The Urinary System: Functional Anatomy and Urine Formation by the Kidneys

U N I T V

Chapter 26

Dr Iman Aolymat

functions of Kidney :-

1 Excretion of Metabolic Waste Products

- Urea (from protein metabolism)
- Uric acid (from nucleic acid)
- Creatinine (from muscle) → very important, if it presents in the urine that indicate an improper function of Kidney
- Bilirubin (from hemoglobin breakdown)
- Hormone metabolites

2 Excretion of Foreign Chemicals and Drugs

- Pesticides
- Food additives
- Toxins
- Drugs

3 Regulation of Water and Electrolyte Balances

very important function of the kidney

Body is trying to keep out the matching the amount of output into the input (water and electrolytes, mainly sodium)

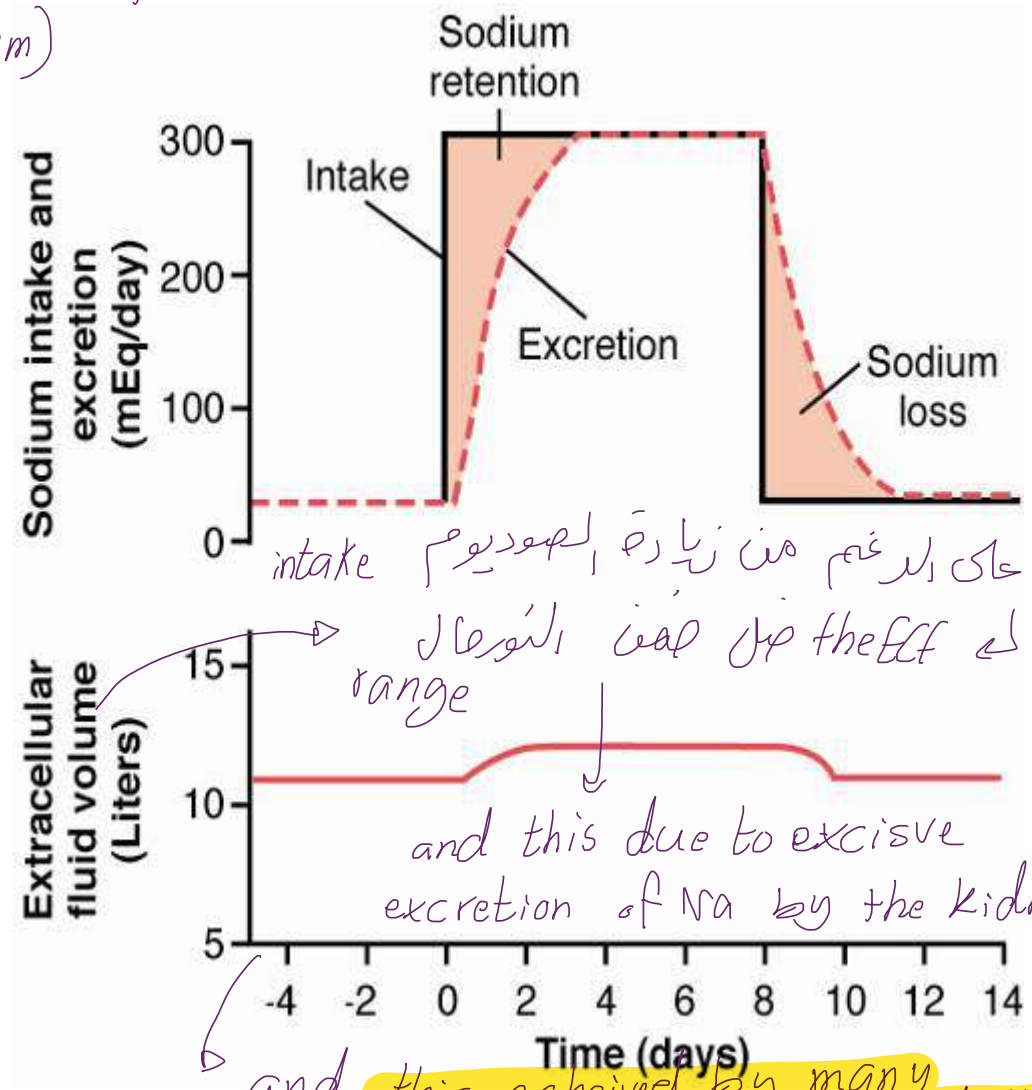
- Input = output

kidney play an important role in excrete the extra Na

Effect of ↑ Na (10X) intake on urinary Na excretion and ECFV

solute by increase the renal excretion

- Within 2-3 days →renal Na excretion ↑
- Modest accumulation of Na →↑ ECFV slightly → triggers hormonal changes & compensatory responses →↑ renal Na excretion
- Same for H2O, K, H^+, Ca, P, Mg



intake حاك الرغم من زيادة الصوديوم

range

and this due to excisve excretion of Na by the kidney

and this acheived by many mechanisms mainly hormonal (compansatory and other mechanisms within the kidney to increase the renal excretion

4 Regulation of Arterial Pressure

- Excretion of Na & H2O
- Secretion of hormones and vasoactive factors
  - Renin-angiotensin system
  - Prostaglandins

or reabsorption of Na & H2O

اذا زاد عدا ال arterial pressure ← الكلية بتحاول تخفضه عن طريق زيادة ال

واذا صار عدا انخفاض بال

hemorrhage shock ← وفي سبب مثلاً arterial pressure

the kidney will try to compansate that by the decrease the excretion of Na^+ & H_2O and this is acheived by hormones and vasoactive factors

5 Regulation of Acid-Base Balance

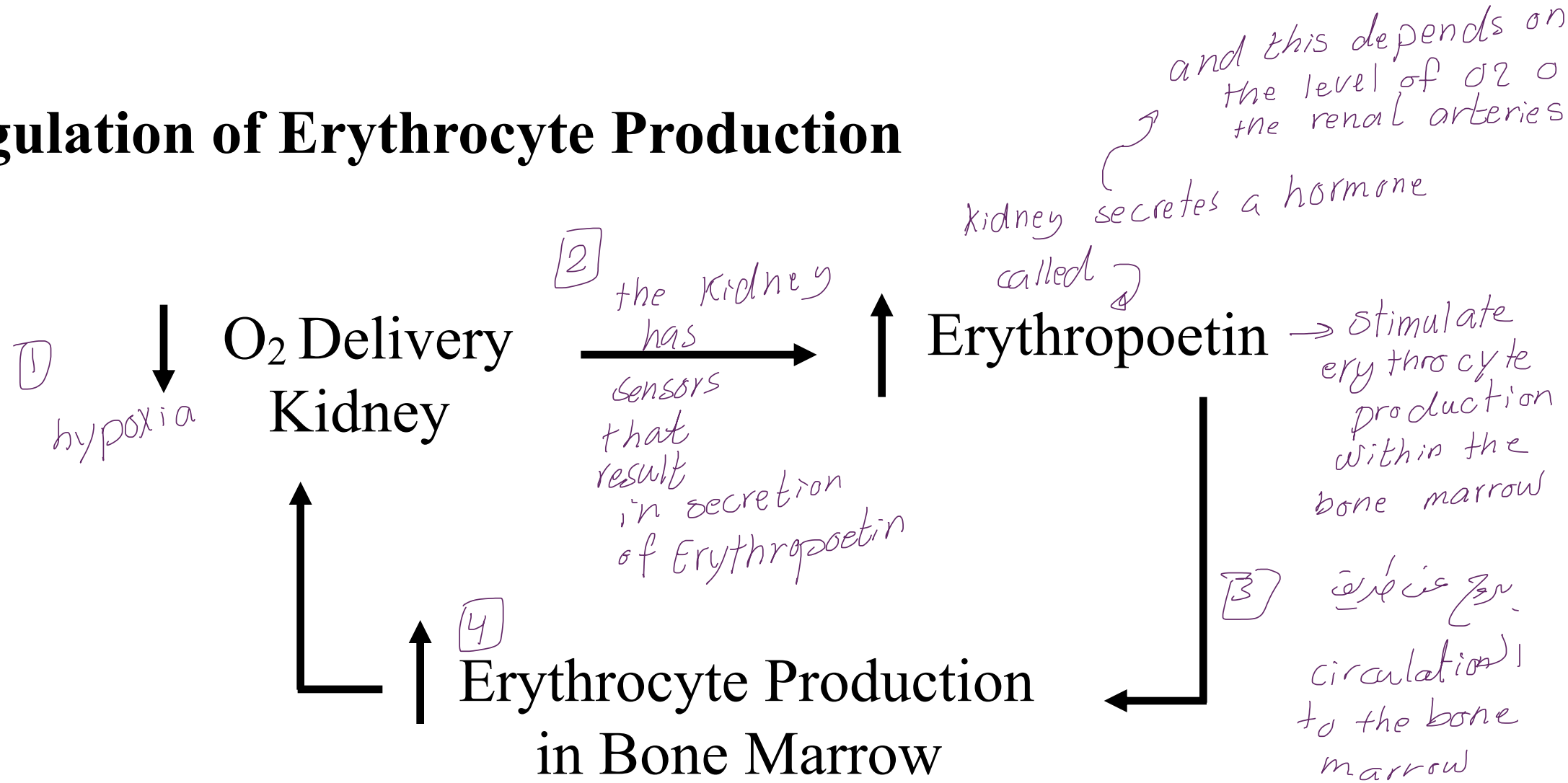
A • Excrete acids (kidneys are the only means of excreting sulfuric acid and phosphoric acid)

B • Regulate body fluid buffers (e.g. Bicarbonate)

also the kidney play an important role in the secretion of proton ions

acid base balance

6 Regulation of Erythrocyte Production



7 Regulation of Vitamin D Activity

Kidney has endocrine function
in term of erythropioten production
- vitamin D activity
- secretions of other hormones

- Kidney produces active form of vitamin D
  (1,25 dihydroxy vitamin D_3)

- Vitamin D_3 is important in Ca & P metabolism

8 Secretion, Metabolism, and Excretion of Hormones

Hormones produced in the kidney

1. • Erythropoietin
2. •Thrombopoietin
3. • 1,25 dihydroxycholecalciferol (Vitamin D)
4. • Renin
5. •Prostaglandins

Hormones metabolized and excreted by the kidney

- Most peptide hormones (e.g. insulin, angiotensin II, etc.)

→ metabolite by the kidneys
→ in diabetic pt → renal failure → so we should adjusment dose of insulin ---
لازم نخفف جرعة الانسولين .

9 Glucose Synthesis

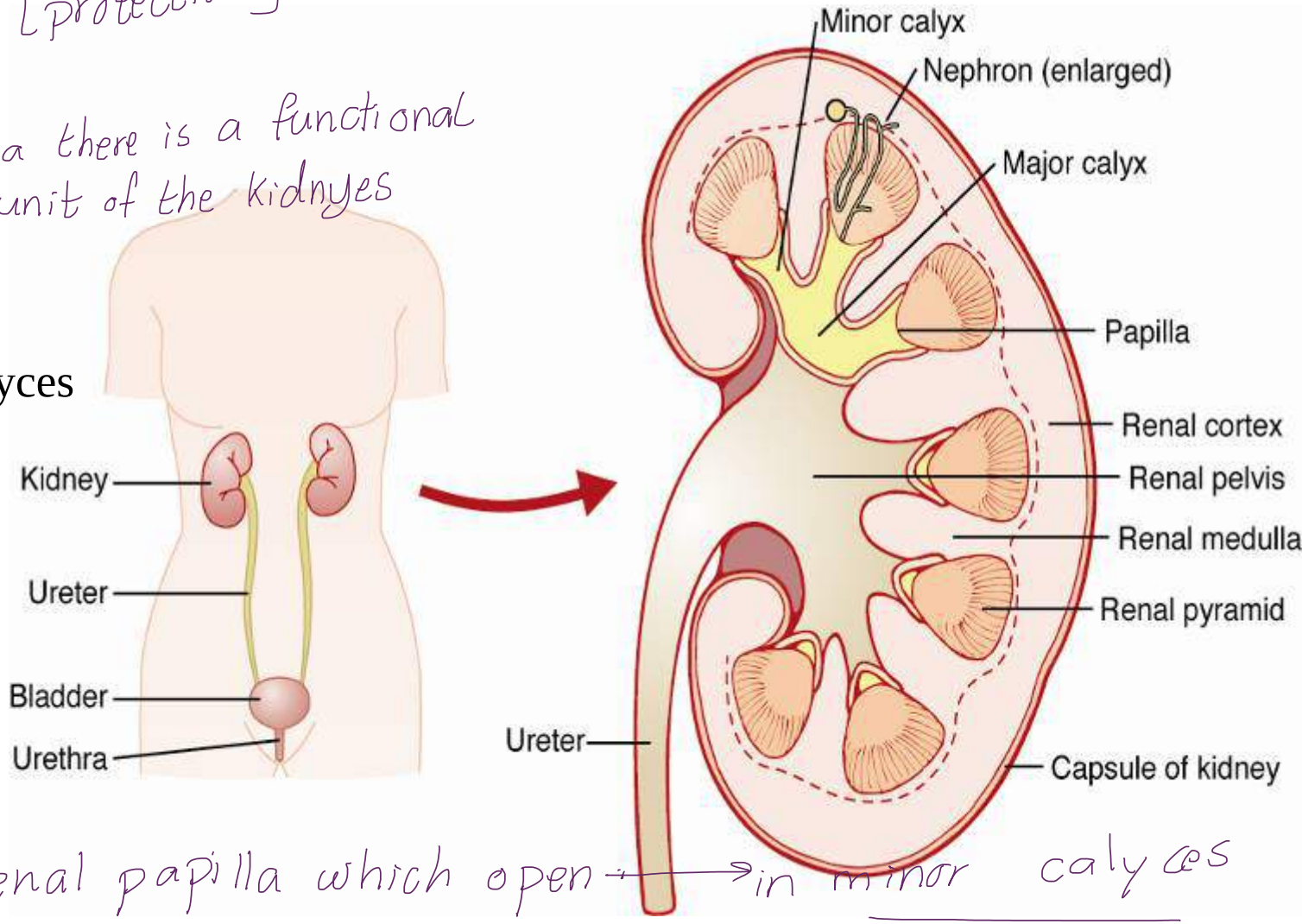
Gluconeogenesis: synthesize glucose from precursors (e.g. amino acids) during prolonged fasting

Urinary system

Kidney is surrounded by a strong fibrous capsul for [protection]

- Cortex & medulla → within the medulla there is a functional unit of the kidnyes
- Renal pyramids→ papilla→renal pelvis
- Renal pelvis→major calyces → minor calyces

→ within it → there is nephrons ↓ functional unit of the Kidneys



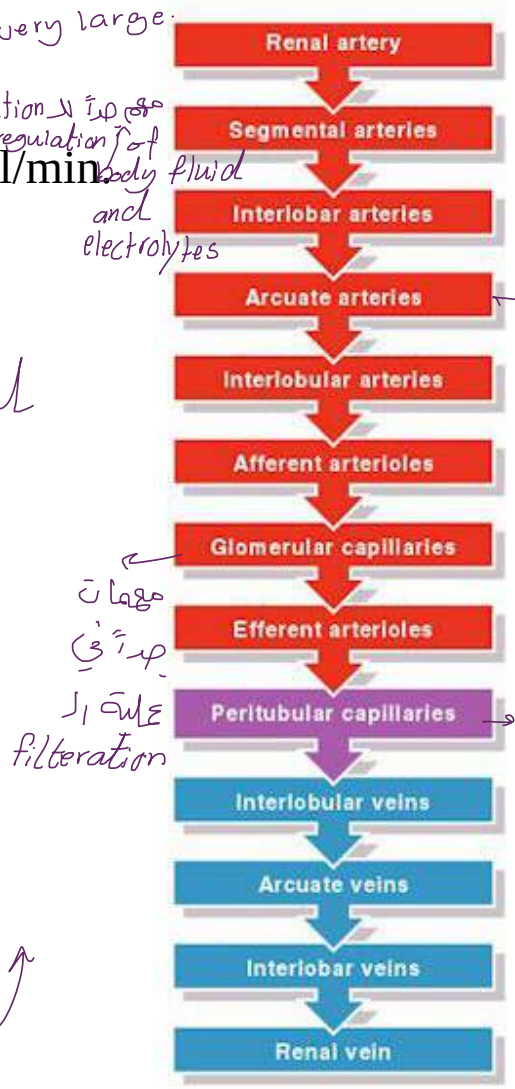
pyramids are empyting into the renal papilla which open → in minor calyces ↓ unit together ← forming major calyces ← وهاي بتفتح في ال Renal pelvis ← and then empyting to the ureter.

