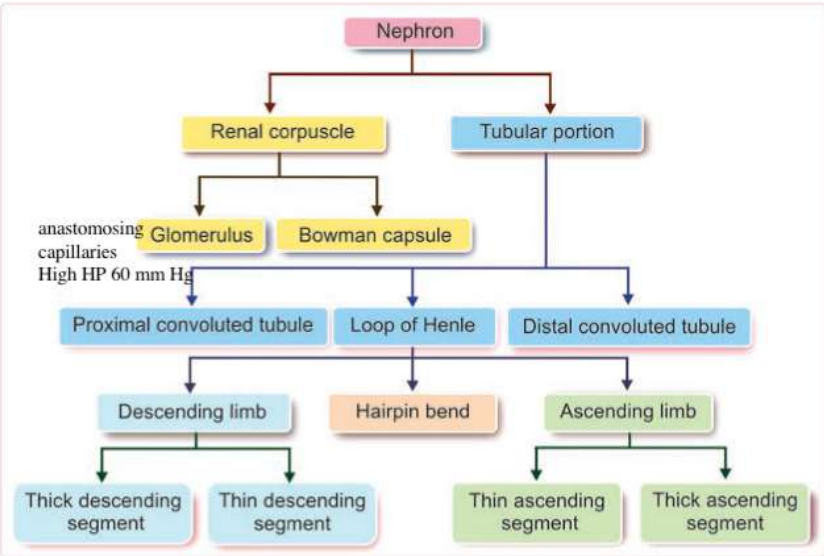
Blood flow to both kidneys~22% CO = 1100 ml/min.

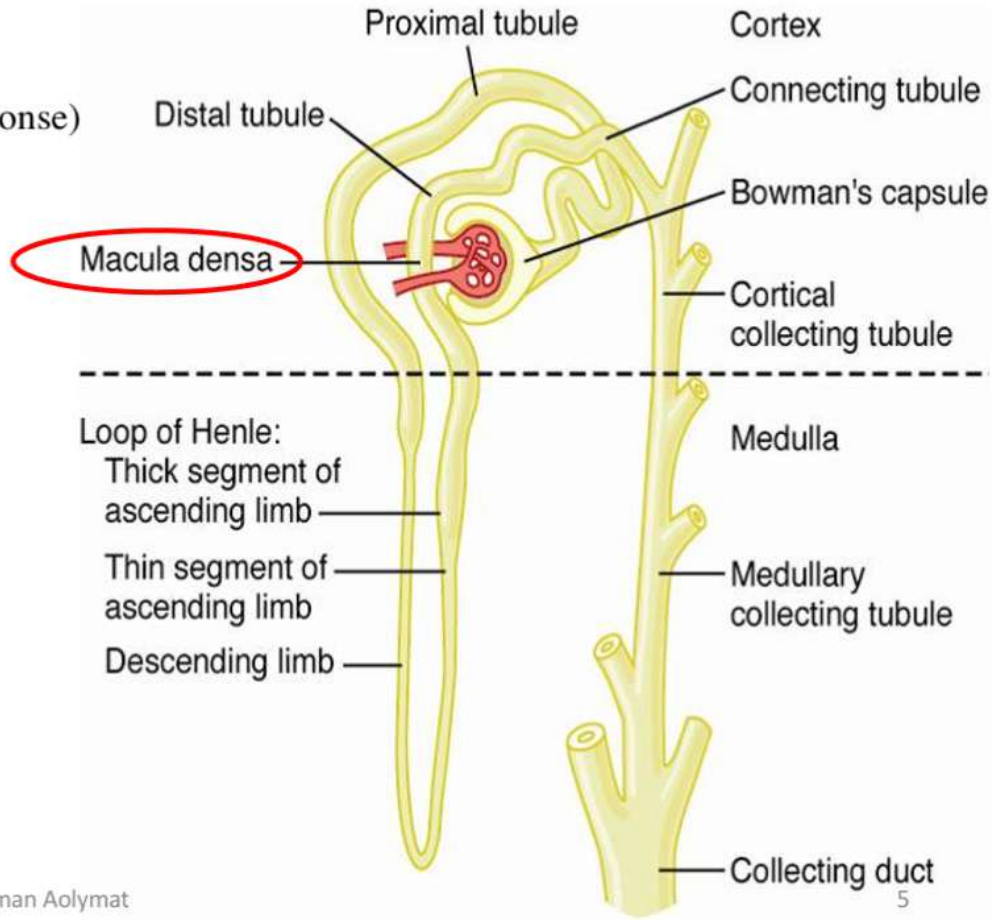




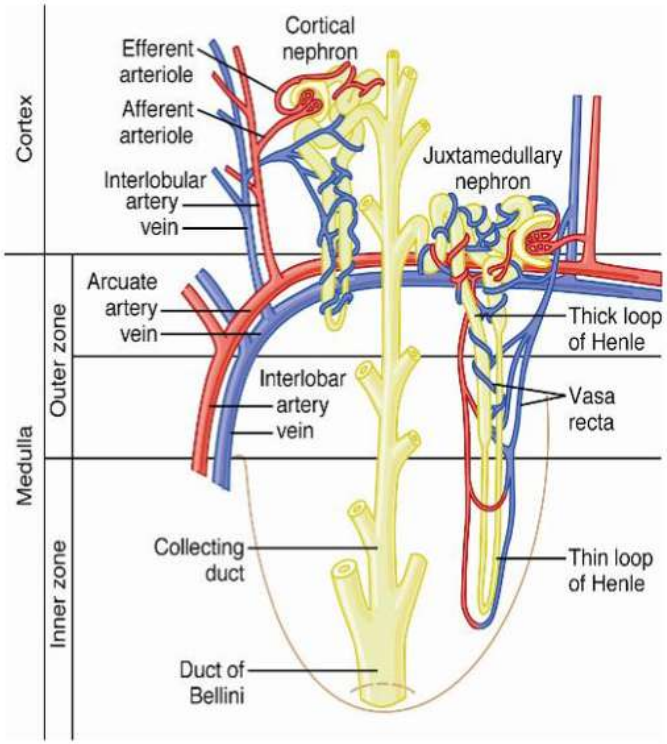
Nephron

Functional unit of the kidney
800K-1M nephrons/kidney, ↓ with ageing (adaptive response)





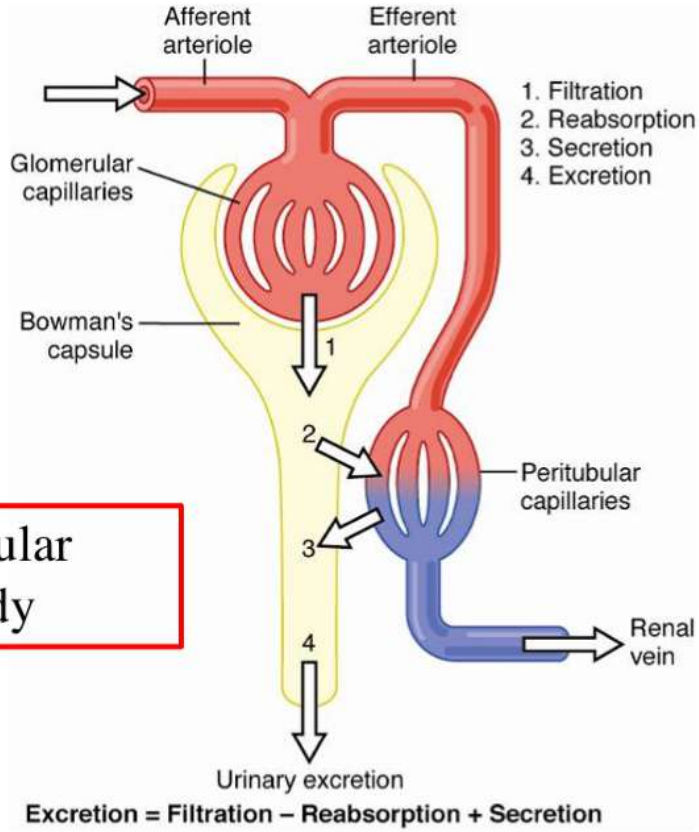
Regional differences in nephron structure: cortical & juxtamedullary nephrons



Features	Cortical nephron	Juxtamedullary nephron
Percentage	85%	15%
Situation of renal corpuscle	Outer cortex near the periphery	Inner cortex near medulla
Loop of Henle	Short	Long
	Hairpin bend penetrates only up to outer zone of medulla	Hairpin bend penetrates up to the tip of papilla
Blood supply to tubule	Peritubular capillaries	Vasa recta
Function	Formation of urine	Mainly the concentration of urine and also formation of urine

Basic Mechanisms of Urine Formation

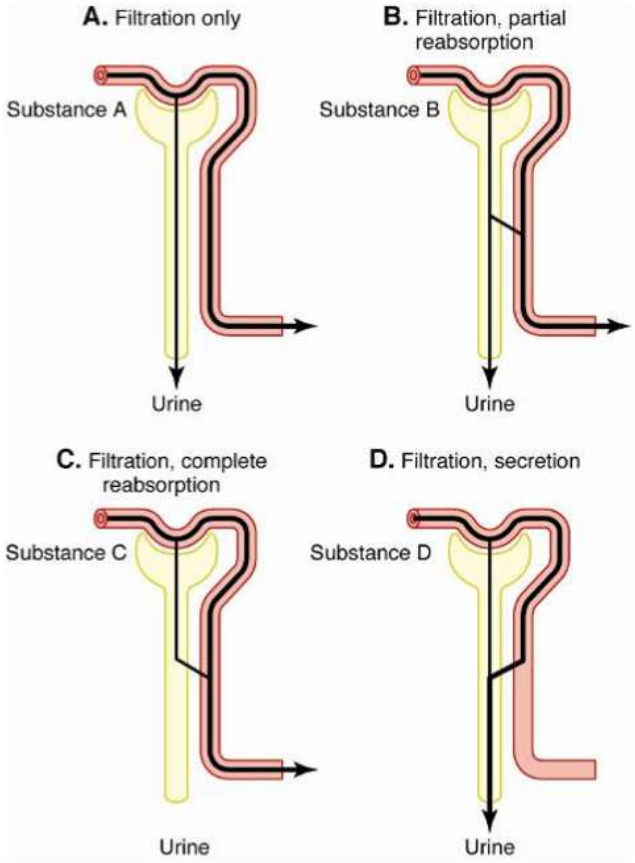
Glomerular filtration, tubular reabsorption, & tubular secretion are regulated according to needs of body



Renal Handling of Different Substances

Creatinine

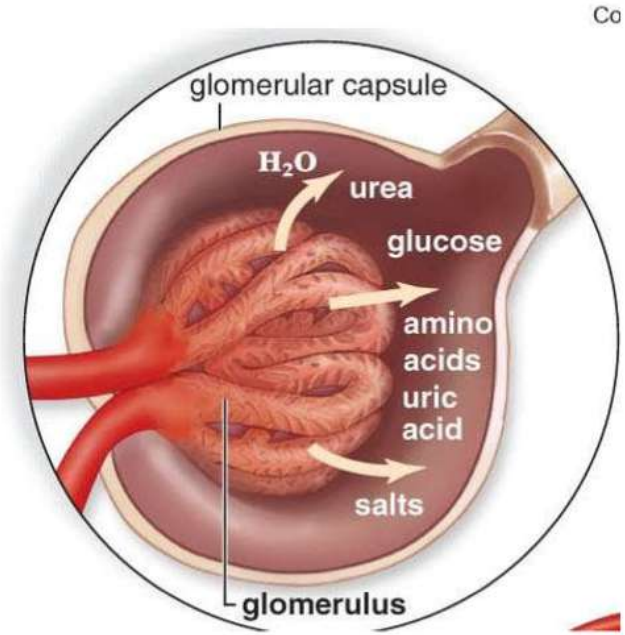
Electrolytes (e.g. Na^+ & Cl^-)



Nutritional substances (amino acids & glucose)

Organic acids and bases

Filtration

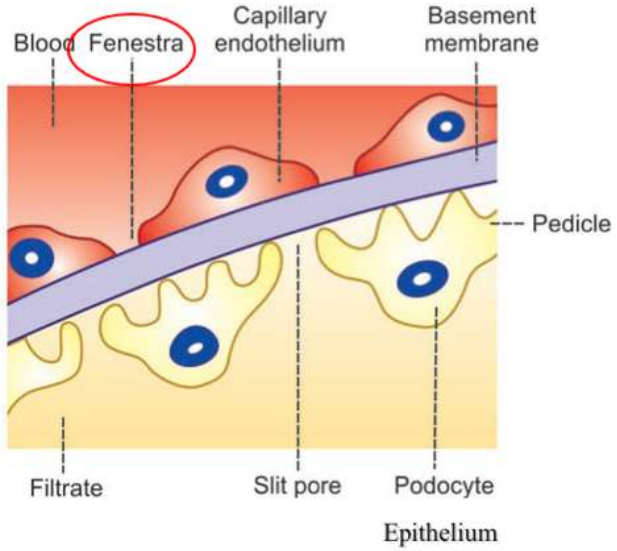

glomerular capsule
H_2O
urea
glucose
amino acids
uric acid
salts
glomerulus

Glomerular capillary filtration barrier

Fenestrated endothelium
- *pores* exclude <u>blood cells and large plasma proteins</u>

Basement membrane
Proteoglycan gel/–ve charge

Epithelium/Podocytes: not continuous footlike processes→ Slit diaphragm pores



Filterability of Solutes Across Glomerular Barrier

- Molecular size (inverse relationship)
- Electrical charge (-ve charged large molecules are filtered **less** easily than +ve charged molecules of equal molecular size due to electrostatic repulsion, any defect→ proteinuria/albuminuria
- Shape (rigid or deformable)

Filterability of solutes across glomerular barrier

Filterability of 1.0 means= substance is filtered as freely as water; [plasma] =[Bowman's capsule]
Filterability of 0.75 =substance is filtered only 75% as rapidly as water.

Table 27-1 Filterability of Substances by Glomerular Capillaries Based on Molecular Weight

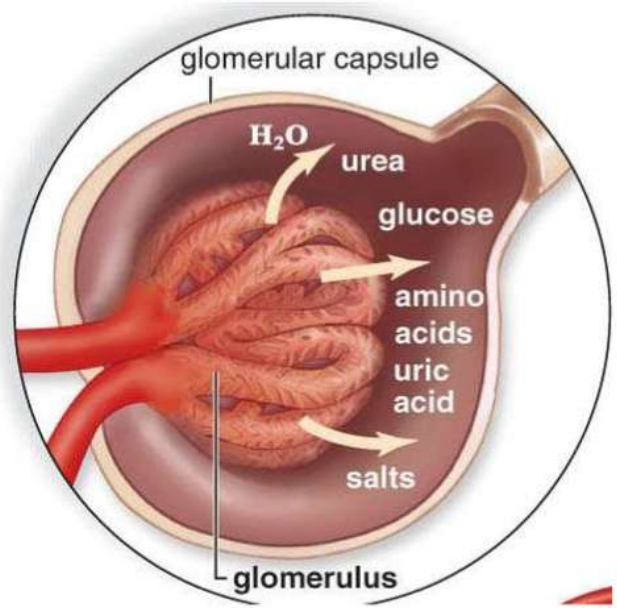
Substance	Molecular Weight	Filterability
Water	18	1.0
Sodium	23	1.0
Glucose	180	1.0
Inulin	5500	1.0
Myoglobin	17,000	0.75
Albumin	69,000	0.005

Filtration

- **Filtration : not selective** → Glomerular filtrate composition is about the same as plasma, except for **large proteins**

- **No blood cells**

- Ca & FA bound to protein→↓[] in filtrate

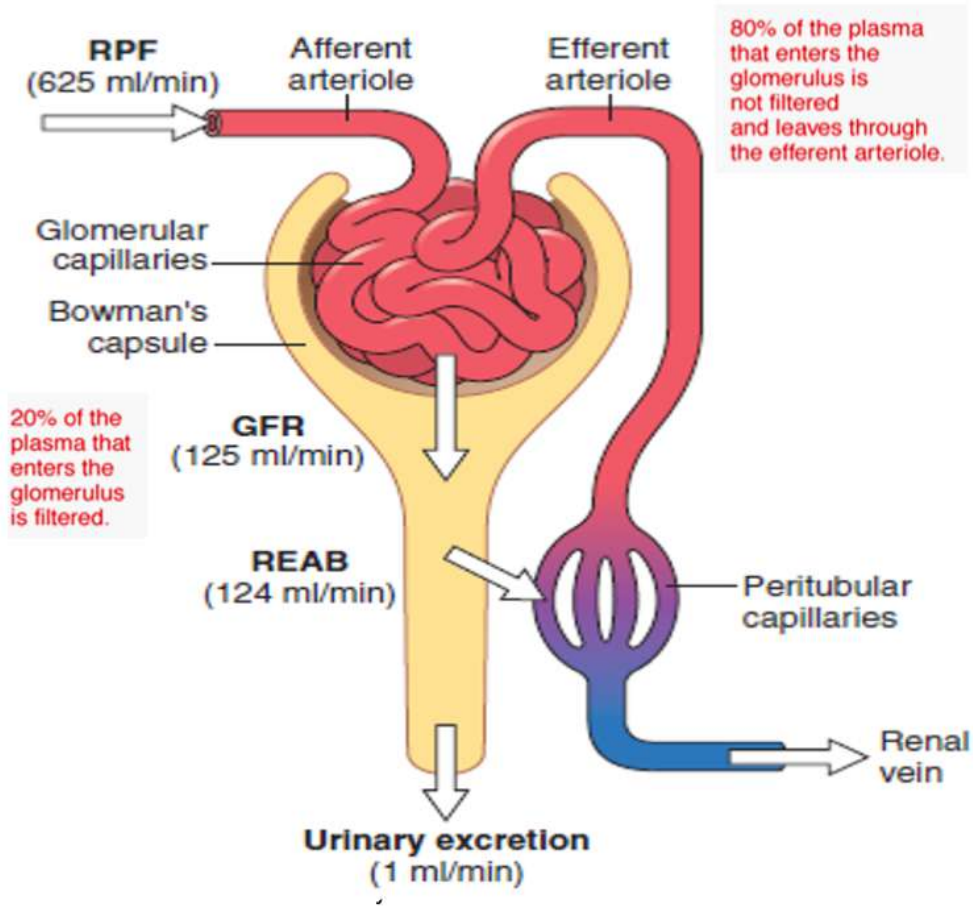


Importance of Glomerular Filtration→ Remove waste products

Average values for total RPF, GFR, tubular reabsorption, and urine flow rate

Renal plasma flow (**RPF**): the volume of blood plasma *delivered* to the kidneys *per unit time* (625 ml/min)

Glomerular filtration rate (GFR): the volume of fluid *filtered* from the kidney's glomerular capillaries into Bowman's capsule *per unit time* (125 ml/min or 180 L/day→ entire plasma can be filtered and processed about 60 times/day.)



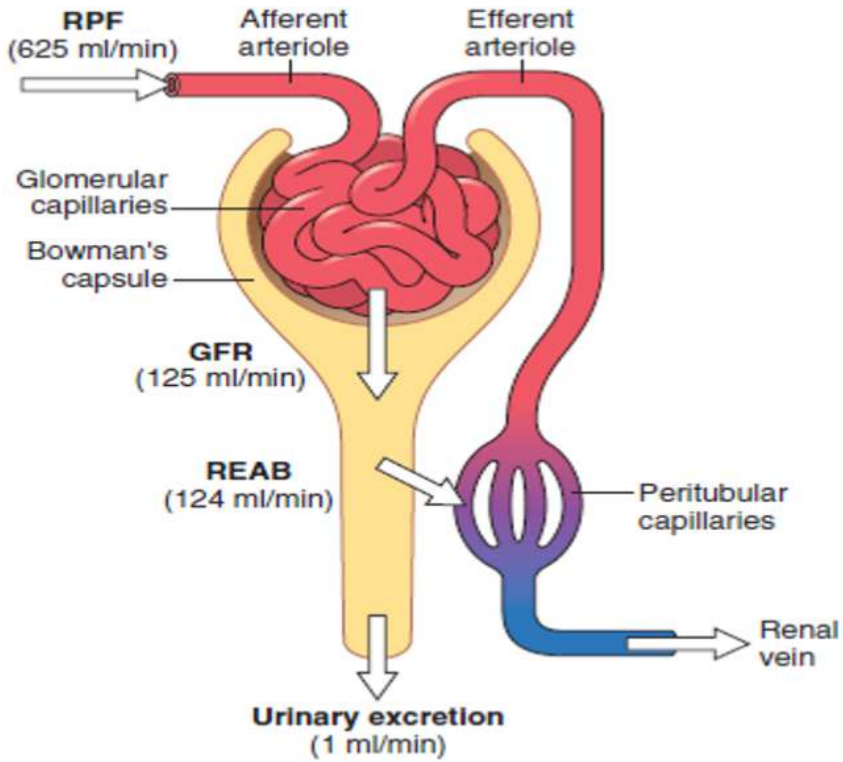
Excretion = Filtration – Reabsorption + Secretion

RPF & GFR

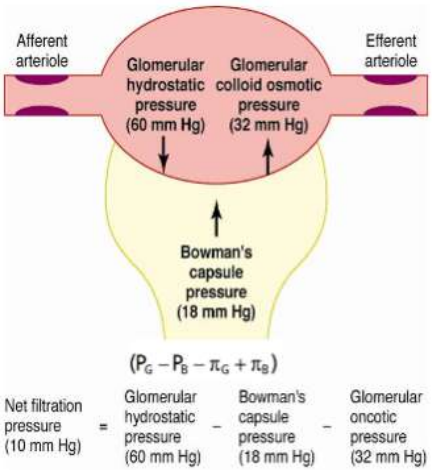
GFR ∝ RPF

GFR= factor * RPF

- Filtration fraction (FF)= GFR/RPF
  125/625= 0.2



Excretion = Filtration – Reabsorption + Secretion



Determinants of GFR

Pressure

- **Glomerular hydrostatic pressure (P_G)**
  - Favors filtration
  - 60 mmHg
  - Due to blood in the capillary "systemic pressure"
- **Bowman hydrostatic pressure (P_B)**
  - Opposes filtration
  - 18 mmHg
  - Due to filtered fluid in the capsule
- **Glomerular Colloid (π_G)**
  - Opposes filtration
  - (28 – 36 mmHg)
  - Average : 32 mmHg
  - Due to plasma protein in the capillary
- **Bowman osmotic pressure**
  - No effect
  - 0 mmHg
  - Due to absent of plasma protein in the capsule

Capillary filtration coefficient (K_f)

- Surface area
- Permeability

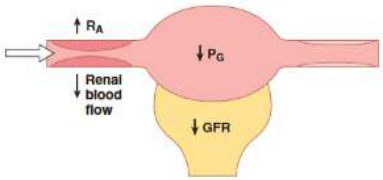
Determinants of P_G

$\uparrow P_G \rightarrow \uparrow$ GFR

Changes in P_G serve as the **means for physiological regulation of GFR.**

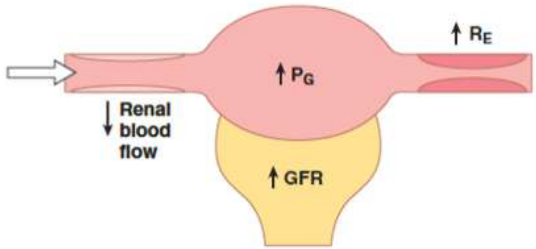
Determinants of P_G

- Afferent arteriolar resistance (Inverse)
- Efferent arteriolar resistance (Proportional ; *certain limit*)
- Arterial pressure (buffered by autoregulation)

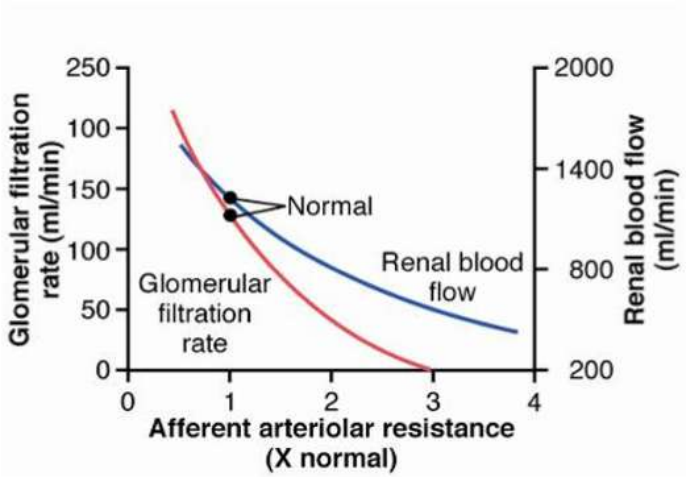


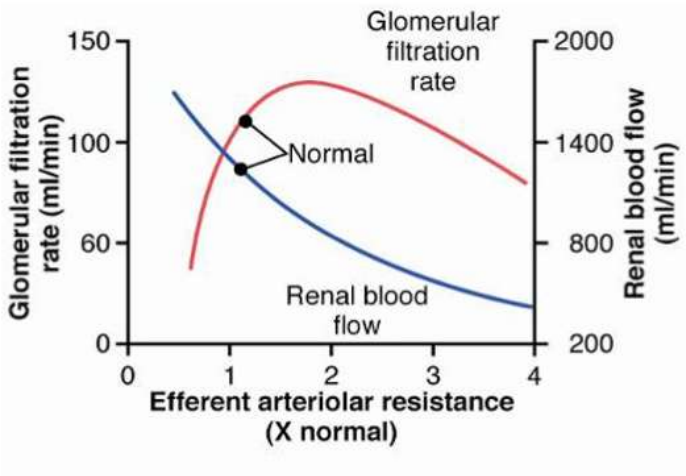
Efferent arteriolar constriction→**↓reduces renal blood flow**

$\uparrow R_E \rightarrow \uparrow$ FF & $\pi_G \rightarrow \pi_G > P_G \rightarrow$ net ↓GFR



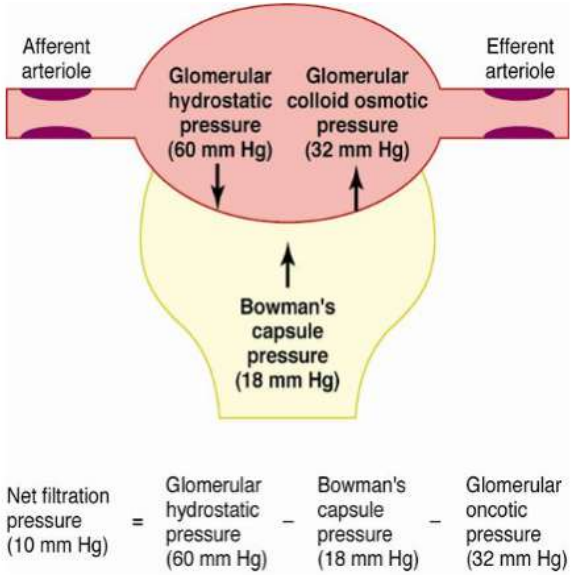
Effect of changes in afferent arteriolar or efferent arteriolar resistance