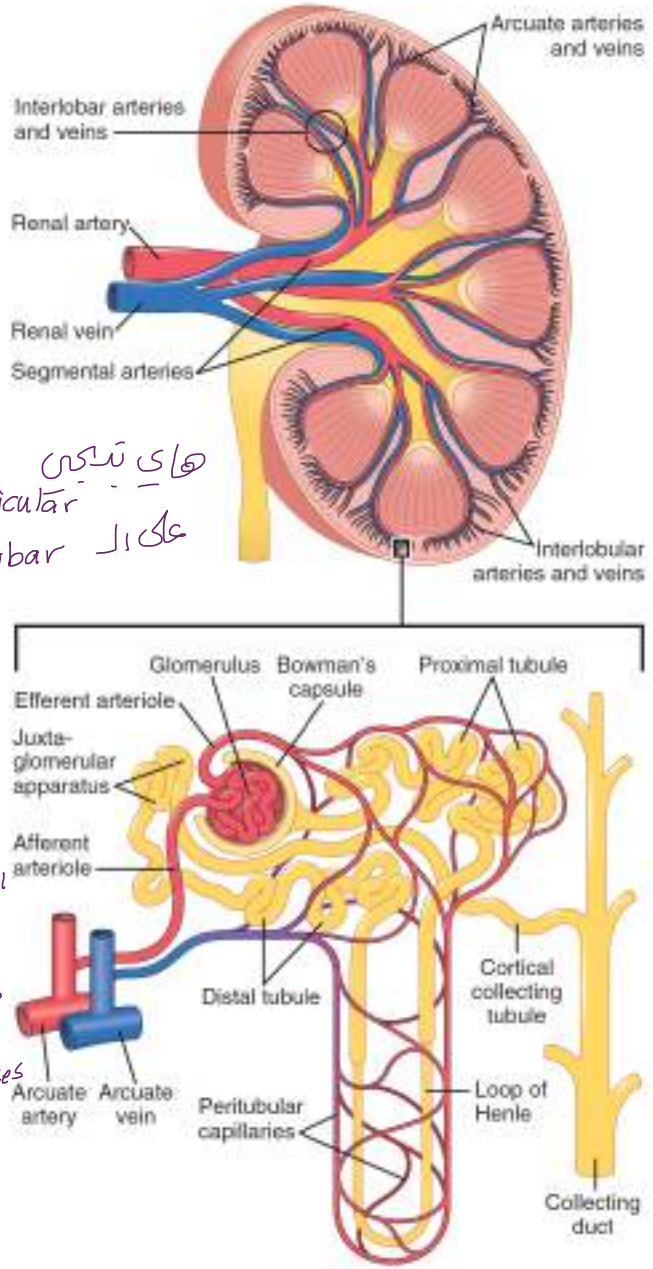
Renal Blood Supply

↳ is unique

- Blood flow to What does ~22% CO = 1100 ml/min.
- 2 capillary beds (glomerular (60 mm Hg) & peritubular (13 mm Hg)→reabsorption.

Blood supply directely from abdominal aorta → renal artery يدخل عن طريق الـ hailum into pelvis وهون بلش تتقسم إلى segmental arteries → interlobar arteries وهاي بتتقسم إلى



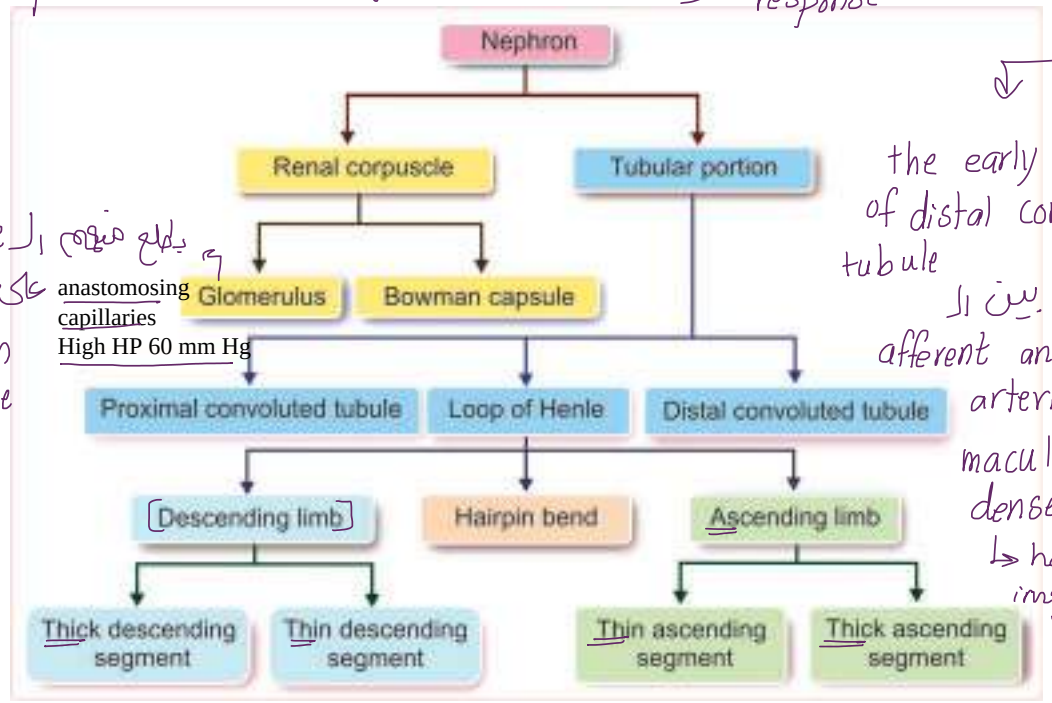


Nephron Tubular Segments

↳ structural unit of the kidney.

800K-1M nephrons, ↓ with ageing (adaptive response)

nephrons في الكلية حتى تعوض النقصان في ال adaptive response الناتج في



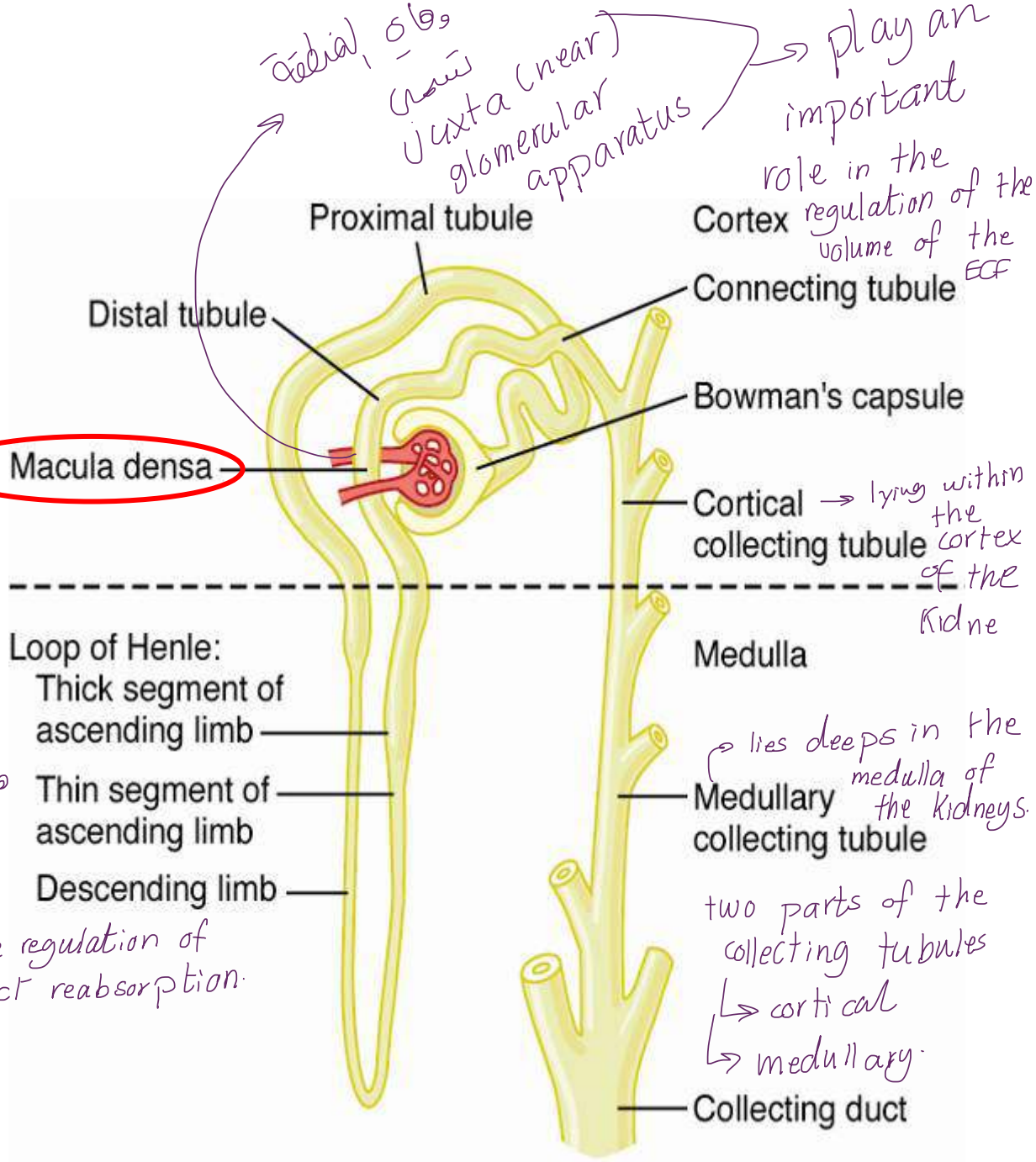
filterate الخارج من الدم على ال Bowman capsule

anastomosing capillaries
High HP 60 mm Hg

the early part of distal convoluted tubule

التي تقع بين ال afferent and efferent arterioles من ال macula dense

↳ has an important role in the regulation of Na and Cl reabsorption.



Extra glomerular cells, تسمى Juxta (near) glomerular apparatus → play an important role in the regulation of the volume of the ECF

→ lying within the cortex of the kidney

→ lies deeps in the medulla of the kidneys.

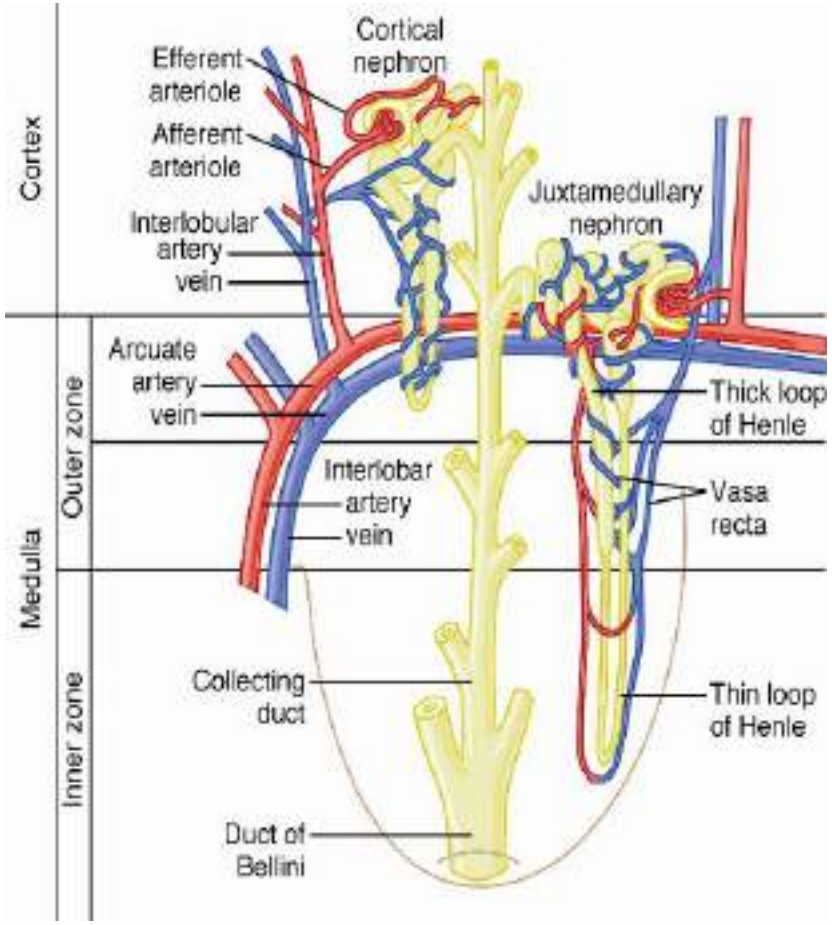
two parts of the collecting tubules
↳ cortical
↳ medullary.

* we have 2 types of nephrons

Regional Differences in Nephron Structure: Cortical & Juxtamedullary Nephrons

1

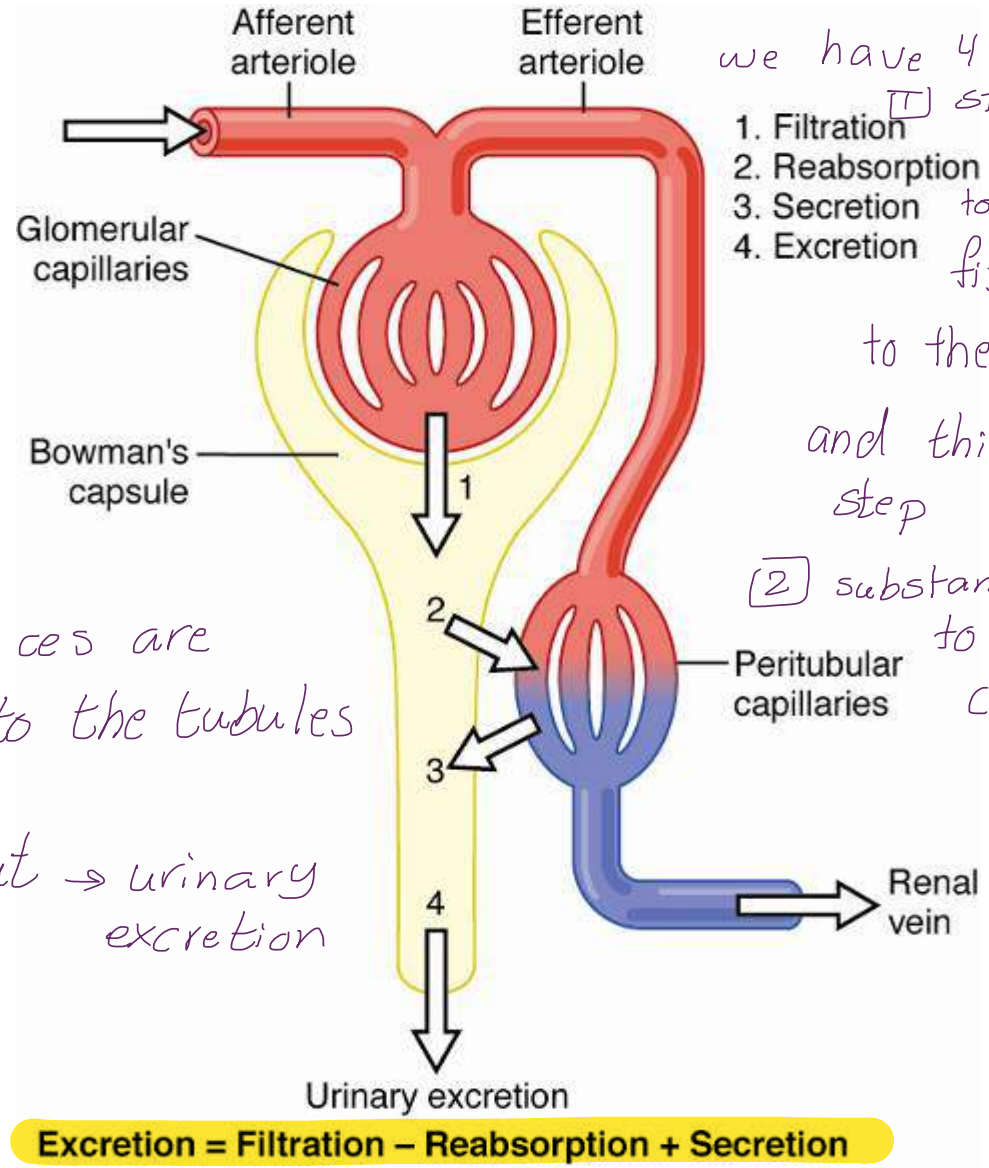
2



most abundant

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 Hairpin bend penetrates only up to outer zone of medulla	Long 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



we have 4 processes
1 start from Renal blood flow to the glomeruli فيلتر الدم
to the bowman capsule
and this is the first step

2 substances → reabsorption to the peritubular capillaries

3 substances are secreted to the tubules

4 final output → urinary excretion

1. filtration

① * first process of the urine formation

② this happens within the renal glomerulus

③ filtration here is not specific يعني تمريت

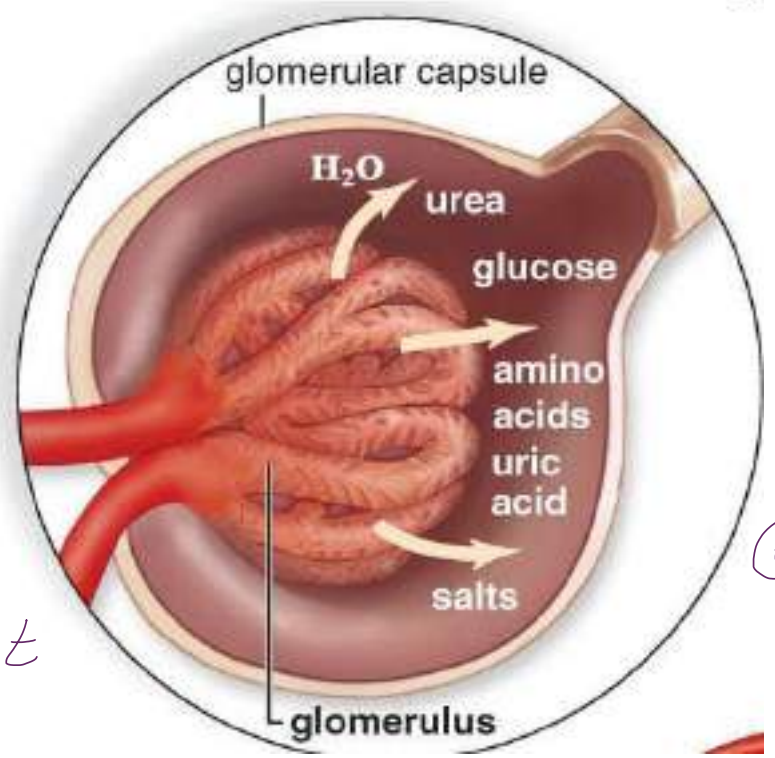
most of the things within the plasma is filtered

water, nutrinionad substances like glucose, a.a

all salts filtered within the glomerulus

and then go to bowman capsule

④ proteins and RBCs are not filtered (very important)



-blood pressure forces small molecules from the glomerulus to the capsule

⑥ high blood pressure within the capillaries ↑ filtration

Filtrates: glucose, amino acids uric acid, urea

Filtration : somewhat variable, not selective (except for proteins), averages 20% of renal plasma flow

⑤ and RBCs

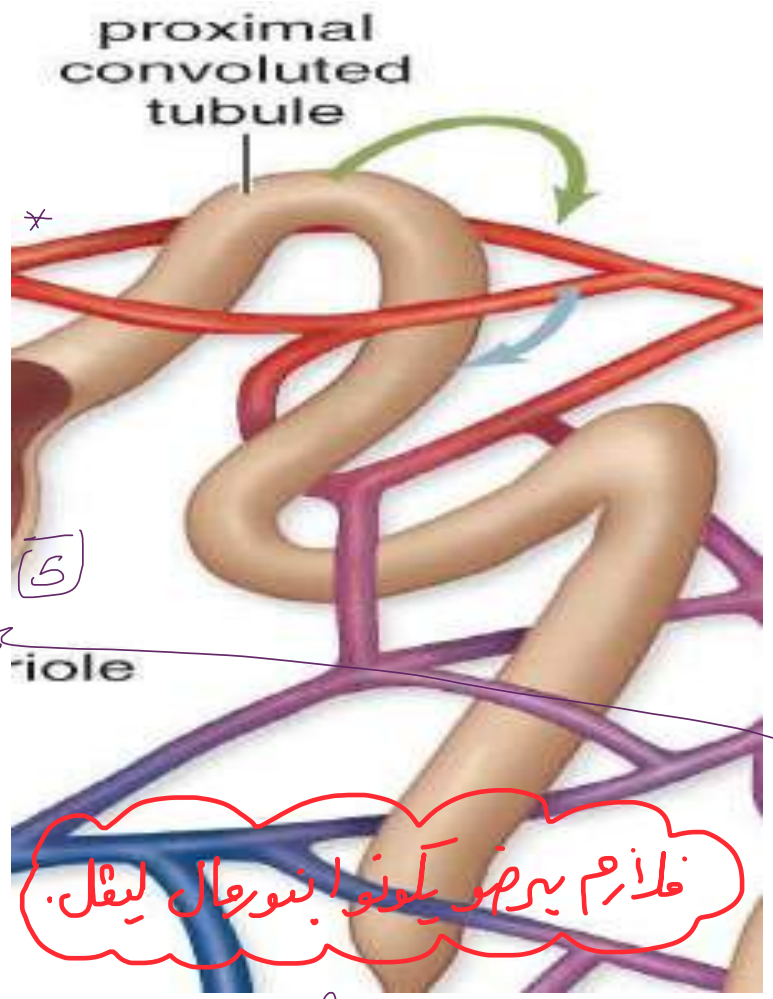
%80 ينزل not filtered

⑦ filtered substances go from bowman capsule into tubules and further processing take place

mainly PCT و tubules من الـ reabsorption عملية بصير فيها ← 1
↳ to the peritubular capillaries.

2. Tubular Reabsorption

7 → كل شي excreted في الـ urine بعطيني indicator about the kidney function.



* اذا في glucose بتكون في الـ diabetes

glucose الـ ↑ + a.a almost reabsorbed يعني ما بالعواني الـ urine ولو كانو موجودين يعني في عنا خلل this sugests sth wrong

5

فلازم يرجعو لانو عال ليقل.

اذا كانو موجودين بكميات كبيرة معناته عنده تروبات

2 * two types of reabsorption :-

-return of filtrates tubules through diffusion 1 and 2 active transport

حسب حاجة الجسم

3 • highly variable and selective

4 • most electrolytes (e.g. Na^+, K^+, HCO_3^-, Cl^-), nutritional substances (e.g. glucose) are almost completely reabsorbed

6 • most waste products (e.g. urea, creatinine, uric acid, urates) poorly reabsorbed

body doesn't want them.

filtered ← حكينا انه مش كل البلازما ✱ ①

20 % is filtered
80 % not filtered

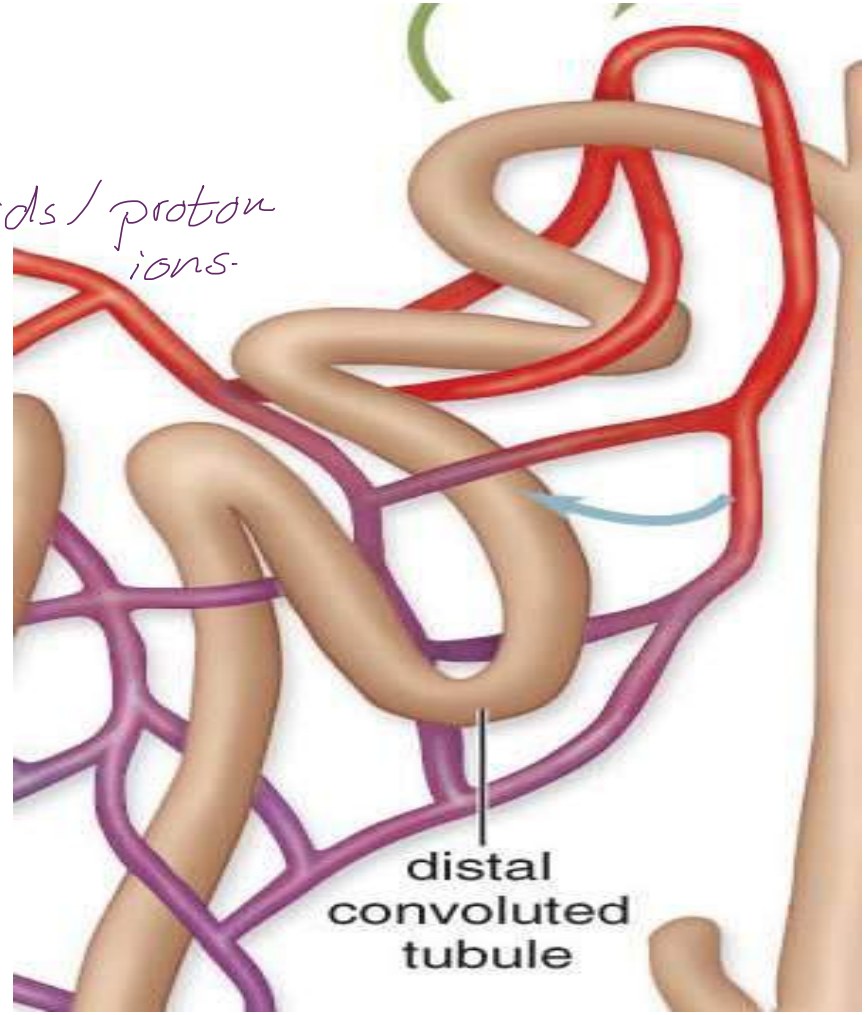
3. Tubular Secretion

highly variable; important for rapidly excreting some waste products (e.g. H^+). ③

acids / proton ions.

من substances في عندي ②
ضمن الـ 20% ما بدنا ايا هم filtered

وبرجع بحير عنا عملية secretion
↳ variable
حسب حاجة الجسم



-movement of molecules from blood into the tubule

④ **Molecules: drugs and toxins**

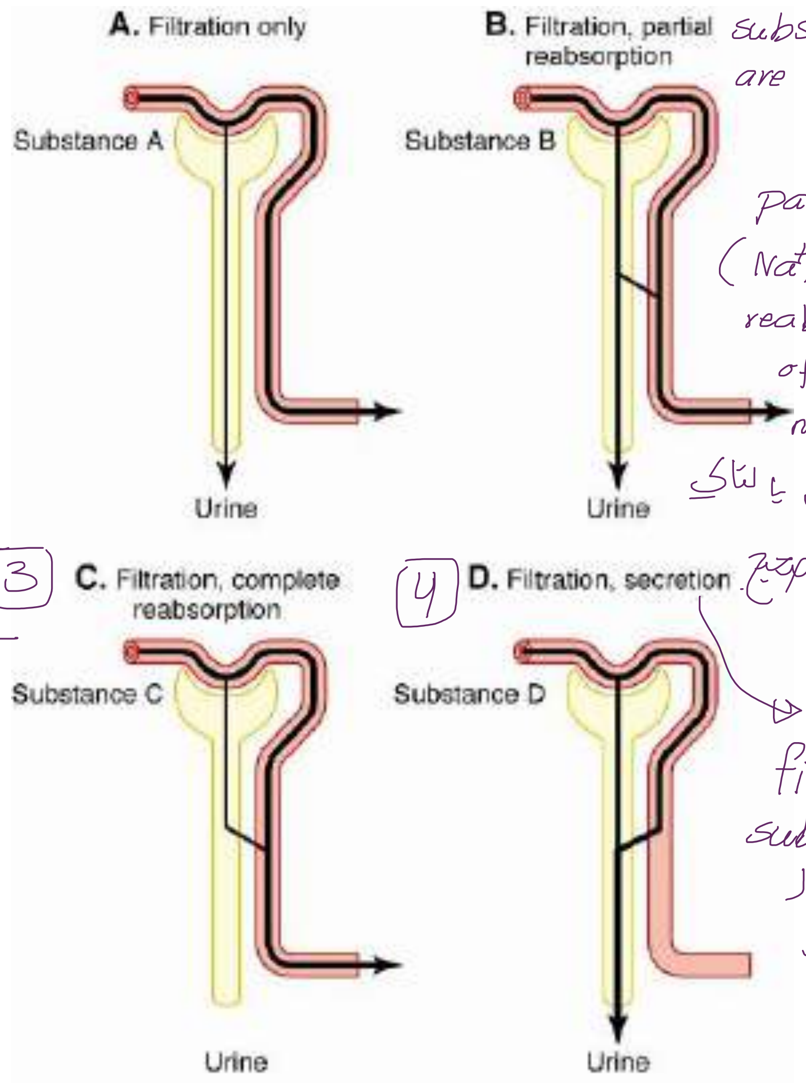
Renal Handling of Different Substances

1 creatinine

هو ← waste product
so all the creatinine will be filtered
بما انه all filtered ← ح يصير all excreted
ما في عنا reabsorption & secretion.

2 electrolytes (e.g. Na^{+} & Cl^{-})

يكون في عنا substances are filtered
فمنها يصير لها partial reabsorption
(Na^{+}, Cl^{-} → the body reabsorbed most of them as the need of body)
فلا عنا ↑BP يا ناس



3 nutritional substances
amino acids & glucose

فعلا يصير عنا filtration وبرجع يصير عنا complete reabsorption
↳ mostly a.a and glucose
وعشان هيك حكينا انه ممنوع يبينوا في ال urine

4 organic acids and bases

ال excretion more than reabsorption بعكس ج
يكون عنا filtered substances وبرد يرجع لعملية ال secretion
زي ال

5 حكينا انه الـ secretion شغلة بسيطة فلو صار فيها تغيرات ما ح تأثر كثير على الـ volume of urine

6 لكن اي تغير في الـ filtration والـ reabsorption ← يعني صار في خلل (مثلاً زاد الـ filtration ، reabsorption ضل ثابت) ح يصير عنا كمية الـ urine زيادة بعنوان البترات بشكل هائل

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

4 Changes in glomerular filtration and tubular reabsorption usually act in a coordinated manner to produce the necessary changes in renal excretion.

ح تأثر بشكل كبير على الـ volume of urine

2 * عملية الـ excretion ← بشبه ثابتة الجسم بعرف انه مثلاً الـ creatinine ح يطلع بطلع ح يطلع الـ arate

3 * لكن في اشيا filtered وبصيرلها reabsorbed بتختلف حسب حاجة الجسم

7 so the kidney has an important regulatory mechanism which is intrinsic within the kidney called autoregulation

there is a matching reabsorption ← filtration في الـ (يعني ↑filtration ح يزيد الـ reabsorption لتكون صحيح)

Micturition

after the formation of urine → evacuation of the substances or the urine.

tension تعتمد على ال within the wall

- Process by which Urinary Bladder empties, when it becomes filled →tension in its walls > threshold level→ micturition reflex

to expil the urine

filling of the bladder ← stretching on the walls ← threshold level ← وبالتالي يصير عنا ← تخطى ال

most important thing in micturition reflex

- Contraction of detrusor muscle→↑pressure in bladder to 40-60 mm Hg →is a major step in emptying the bladder

- Internal sphincter→prevents emptying of bladder until pressure in bladder > threshold level

involuntary

- External sphincter→ voluntary skeletal muscle, used to consciously prevent urination

inhibition ← لما يصير ل

relaxation on the conscious level ?