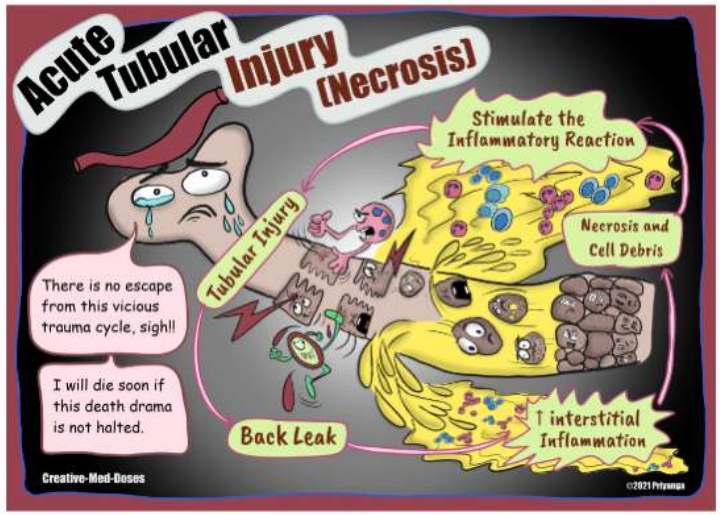




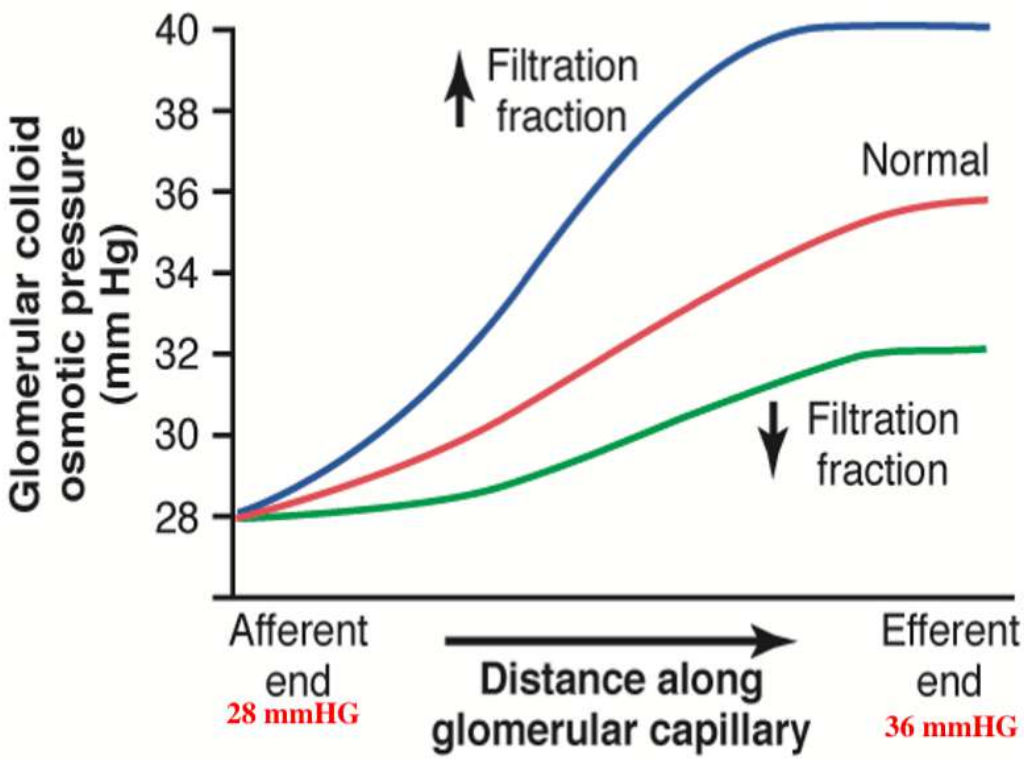
Bowman's Capsule hydrostatic Pressure (P_B)

- Tubular Obstruction
  kidney stones
  tubular necrosis $\longrightarrow$ ↓GFR
- Urinary tract obstruction
  Prostate hypertrophy/cancer





Increase in colloid osmotic pressure in plasma reduces GFR



[plasma protein] ↑about 20%, due to filtration of plasma→ concentrating glomerular proteins

Factors Influencing Glomerular Capillary Oncotic/colloid Pressure (π_G)

++ intra-capillary proteins

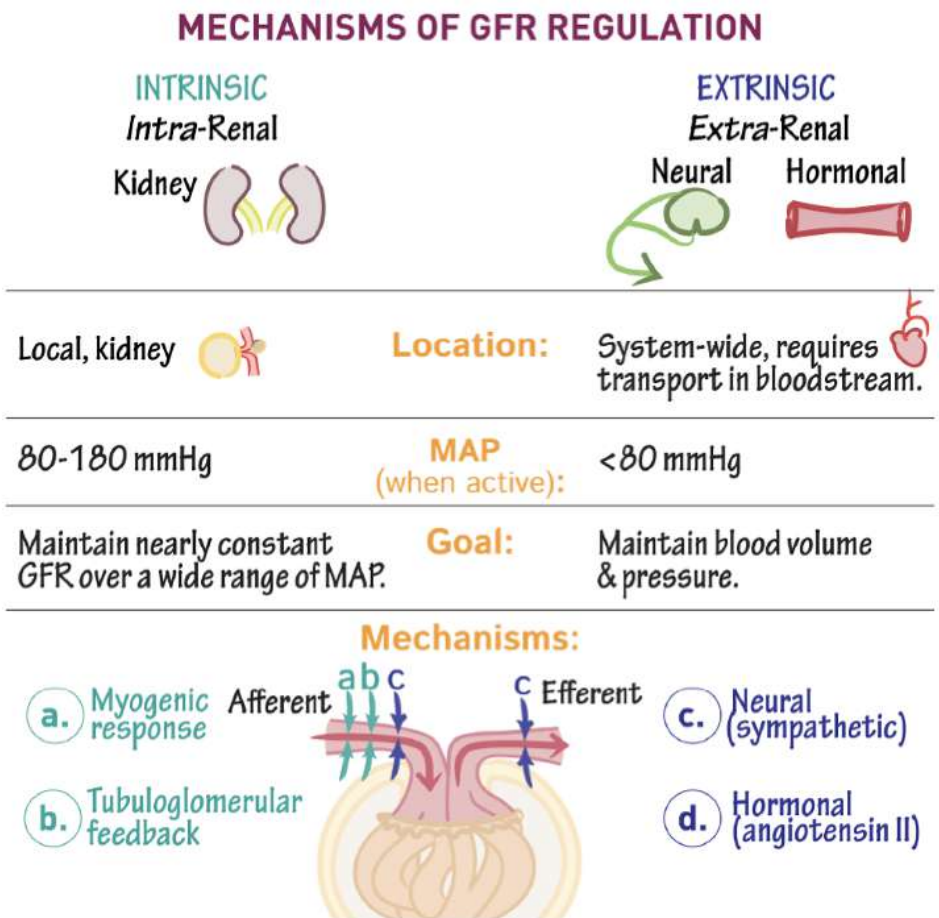
- Arterial Plasma Oncotic Pressure (π_A)

$$\uparrow \pi_A \longrightarrow \uparrow \pi_G \longrightarrow \downarrow GFR$$

- Filtration Fraction (FF)

$$\uparrow FF \longrightarrow \uparrow \pi_G \longrightarrow \downarrow GFR$$

Control of GFR and RBF



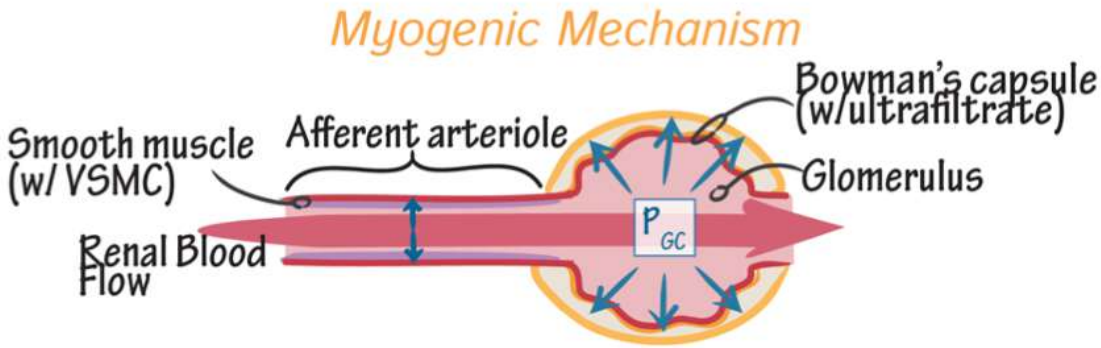
Autoregulation

Intrinsic ability of kidneys to regulate its own **blood flow <u>to maintain constant GFR</u>**

Autoregulation → constant RBF & GFR over P changes 80-170 mmHg

Two mechanisms involved in renal autoregulation:
1. Myogenic response
2. Tubuloglomerular feedback

Myogenic response



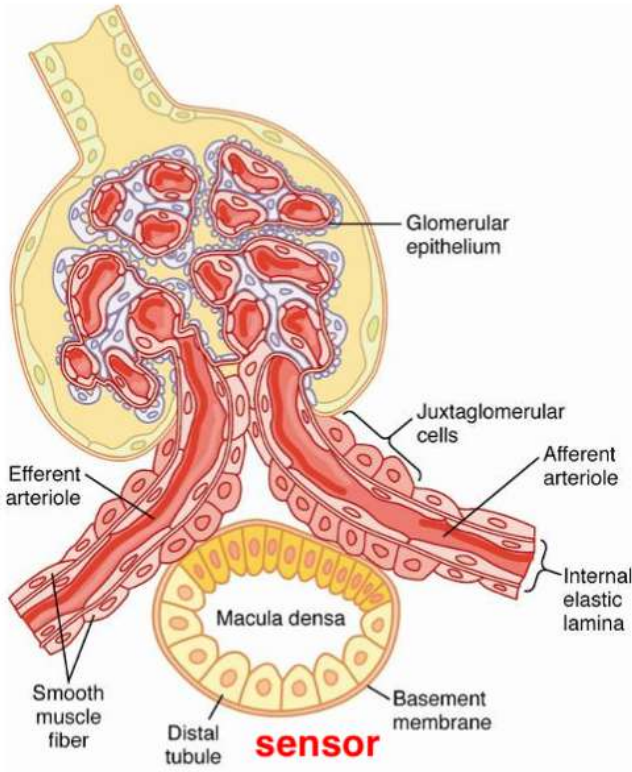
1. ↑RBF = ↑Hydrostatic pressure against the walls of the afferent arteriole.

↑flow of Ca from ECF into cells

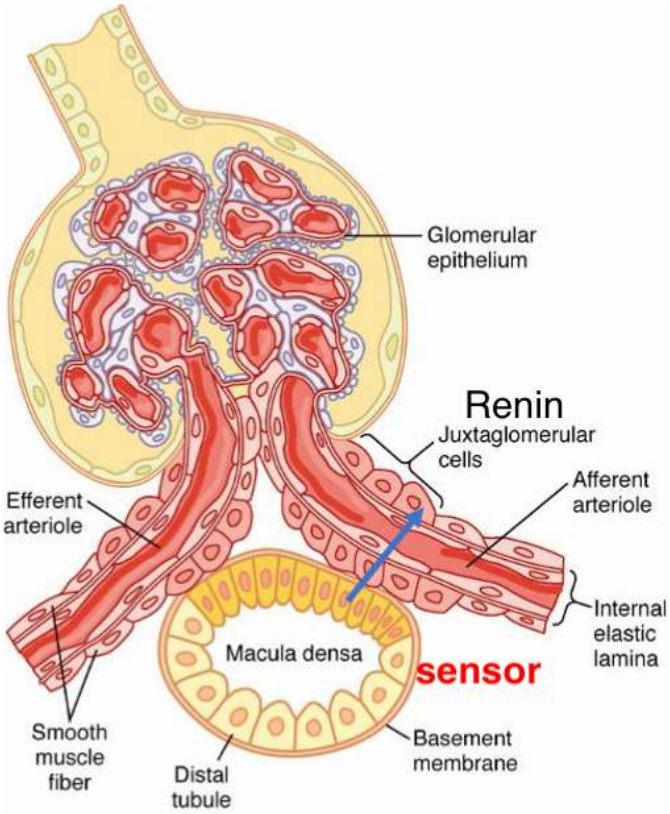
2. Stretch receptors in VSMC initiate VASOCONSTRICTION.

Juxtaglomerular apparatus

- The juxta-glomerular apparatus is a specialized structure formed by the **distal convoluted tubule and the glomerular afferent arteriole**
- Its main function is to **regulate blood pressure** and GFR
- It's made up of **juxtaglomerular cells and the macula densa**
- The macula densa is a collection of specialized epithelial cells in the *distal convoluted tubule* that **detect Na concentration** of the fluid in the tubule



Juxtaglomerular apparatus

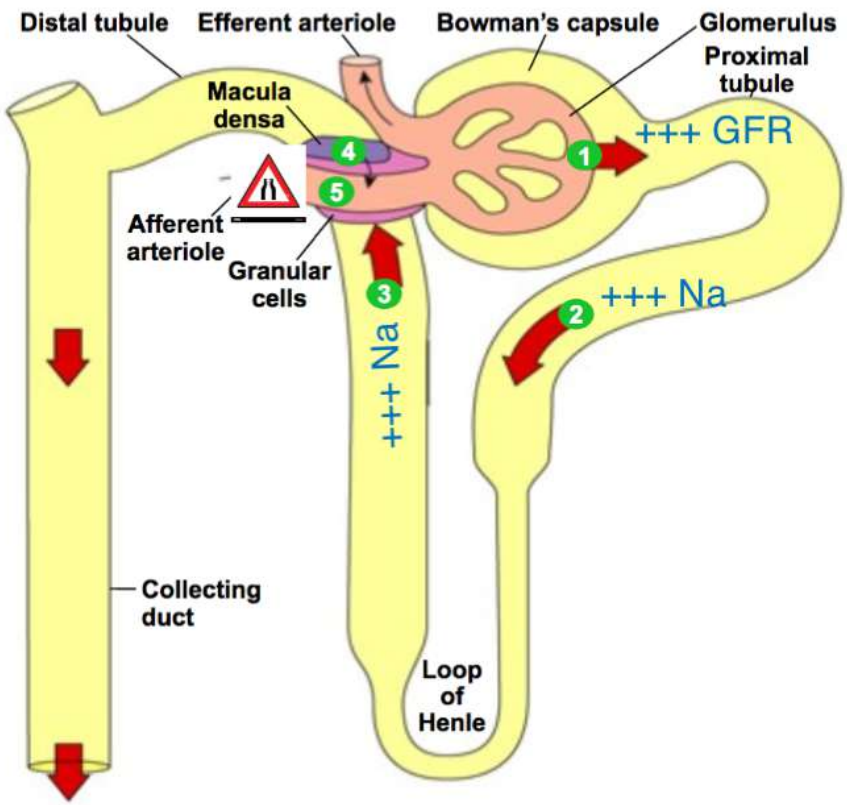


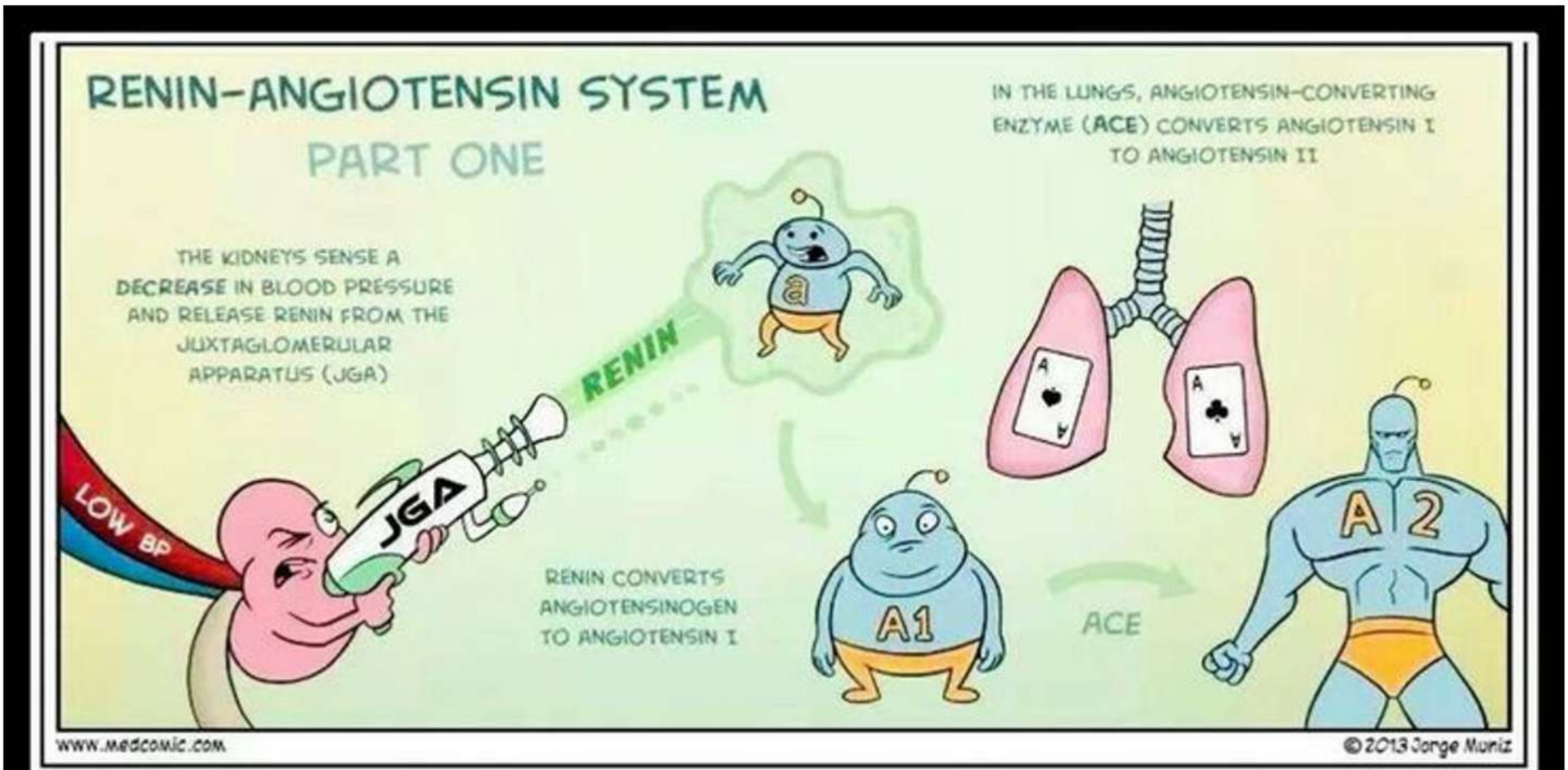
Tubuloglomerular feedback

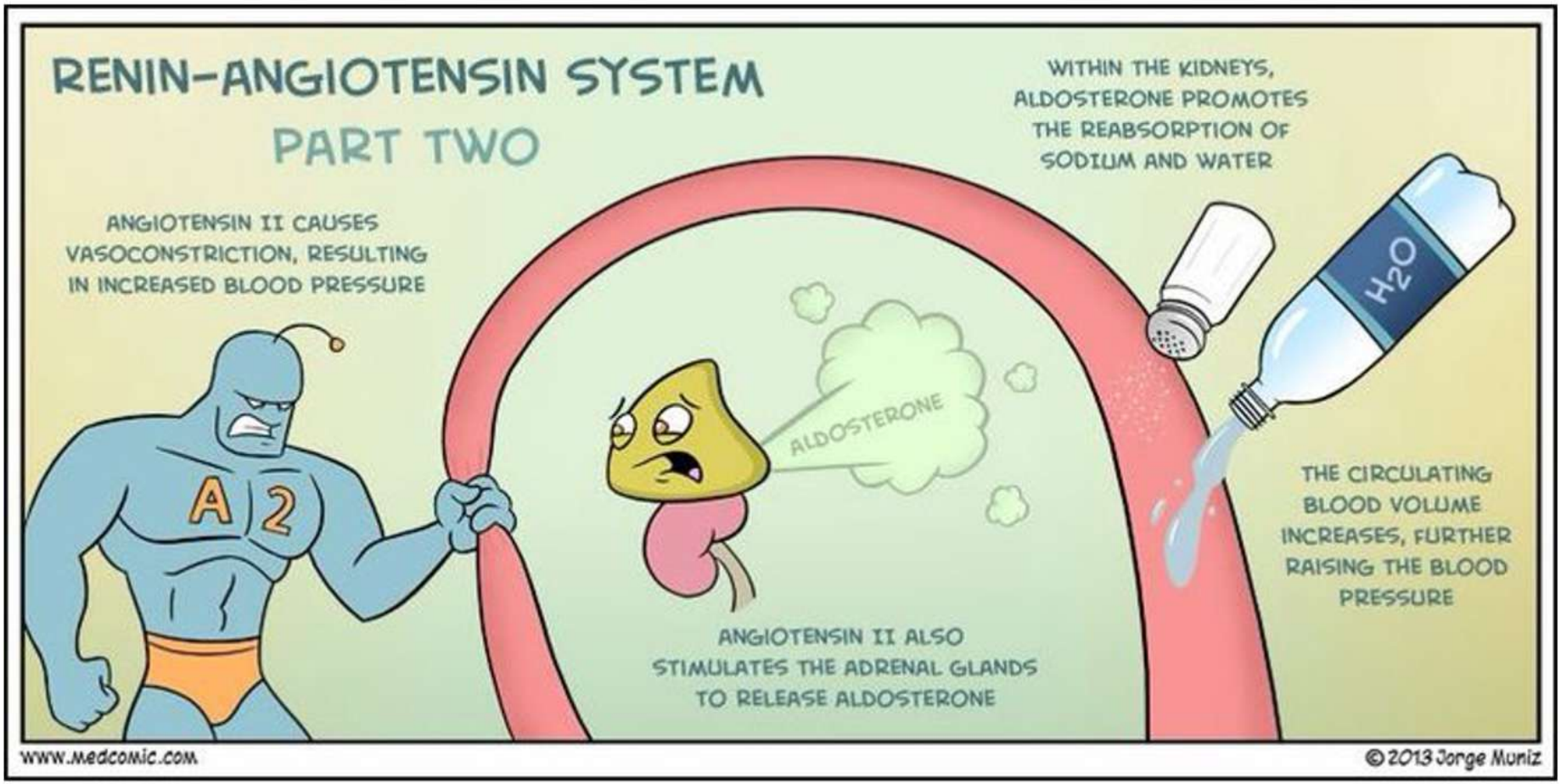
High Na→
↑ adenosib→ VC of A } ↓↓ GFR

Low Na→
↑ NO & PG→ VD of A
↑ Renin—angio II→ VC of E & Aldosterone secretion } +++ GFR

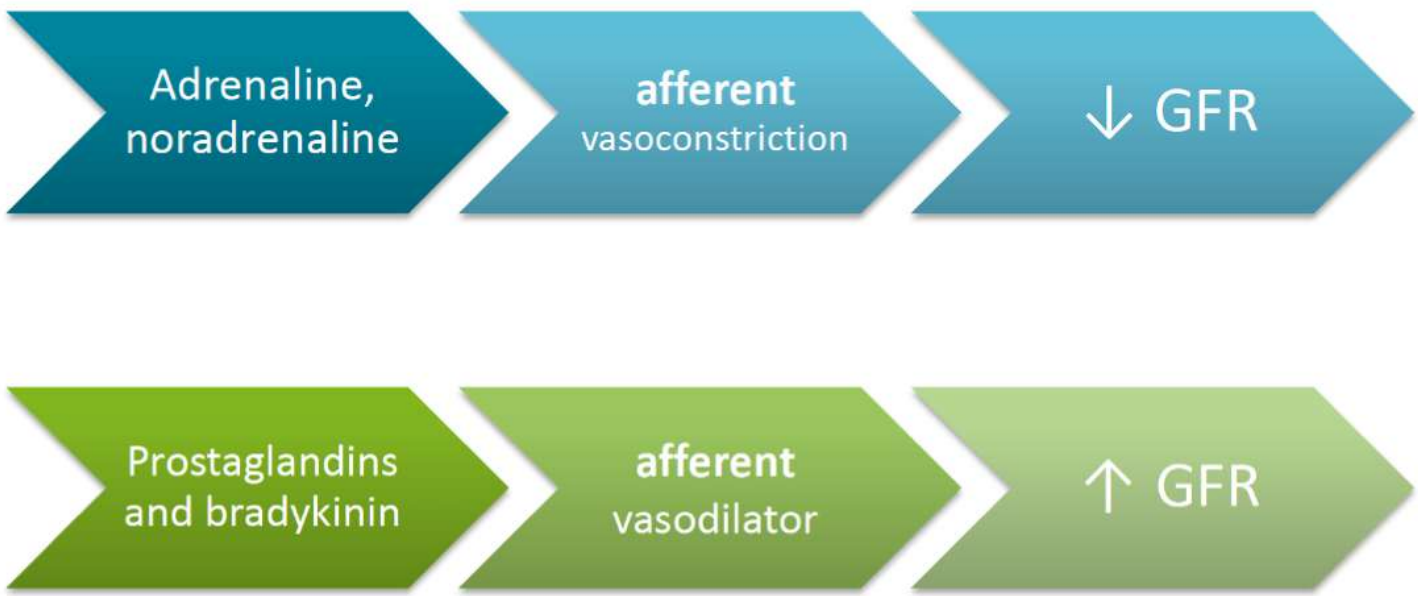
Tubuloglomerular feedback




RENIN-ANGIOTENSIN SYSTEM
PART ONE
THE KIDNEYS SENSE A DECREASE IN BLOOD PRESSURE AND RELEASE RENIN FROM THE JUXTAGLOMERULAR APPARATUS (JGA)
LOW BP
JGA
RENIN
a
RENIN CONVERTS ANGIOTENSINOGEN TO ANGIOTENSIN I
A1
ACE
IN THE LUNGS, ANGIOTENSIN-CONVERTING ENZYME (ACE) CONVERTS ANGIOTENSIN I TO ANGIOTENSIN II
A2
www.medcomic.com
©2013 Jorge Muniz

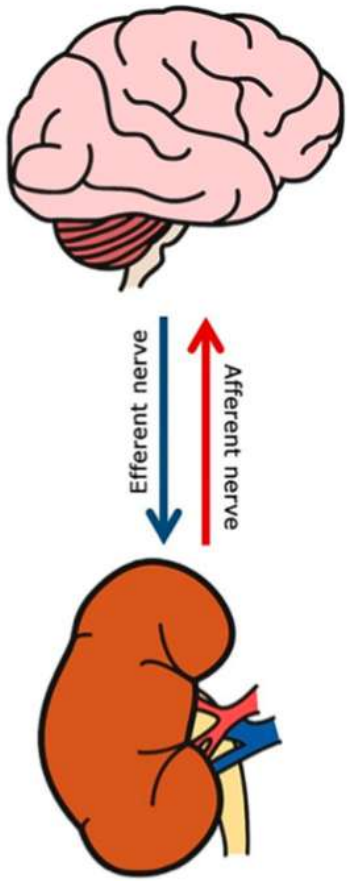

RENIN-ANGIOTENSIN SYSTEM
PART TWO
ANGIOTENSIN II CAUSES VASOCONSTRICTION, RESULTING IN INCREASED BLOOD PRESSURE
A2
ALDOSTERONE
ANGIOTENSIN II ALSO STIMULATES THE ADRENAL GLANDS TO RELEASE ALDOSTERONE
WITHIN THE KIDNEYS, ALDOSTERONE PROMOTES THE REABSORPTION OF SODIUM AND WATER
H2O
THE CIRCULATING BLOOD VOLUME INCREASES, FURTHER RAISING THE BLOOD PRESSURE
www.medcomic.com
©2013 Jorge Muniz

Other Hormonal regulation of GFR



Nervous regulation of GFR and RBF

Strong sympathetic stimulation→ vasoconstriction (Afferent) →↓GFR
Moderate sympathetic stimulation→ little effect
Sympathetic have **little** influence on RBF (↓RBF).
sympathetic stimulation→ ↑ Renin



Sympathetic is important in acute disturbances (e.g. defense reaction, brain ischemia, or severe haemorrhage)

Clearance

- Volume of plasma completely cleared of a substance by both kidneys per unit time.