[سؤال]

ال ← renal BP ما بتتغير تعاكس ال systemic BP

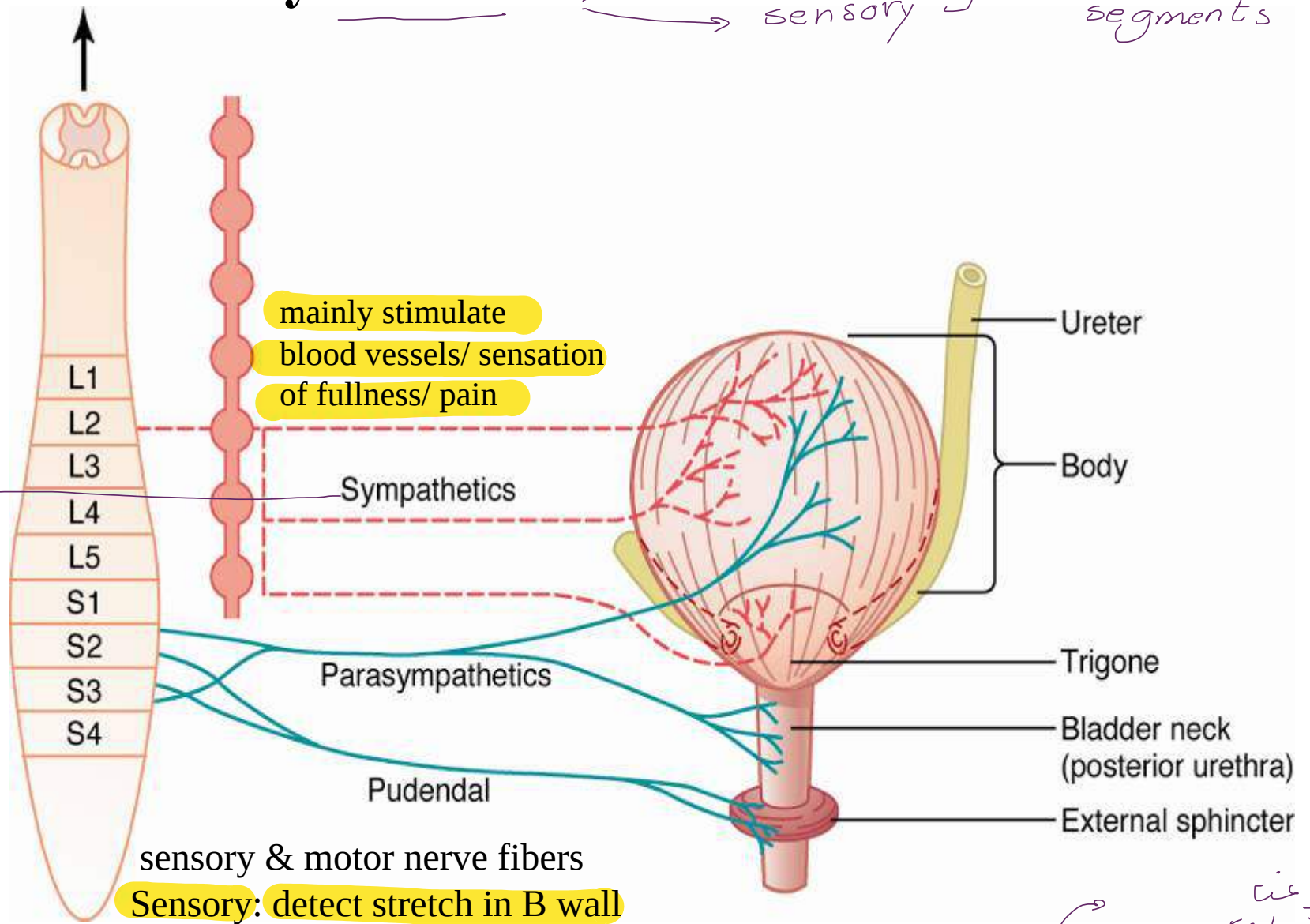
وأي تغيير ال afferent أو ال efferent

Resistance

BP within the glumerali ح تنعكس على

Innervation of urinary bladder

motor
sensory
} mainly from sacral segments



mainly stimulate blood vessels/ sensation of fullness/ pain

S nerve supply to the bladder
↳ this is mainly directed to the BV control of the BV diameters.
sensation of fullness and pain

sensory & motor nerve fibers

Sensory: detect stretch in B wall

Motor: PS (detrusor), skeletal motor fibers (external sphincter)

relaxation.

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

controlled by the nervous system

urine وحركة ال within these structures is mediated by peristalsis. ← that pushing the urine toward its final distination.

evacuation عملية ال of urine from urinary bladder to other (mainly to urethra)

urethra من آلية تنفسها ما في أي تغيرات ال compistion of urine

collecting duct من ال urine مجرد ما يطلع ال في أي تغيرات على ال compistion of urine

--- secretion ، reabsorption

Flow of urine from ureter into urinary bladder

1. • Peristalsis in ureters forces urine into urinary bladder → يصير له storage في الـbladder حتى زيادة الـvolume ويصير stretch في الـwall of the bladder and the evacuation of the urine.

3. • Oblique course+ compressed by detrusor muscle tone→Prevents Vesicoureteral Reflux

4. لـ متى يمنع الـ reflex من الـ urinary B back to the ureters

5. • Reflux →enlargement of ureters+ ↑pressure in renal calyces & medulla, →damage

is not good ← شائع في الأطفال

6. because the urine is going back → بمراحل معينة على يوصل لـ hydronephrosis renal failure

2. Course of the ureter within the posterior wall of the bladder is oblique like a functional sphincter ← متى يصير عنا

Clinically مهم

Pain sensation in Ureters

- Well supplied with pain nerve fibers

يعني أي block / obstruction أي شي ينتج within the ureters (such as ureter stones or tumor) and this will result in a severe stimulation of the pain nerves which is very very painful to pt

most common in Jordan.

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

Sympathetic reflex back to kidney To ↓the urine output **Ureterorenal reflex→**

* **preventing excessive flow of fluid into pelvis**

damage لحد معين وبعد هاد بكد يصير عنا

* first managment in renal colic or renal stones pt → releive the pain

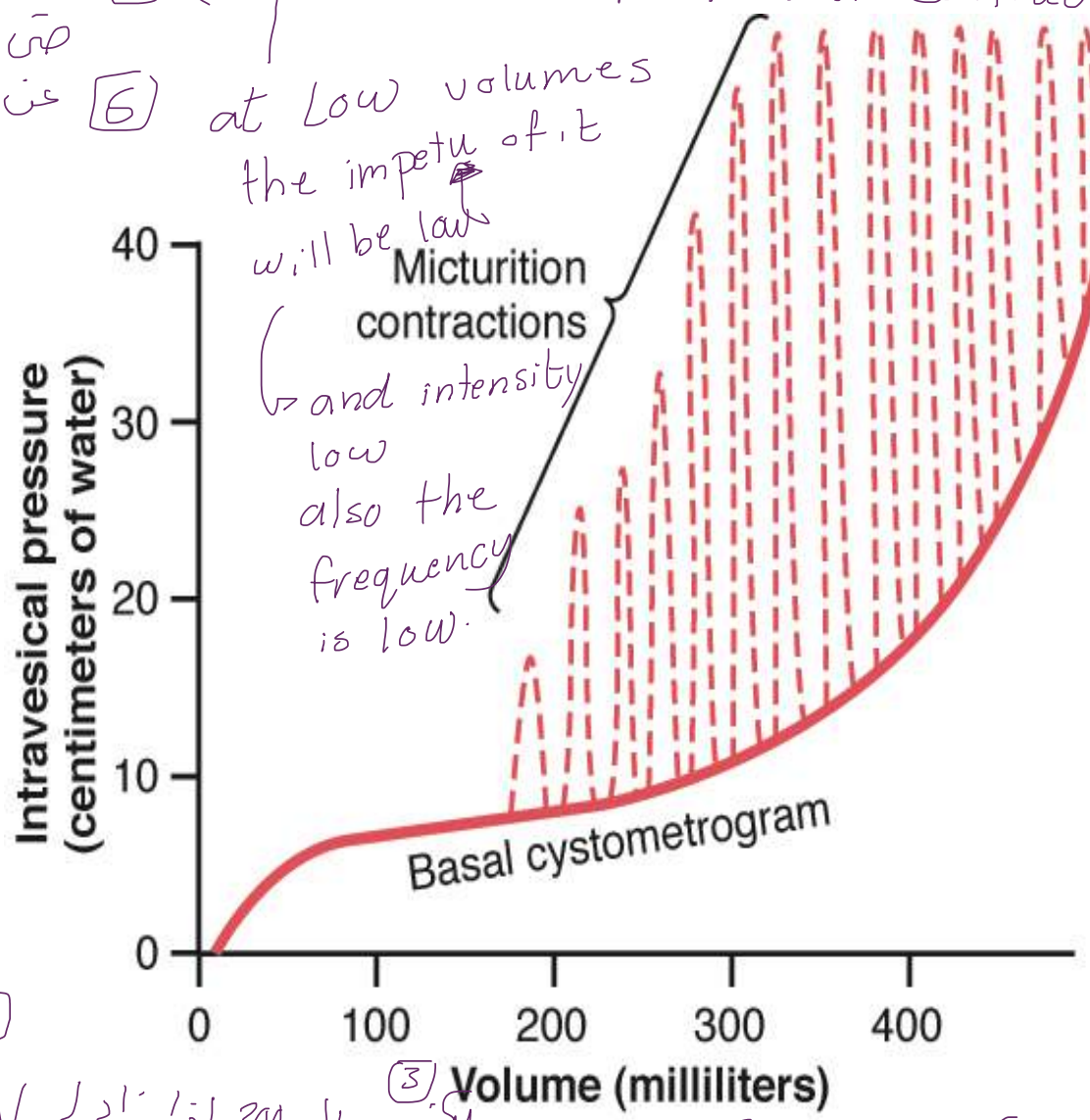
Filling of Bladder and Bladder Wall Tone; Cystometrogram

Tonic pressure changes

- No urine in bladder→intravesicular pressure is about 0
- 30-50 ml of urine →pressure rises to 5 -10 cm H2O
- 200-300 ml—only small additional rise in pressure; caused by intrinsic tone of the bladder wall.
- Beyond 300-400 ml→pressure rise rapidly

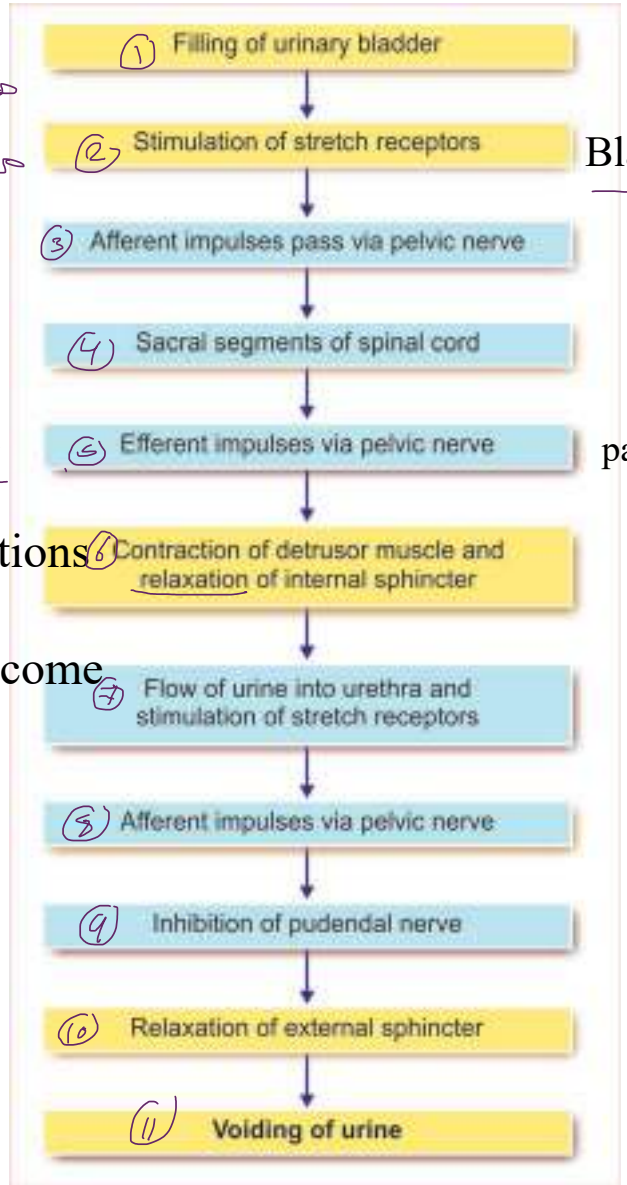
Micturition waves

- Superimposed on the tonic pressure changes during filling
- Periodic acute increases in pressure (few->100 cm H2O)
- Caused by the micturition reflex.



Micturition Reflex

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



- When bladder is partially filled →micturition contractions usually relax.
- As bladder continues to fill → Micturition reflexes become more **Frequent** and **Powerful**

higher centers

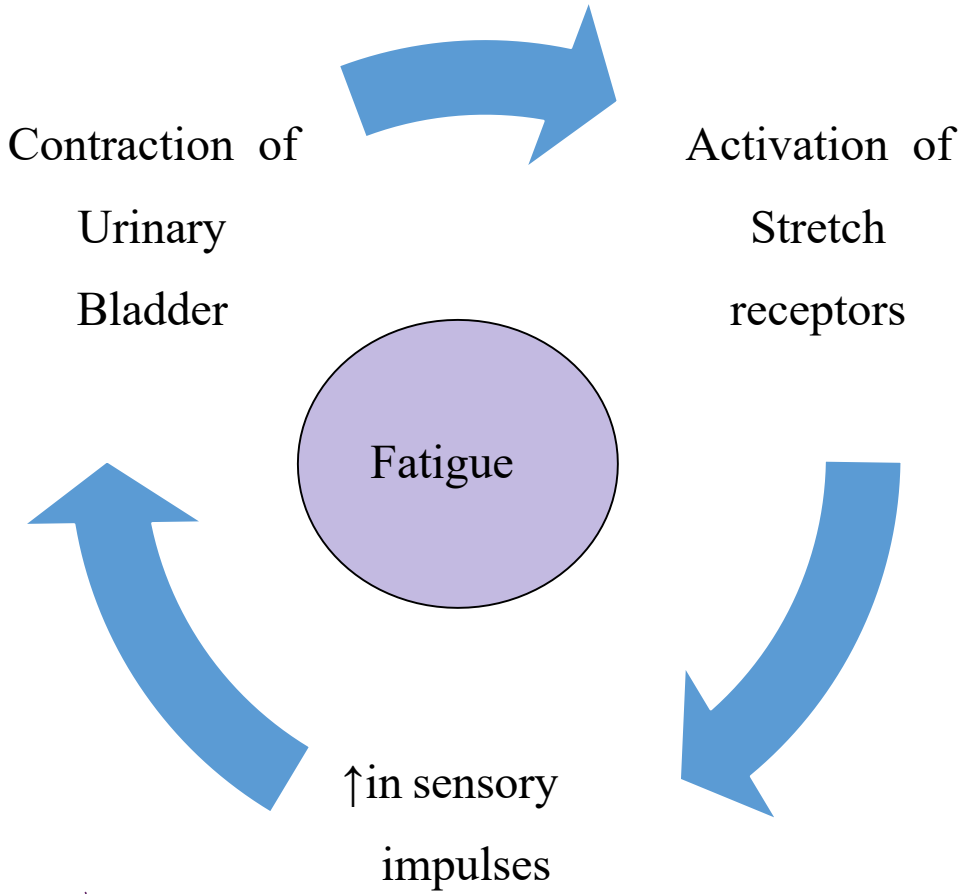
Self-Regenerative Reflex:

a single complete cycle of:

i.Progressive and Rapid increase of Pressure

ii.Sustained Pressure

ii. Relaxation



inhibition of the reflex

لحد معين وبعد هاد كل حابتقدر نعمله

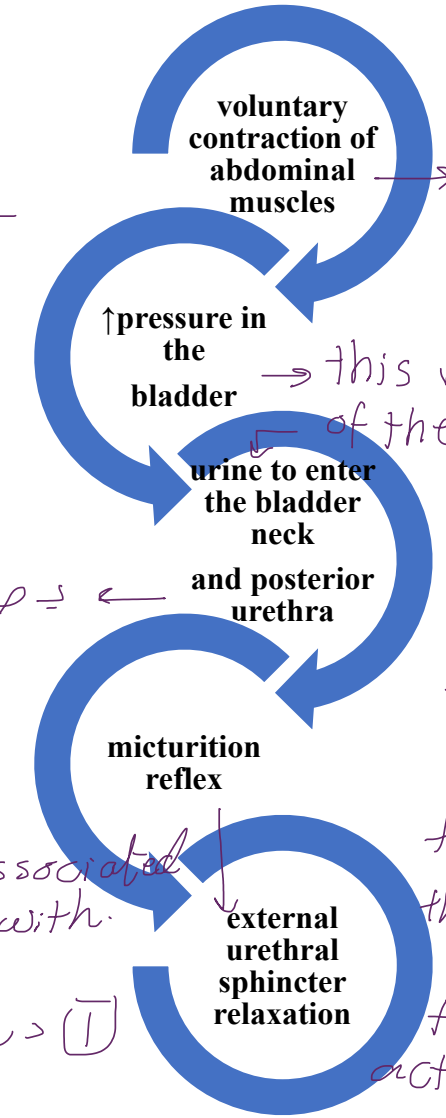
Control by Higher Centers

- Pons mainly
  Facilitatory & inhibitory
- Cerebral corte mainly involved in consious control of the urine voiding
  Normally inhibits the External sphincter

Higher centers normally exert final control of micturition

- Partial inhibition of micturition reflex, except when micturition is desired.
- 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 & inhibit external sphincter

Voluntary urination



proper time of urination
the cortical sensors facilitate the activity of the micturition reflex

micturition reflex suppression of the micturition by control of the external sphincter

The end

Glomerular Filtration, Renal Blood Flow, and Their Control

U N I T V
Chapter 27

Importance of Glomerular Filtration

1. • Remove waste products
2. • Waste products are poorly reabsorbed by the tubules like creatinine , urea

يعادل ٣ لتر من البلازما

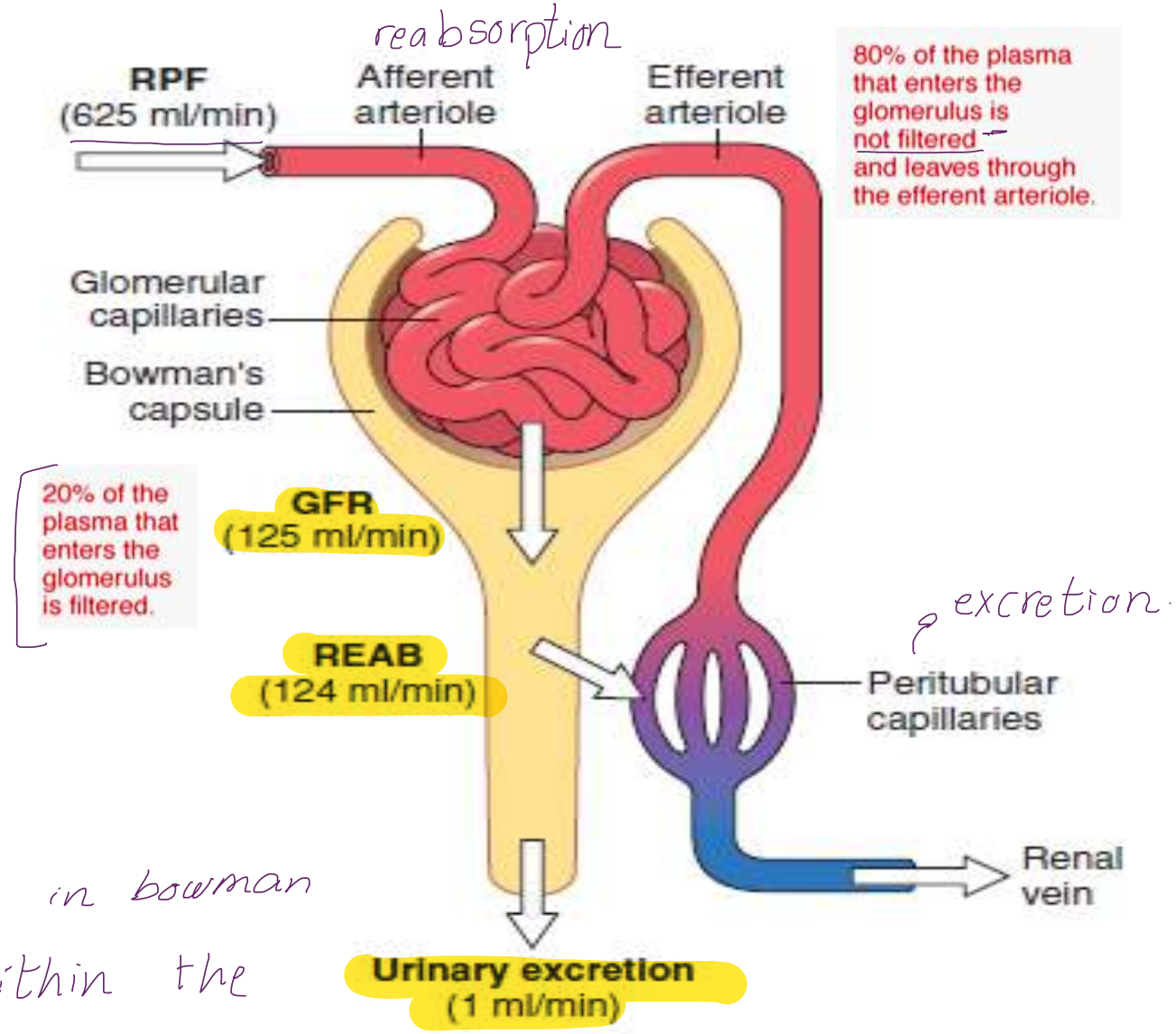
plasma volume= 3 L, GFR is about 180 L/day → entire plasma can be filtered and processed about 60 times/day. This high GFR allows the kidneys to precisely and rapidly control the volume and composition of the body fluids.

Average values for total renal plasma flow (RPF), glomerular filtration rate (GFR), tubular reabsorption (REAB), and urine flow rate

- Glomerular filtrate composition is about the same as plasma, except for large proteins

No blood cells

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



filtration is not selective

أي شي في الـ capillaries ع بيبن ويدخل

عـ الـ bowman capsule

ما عدا البروتين مثل RBCs

So the concentration of the fitrate in bowman capsule same the concentration within the glomerular capillaries

Glomerular capillary filtration barrier

1 * very important in the function of capillaries

2 prevention of the filtration of the proteins and other substances

3 **Fenestrated endothelium** → filtration

4 NO RBCs, NO a.a.

- pores exclude blood cells and large plasma proteins (-ve charges)

5 basement membrane

6 **Basement membrane** mainly

- Proteoglycan gel -excludes molecules –ve charge

(podicles)

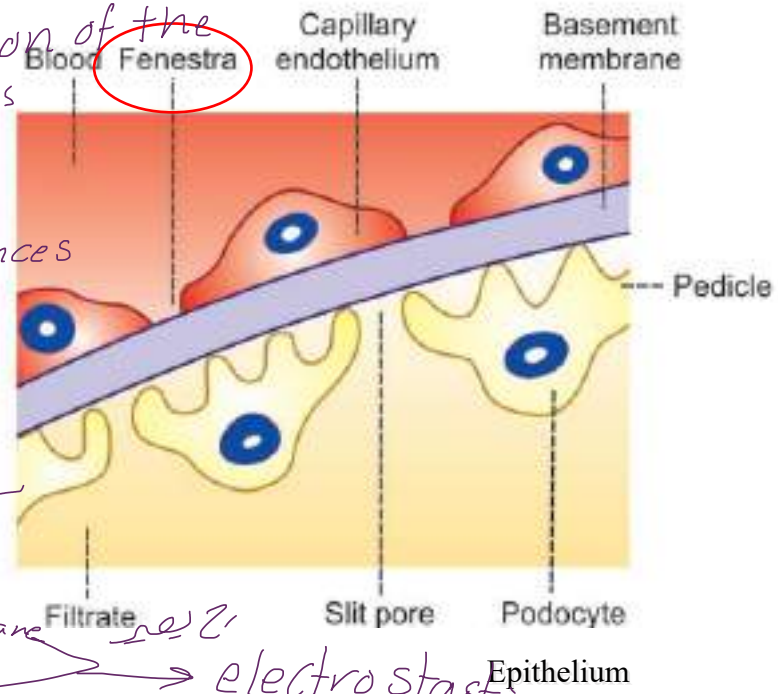
9 **Podocytes not continuous footlike processes** (-ve charges)

epithelium → bowman capsule → filtration

Slit diaphragm pores

Excludes particles

7 -ve basement membrane
-ve endothelium
-ve endothelium are -ve charge



electrostastic repulsion

8 filtration of large proteins

Filterabilty of Solutes Across Glomerular Barrier

depends on:-

1. • Molecular size (inverse relationship)
2. • 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
3. • Shape (rigid or deformable)

can't / can

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

freely filtered.

is filtered same as water

very very low is nearly that not filtered.

Determinants of Glomerular Filtration Rate (very very important)

Normal Values:

GFR = 125 ml/min or 180 L/day

125 625

- Filtration fraction (GFR/Renal Plasma Flow)

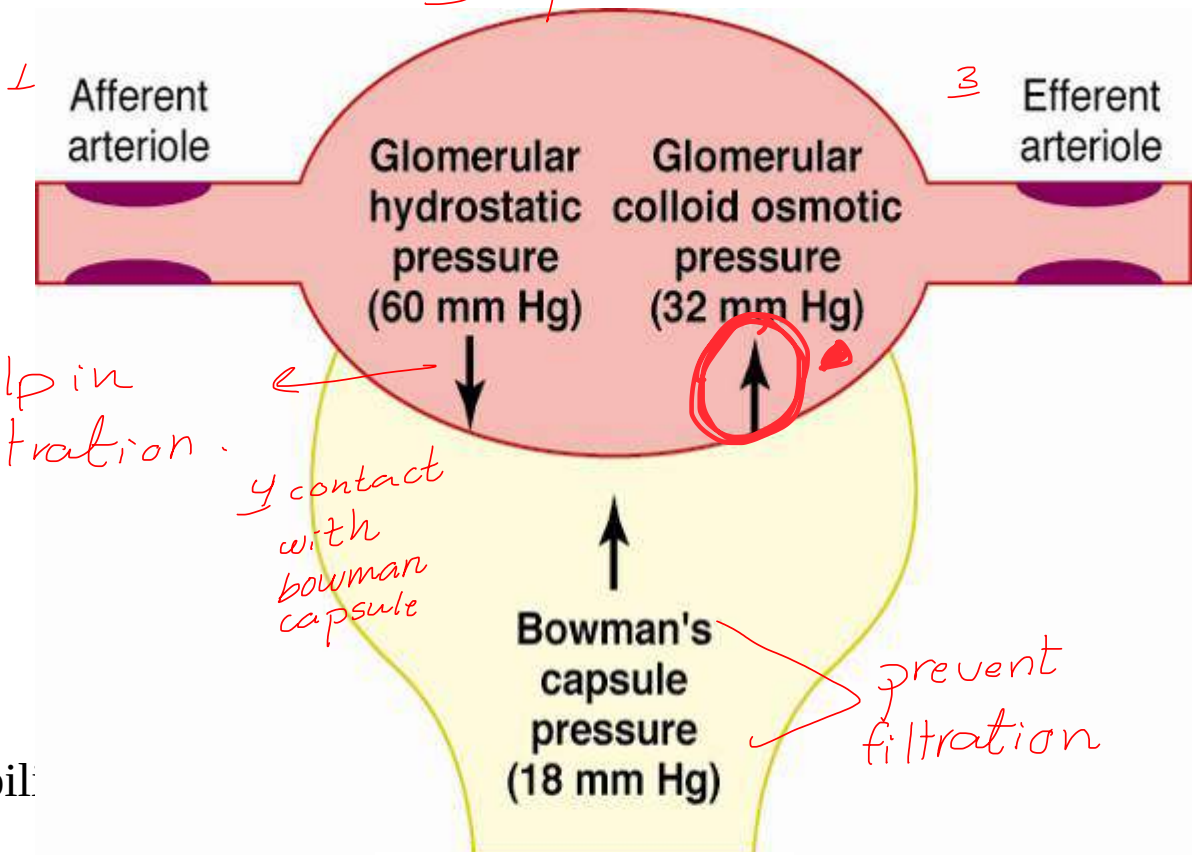
  125/625= 0.2 ↑ff → ↑ GFR

GFR is determined by:

(1) balance of hydrostatic & colloid osmotic forces acting across capillary membrane

(2) capillary filtration coefficient (Kf), product of permeabil (1) and filtering surface area of capillaries (2)

↑Kf → ↑ GfR



$$(P_G - P_B - \pi_G + \pi_B)$$

Net filtration pressure (10 mm Hg) = Glomerular hydrostatic pressure (60 mm Hg) − Bowman's capsule pressure (18 mm Hg) − Glomerular oncotic/colloid pressure (32 mm Hg)

* في عنا different pressure within the capillaries it self or in bowman capsule

← هدول اللي بيتحكموا في ال filtration Rate

1 hydrostatic pressure

hydrostatic pressure within the capillaries ← يقابله → pressure within the capsule.
- very high (60 mmHg)
  - help in filtration
- prevents (oppose the filtration)

2 coloid osmotic pressure expressed by protein
- موجود في ال capillaries and bowman capsule → filtered ما في بروتين في ال value of colloid P in capsule = zero
- oppose filtration نظراً لوجود البروتين

opposing pressure within the capillaries and bowman capsule

---

so we have 3 factors
1- hydrostatic P within capillaries (facilitate filtration) →
2. hydrostatic P within capsule
3. colloid P within capillaries
→ prevent / oppose filtration

regulatory عوامل تنظم factor in the process of GF

* كل ما يمشي ال blood من ال afferent arterioles تفقد سوائل وبنزلوا على ال bowman capsule

بالمقابل البروتينات بصير أكثر ← condensated proteins

بزداد تركيز باتجاه ال efferent له

بالتالي ال ↑ oncotic P

* من ال afferent إلى efferent end ← بزيد ال colloid pressure لأنه كمية ال fluid ال filtered قلت بالتالي ال concentration صار أعلى

Filtration coefficient

Kf = GFR/Net filtration pressure

Normally, GFR=125 ml/min, Net filt. P= 10
Kf=125/10
=12.5 ml/min/ mm Hg
Very high compared to other body capillaries Kf (0.01)→rapid rate of filtration

* لذلك الكلية تستطيع تصفي الدم ٦٥ مرة باليوم.

Glomerular Capillary Filtration Coefficient (K_f)

- ↑ Kf→↑GFR
- ↓ Kf →↓GFR

هاد مهم لكن مش ال normal physiological conditions

very important

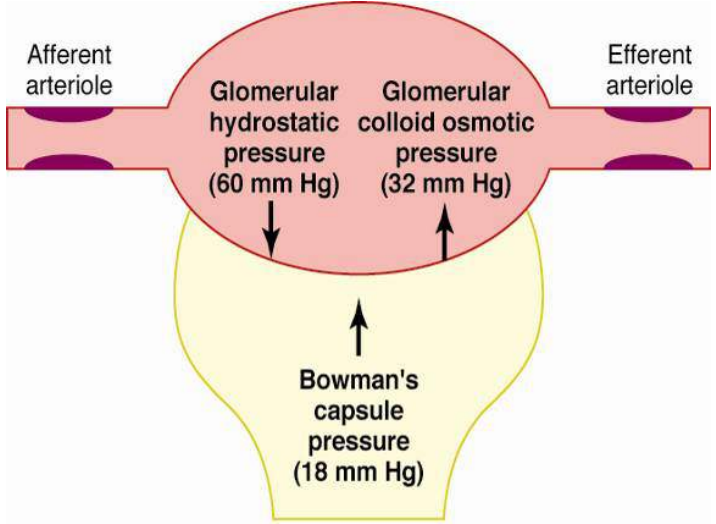
The GFR is mainly regulated by hydrostatic pressure

- Changes in Kf probably do not provide a primary mechanism for normal day-to-day regulation of GFR.