- To quantify renal function (RBF, GFR, reabsorption & secretion)

Clearance Technique

$$Cs \times Ps = Us \times V$$

$$Cs = \frac{Us \times V}{Ps} = \frac{\text{urine excretion rate}}{\text{Plasma conc.}}$$

Where : Cs = clearance of substance S

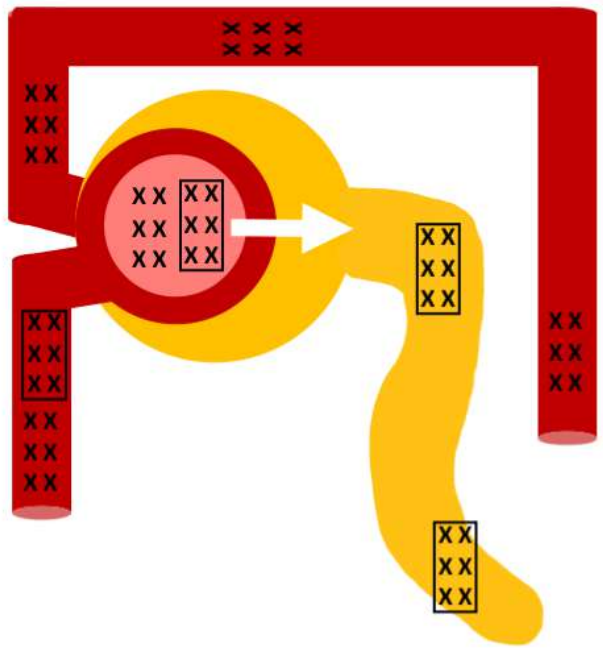
Ps = plasma conc. of substance S

Us = urine conc. of substance S

V = urine flow rate

Use of clearance to measure GFR

For a substance that is freely filtered, but <u>not</u> reabsorbed or secreted (inulin, ^{125} I-iothalamate, creatinine), renal clearance is <u>equal</u> to GFR



Amount filtered = Amount excreted

$$GFR \times P_{in} = U_{in} \times V$$

$$GFR = \frac{U_{in} \times V}{P_{in}}$$

Creatinine clearance to estimate GFR

Advantages:

- Cleared from the body fluids *almost entirely* by glomerular filtration
- Not require intravenous infusion

Disadvantages

- not perfect marker of GFR because a small amount of it is **secreted** by the tubules→ amount of creatinine excreted > amount filtered→ a slight error in measuring plasma creatinine

Use of clearance to estimate RPF

Theoretically, if a substance is <u>completely</u> cleared from plasma→ its clearance rate =<u>renal plasma flow (RPF)</u>

Amount of substance delivered to kidneys in blood= Amount excreted in urine

$$(RPF \times Ps) = (Us \times V)$$

$$RPF = Us \times V / Ps$$

Cx = renal plasma flow

Use of PAH clearance to estimate renal plasma flow

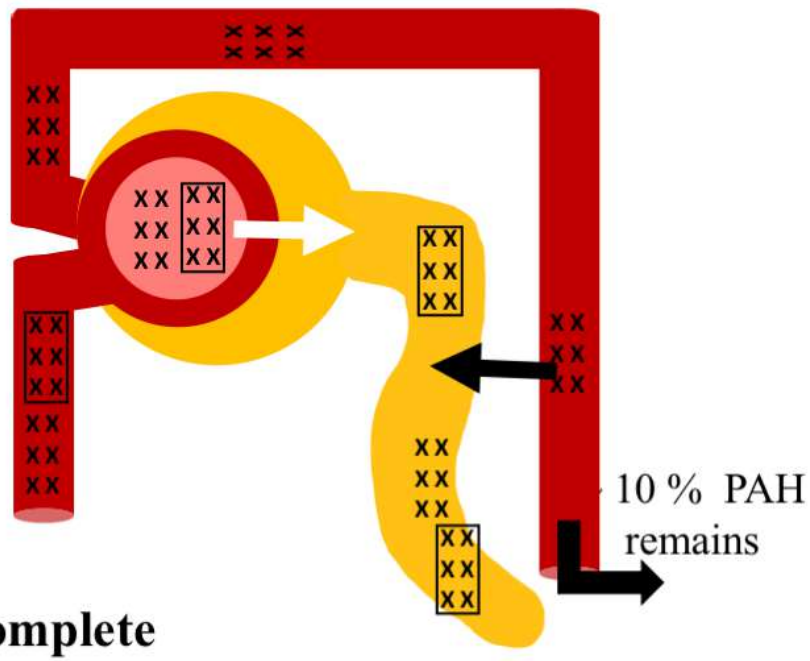
Paraminohippuric acid (PAH) is 90% filtered and secreted and is almost completely cleared from the renal plasma

amount entered $\cong$ amount excreted

$$RPF \times P_{pah} = U_{PAH} \times V$$

$$RPF = \frac{U_{PAH} \times V}{P_{PAH}}$$

$$RPF = \text{Clearance PAH}$$



To calculate <u>actual</u> RPF , one must correct for incomplete extraction of PAH

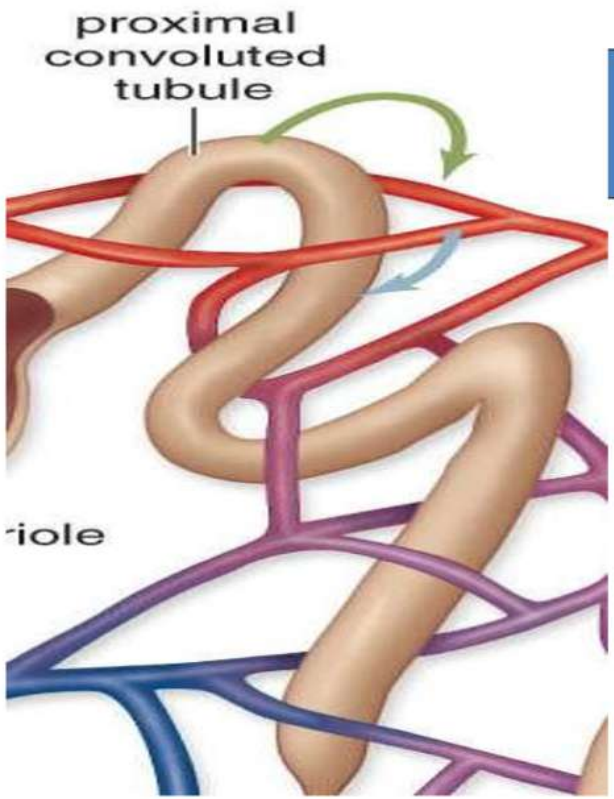
Calculation of tubular reabsorption/excretion

- If the rates of **glomerular filtration** and **renal excretion** of a substance are known, one can *calculate whether there is a net reabsorption or a net secretion* of that substance by the renal tubules.

- If the rate of **excretion** of the substance (Us x V) < the **filtered load** of the substance (GFR x Ps), then some of the substance must have been **reabsorbed** from the renal tubules.

- If the **excretion rate** of the substance > **filtered load**, then the rate of excretion= **sum of the rate of glomerular filtration plus tubular secretion.**

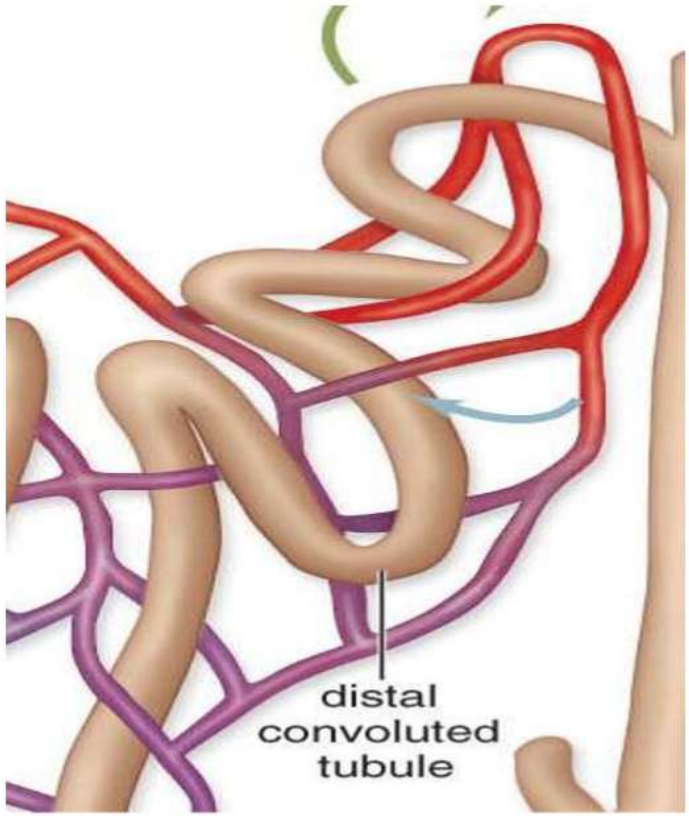
Tubular eabsorption



return of filtrates from tubules through diffusion & active transport

- Selective
- Most electrolytes (e.g. Na^+, K^+, HCO_3^-, Cl^-), nutritional substances (e.g. glucose) are almost completely reabsorbed
- Most waste products (e.g. urea, creatinine, uric acid, urates) poorly reabsorbed

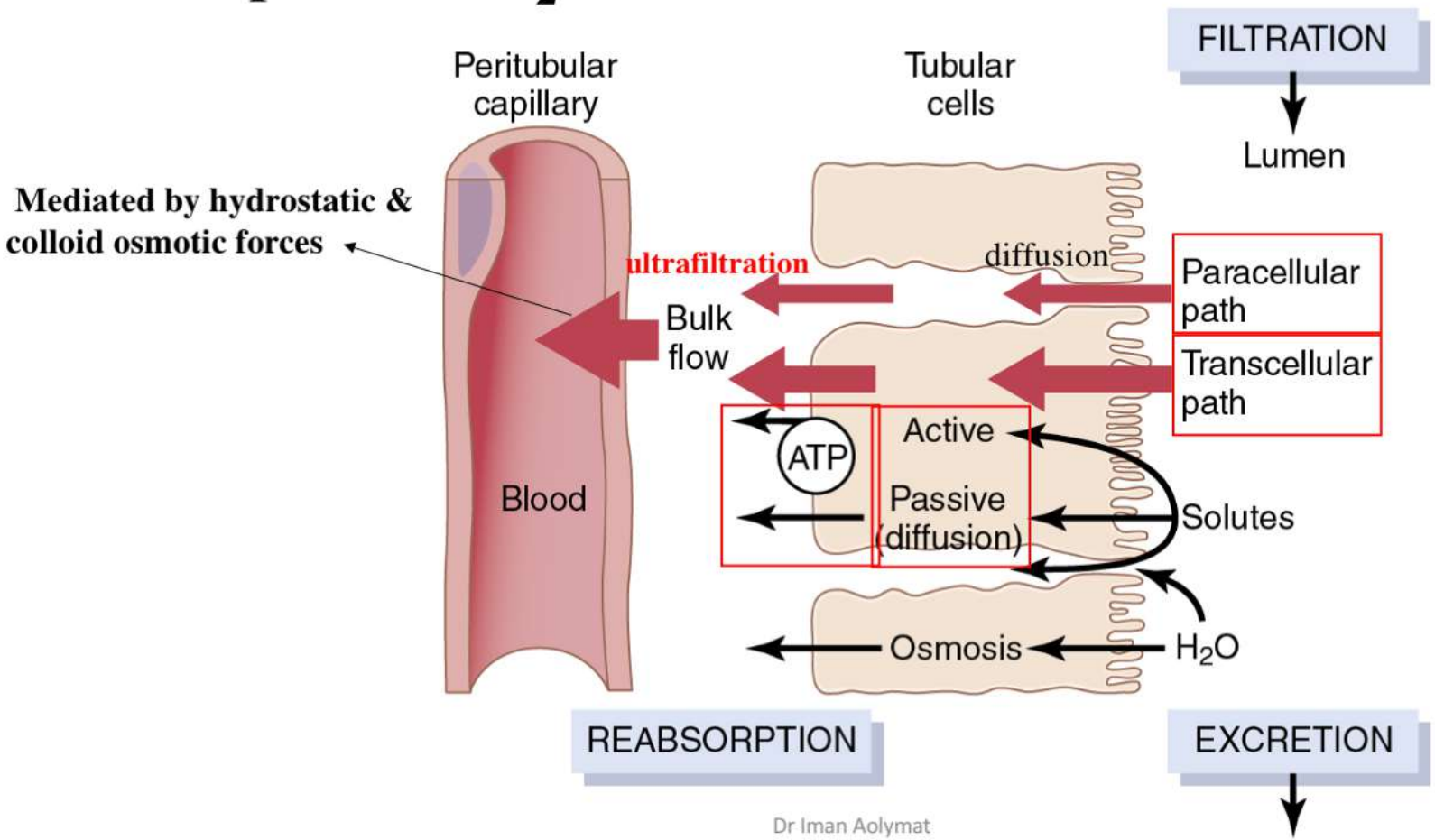
3. Tubular Secretion



Movement of molecules from blood into tubule

Excretion of waste products (e.g. H+, drugs and toxins).

Reabsorption of H_2O and solutes



ACTIVE TRANSPORT

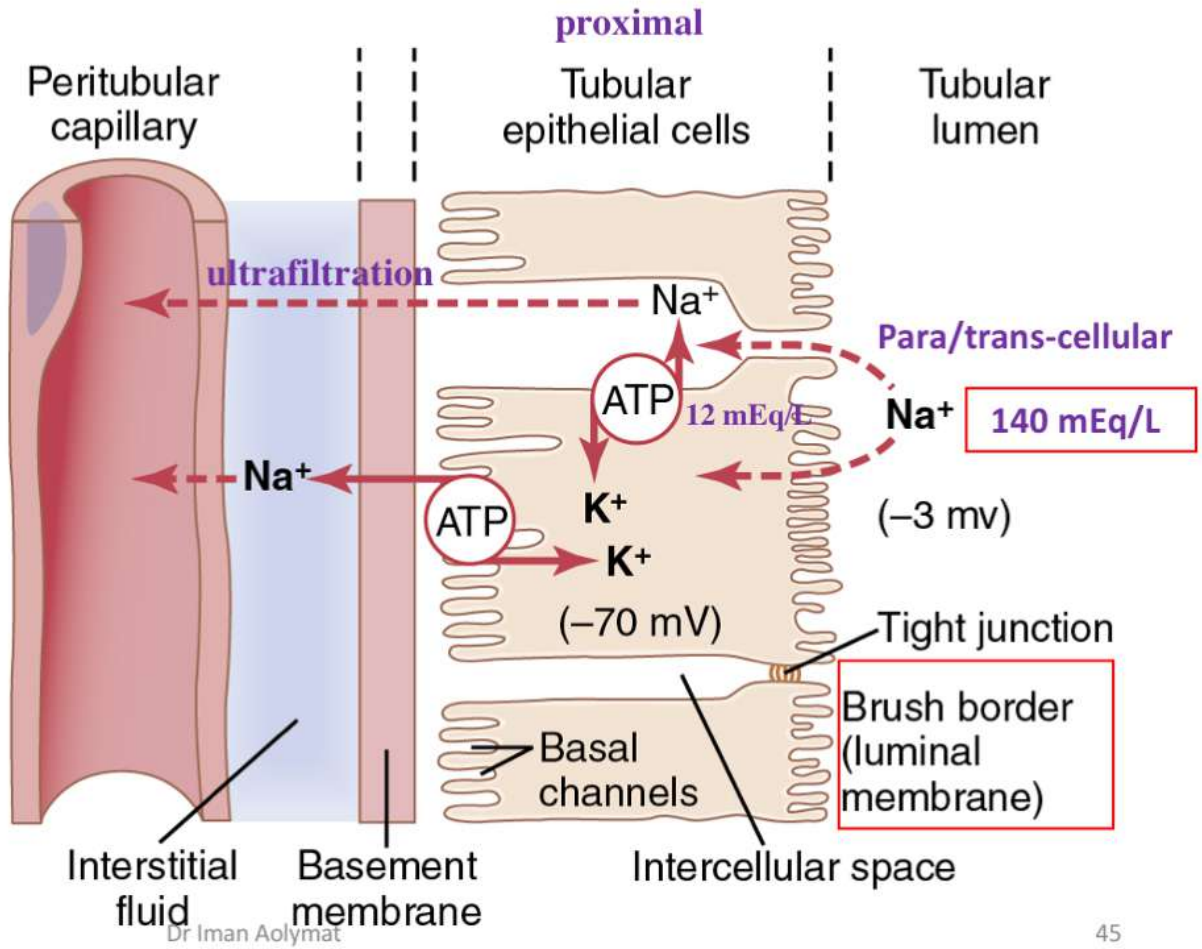
- Moved against electrochemical gradient
- ATP-dependent

- Primary active transporters in kidneys:
- Na^+ -K^+ ATPase
- H^+ ATPase
- H^+ -K^+ ATPase
- Ca+ ATPase

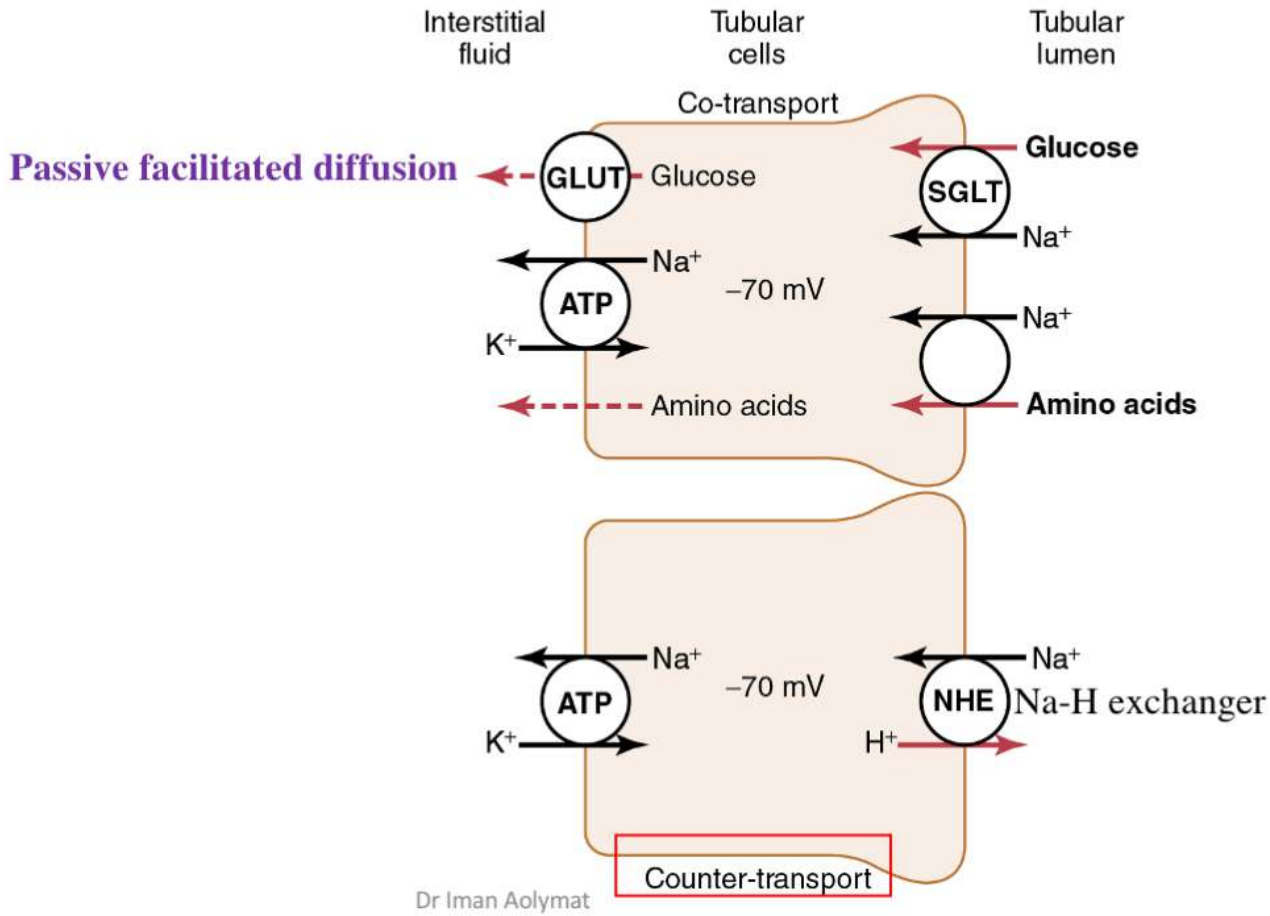
Reabsorption of H_2O & solutes is coupled to Na^+ reabsorption

Primary active transport of Na^+

Passive diffusion of Na
1) Concentration gradient difference
2) -70 mV intracellular potential attracts positive Na



Mechanisms of secondary active transport.



Reabsorption of H_2O & solutes is coupled to Na^+ reabsorption

- H_2O is absorbed by **osmosis** through aquaporins/tight junctions
- Proximal tubules are **highly permeable** to H_2O
- H_2O osmosis drag other solutes (Na, Cl, K, Ca & Mg) mainly in *proximal T.*

Reabsorption of Cl & urea

- Cl reabsorption

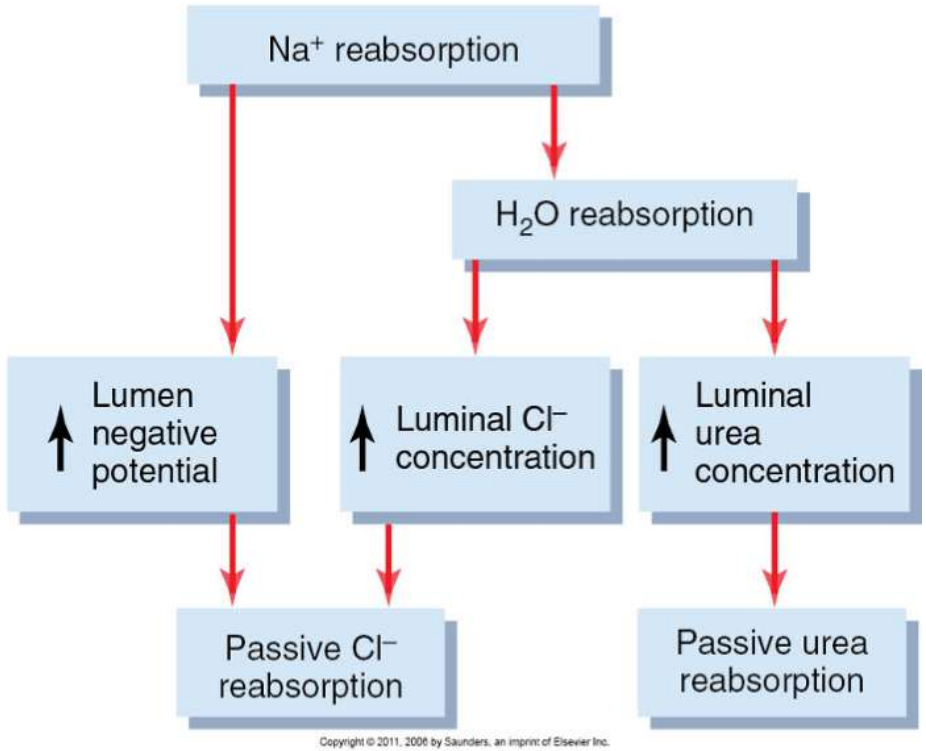
  - **Passive diffusion** (paracellular pathway) due to **Na (+ve)** and water reabsorption

  -Secondary active transport → Na-Cl cotransport

- Urea reabsorption

  -passive

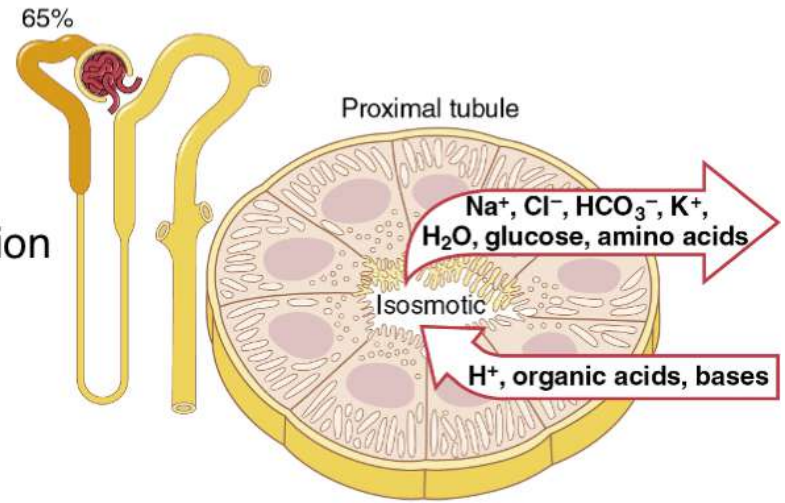
  -Urea transporters



Transport Characteristics of Proximal Tubule (PT)

- **Proximal tubules**
- Extensive brush border on luminal side→ ↑ SA
- Extensive intercellular and basal channels
- High capacity for active (mitochondria) & passive reabsorption

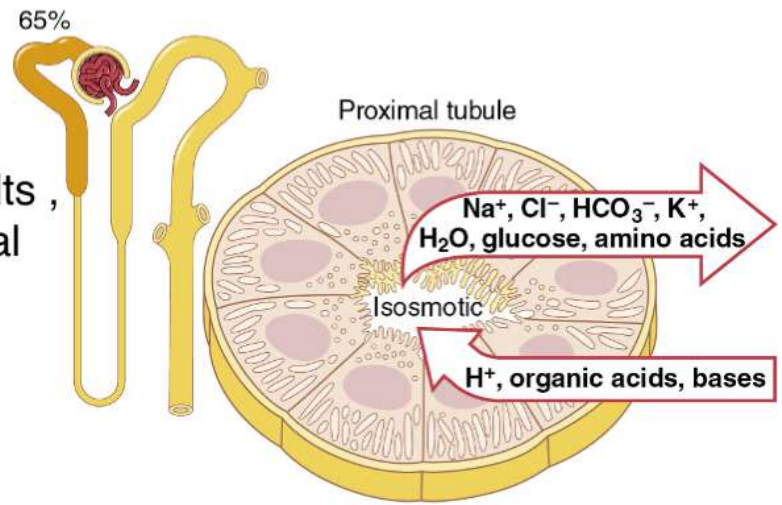
- **Reabsorption:**
- **65% of filtered Na, Cl, HCO_3 & K**
- *Na* is mainly reabsorbed by *primary transport*
- In 1st ½ of PT→ Na, GLU & AA → **COTRANSPORT**
- Reabsorb **all** filtered *glucose and amino acids*
- In 2nd ½ of PT → **high Cl** →diffusion through intercellular j.

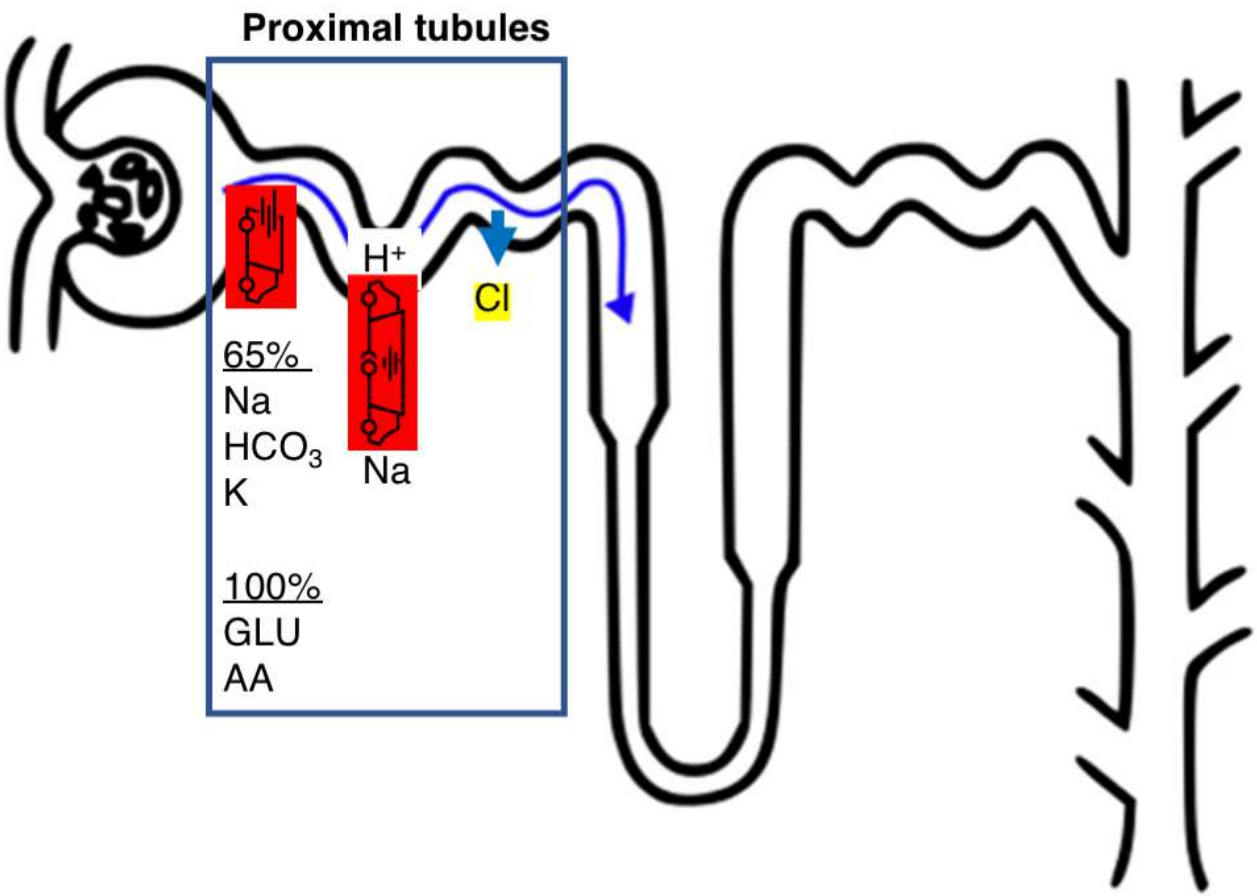


Transport Characteristics of Proximal Tubule (PT)

- **Secretion:**

- Secretes organic acids, bases, & H^+ into lumen.
- H^+ secretion binds HCO_3^- → H_2CO_3→H_2O +CO_2
- Secretion of drugs (penicillin and salicylates),toxins, bile salts , ureat oxlate and catcholamines are secreted by the proximal tubule.




Proximal tubules
H+
Cl
65%
Na
HCO3
K
Na
100%
GLU
AA

Glucose Transport Maximum

- In healthy adult, all filtered glucose is reabsorbed and no glucose will appear in urine.
- If plasma glucose (P_G) reaches 200 mg/dl, glucose appear in the urine – this level is the "Renal threshold"

- The amount of reabsorbed glucose at very **high** filtered glucose, remains **constant**, this is called **glucose transport maximum** (TmG)= 375 mg/min

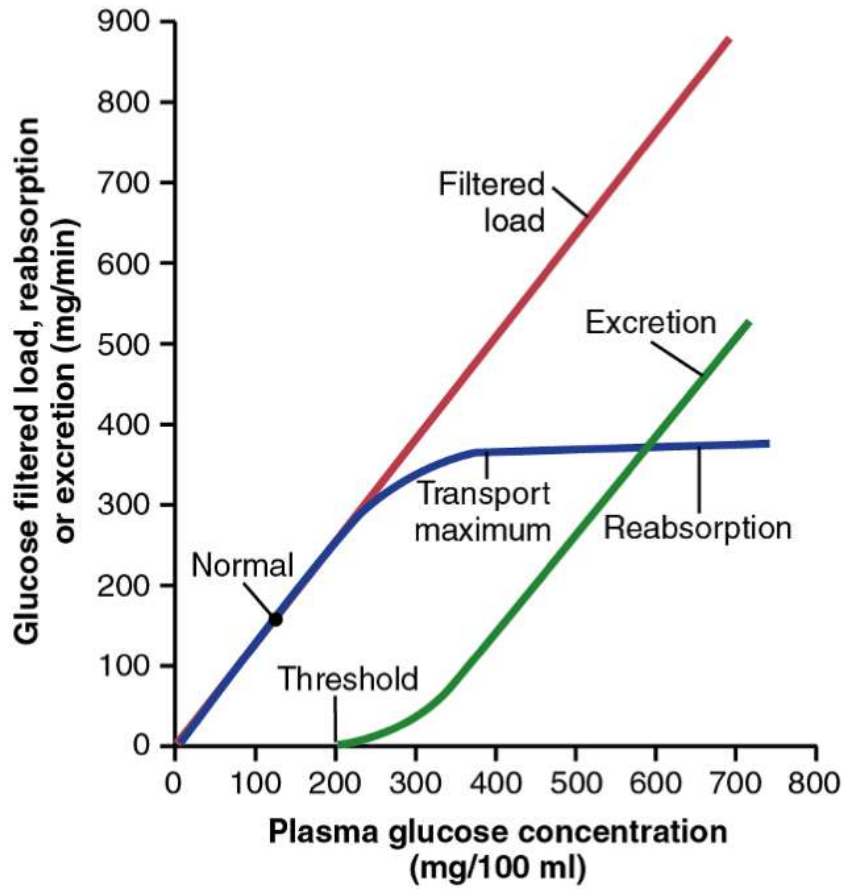
Glucose Transport Maximum

Normally **No** glucose in the urine

when filtered load > Tm →urinary excretion of glucose

Appearance of glucose in urine (at the threshold) occurs before transport maximum is reached.!!
Why?
Not all nephrons have the same transport maximum for glucose→ some of nephrons begin to excrete glucose before others have reached their transport maximum.

The overall transport maximum for the kidneys is reached when **all** nephrons have reached their maximal capacity to reabsorb glucose →no more glucose can be transported.



Transport characteristics of loop of Henle

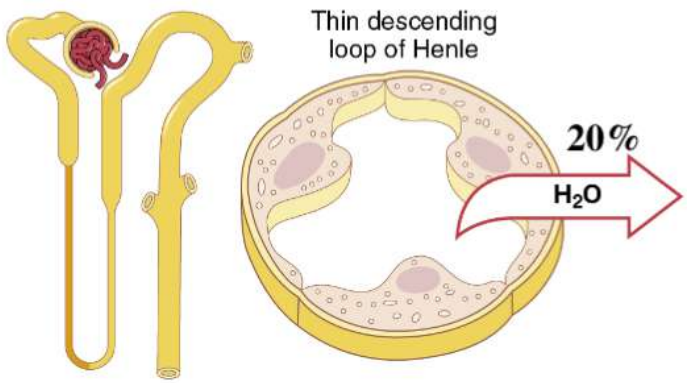
3 functionally segments:

1- Thin descending

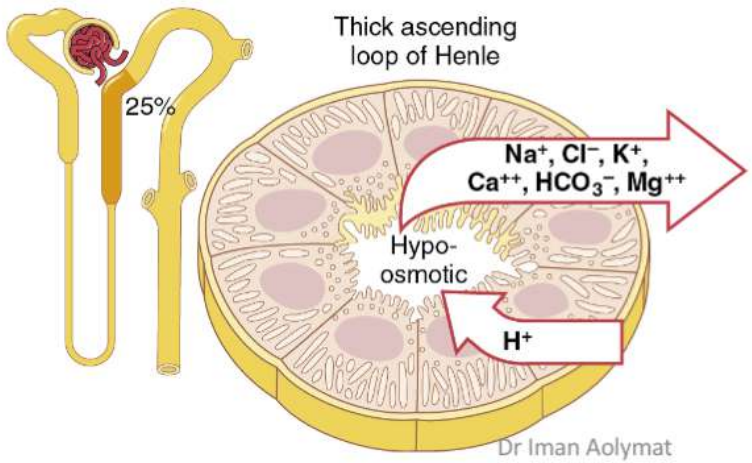
2- Thin ascending

3- Thick ascending

Transport characteristics of loop of Henle



Thin epithelium
No brush borders
Few mitochondria
Highly permeable to H2O



- Reabsorption of
  Na^+, Cl^-, K^+, HCO_3^-,Ca^{++}, Mg^{++}
- <u>Secretion of H^+</u>
- **Not permeable to H_2O**

Transport characteristics of loop of Henle

Cotransport

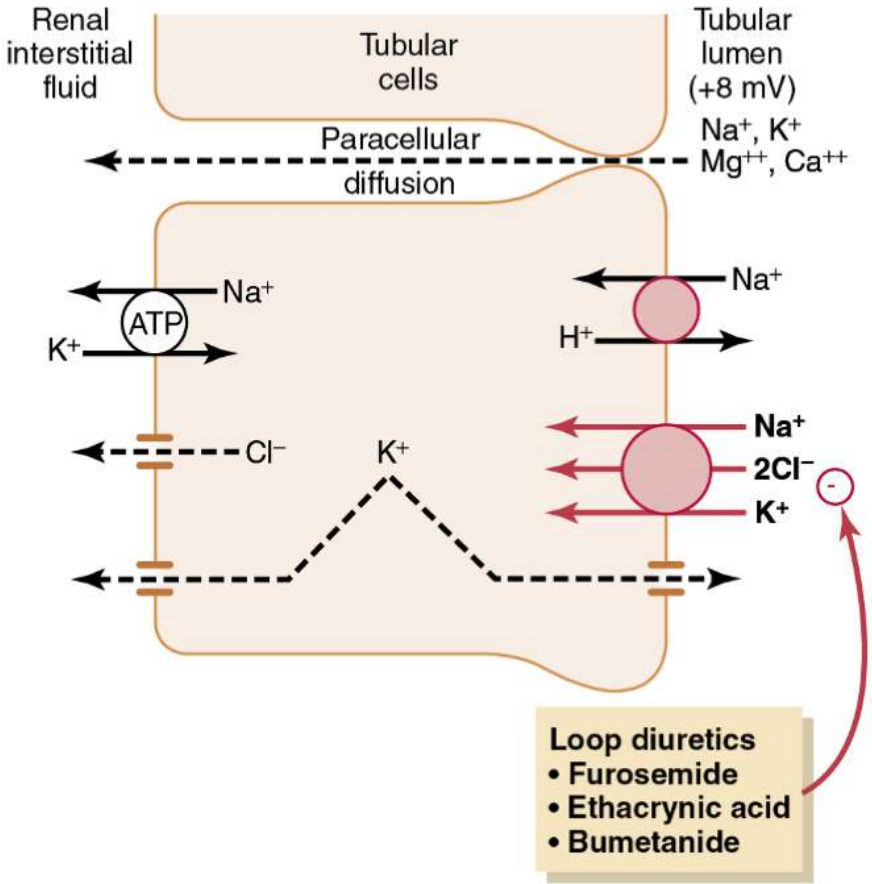
- NaCl & K transport in thick ALH
- DEPENDS on **Na+-K+ATPase** in basolateral membrane

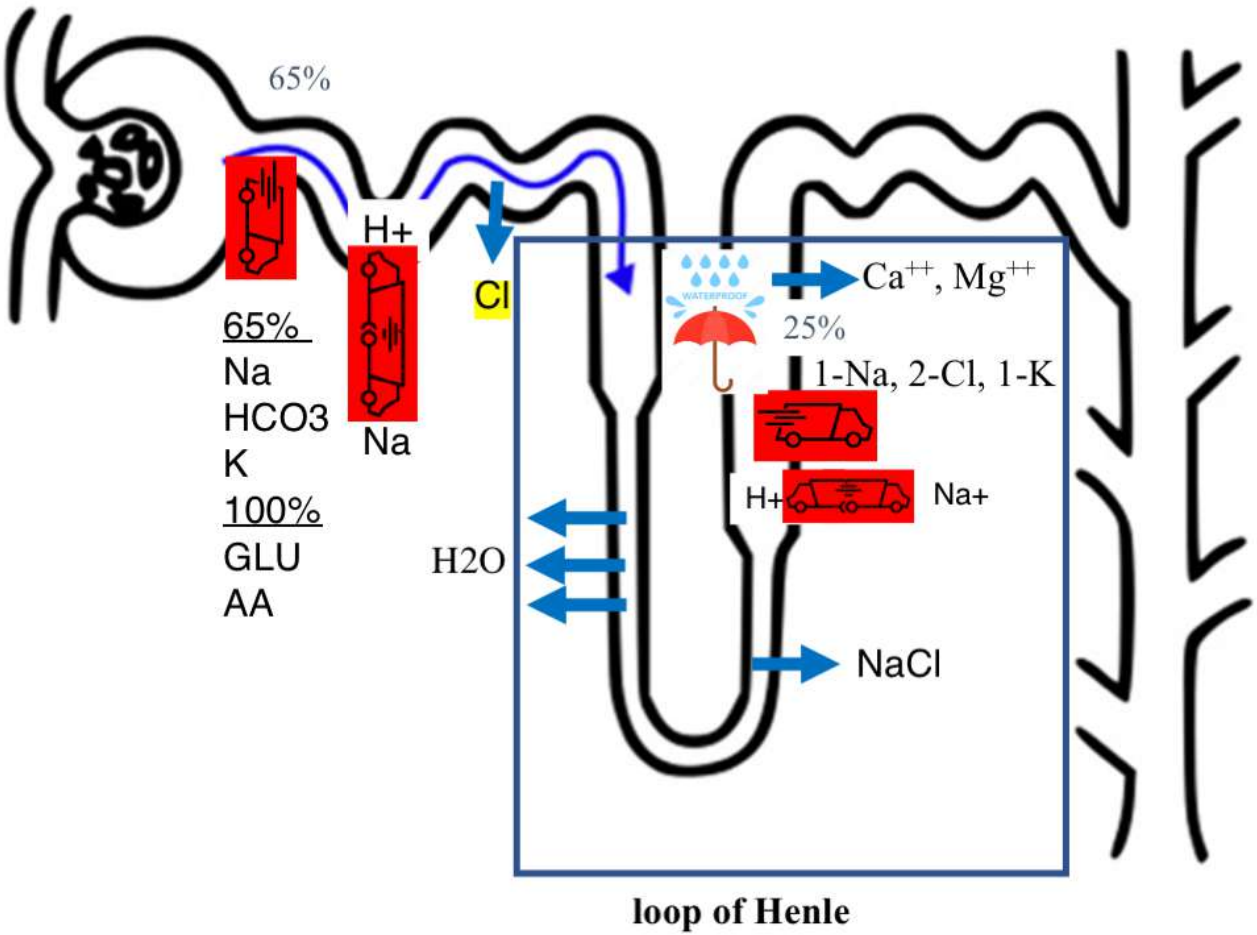
- Na+-K+ATPase →↓ intracellular Na→ Na diffusion from tubule to cell.

- Movement of Na is mediated primarily by a 1-Na, 2-Cl, 1-K co-transporter

Counter transport

Na-H counter-transport mechanism



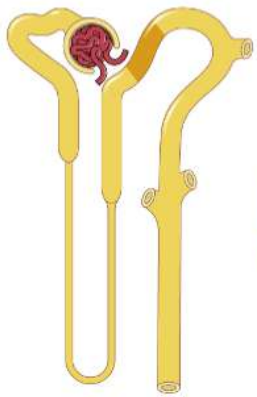


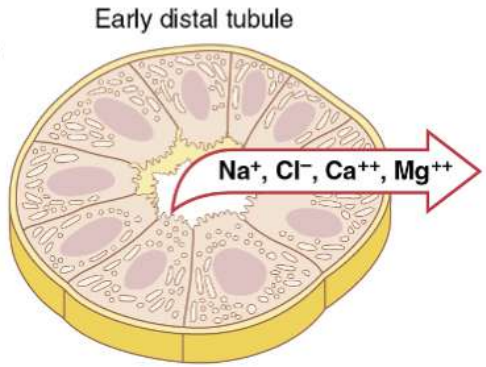
loop of Henle

Early Distal Tubule

- ***Not permeable to water***

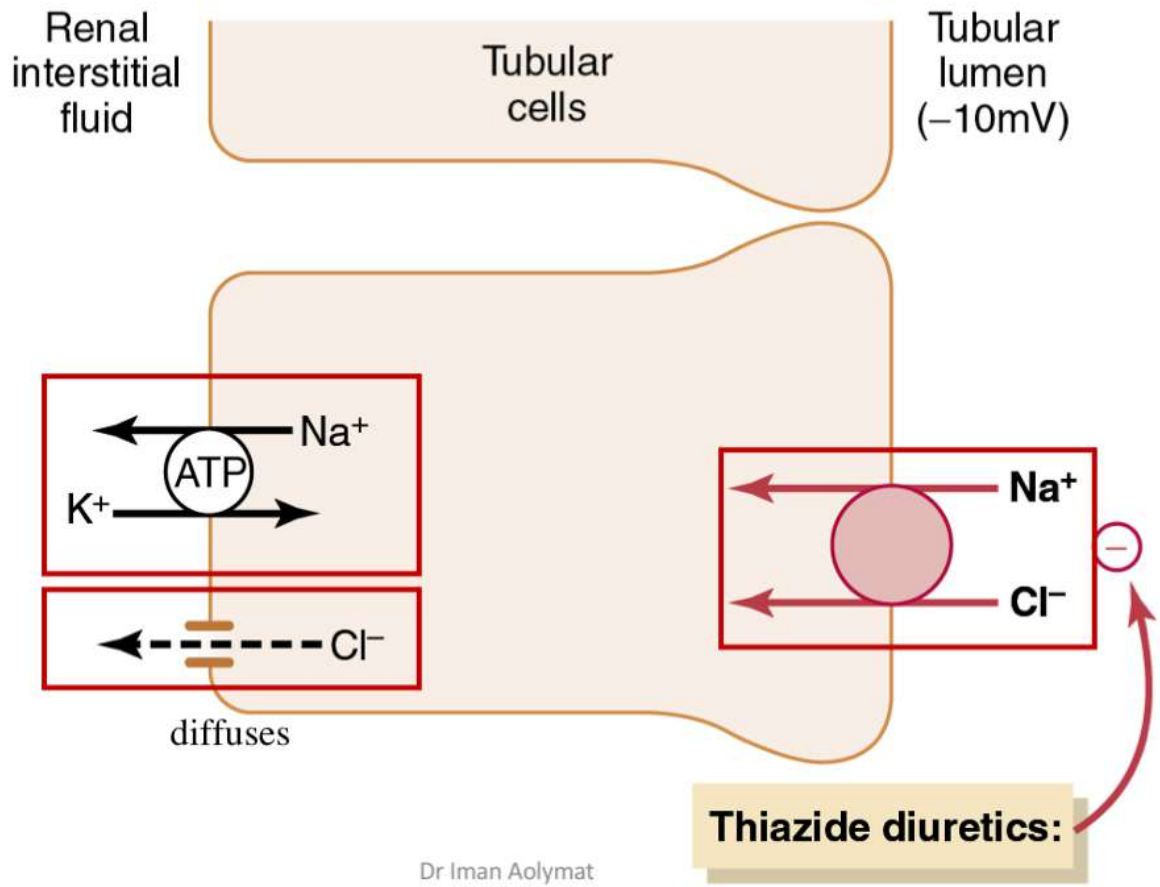
- ***Impermeable urea.***
- Called *diluting segment*

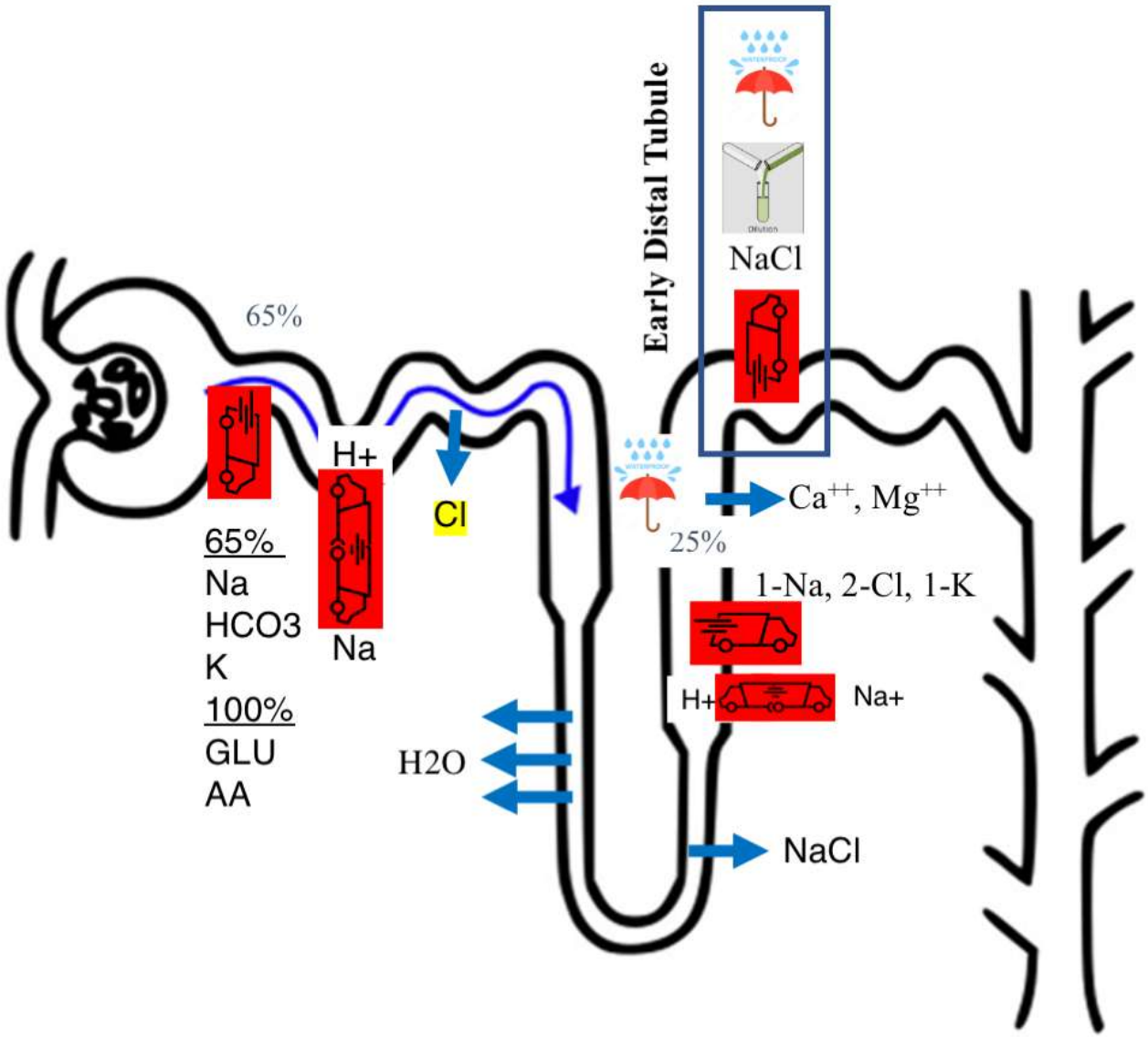




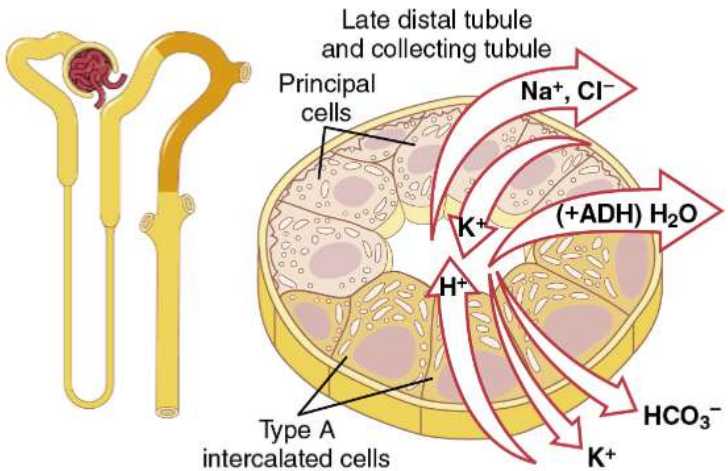
- **Active** reabsorption of Na^+, Cl^-, K^+, Mg^{++}

Early Distal Tubule




Early Distal Tubule
NaCl
65%
H+
Cl
65%
Na
HCO3
K
100%
GLU
AA
Na
H2O
Ca++, Mg++
25%
1-Na, 2-Cl, 1-K
H+
Na+
NaCl

Late Distal Tubules and Collecting Tubules.



- Control dilution or concentration of urine
- Permeability to H_2O depends on **ADH**

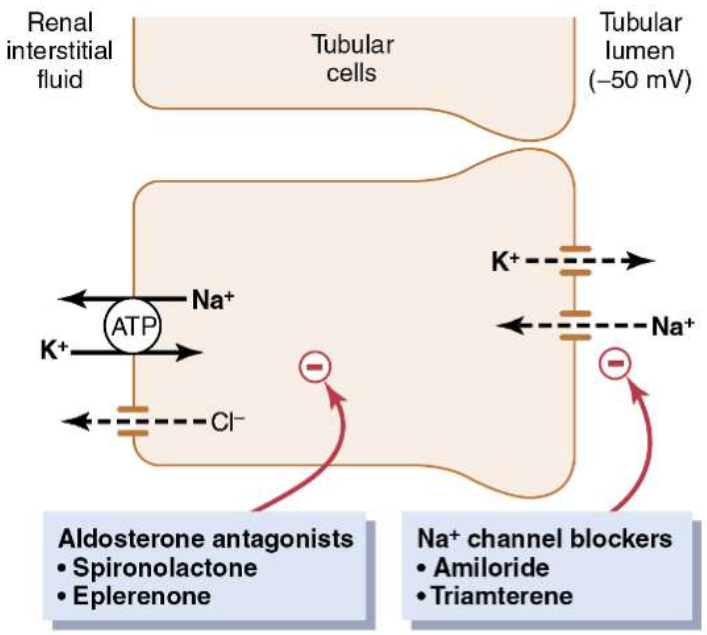
↑ ADH → ↑ permeability

↓ADH → ↓ permeability

- ***Not very permeable to urea***

Principal Cells

- Na+-K+ATPase pump basolateral membrane.
- Low Na & High K intracellular →Na diffusion IN & K diffusion OUT
- **Aldosterone** ++Na reabsorption & K excretion
- Sites of action of the K-sparing diuretics.
- Aldosterone antagonists
- Na channel blockers

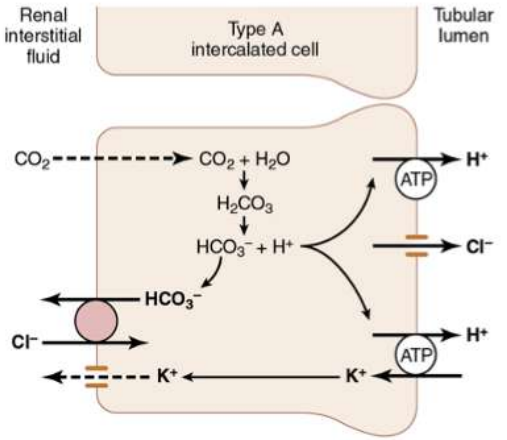


Intercalated Cells- in acid-base regulation

BEAR (Beta cells excrete HCO3, Alpha cells reabsorb it)

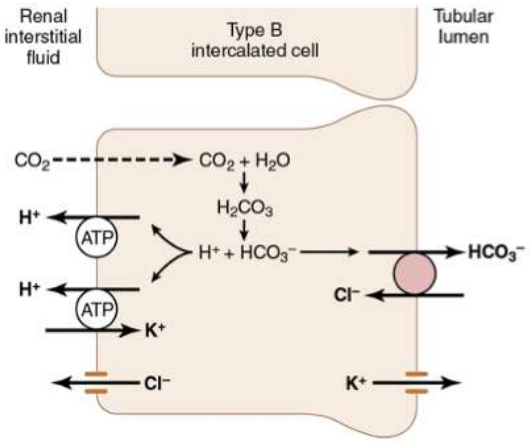
Type A intercalated cells

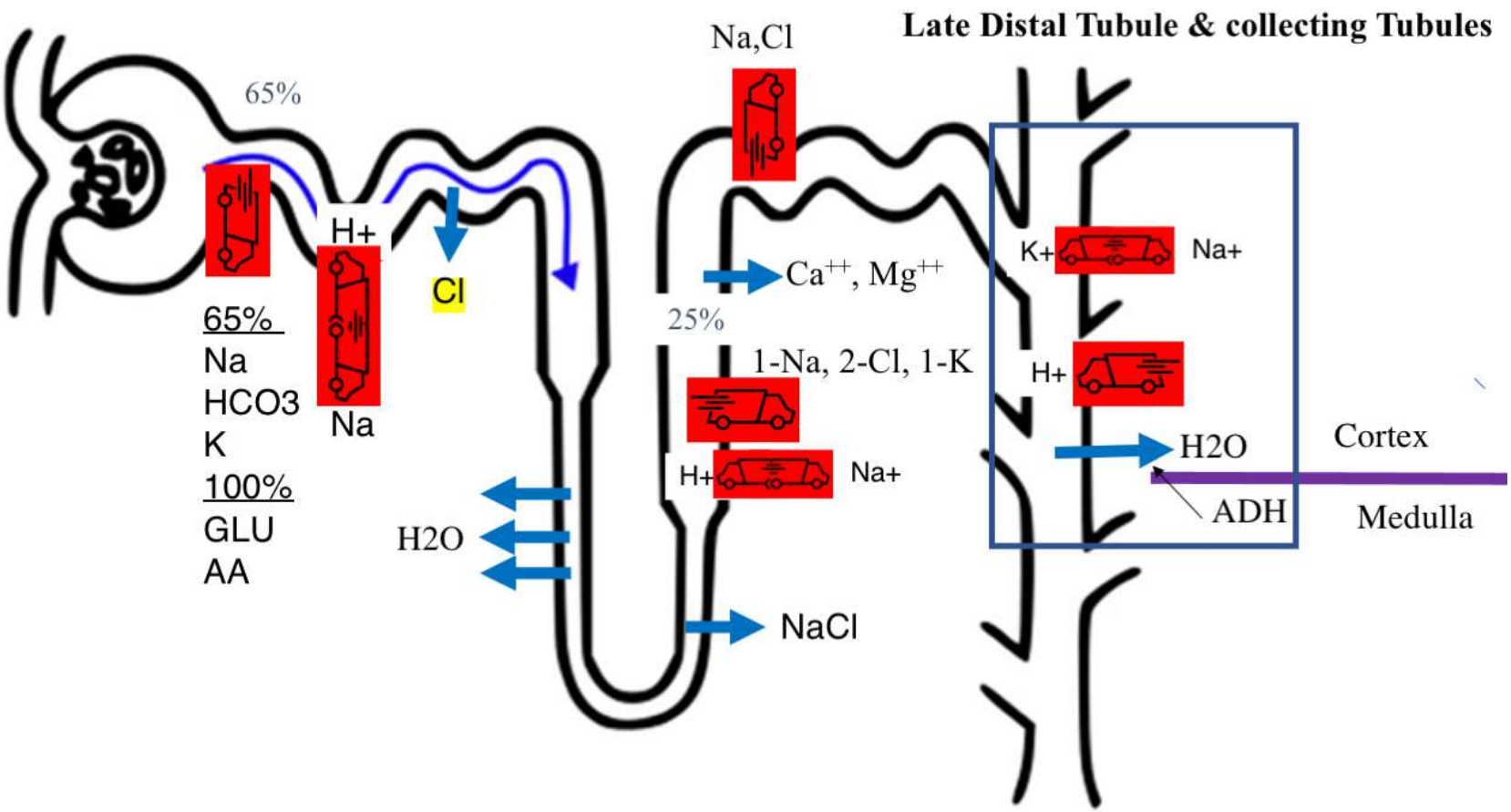
- H^+ secretion is mediated by a H-ATPase
- H^+ source?
- Reabsorb K
- for each H^+ secreted, HCO_3 reabsorbed across **the basolateral membrane**.