- Disease that can reduce K_f and GFR
  - chronic hypertension
  - obesity/diabetes mellitus
  - glomerulonephritis

Bowman's Capsule hydrostatic Pressure (P_B)

[oppose the filtration]



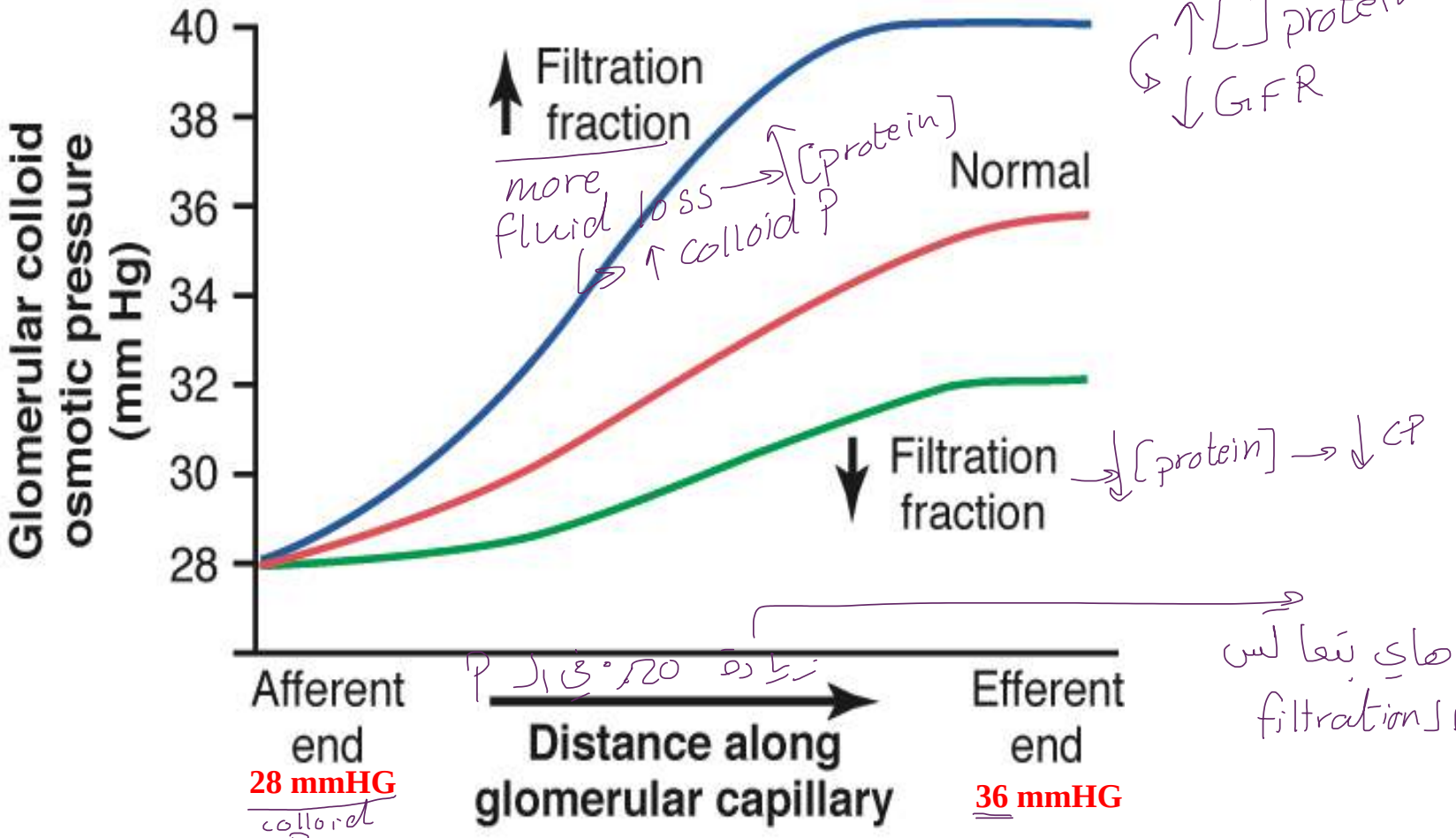
- Normally changes as a function of GFR, not a physiological regulator of GFR
- Tubular Obstruction
  - kidney stones
  - tubular necrosis

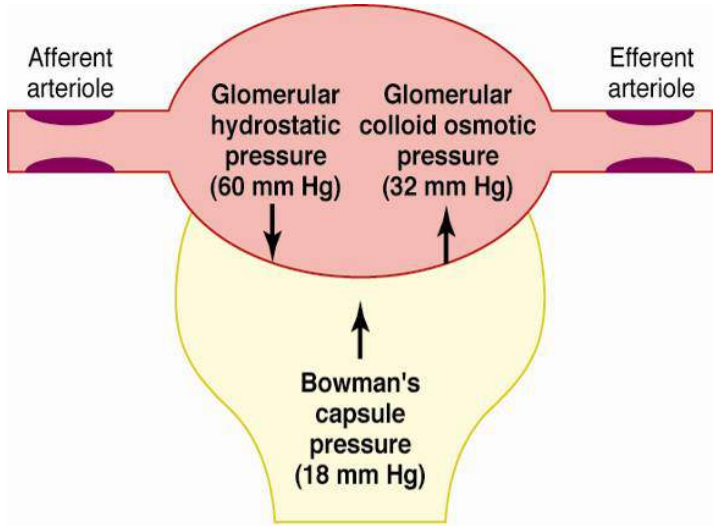
↑ HPin bowman's capsule. → ↓GFR

- Urinary tract obstruction
  - Prostate hypertrophy/cancer

narrowing urethra. → hydronephrosis

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)

1. • Arterial Plasma Oncotic Pressure (π_A)

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

2. • Filtration Fraction (FF)

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

$$FF = GFR/Renal\ plasma\ flow$$

$$GFR \propto Renal\ plasma\ flow$$

proportional (طردي) . كد معين *

↑ P_G → ↑ GFR

Glomerulus hydrostatic pressure.

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

Factors affecting Glomerular Capillary hydrostatic Pressure (P_G):

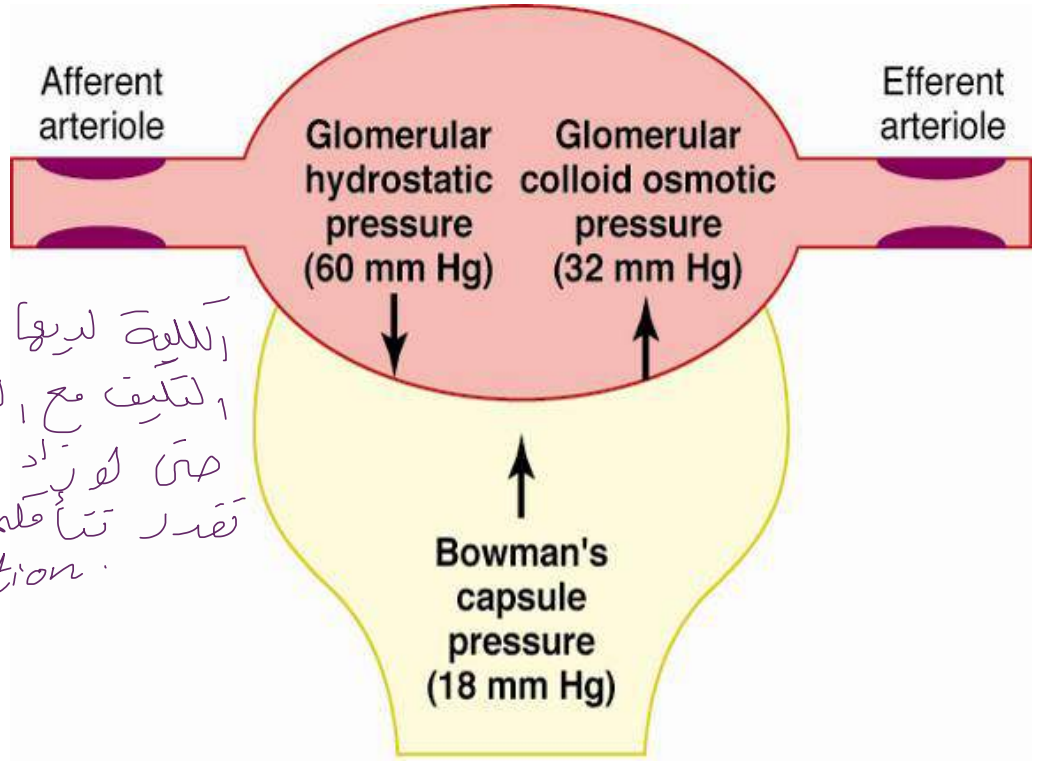
systemic P.

1-Arterial pressure (Proportional, buffered by autoregulation (constant P_G)

2- Afferent arteriolar resistance

3- Efferent arteriolar resistance

الكلية لديها لقدرة على التكيف مع التغيرات الـ PG حتى لو زاد إلى 180 تقدر تتأقلم عن طريق الـ autoregulation.



Net filtration pressure (10 mm Hg)	=	Glomerular hydrostatic pressure (60 mm Hg)	–	Bowman's capsule pressure (18 mm Hg)	–	Glomerular oncotic pressure (32 mm Hg)

$\uparrow P_G \rightarrow \uparrow GFR$

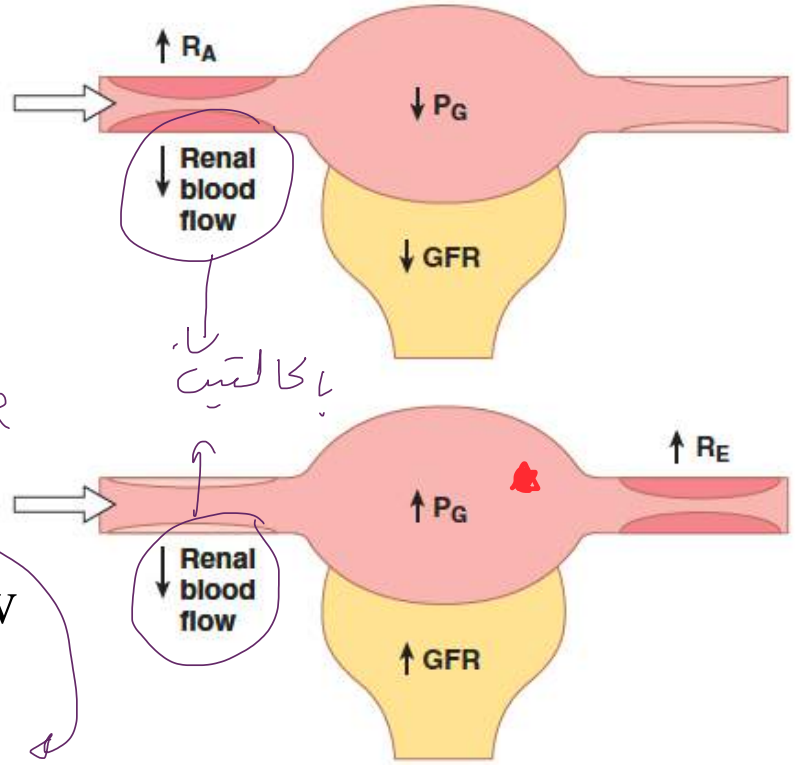
Factors affecting Glomerular Capillary hydrostatic Pressure (P_G) :

2- ↑ Afferent arteriolar resistance (Inverse) ↓PG → ↓GFR

3- ↑ Efferent arteriolar resistance (Proportional) ↑PG → ↑GFR في البداية (initial effect)

efferent arteriolar constriction → ↓reduces renal blood flow

$\uparrow R_E \rightarrow \uparrow$ FF & $\boldsymbol{\pi_G} \rightarrow \boldsymbol{\pi_G} > \mathbf{P_G} \rightarrow$ net ↓GFR



بعدين تنبيه الـ concentration of the proteins ↓ بتصير الـ consentation بالبلازما الـ colloid pressure بصير أعلى من PG وبالتالي بصير عنا net ↓GFR

Effect of changes in afferent arteriolar or efferent arteriolar resistance

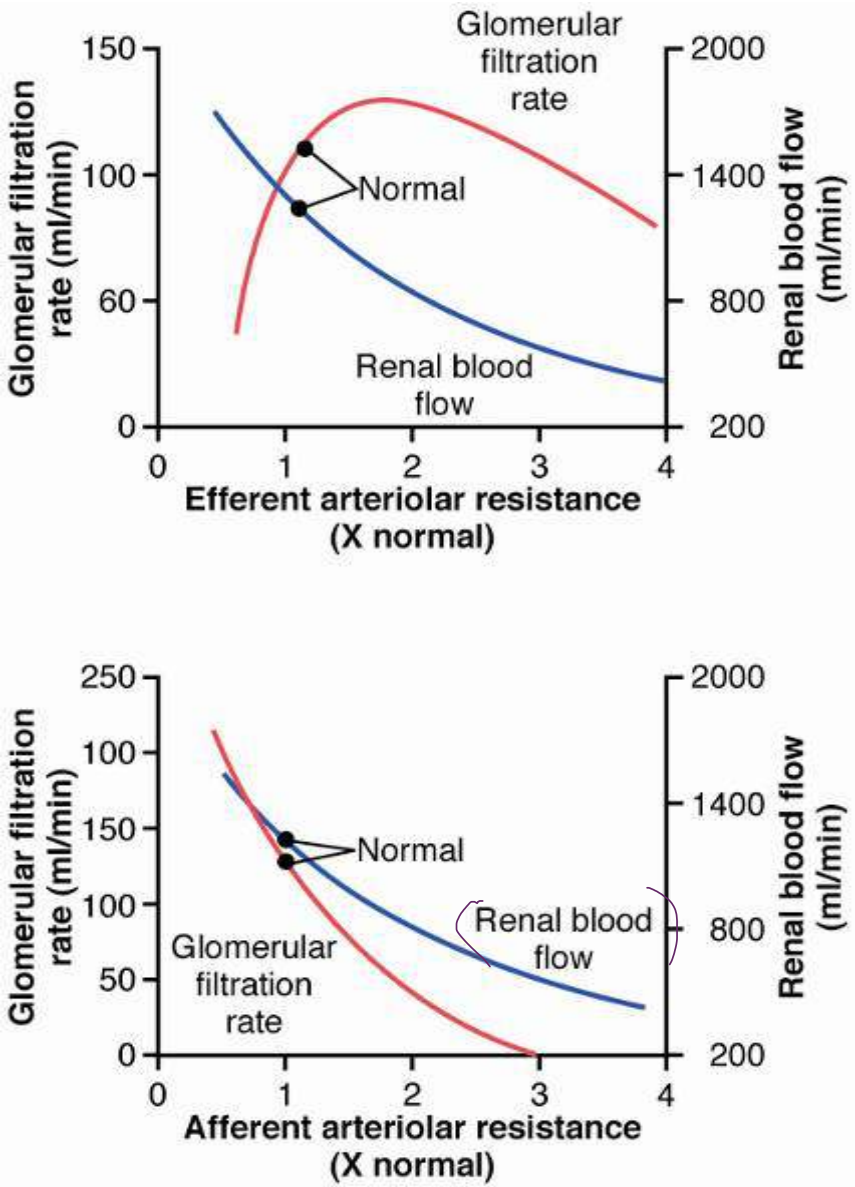


Figure 26-15

Table 27-2 Factors That Can Decrease the Glomerular Filtration Rate

Physical Determinants*	Physiological/Pathophysiological Causes
$\downarrow K_f \rightarrow \downarrow GFR$	Renal disease, diabetes mellitus, hypertension
$\uparrow P_B \rightarrow \downarrow GFR$	Urinary tract obstruction (e.g., kidney stones)
$\uparrow \pi_G \rightarrow \downarrow GFR$	↓ Renal blood flow, increased plasma proteins
$\downarrow P_G \rightarrow \downarrow GFR$ $\downarrow A_P \rightarrow \downarrow P_G$	↓ Arterial pressure (has only a small effect because of autoregulation)
$\downarrow R_E \rightarrow \downarrow P_G$	↓ Angiotensin II (drugs that block angiotensin II formation)
$\uparrow R_A \rightarrow \downarrow P_G$	↑ Sympathetic activity, vasoconstrictor hormones (e.g., norepinephrine, endothelin)

Renal blood flow

- High blood flow (1100 ml/min ~22% of cardiac output)
- High blood flow needed for high GFR
- Oxygen and nutrients delivered to kidneys normally greatly exceeds their metabolic needs
- A large fraction of renal oxygen consumption is related to renal tubular Na reabsorption

كل ما زاد الـ Na reabsorption ④ the O_2 consumption is increased.