Type B intercalated cells

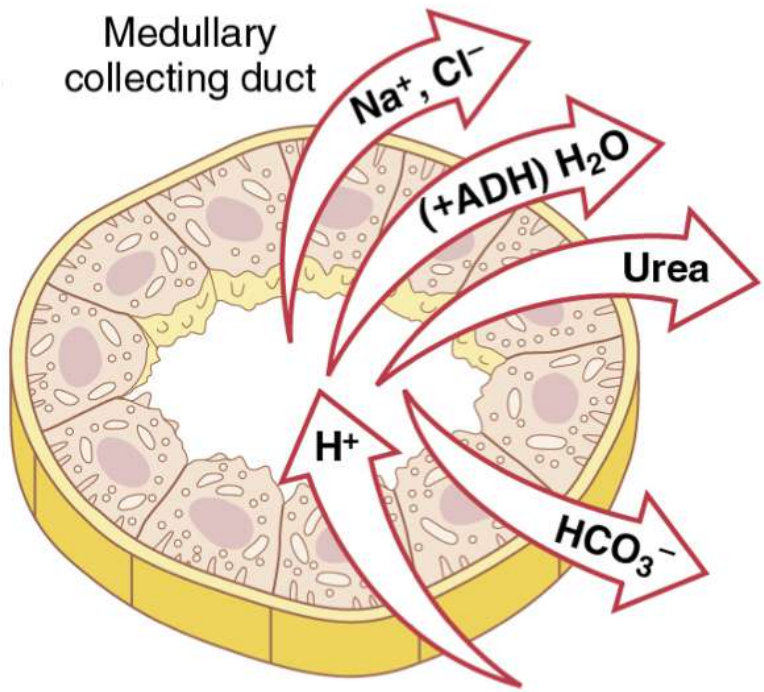
- Functions is opposite to those of type A cells (**in alkalosis**)
- HCO_3 to lumen
- H^+ reabsorption via H-ATPase
- Secrete K




Late Distal Tubule & collecting Tubules
Na,Cl
65%
H+
Cl
65%
Na
HCO3
K
100%
GLU
AA
Na
Ca++, Mg++
25%
1-Na, 2-Cl, 1-K
H+
Na+
H2O
NaCl
K+
Na+
H+
H2O
ADH
Cortex
Medulla

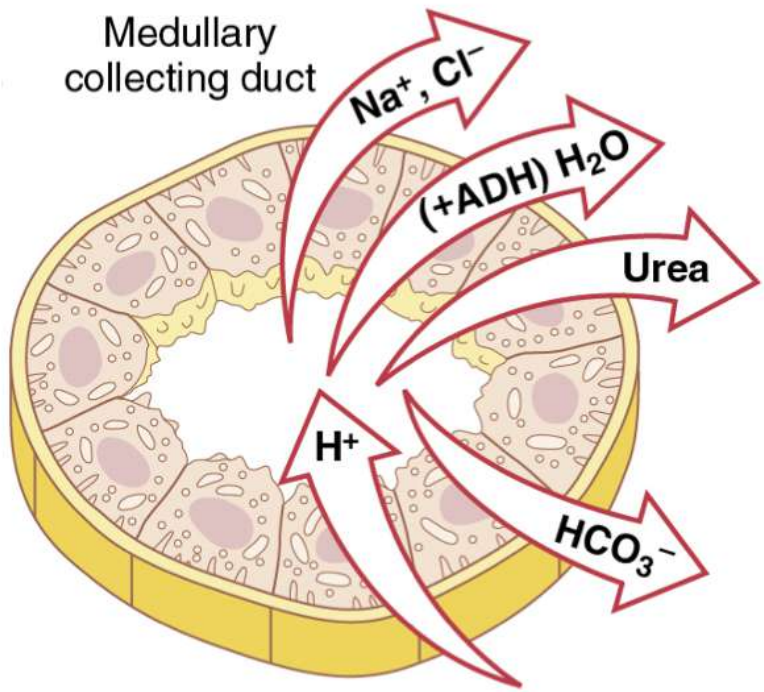
Medullary collecting ducts

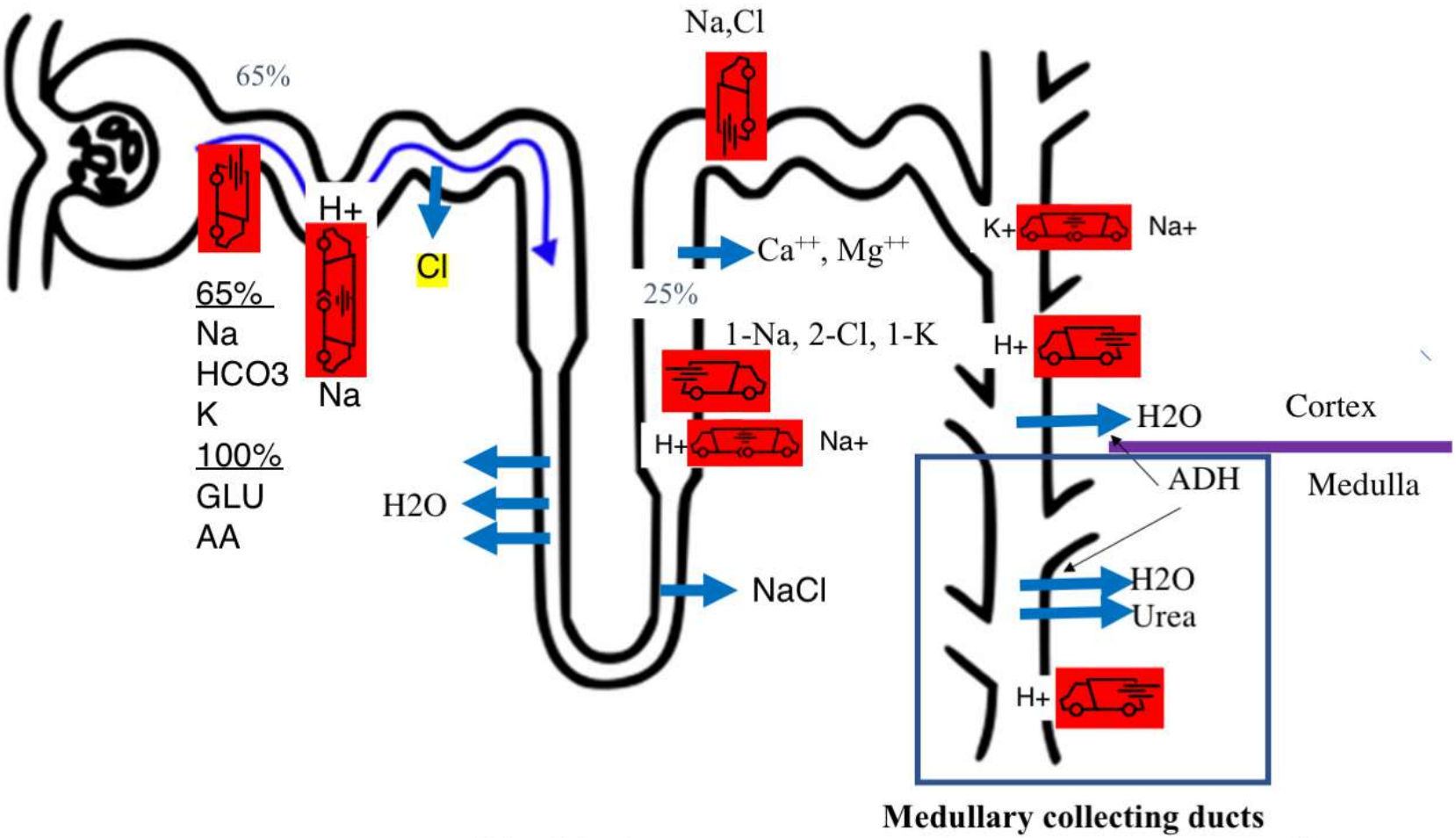
- Reabsorb <10% of filtered H_2O & Na.
- Play an extremely important role in determining the final urine output of water and solutes.
- **Secretes H+** against a large concentration gradient→ plays a key role in regulating **acid-base balance**.



Medullary collecting ducts

- H_2O permeability → controlled by **ADH**.
- **Permeable to urea**→urea is reabsorbed into **medullary interstitium** → helping to raise the **osmolality** in this region of the kidneys and contributing to the kidneys' overall ability to form a **concentrated** urine.




Na,Cl
65%
H+
Cl
65%
Na
HCO3
K
100%
GLU
AA
Na
Ca++, Mg++
25%
1-Na, 2-Cl, 1-K
H+
Na+
H2O
NaCl
K+
Na+
H+
H2O
Cortex
Medulla
ADH
H2O
Urea
H+
Medullary collecting ducts

Regulation of Tubular Reabsorption

-To maintain balance between **tubular reabsorption** and **glomerular filtration**.

Glomerulotubular Balance

↑ GFR → ↑ *filtered load* → ↑ **reabsorption** = Glomerulotubular balance.

-Glomerulotubular balance acts as another line of defence to buffer the effects of spontaneous changes in the GFR on urine output.

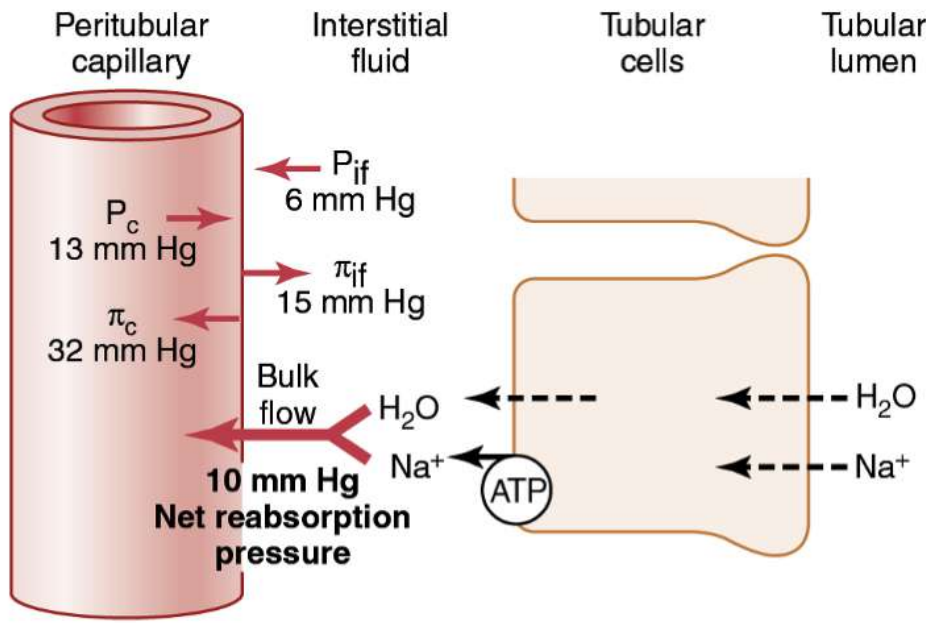
Peritubular Capillary Reabsorption

- Hydrostatic & colloid osmotic forces
- Normal rate of peritubular capillary **reabsorption** is about 124 ml/min.

a. Hydrostatic P. in capillary (Pc) **opposes** – (13 mmHg)
b. Hydrostatic P In interstitium (Pif) **favors** – (6 mmHg)
c. Colloid osmotic P in capillary (πc) **favors** – (32 mmHg)
d. Colloid osmotic P in intrst. (πif) **opposes** –(15 mmHg)

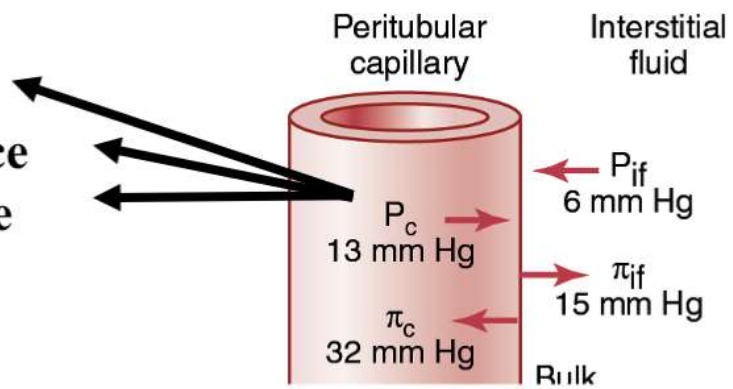
Net reab. P 10 mmHg

Reabsorption = K_f x Net reabsorptive P
=12.4 x 10
= 124 ml/min

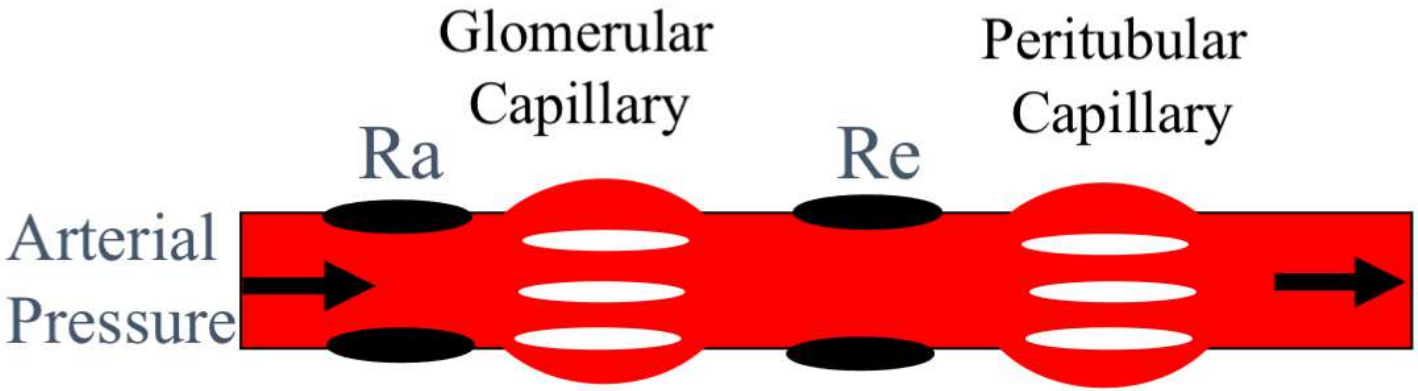


Determinants of Peritubular Capillary Hydrostatic Pressure

- **Arterial BP**
- **Afferent arteriole resistance**
- **Efferent arteriole resistance**



Peritubular Capillary Hydrostatic Pressure



↑ Arterial Pressure → ↑ Pc → ↓ Reabs.

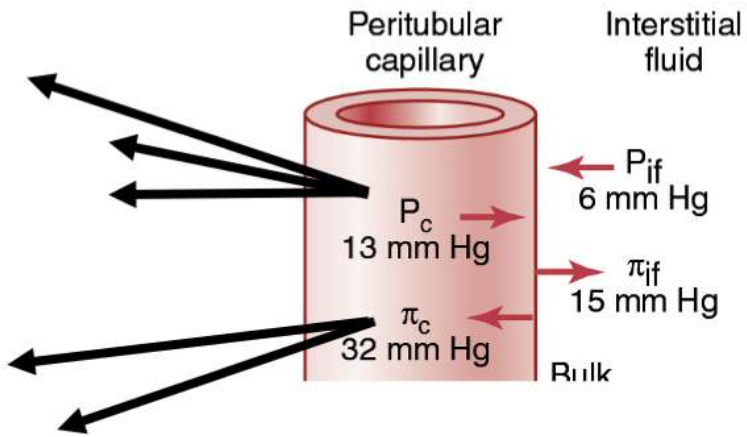
↑ Ra → ↓ Pc → ↑ Reabs.

↑ Re → ↓ Pc → ↑ Reabs.

Determinants of Colloid Osmotic Pressure

- Arterial BP
- A arteriole resistance
- E arteriole resistance

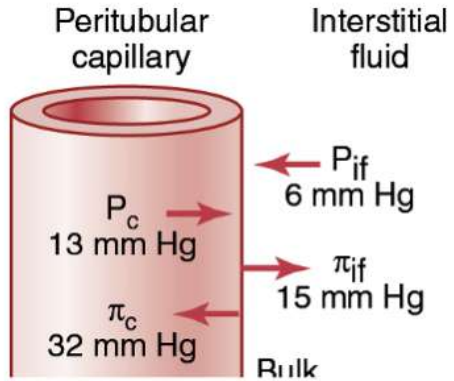
- **[Systemic plasma protein]**
- **FF**

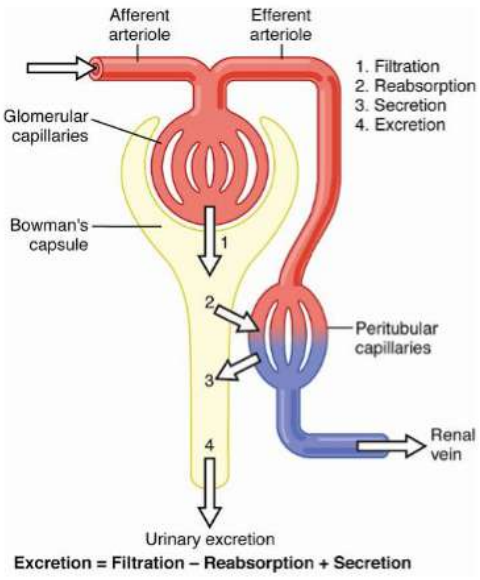


Colloid Osmotic Pressure

↑ [Systemic plasma protein] → ↑π_C → ↑Reabsorption

↑ FF → ↑π_C → ↑Reabsorption

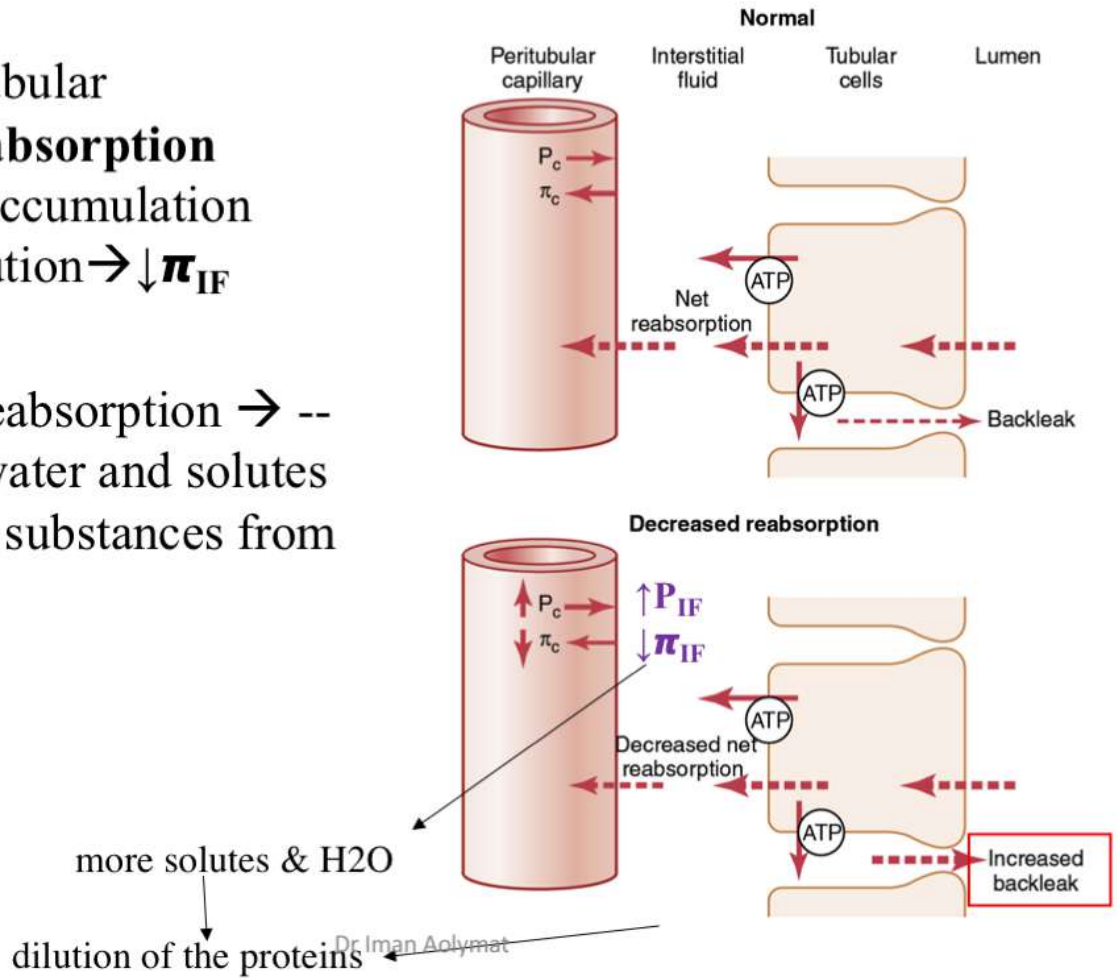




Renal Interstitial Hydrostatic and Colloid Osmotic Pressures

++ Pc / or -- π_c in peritubular capillaries → **reduce reabsorption**
Why? fluid and solutes accumulation
IF→++P_{IF} & protein dilution→↓π_{IF}

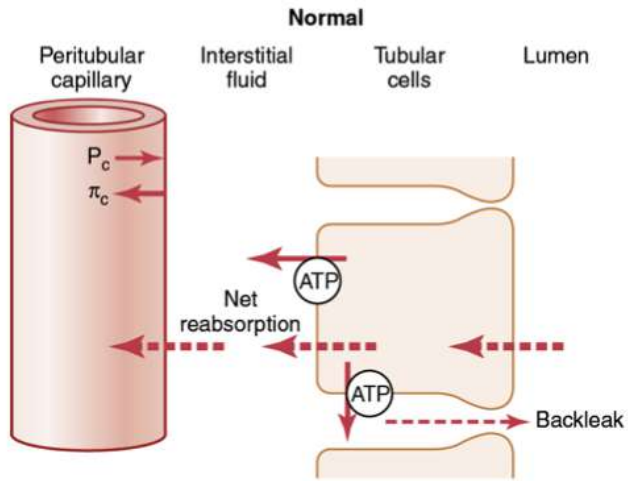
-- peritubular capillary reabsorption → -- tubular reabsorption of water and solutes & **backleak** of absorbed substances from IF to the tubular lumen .



Renal Interstitial Hydrostatic and Colloid Osmotic Pressures

++peritubular capillary reabsorption → ++reabsorption from tubules

Why? Reabsorption to capillaries – P_{IF} & ++ $\boldsymbol{\pi}_{IF}$ → ++tubular reabsorption



Pressure diuresis and pressure natriuresis

- ↑ BP → kidneys excrete large amounts of H_2O & Na

- Diuresis & natriuresis→↓ECFV & blood volume→ brings the arterial blood pressure back to normal level.

Mechanisms

- Impaired autoregulation → ↑ GFR
- ++ Pc in vasa recta→++P_{if}→ prevent Na & H_2O reabsorption+ ↑backleak
- ↓ Angiotensin II→ direct effect → ↓Na reab, indirect ↓aldosterone→ ↓ Na reabsorbtion

Hormonal control of tubular reabsorption

Angiotensin II

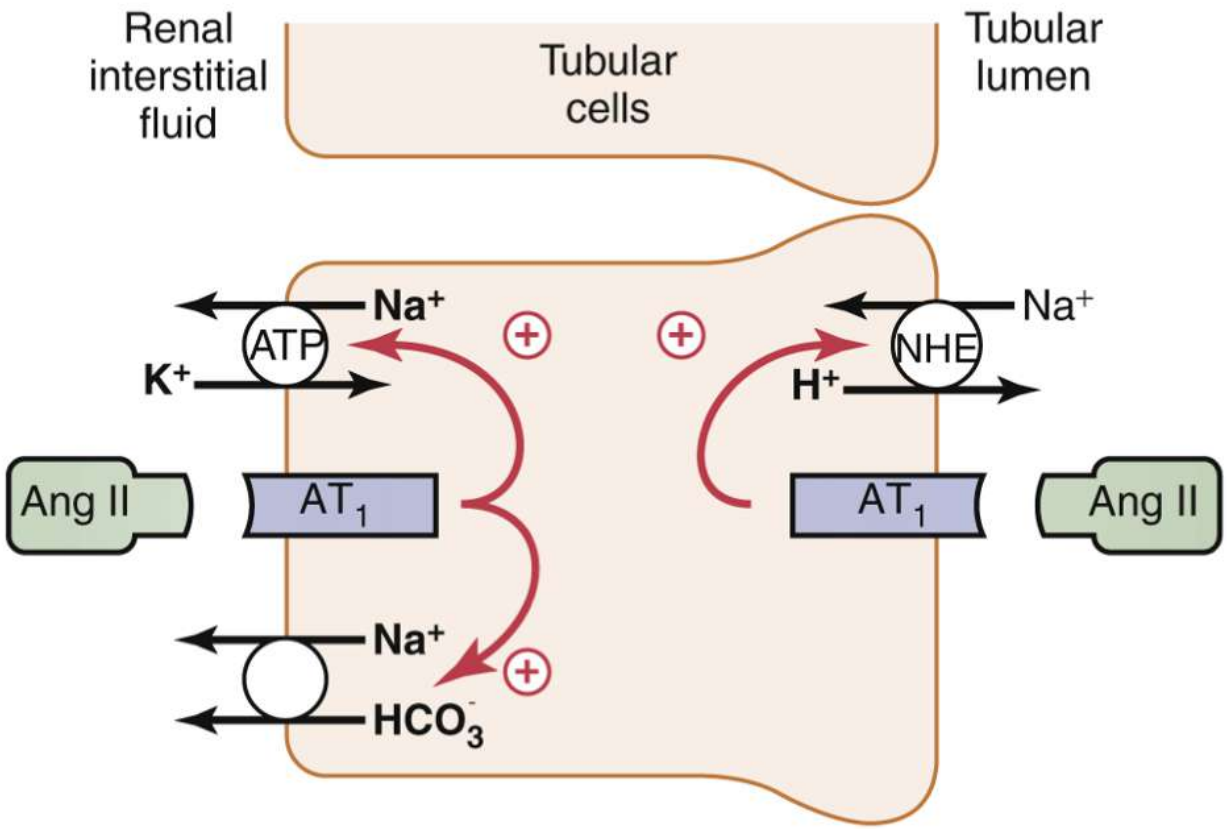
Stimuli

- Na and volume depletion or low blood pressure

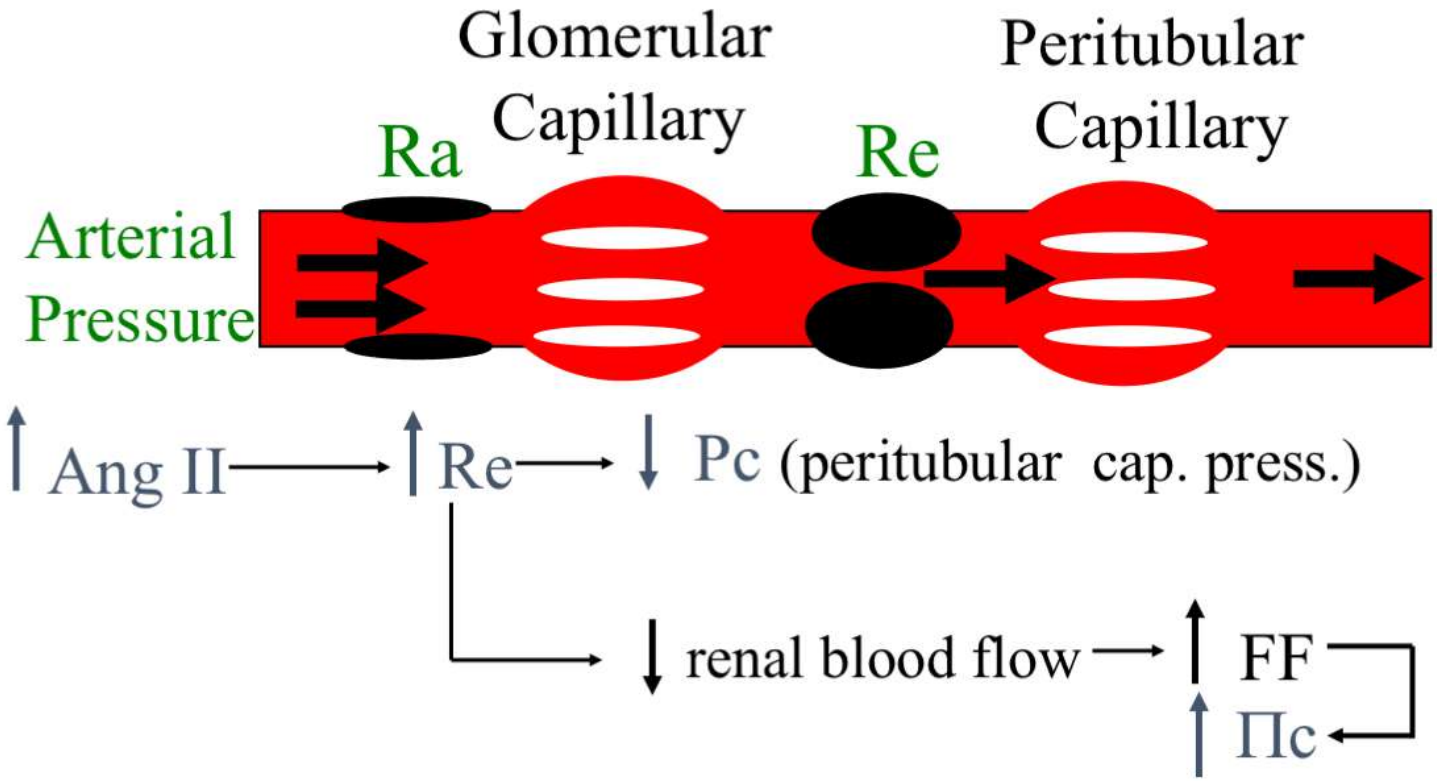
Results

- Constricts **efferent** arterioles
  - -- peritubular capillary hydrostatic pressure
  - ++ FF → ++ peritubular colloid osmotic pressure
- ++ aldosterone secretion → increases Na^+ reabsorption

Angiotensin II increases renal tubular sodium reabsorption



Effect of Angiotensin II on Peritubular Capillary Dynamics

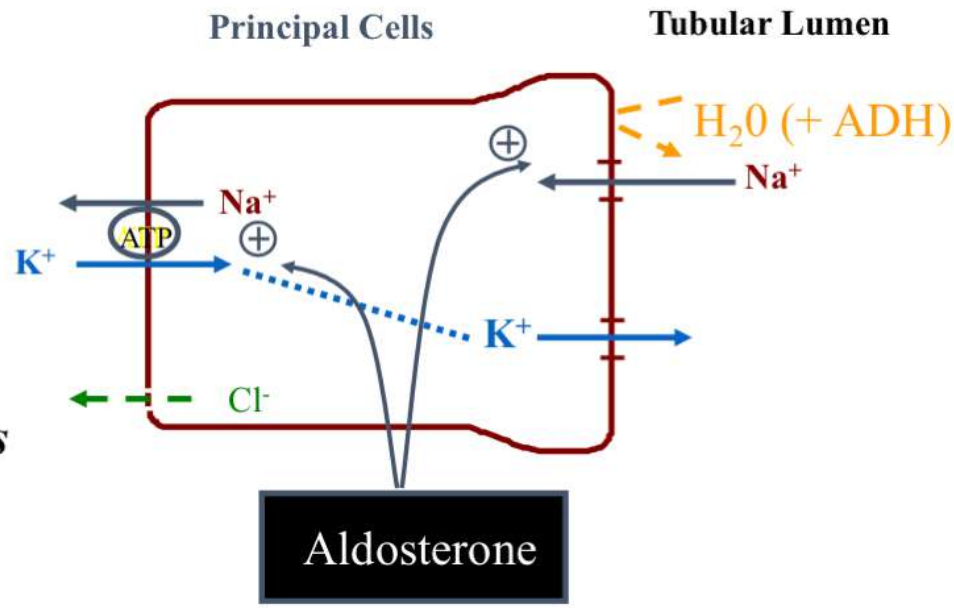


Angiotensin II blockade decreases Na^+ reabsorption and BP

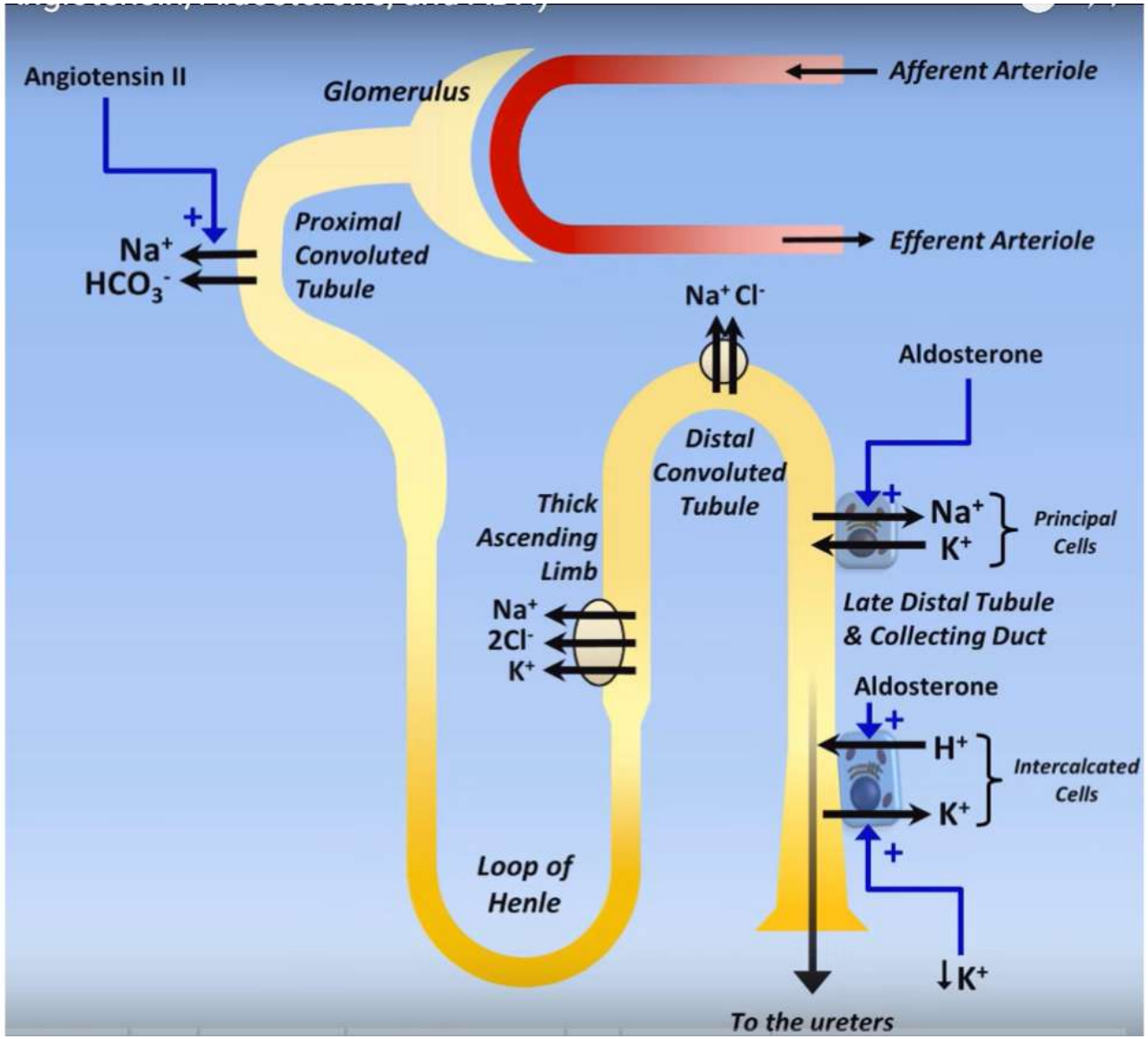
- ACE inhibitors (captopril, benazipril, ramipril)
- Ang II antagonists (losartan, candesartin, irbesartan)
- Renin inhibitors (aliskirin)
  - decrease aldosterone
  - directly inhibit Na^+ reabsorption
  - decrease efferent arteriolar resistance

Natriuresis and Diuresis + ↓ Blood Pressure

Aldosterone



- Released in response to *angiotensin II*
- Acts on the ***distal tubule and collecting ducts*** **(principal cells)**
- Increases the number of Na+/K+ ATPase pump
- ++NaCl , H2O reabs.
- ++ K+ & H^+ secretion.


Angiotensin II
Glomerulus
Afferent Arteriole
Efferent Arteriole
Proximal Convoluted Tubule
Na+
HCO3-
Na+ Cl-
Aldosterone
Distal Convoluted Tubule
Thick Ascending Limb
Na+
2Cl-
K+
Na+
K+
Principal Cells
Late Distal Tubule & Collecting Duct
Aldosterone
H+
K+
Intercalcated Cells
Loop of Henle
↓K+
To the ureters

Control of Aldosterone Secretion

Factors ++ aldosterone

- Hormones: Angiotensin II & ACTH
- Increased K^+

Factors -- aldosterone

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

Atrial natriuretic peptide increases Na^+ excretion

- Secreted by cardiac atria in response to stretch (increased blood volume)
- Directly -- Na^+ reabsorption (mainly from **collecting ducts)**
- -- renin and aldosterone release
- ++ GFR

Antidiuretic Hormone (ADH)

- Increases H_2O permeability and reabsorption in **distal and collecting tubules**→ control of extracellular fluid *osmolarity*

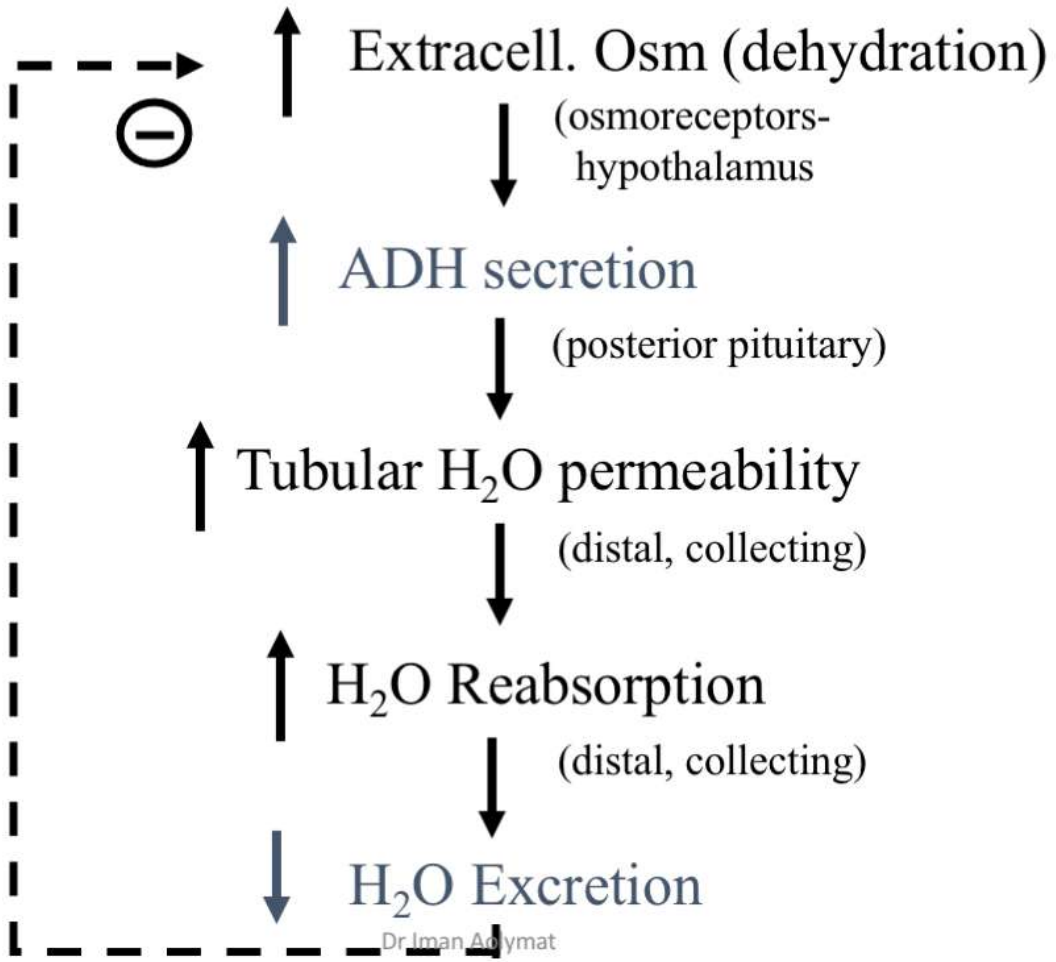
- Inducing vasoconstriction- Vasopressin

Stimuli for ADH Secretion

- ++ osmolarity
- -- blood volume/ P

- Other stimuli :
  - input from cerebral cortex (e.g. fear)
  - angiotensin II
  - nausea
  - nicotine
  - morphine

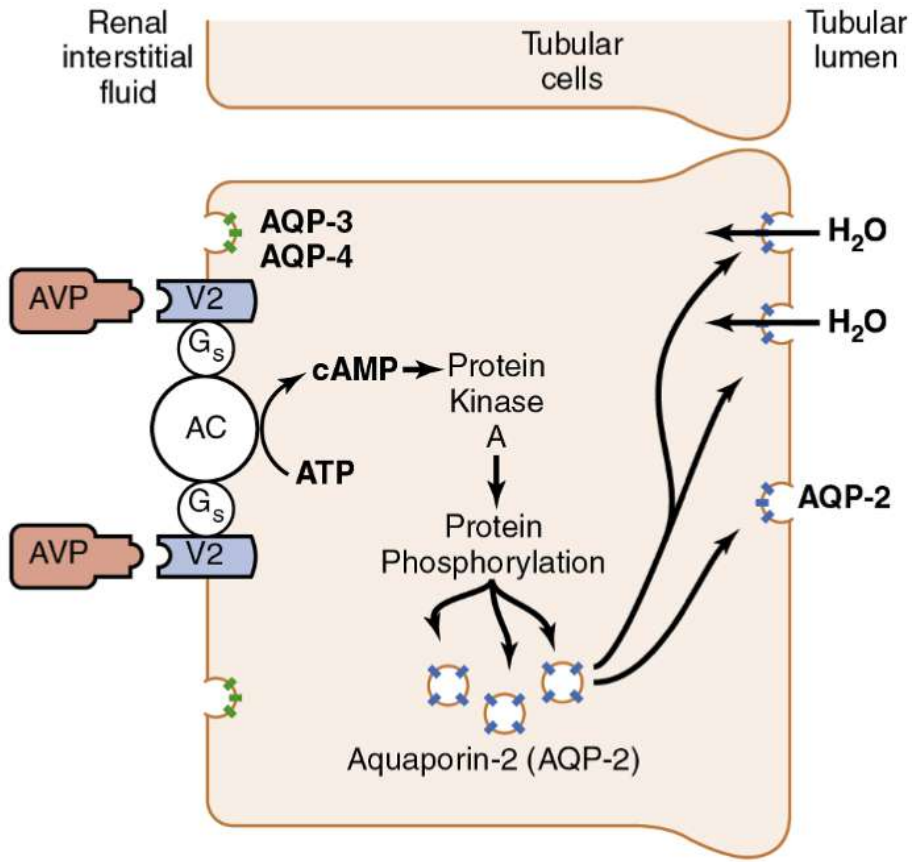
Feedback Control of Extracellular Fluid Osmolarity by ADH



Mechanism of action of ADH in distal and collecting tubules

Binds V2 receptors→ form cyclic AMP →++ AQP

- When ADH decreased → AQP back to cytoplasm



Factors That Decrease ADH Secretion

- -- osmolarity
- ++ blood volume/ P

- Other factors :
  - alcohol
  - clonidine (antihypertensive drug)
  - haloperidol (antipsychotic)

ADH is considerably more sensitive to small changes in osmolarity than to changes in blood volume

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)

Concentration and Dilution of the Urine

- Kidneys excrete **excess water** by forming dilute urine

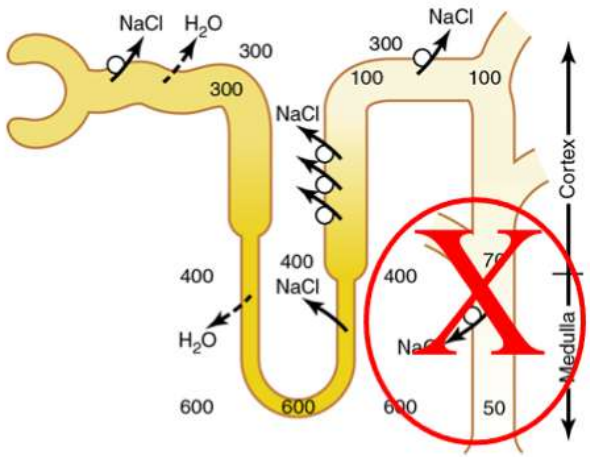
- Maximal urine concentration (H_2O deficit)
  = 1200 - 1400 mOsm / L
- Minimal urine concentration (high H_2O)
  = 50 - 70 mOsm / L

- Kidneys can excrete diluted/concentrated urine **without major changes** in rates of excretion of solutes such as Na & K

- Obligatory urine volume: is the minimum urine **volume** in which the excreted solute can be dissolved and excreted = 0.5 L/min (*lower than this indicates renal function problem*)

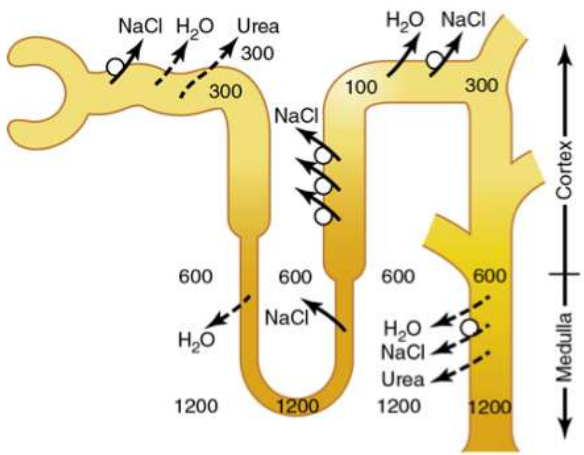
Diluted urine

- LESS (↓) water reabsorption→ By ↓ ADH release

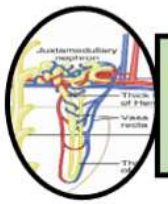


Concentrated Urine

More (↑) water reabsorption→ → By ↑ ADH release/High osmolarity of medulla/ Countercurrent flow of tubular fluid



Concentration of urine - Juxtameddullary nephrons

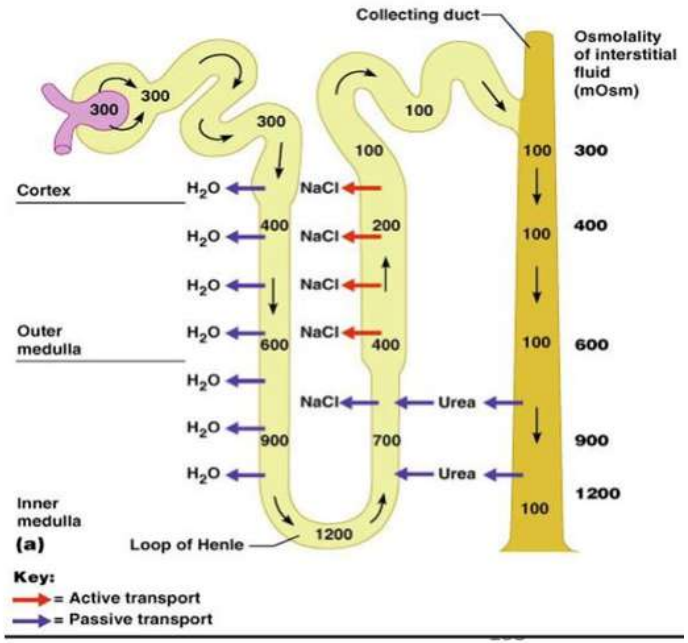


•Juxtamedullary nephron: Special anatomical arrangement of the loops of Henle and vasa recta of renal medulla.

•Requires **<u>hyperosmolar</u>** medullary interstitium –

How?

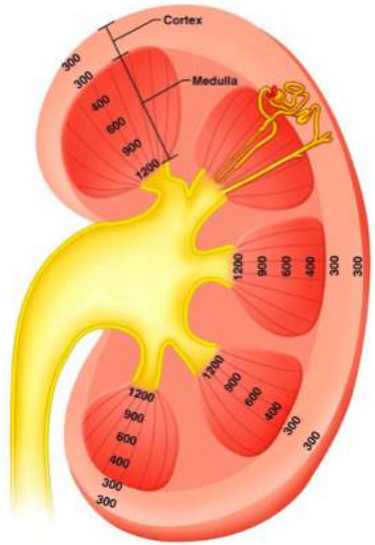
1. Movements of **electrolytes & urea** from thick ascending loop of Henle & collecting ducts into medullary interstitium
2. Diffusion of **small** amounts of **H_2O** into medullary interstitium -Most of H2O reabsorption occurs in cortex rather than in the medulla

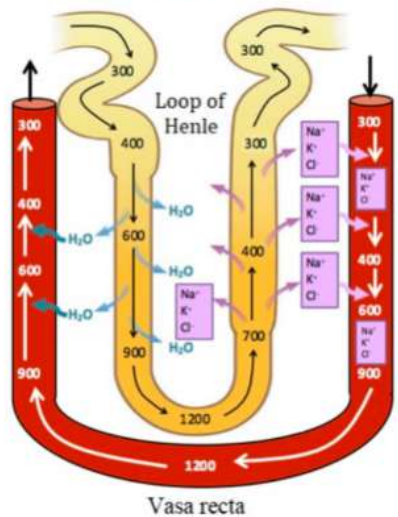


Hyperosmotic renal medullary interstitium

The hyperosmotic renal medullary interstitium:

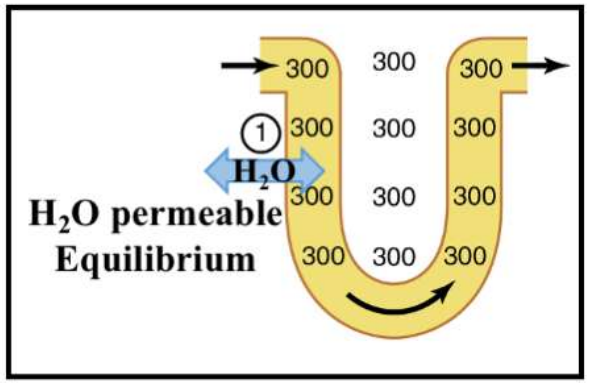
- Produced by Counter-Current Multiplayer .
- Maintained by Counter current Exchanger .

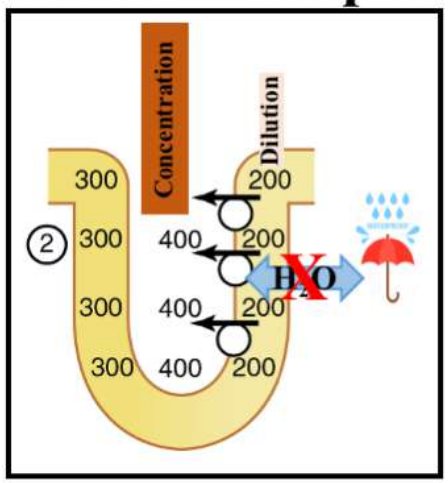


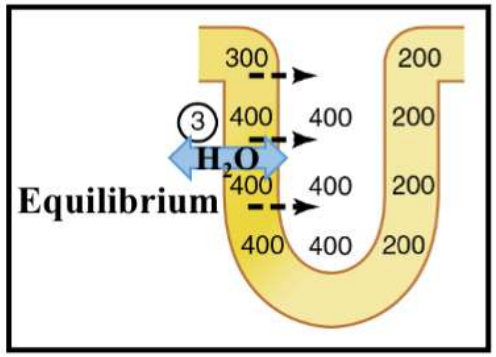


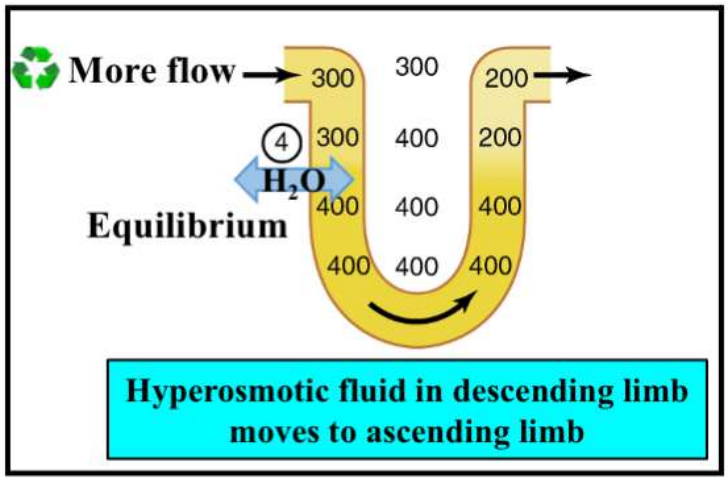
Vasa recta

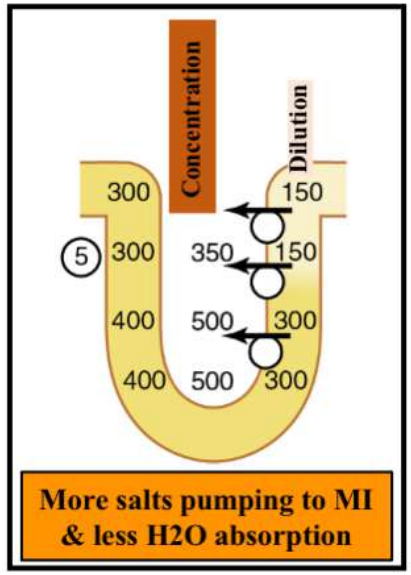
Countercurrent multiplier system in the loop of Henle

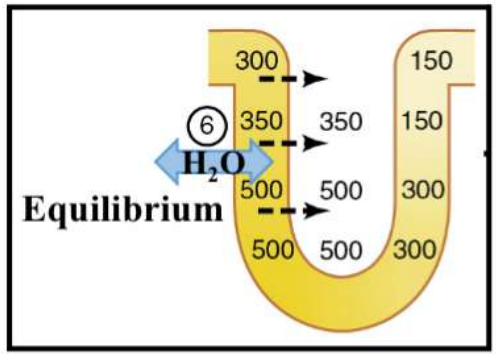




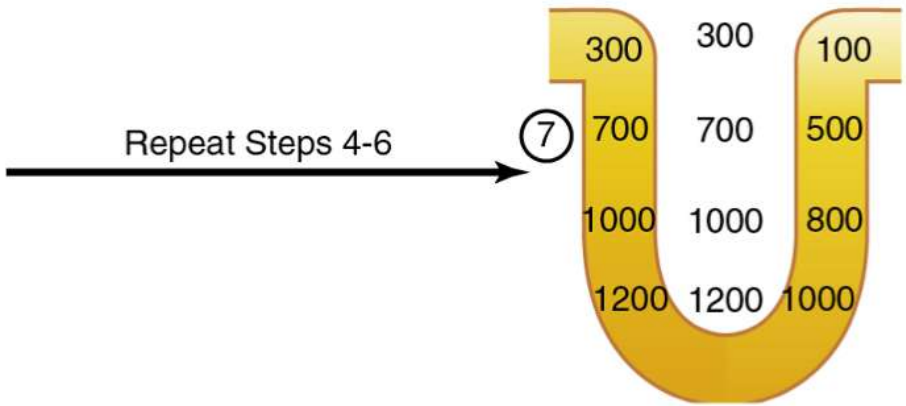


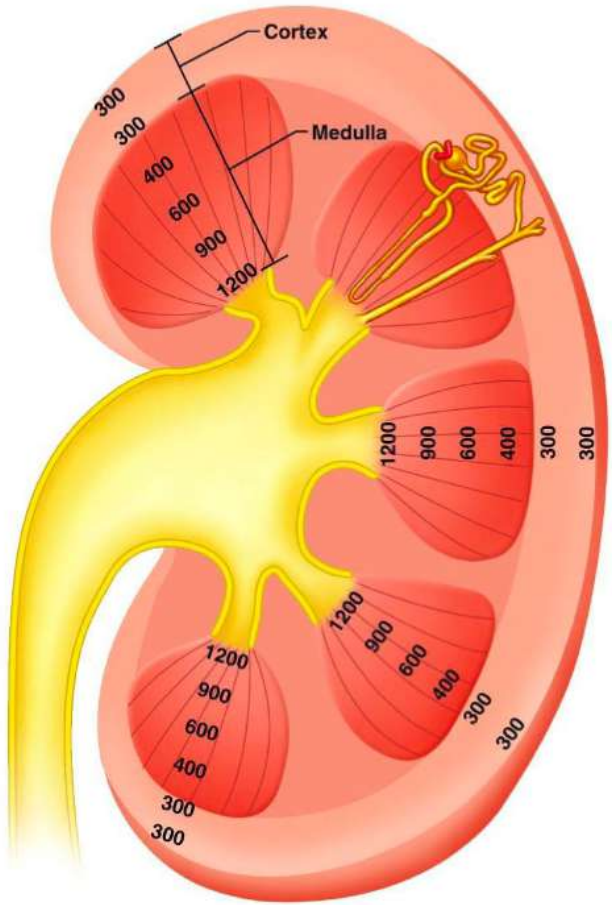






Countercurrent multiplier system in the loop of Henle





Countercurrent multiplier system in the loop of Henle

1. Loop of Henle is filled with fluid having a concentration of 300 mOsm/L, the same as that leaving the proximal tubule.