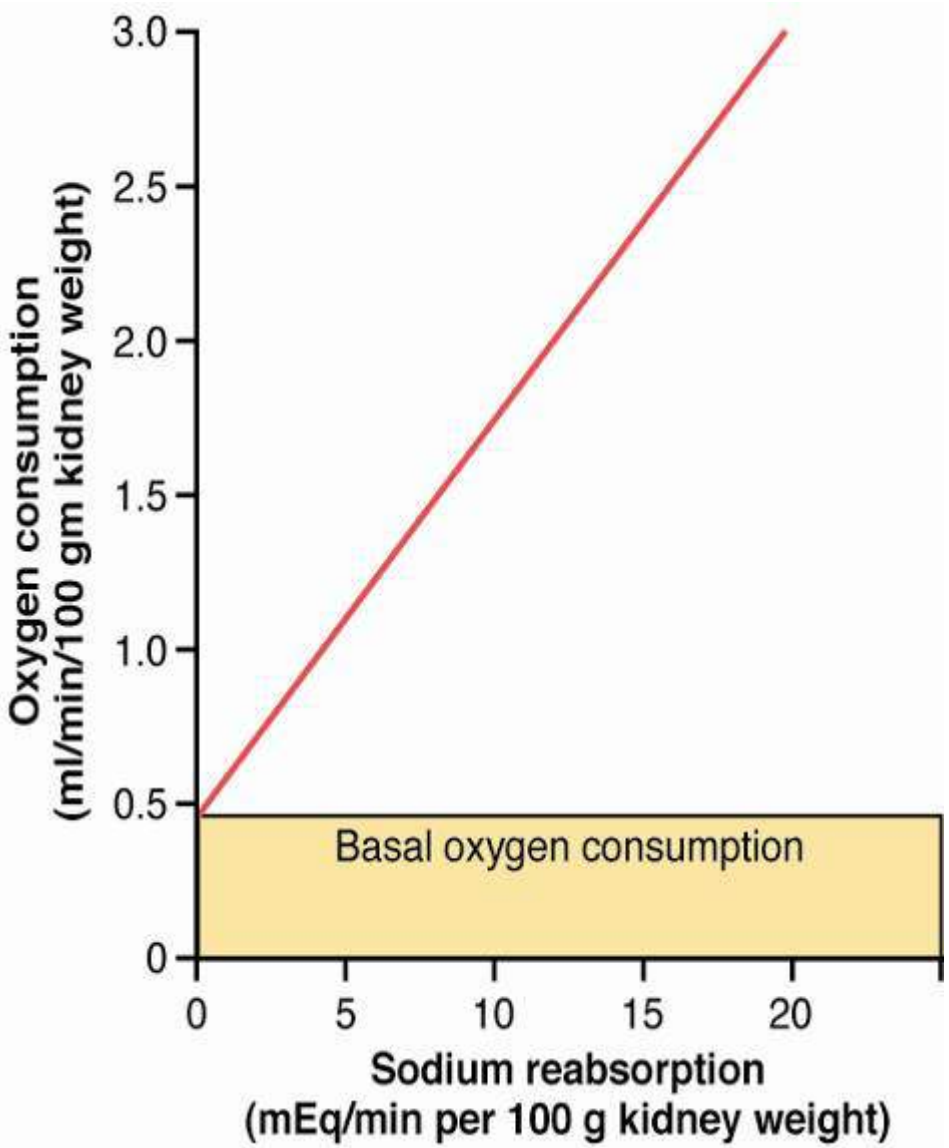
لأن هناك علاقة طردية بين الـ O_2 consumption ① of the kidneys which is important in active transport

② تعكس مدى الـ reabsorption of Na

③ is mediated by active transport

Renal O2 consumption varies in proportion to renal tubular Na reabsorption

↓renal blood flow& GFR →less Na is filtered →less Na is reabsorbed →less O2 consumed



Determinants of Renal Blood Flow (RBF)

$$RBF = \Delta P / R$$ of vascular-

ΔP = difference between renal artery pressure and renal vein pressure

renal artery P=systemic arterial pressure = 120/80

renal vein P=3-4 mmHg

↑ΔP ⟶ ↑ RBf

↑R ⟶ ↓ RBf

R = total renal vascular resistance
= sum of all resistances in kidney vasculature (arteries, arterioles, capillaries &veins)

Determinants of Renal Blood Flow (RBF)

Most of renal vascular resistance resides in:

1-interlobular arteries

2-afferent arterioles

3-efferent arterioles

↑ resistance of any of vascular segments of kidneys →↓RBF and vice versa if renal artery & renal vein pressures remain constant.

Autoregulation

Intrinsic ability of kidneys to regulate its own **blood flow** to maintain GFR

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

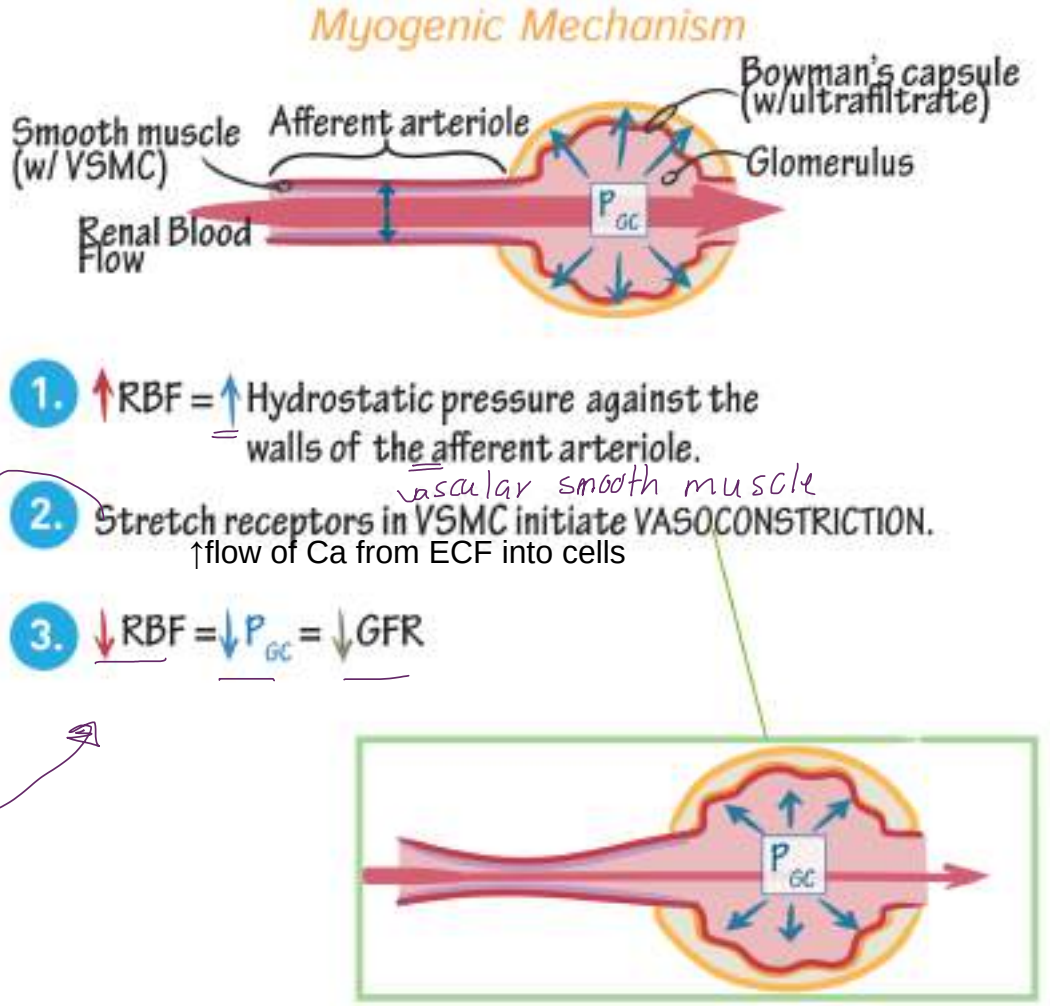
Two mechanisms involved in renal autoregulation:

1. Myogenic response
2. Tubuloglomerular feedback

Myogenic response

Myogenic Mechanism Pressure dependent mec

by the detection in the change of the pressure within the arterioles



Ca ينتج عنه دخول ال ← Action potential

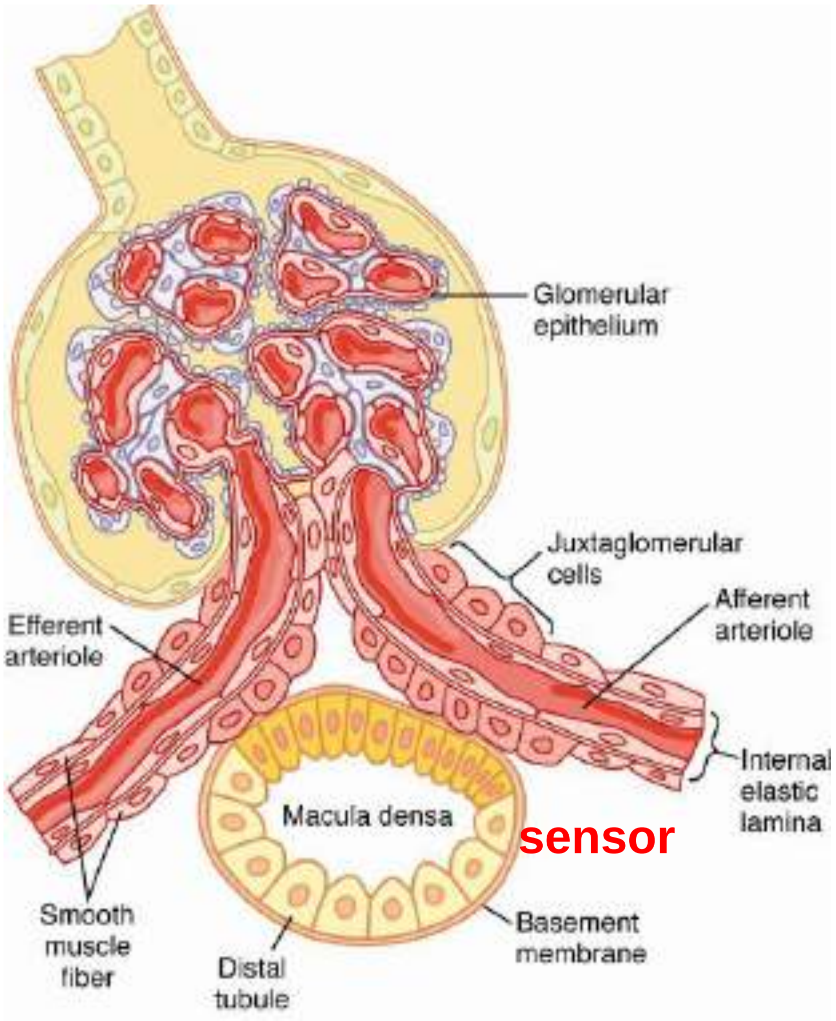
from ECF → cells

ينتج عنه

vascular smooth muscle

VC في يحفز ال

Tubuloglomerular feedback



first part of distal tubule
between afferent and effent arterioles

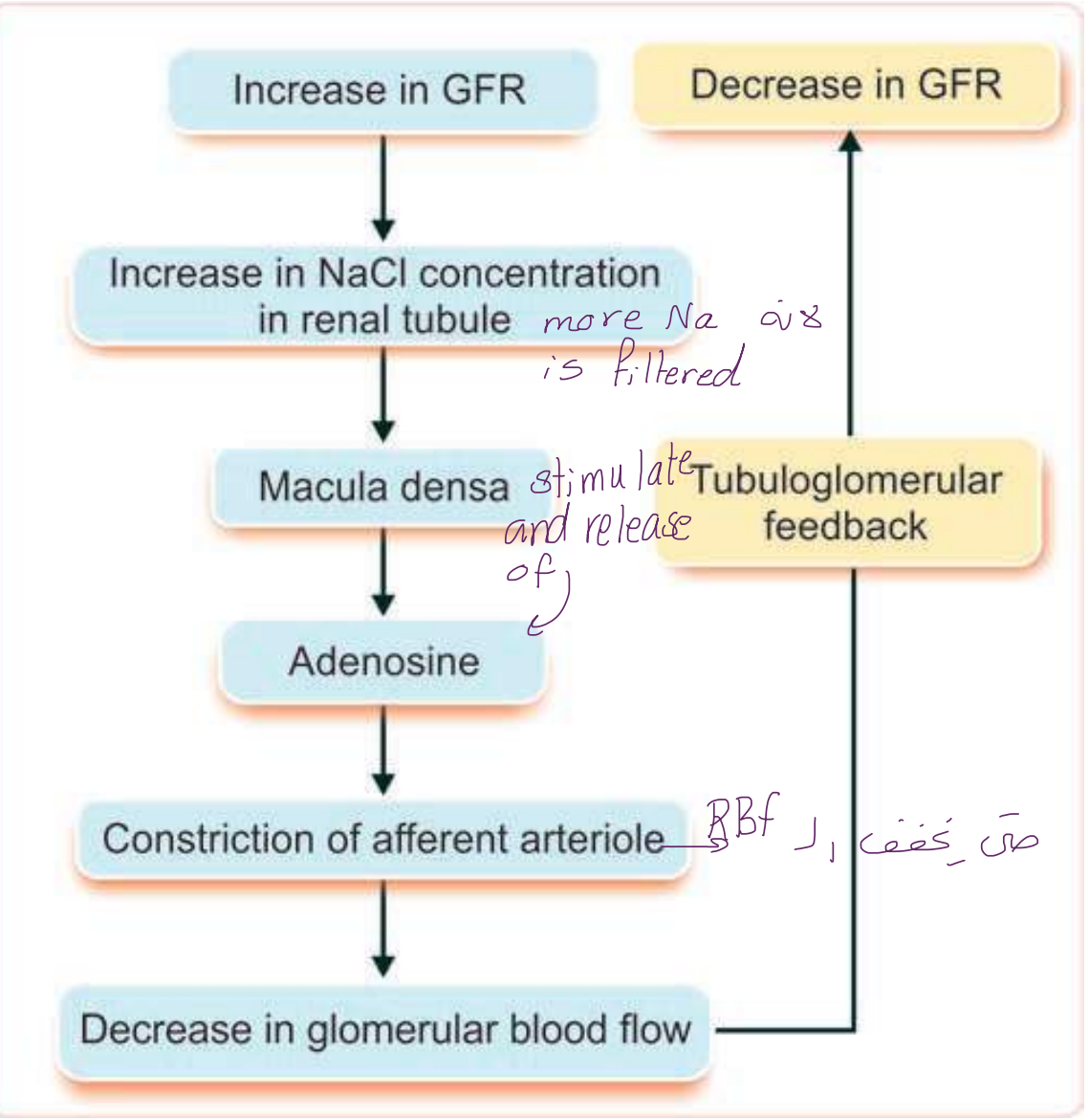
Macula densa of juxtaglomerular apparatus in the terminal portion of thick ascending limb is sensitive to the NaCl in the tubular fluid