2. Active ion pump of **thick ascending** limb on the loop of Henle **reduces** the concentration inside the tubule and raises the interstitial concentration; this pump establishes a 200-mOsm/L concentration gradient between the tubular fluid and interstitial fluid.

3. Tubular fluid in the **descending limb** of the loop of Henle and interstitial fluid quickly reaches osmotic equilibrium due to **osmosis of water out of the descending limb**. The interstitial osmolarity is maintained at 400 mOsm/L because of *continued transport of ions out of the thick ascending loop of Henle.*

4. Additional flow of fluid into the loop of Henle from the proximal tubule, which causes the *hyperosmotic fluid previously formed in the descending limb to flow into the ascending limb.*

Countercurrent multiplier system in the loop of Henle

5. Once fluid is in the ascending limb, *additional ions are pumped into the interstitium* and **water remains** in the tubular fluid. The interstitial fluid osmolarity rises to 500 mOsm/L.

6. Fluid in the descending limb reaches equilibrium with the hyperosmotic medullary interstitial fluid..

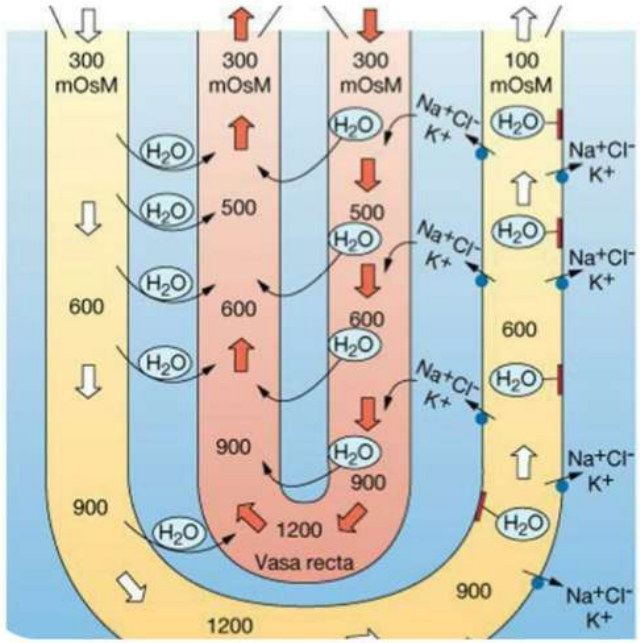
These steps are repeated over and over, with the net effect of adding more and *more solute to the medulla in excess of water*. With sufficient time, this process gradually traps solutes in the medulla and multiplies the concentration gradient established by the active pumping of ions out of the thick ascending loop of Henle, eventually raising the interstitial fluid osmolarity to 1200 to 1400 mOsm/L, as shown in step 7.

The Vasa Recta Preserve Hyperosmolarity of Renal Medulla

- Vasa recta blood flow is **low** (only 1-2 % of total renal blood flow) **minimizing washout of solutes** from the medullary interstitium.

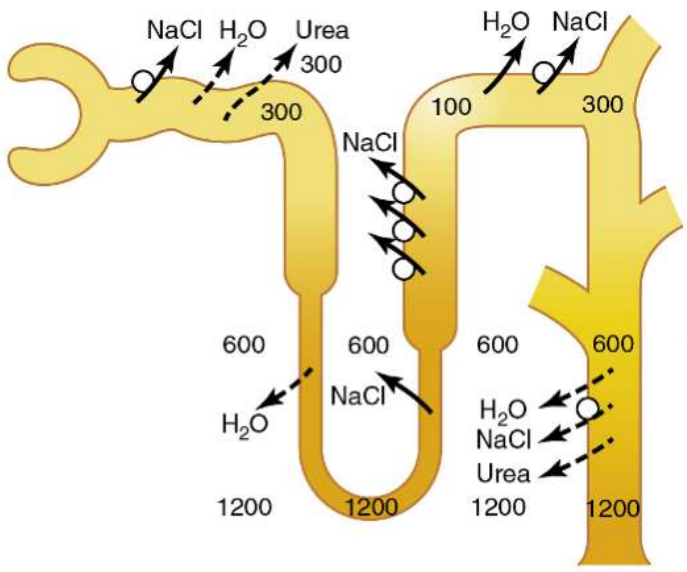
- The vasa recta serve as **countercurrent exchangers**:
- Descending limb → **hyperosmotic** (water out & solutes in)
- Ascending limb → solutes out and water in

Large amounts of solutes would be lost from the renal medulla without the U shape of the vasa recta capillaries.



Role of distal T & collecting ducts in excreting concentrated urine

Distal tubule **→dilutes tubular fluid**
Active reabsorption of NaCl
Impermeable to H2O

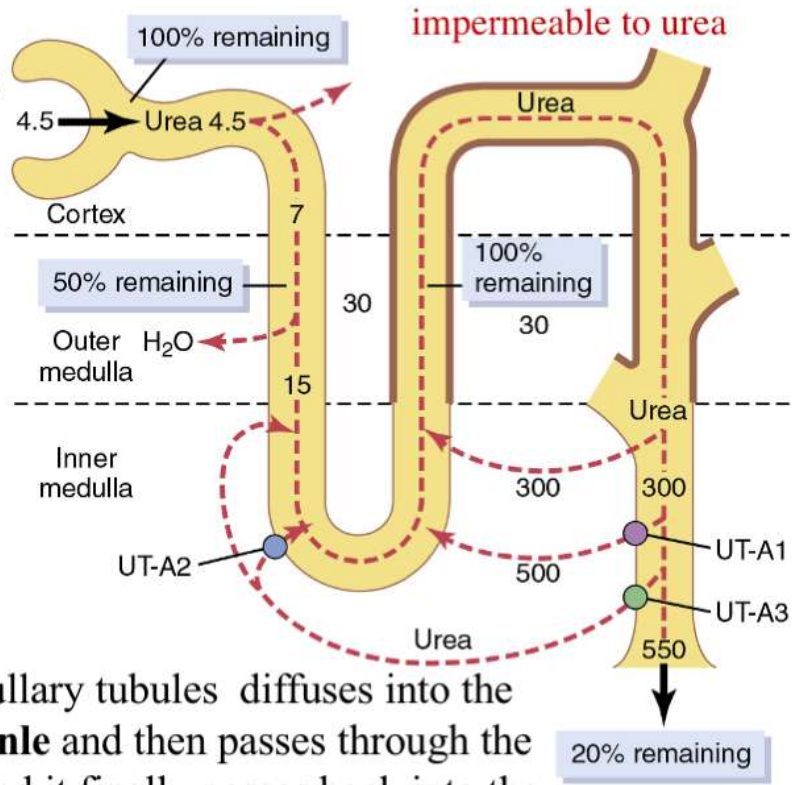


Cortical collecting tubule
ADH dependent H2O reabsorption **TO CORTEX NOT MEDULLA→** maintain hyperosmolar medulla
Continues to reabsorb solutes

Medullary collecting ducts
ADH dependent H_2O reabsorption → carried away by **vasa recta** into venous blood.
Urea passive reabsorption- UT-A1 and UT-A3.

Urea Recirculation

- 50% of urea is **passively** reabsorbed in **proximal tubule**
- Distal and collecting tubules → impermeable to urea
- Medullary collecting tubule **highly permeable** to urea → diffuses into medullary interstitium
- ADH increases urea permeability of medullary collecting tubule by activating urea transporters (UT-A)



Urea from medullary tubules diffuses into the **thin loop of Henle** and then passes through the distal tubules, and it finally passes back into the collecting duct.

Micturition

Transport of urine to urinary bladder

- No change in composition
- Urine from Collecting Duct→ Calyces (↑Pacemaker activity → peristalsis) →Pelvis→ Ureter →Urinary Bladder

Sympathetic stimulation:
↓Peristalsis
Parasympathetic stimulation:
↑Peristalsis

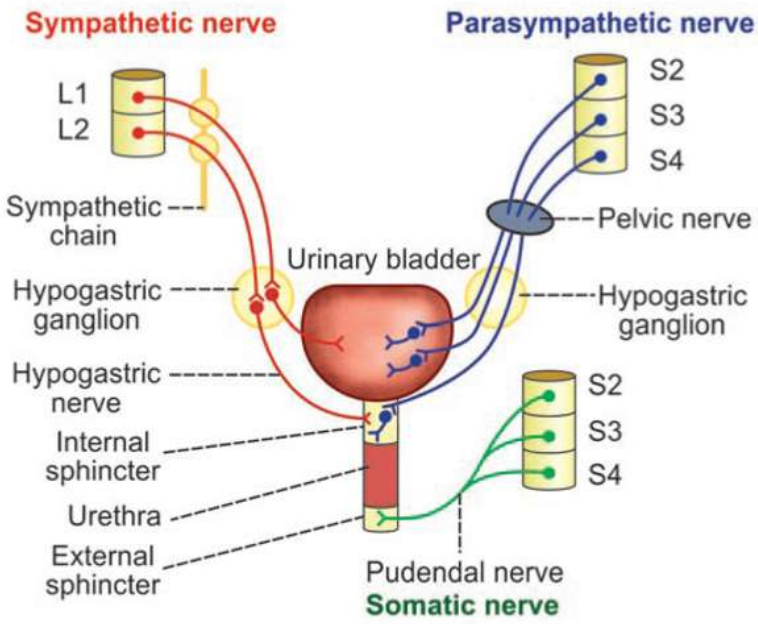
- Oblique course U+ compressed by detrusor muscle tone→ Prevents Vesicoureteral Reflux
- Reflux →enlargement of ureters+ ↑pressure in renal calyces & medulla →damage

Pain sensation in Ureters

- Well supplied with pain nerve fibers
- Irritation/ block (e.g. stone) → intense stimulation of pain nerve fibers → Intense contraction of ureters (severe pain)

Sympathetic reflex back to kidney→ vasoconctriction of renal arterioles→ ↓the urine output =**Ureterorenal reflex→ preventing excessive flow of fluid into pelvis**

Innervation of urinary bladder



Pelvic nerve has sensory fibers→ impulses from stretch receptors in urinary bladder and urethra →CNS

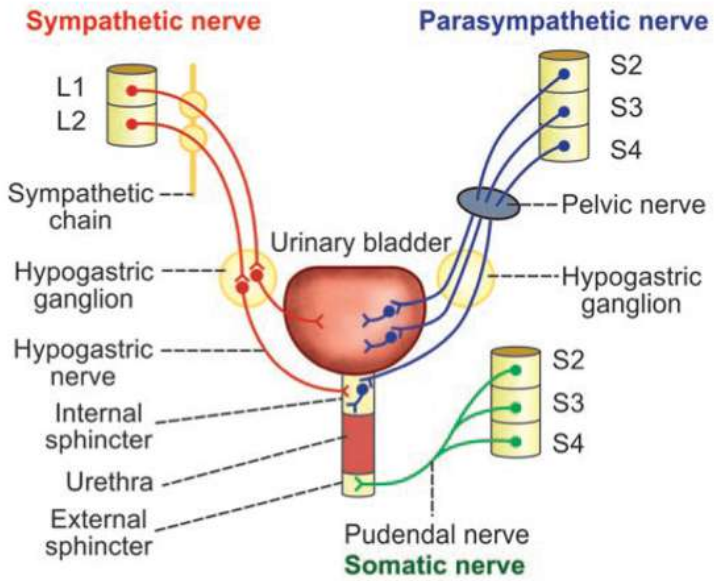
Nerve	On detrusor muscle	On internal sphincter	On external sphincter	Function
Sympathetic nerve	Relaxation	Constriction	Not supplied	Filling of urinary bladder
Parasympathetic nerve	Contraction	Relaxation	Not supplied	Emptying of urinary bladder
Somatic nerve	Not supplied	Not supplied	Constriction	Voluntary control of micturition

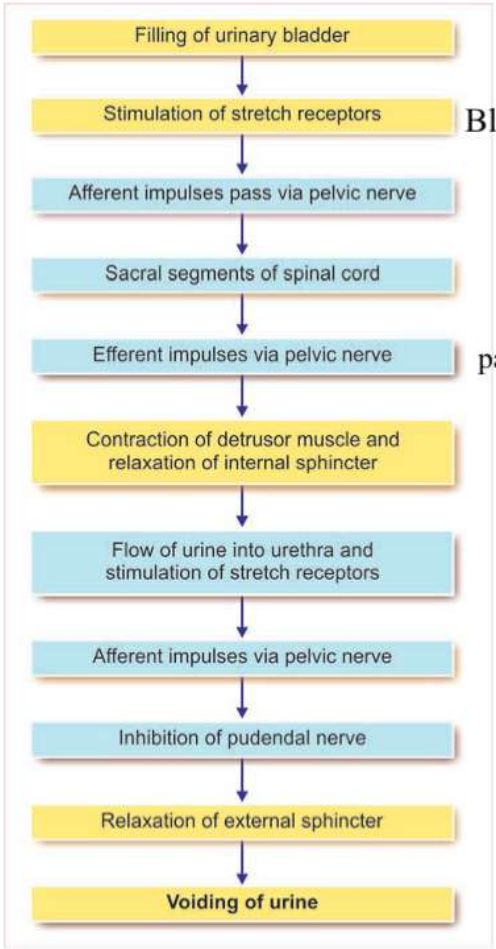
Micturition

- Emptying urinary bladder when it becomes filled →tension in its walls > threshold level→ **micturition reflex**
- Contraction of detrusor muscle→↑pressure in bladder to 40-60 mm Hg → emptying the bladder
- Internal sphincter→ prevents emptying of bladder until pressure in bladder > threshold level
- External sphincter→ voluntary skeletal muscle, used to consciously prevent urination

Micturition Reflex

- Autonomic spinal cord reflex
- Contraction of Detrusor muscle
- Inhibited / facilitated by brain



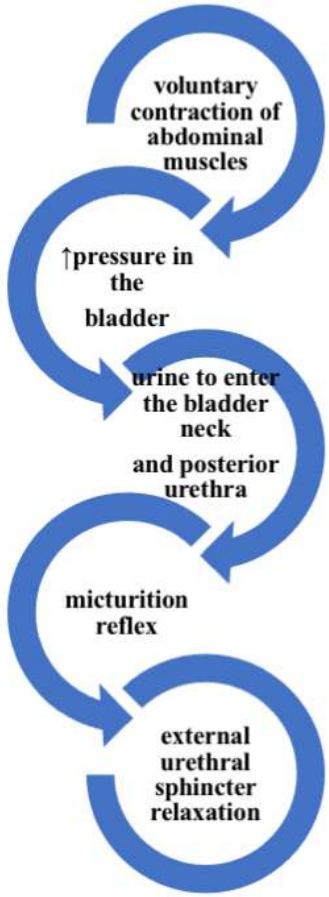


Control by Higher Centers

Higher centres normally exert final control of micturition

- Pon & cerebral cortex
- Partial **inhibition of micturition reflex→** Prevent micturition, even if micturition reflex occurs by **tonic contraction of external urinary sphincter** until a convenient time presents itself.
- Cortical centers can facilitate sacral micturition centers to initiate micturition reflex & relax external sphincter

Voluntary urination



Acid-Base Regulation

- Acid : release H^+ in solutions .
- Bases : accept a hydrogen ions in solution .
- Strong acids & Base: completely dissociate.
- Weak acid & Base : partially dissociate.

- **Acidosis = excess generation of H+**

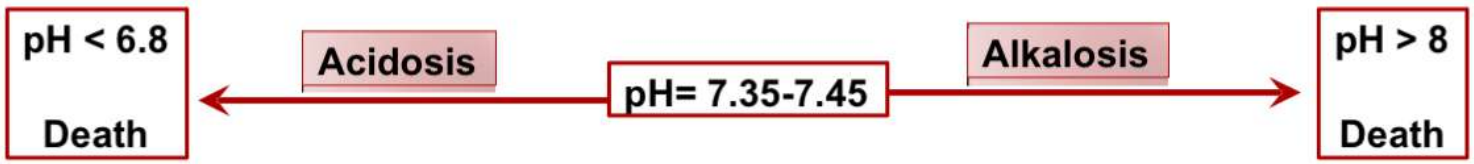
Alkalosis = excess removal of H+ from the body fluids

[H^+] & pH

- [H+] is precisely **regulated** at 0.00004 mEq/L (important for enzyme functions)
- H^+ ion concentrations are expressed as pH.

- pH ∝ - Log [H^+]
  - If the [H^+] increase → pH will decrease (more acidic)
  - If the [H^+] decrease → pH will increase (more alkaline)

Normally pH= 7.35-7.45



Acid Production by the Body

- Acids in the body are of two kinds:
  1. Volatile (CO_2)
  2. Non-volatile “fixed” (sulfuric acid, lactic acid)

The Body's Defense Against Changes in $[H^+]$

Three main systems:

1. ***Body fluid buffers.***

   Works within seconds (bind acid/base→ weaker).

2. ***Lungs***

   Works within minutes (eliminate CO2).

3. ***Kidneys***

   Works within hours-days (EXCRETE ACID/BASE).

   The most powerful of the three.

Chemical Buffer Systems in the Body

- ***There are 3 chemical buffers in the body;***

1. The HCO_3 buffer system.
2. The PO4 buffer system.
3. Proteins.

- They are the 1st line of defence against changes in pH i.e. $[H^+]$, act within seconds.

HCO3 Buffer System

- The main ECF buffer system
- Composed of:
  - A weak acid (H_2CO_3).
  - Its conjugated base (e.g $NaHCO_3$).

1. ***H_2CO_3 forms in the body by the reaction of CO_2 & H_2O***

$$CO_2 + H_2O \xrightleftharpoons{\text{Carbonic anhydrase}} H_2CO_3$$

2. ***H_2CO_3 ionizes weakly to form small amounts of H^+ & HCO_3^-***

$$H_2CO_3 \rightleftharpoons H^+ \,\&\, HCO_3^-$$

3. ***The second component is $NaHCO_3$ which dissociates to form Na^+ & HCO_3^-***

$$NaHCO_3 \rightleftharpoons Na^+ \,\&\, HCO_3^-$$

Other Buffering Systems

The phosphate buffer:

- Plays a major role in buffering intracellular & renal tubular fluid.

- Composed of;
  - $H_2PO_4^-$ (dihydrogen phosphate/ACID)
  - HPO_4^{-2} (Hydrogen phosphate/BASE)

Proteins: PLENTIFUL

- Contributes to buffering inside cells→ H+ /HCO3- diffusion to the cell.
- E.g. Hb.

The Henderson-Hasselbalch Equation

What is the HHE?

- It is an equation that enables the calculation of pH of a solution.

What is it?

$$pH = pK + log \frac{HCO3^-}{0.03\ X\ PCo_2}$$

pK = dissociation constant, pK = 6.1

PCO_2= solubility coefficient of CO_2= 0.03

The Henderson-Hasselbalch Equation

$$pH = pK + \log \frac{[HCO3^-]}{0.03\ X\ PCO2}$$

- ***What do we understand from this equation?***

1. pH ∝ $\frac{HCO3^-}{PCO2}$ — $HCO3^-$: **Regulated by kidneys**; $PCO2$: **Regulated by lungs**

   - ↑↑ HCO_3^- will ↑↑ pH
   - ↑↑ PCO2 will ↓↓ pH

Renal Regulation of Acid-Base Balance

- 3rd line of defense against acid-base disturbances and the most powerful.
- Kidneys conserve HCO_3^- and excrete acidic or basic urine depending on body needs

Mechanisms

- Secretion of non-volatile acids (H_2SO_4, H_3PO_4) (~ 80 mmol/day)
- Secretion of H^+ (~ 4400 mmol/day)
- Filtration of HCO_3^- (~ 4320 mmol/day)
- Reabsorption of HCO_3^- (~ 4319 mmol/day)
- Excretion of HCO_3^- (1 mmol/day)
- Production of new HCO_3^- (~ 80 mmol/day)

H+ is NOT excreted as free H+ but rather in combination with other **urinary buffers**, especially **phosphate** and **ammonia**.

Renal compensation of Acid-Base Balance

- Acidosis:
  - increased H^+ secretion
  - increased HCO_3^- reabsorption
  - production of new HCO_3^-

Result

Less H+ in body
More HCO_3 in body

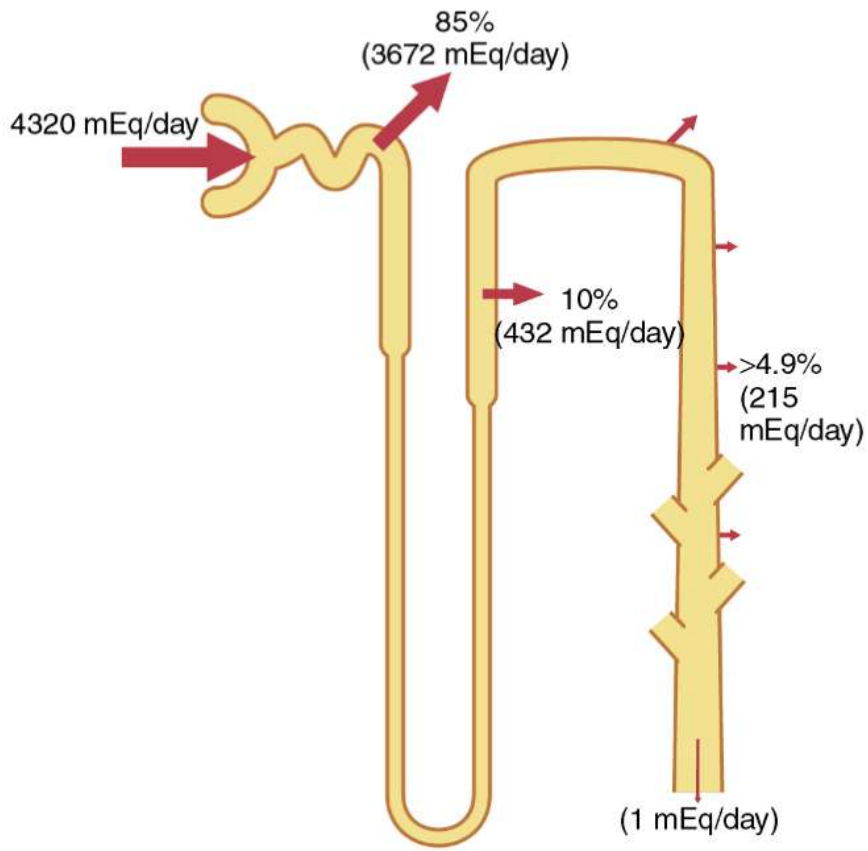
- Alkalosis:
  - decreased H^+ secretion
  - decreased HCO_3^- reabsorption
  - loss of HCO_3^- in urine

Result

More H+ in body
Less HCO_3 in body

HCO_3 reabsorption & secretion of H^+ in renal tubule

<u>Key point:</u>
For each HCO_3^- reabsorbed, there must be a H^+ secreted



Mechanisms of HCO_3^- reabsorption and Na^+-H^+ exchange

PT, thick loop of Henle & early DT

Na-K ATPase→ IC Na→++ [Na] gradient

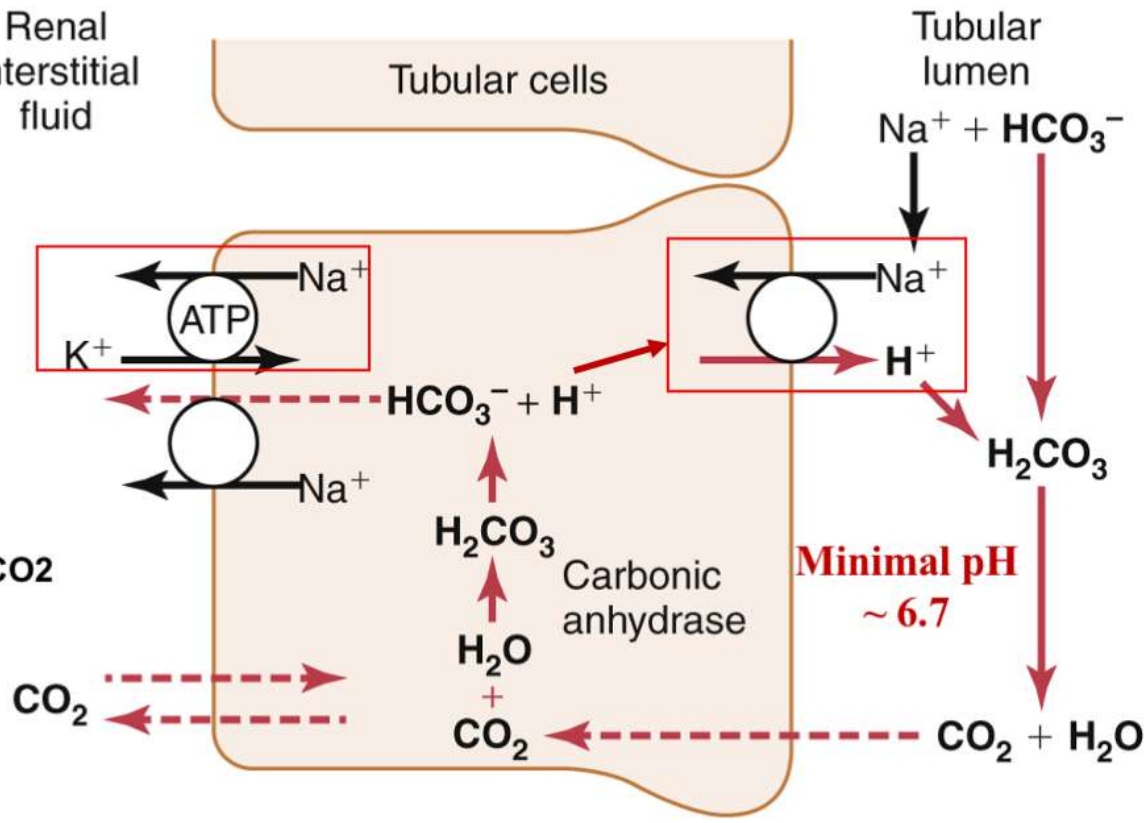
↓

H+ secretion into the tubular fluid by Na-H counter-transport

NO CHANGE IN LUMINAL pH

HCO3 reabsorption starts with formation of H2CO3→ CO2 reabsorption→ Na-HCO3 co-transport

Replacement of filtered HCO3



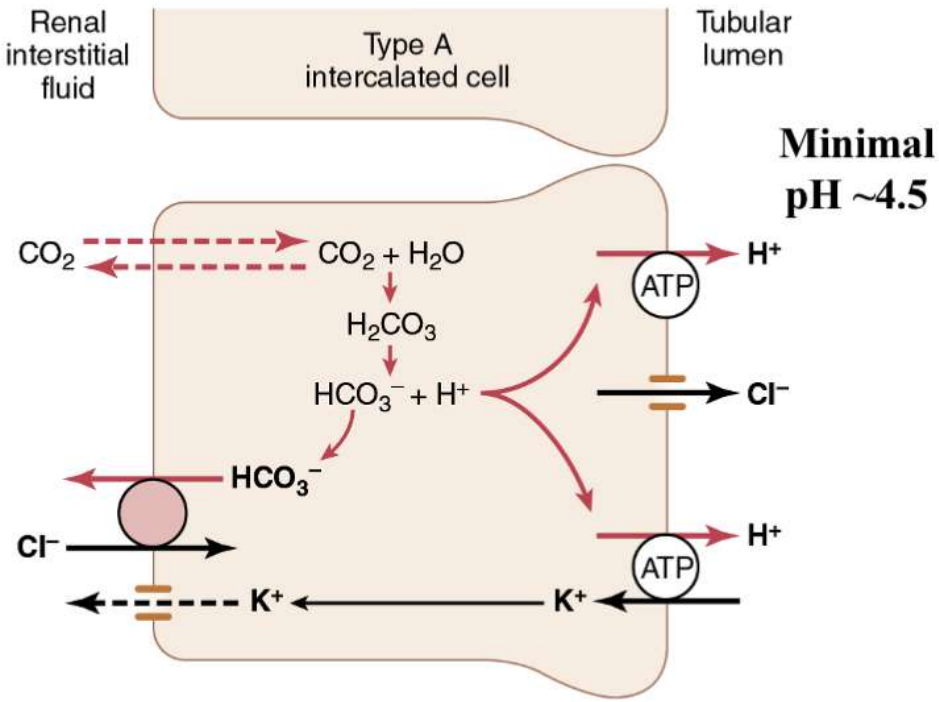
HCO_3^- reabsorption and H^+ secretion

Intercalated cells of late distal and collecting tubules

Primary Active secretion of H+
H+–ATPase
H+-K+-ATPase

CHANGE IN LUMINAL pH→ acidification of U

one HCO3 is absorbed for each H+ secreted→
HCO3-Cl counter transport
one Cl is passively secreted.

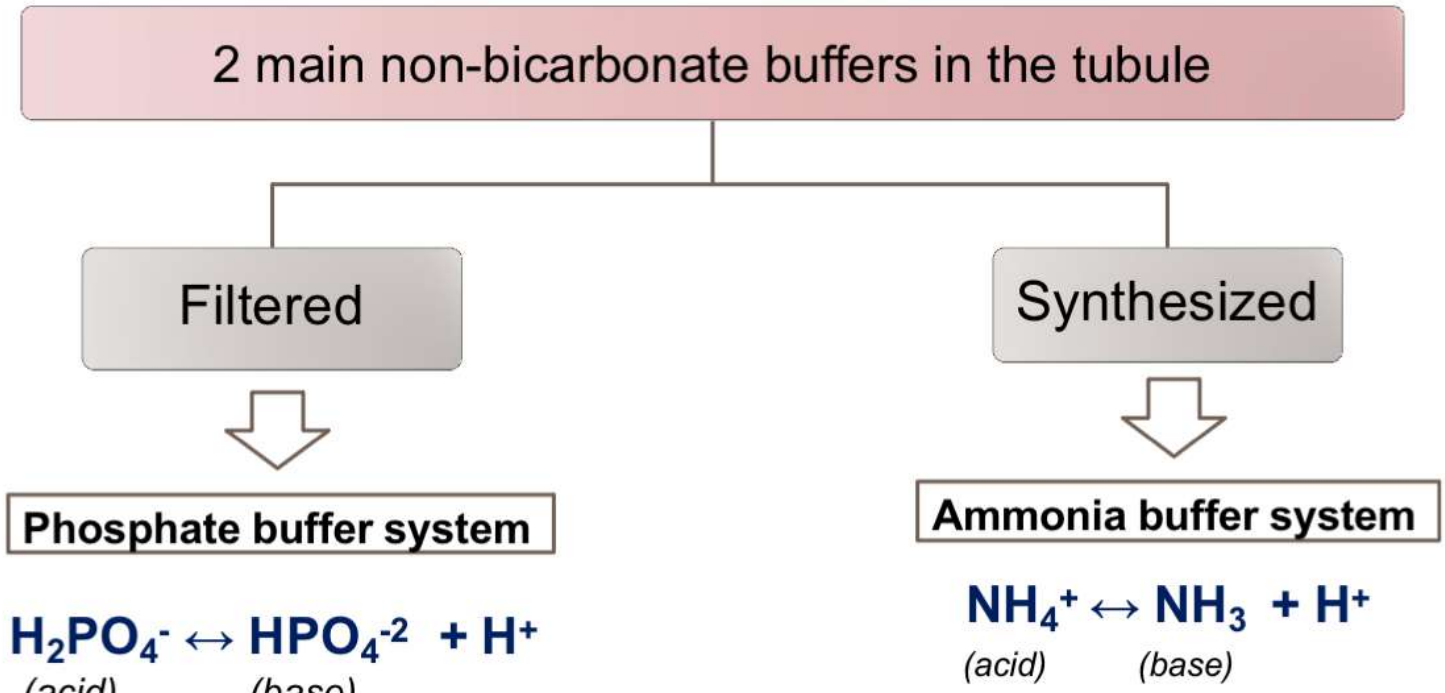


H^+ secretion

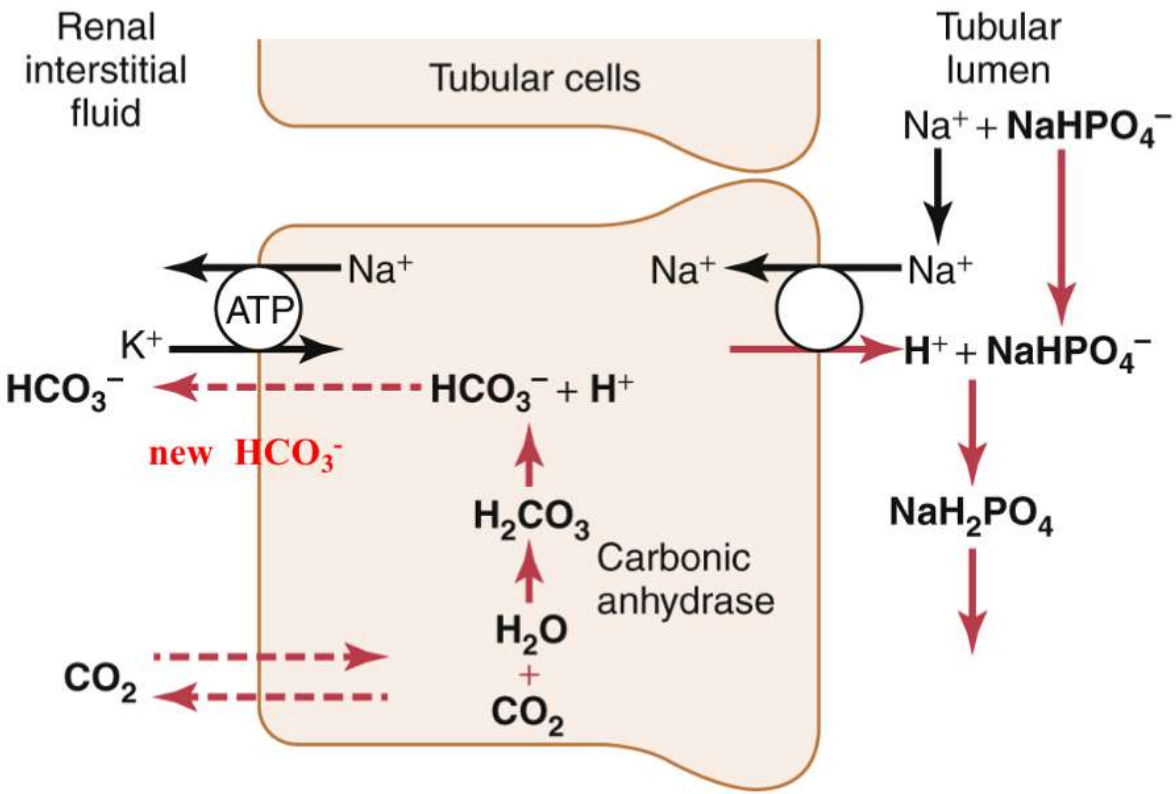
- Only a **limited** number of H^+ can be excreted in its **free form** in urine.
- Lowest possible urine pH=4.5 → ≈ 0.04 mmol/L of free H^+.
- ***How does the kidney excrete the extra H^+?***

Non-Bicarbonate Buffers in the Tubular Lumen

The extra H^+ secreted will need to be buffered in the tubular lumen

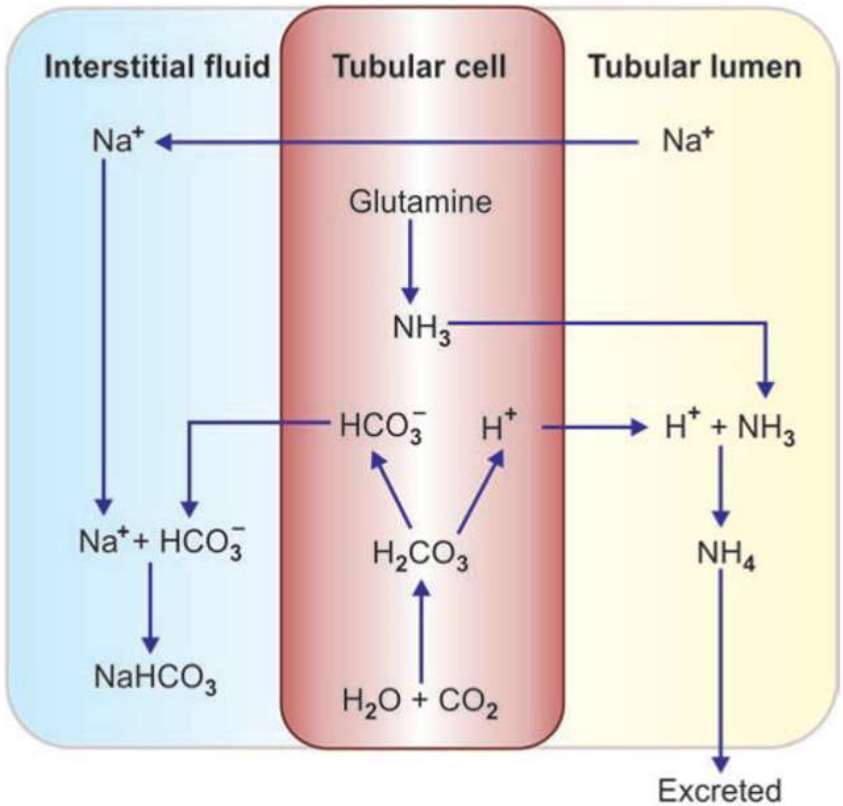


Buffering of secreted H^+ by filtered phosphate ($NaHPO_4^-$) and generation of "new" HCO_3^-

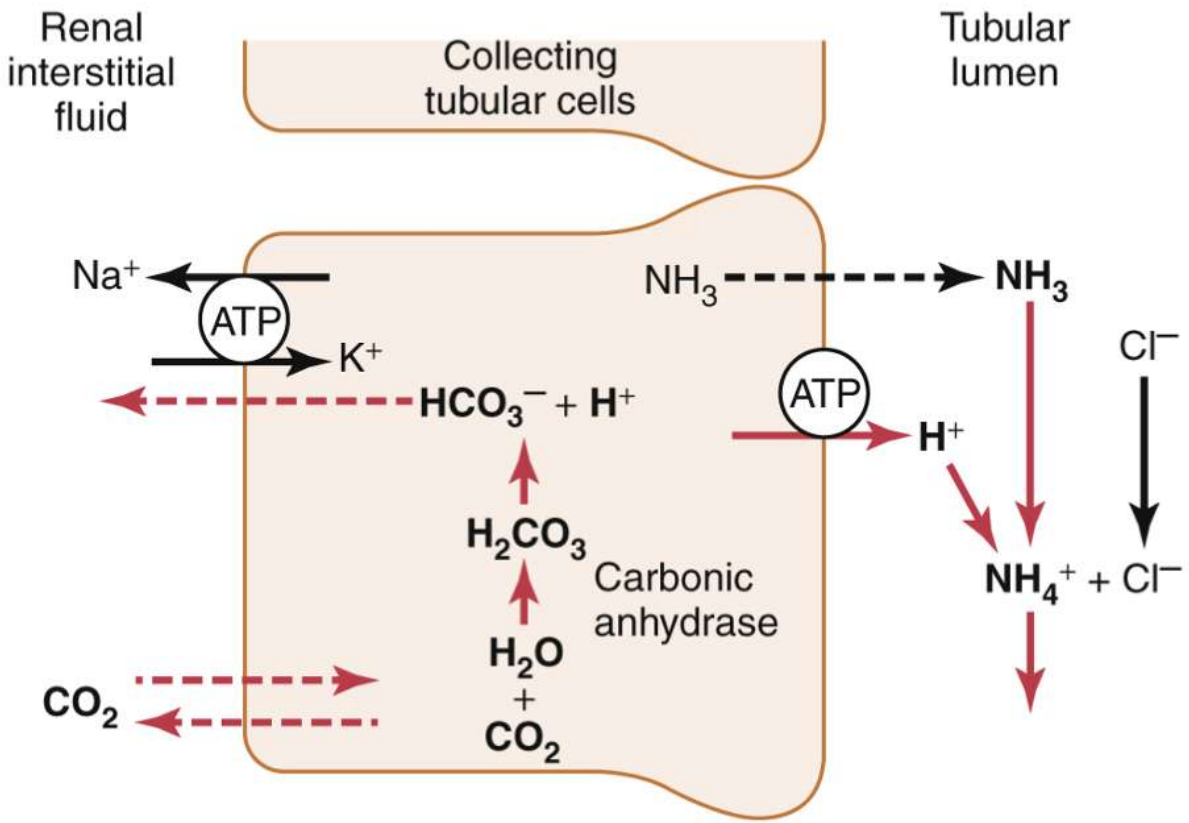


Production and secretion of NH_4^+ and HCO_3^- by proximal, thick loop of Henle and distal tubules

- Quantitatively, **NH4+** system is more important than the **phosphate** buffer system for H^+ excretion in urine.
- It is the most important system in case of **acidosis**.
- Ammoniagenesis→ from glutamine



Buffering of H^+ by NH_3 in collecting tubules



Renal correction of acidosis

pH	$HCO3^-$	PCO_2	H^+
7.35-7.45	22-26	35-45	40

Acidosis → ↓pH

$$pH \propto \frac{HCO3}{PCO2}$$

	Acidosis pH< 7.35/Acidosis pH< 7.35/Acidosis pH< 7.35/Acidosis pH< 7.35	
Type	Metabolic	Respiratory
Change	↓ HCO3	↑PCO2
Causes	excessive H+ → Metabolic dis (e.g DM, shock)/ Ingestion of Acids→a spirin Impaired acid secretion HCO3- loss→ diarrhea & RF	Any condition causes **HYPO**ventilation- respiratory centers damage Airways obstruction Impaired exchange of gases Neuromuscular dis
Compensation **↑ pH**	Respiratory→ ↓PCO2 = hyperventilation Renal→ ↑HCO3 reabsorption	Renal→↑HCO3 reabsorption
Diagnosis	pH ↓ ↓ HCO3 ↓PCO2	pH ↓ ↑PCO2 ↑HCO3

Renal correction of alkalosis

pH	$HCO3^-$	PCO_2	H^+
7.35-7.45	22-26	35-45	40

Alkalosis → ↑pH $pH \propto \frac{HCO3}{PCO2}$

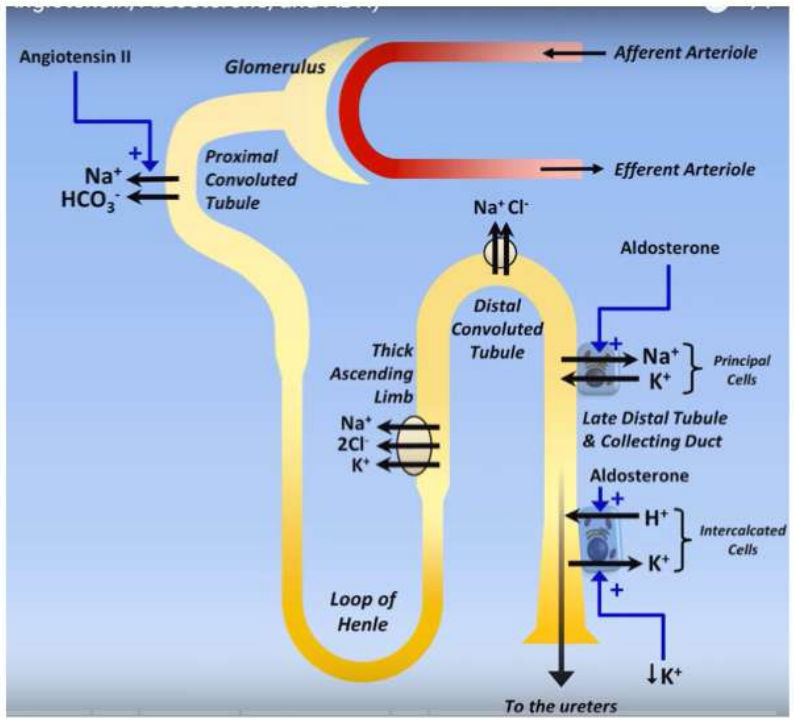
	Alkalosis pH> 7.45/Alkalosis pH> 7.45/Alkalosis pH> 7.45/Alkalosis pH> 7.45	
Type	**Metabolic**	**Respiratory**
Change	**↑HCO3**	**↓PCO2**
Causes	**-Acid loss→ persistent vomiting** **-↑HCO3- →** **thiazides/loop diuretics** **Hypovolemia** **Ingestion of alkaline drugs (NaHCO3)** **↑aldosterone & cortisol**	**Hyperventilation-** **fever, psychoneurosis, meningitis, early exercise, ascending to high altitude**
Compensation ↓ pH	**Respiratory→ hypoventilation (limited)→↑ PCO2** **Renal→↓HCO3 reabsorption**	**Renal→↓HCO3 reabsorption**
Diagnosis	**pH ↑** **↑HCO3** **↑PCO2**	**pH ↑** **↓PCO2** **↓ HCO3**

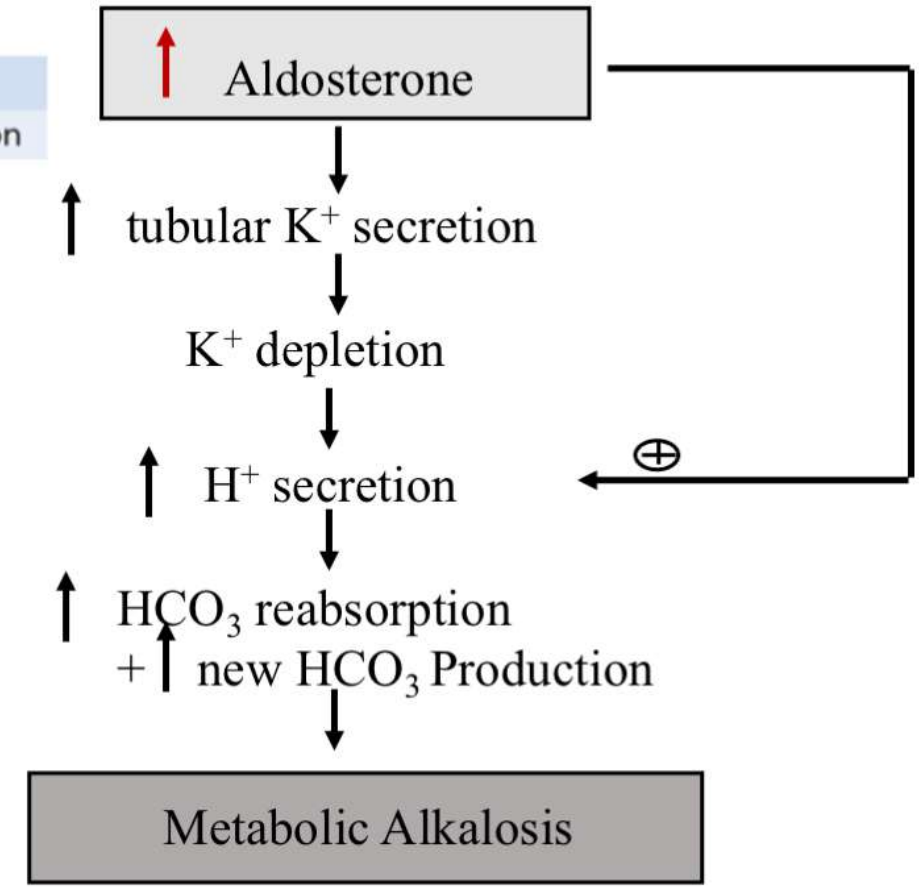
Table 31-2 Plasma or Extracellular Fluid Factors That Increase or Decrease H^+ Secretion and HCO_3^- Reabsorption by the Renal Tubules

Increase H^+ Secretion and HCO_3^- Reabsorption	Decrease H^+ Secretion and HCO_3^- Reabsorption
↑ P_{CO_2}	↓ P_{CO_2}
↑ H^+, ↓ HCO_3^-	↓ H^+, ↑ HCO_3^-
↓ Extracellular fluid volume	↑ Extracellular fluid volume
↑ Angiotensin II	↓ Angiotensin II
↑ Aldosterone	↓ Aldosterone
Hypokalemia	Hyperkalemia

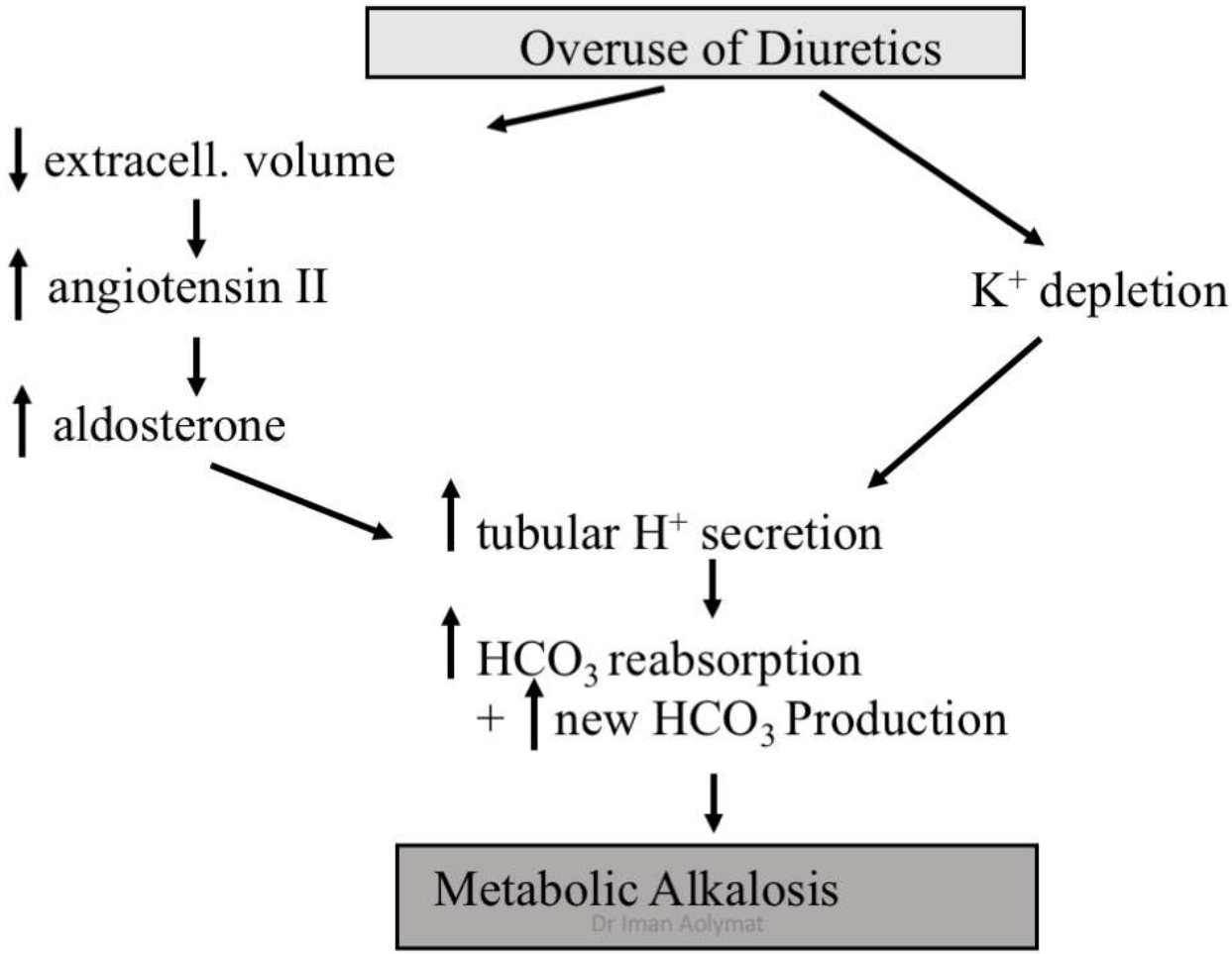
Hyperaldosteronism (aldosteronism) and acid base disturbances

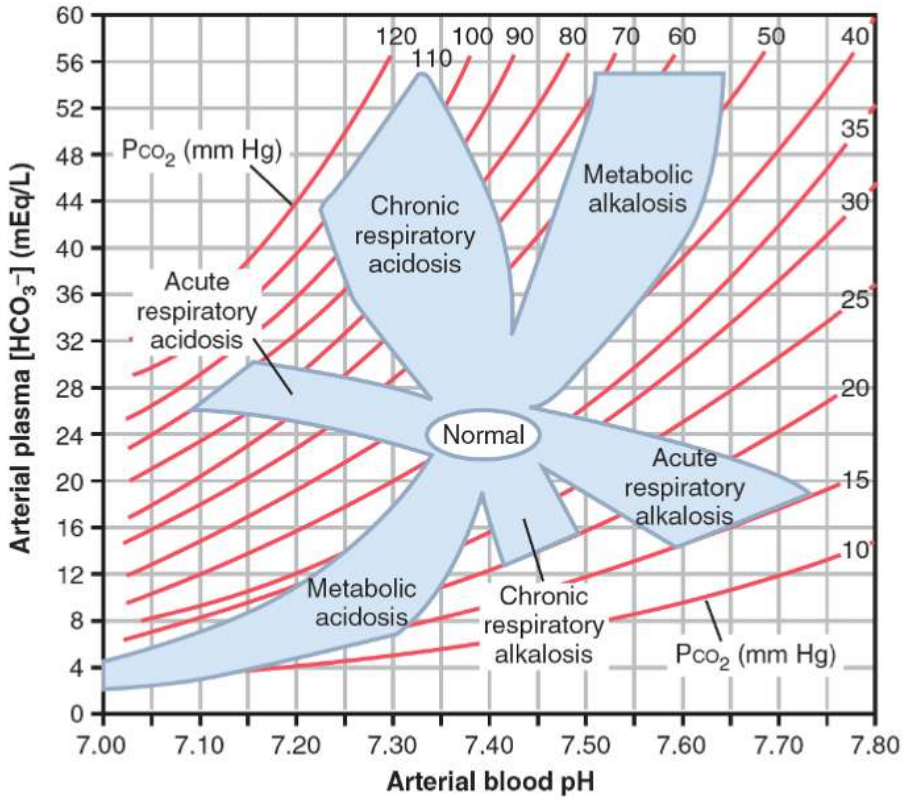
Hormone	Effects
Aldosterone	↑ NaCl, H_2O reabsorption, ↑ K^+ secretion, ↑ H^+ secretion





Acid base disturbances caused by overuse diuretics





Mixed disorders

The end