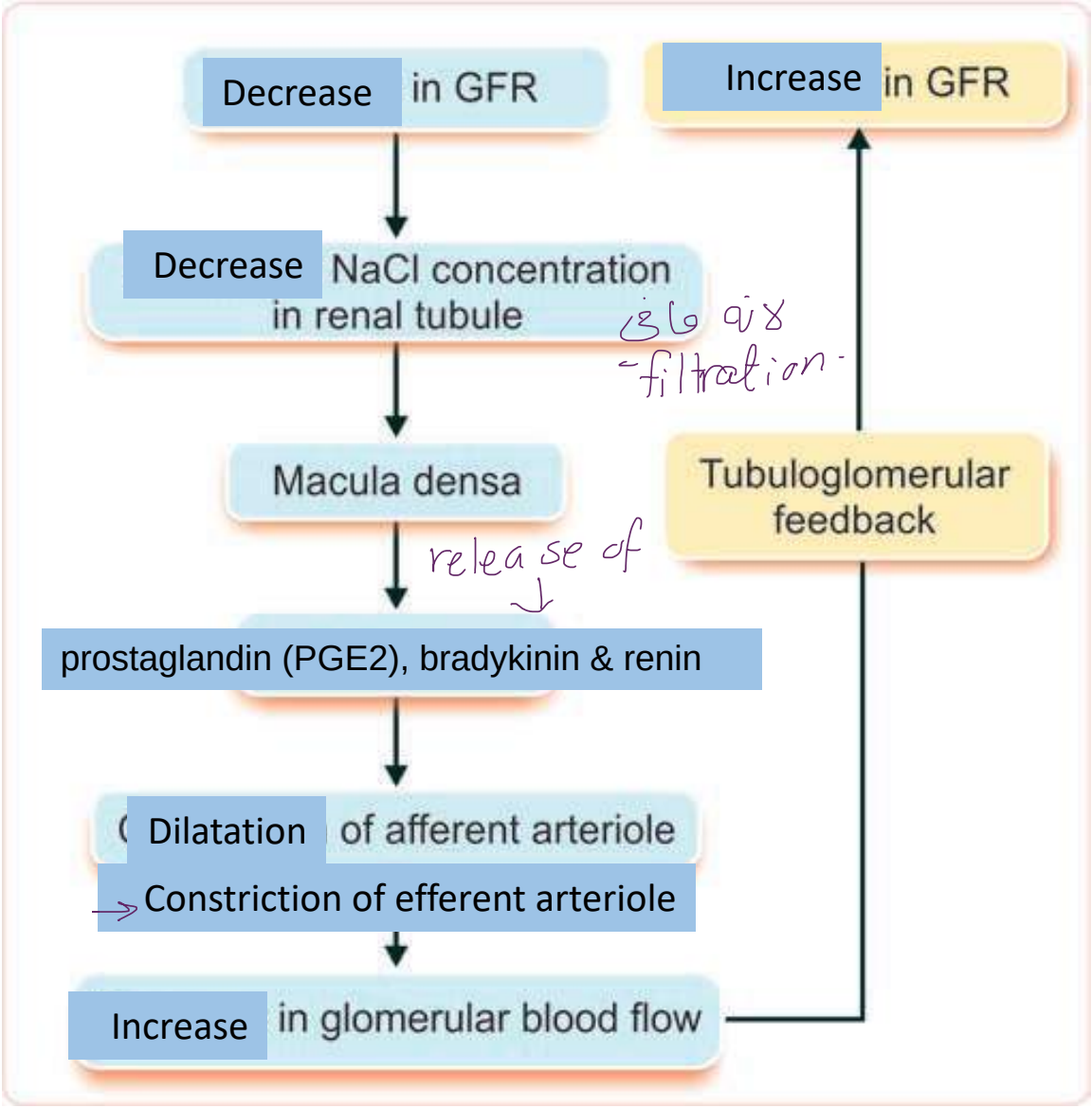
act as a sensor
of (how much Na within the filterate)
حسب حاجة الجسم

* اذا زاد ال GFR ← يقل ال [Na]
in renal tubules

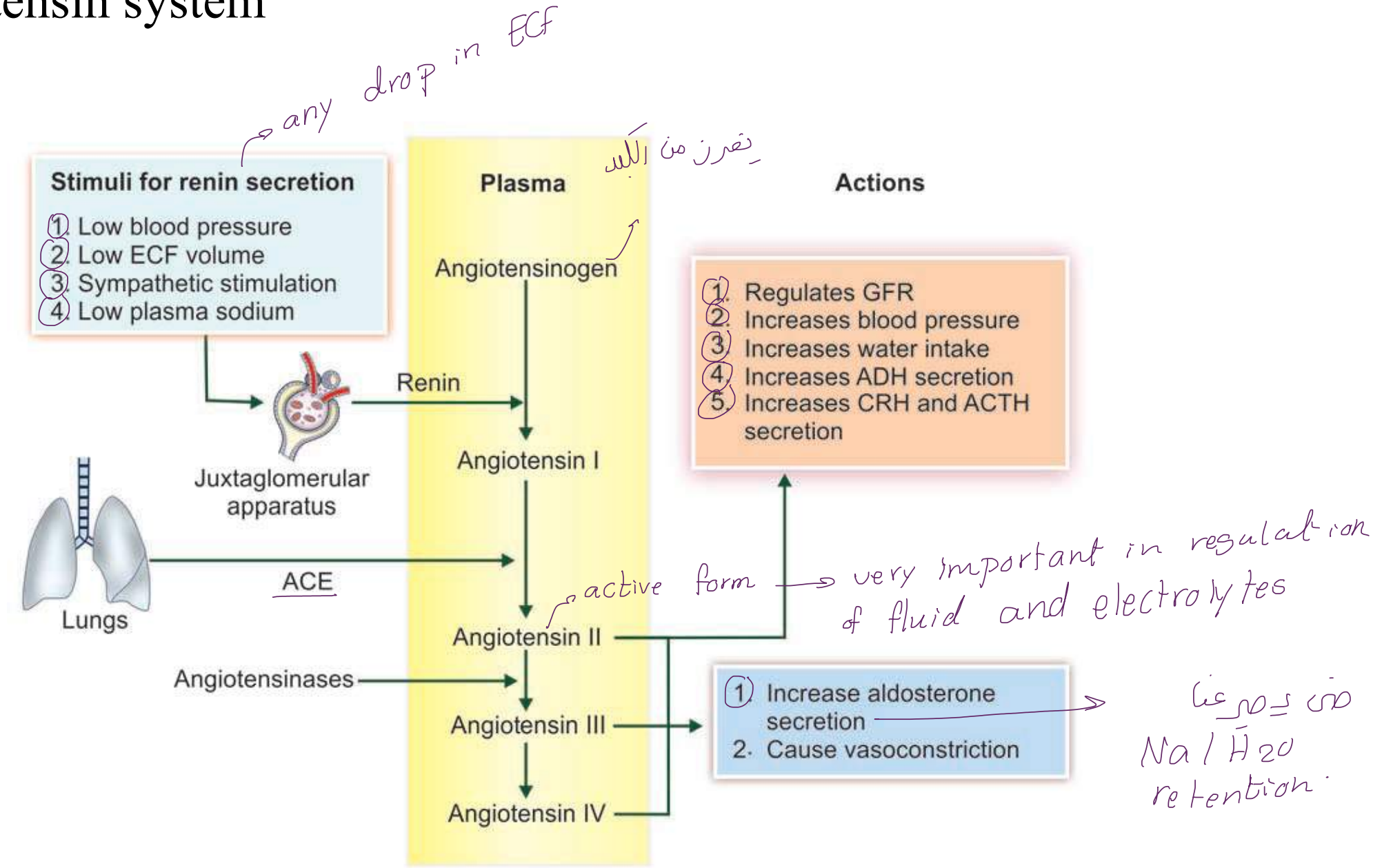
يزيد ←

Tubuloglomerular feedback





Renin-Angiotensin system



Tubuloglomerular feedback

- **Factors increasing the sensitivity of tubuloglomerular feedback:**

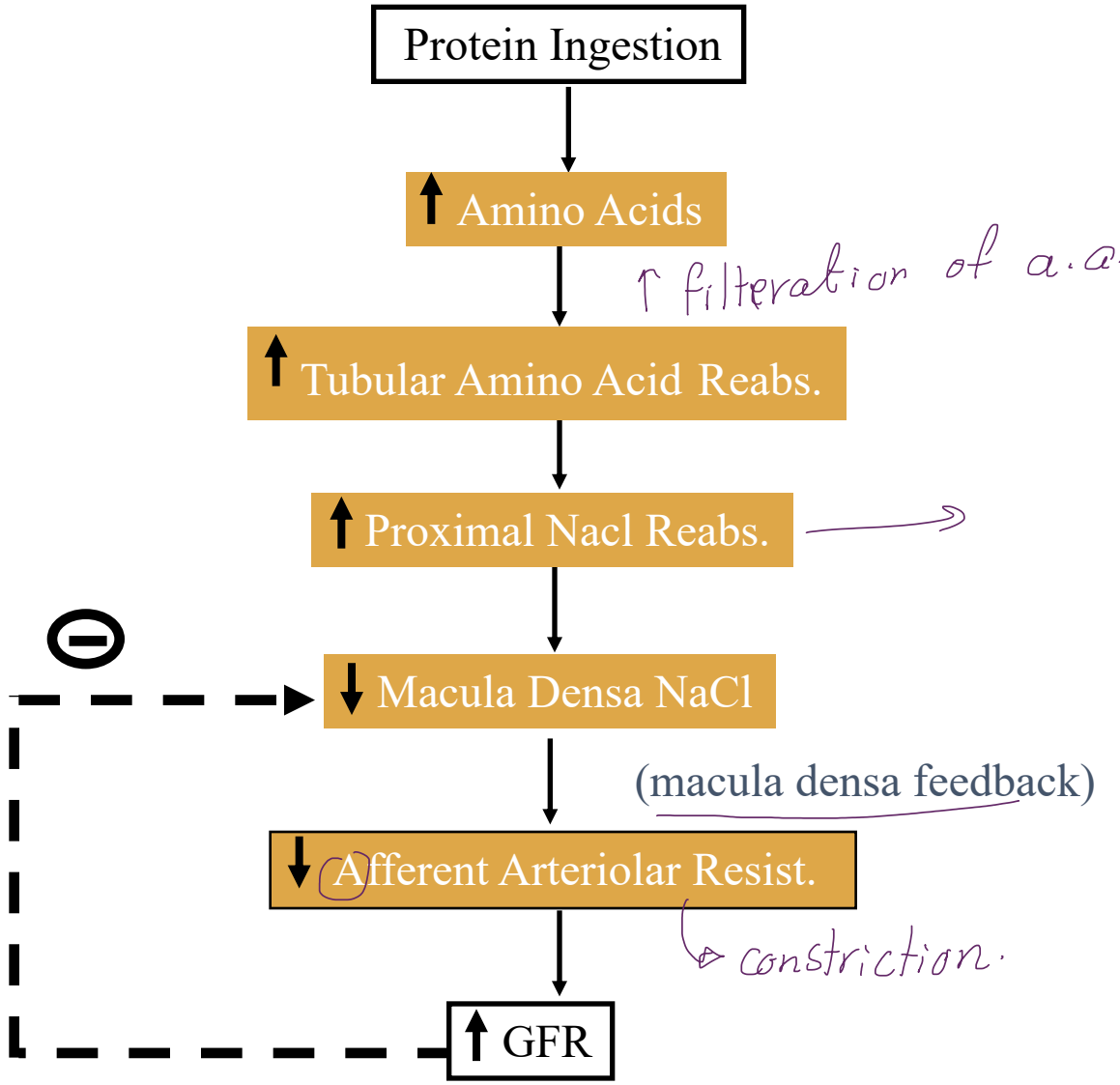
  i. Adenosine
  ii. Thromboxane
  iii. Prostaglandin E2

  Factors decreasing the sensitivity of tubuloglomerular feedback:

  i. Atrial natriuretic peptide
  ii. Prostaglandin I2
  iii. Cyclic AMP (cAMP)
  iv. Nitrous oxide.

Other Factors That Influence GFR

- Fever, pyrogens: increase GFR
- Glucorticoids: increase GFR
- Aging: decreases GFR 10%/decade after 40 yrs
- Hyperglycemia: increases GFR (diabetes mellitus)
- Dietary protein: high protein increases GFR
  low protein decreases GFR



reabsorption of a.a
Na ⇒ بروتين

because the protein reabsorbed actively by 2ndry active transport ↓ depends on Na.

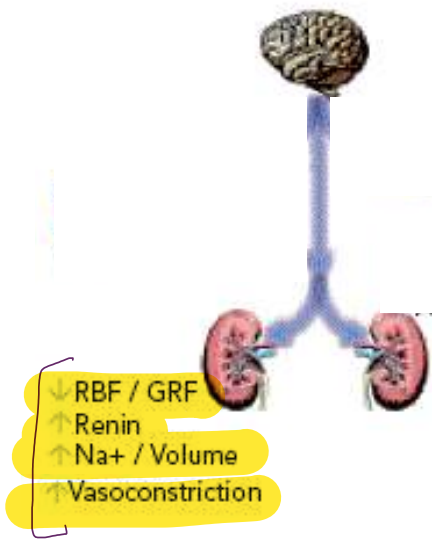
Control of GFR and RBF

Control over P_G & π_G

- Neurohormonal
- Local (autacoids, Intrinsic)

Neurohormonal regulation of GFR and RBF

Strong Sympathetic stimulation ⟶ ↑ VC ⟶ ↓ RBF
↓ GFR



- In healthy person, sympathetic have little influence on RBF.
- Sympathetic is important in acute disturbances (e.g. defense reaction, brain ischemia, or severe haemorrhage)

and shock

Hormonal regulation of GFR and RBF

- Constrict **Efferent** arterioles
- Powerful
- Physiological conditions
- low Na diet, volume depletion & ↓ arterial P
- prevents ↓ P_G & GFR
- ↓ flow in peritubular capillaries ↑ Na reabsorption
- NO & PG Counteract the angiotensin II mediated vasoconstriction in afferent A.

Table 27-4 Hormones and Autacoids That Influence GFR

Hormone or Autacoid	Effect on GFR
Norepinephrine	↓
Epinephrine	↓
Endothelin	↓
Angiotensin II	↔ (prevents ↓)
Endothelial-derived nitric oxide	↑
Prostaglandins	↑

Constrict Renal Blood Vessels
Little effect normally
Hrrge
Toxemia of preg
ARF
Chronic uremia

- vasodilator
- Help in Na & H2O excretion

- vasodilator
- important only when there are

other disturbances that are already tending to lower GFR

- Inhibited by NSAIDs

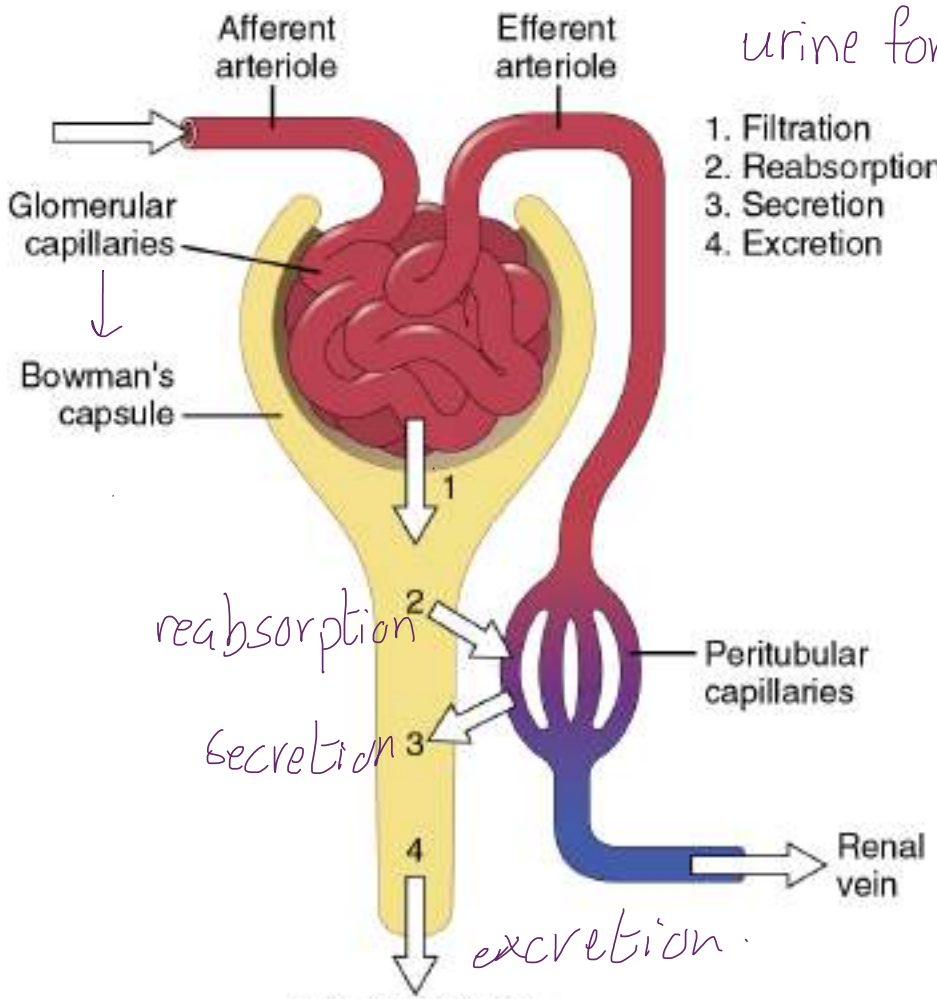
Renal Tubular Reabsorption and Secretion-I

Unit V

Chapter 28

Dr Iman Aolymat

Basic Mechanisms of Urine Formation



urine formation includes several stages starts from G filtration to the bowman capsule

reabsorption

secretion

excretion.

Excretion = Filtration – Reabsorption + Secretion

total excreted volumes

لـ يلعب دور مهم في تنظيم

change بواحد

large numbers

Glomerular filtration

- Filtration = GFR × Plasma concentration
- Assuming that substance is not bound to plasma proteins

large quantities

small quantities

Table 28-1 Filtration, Reabsorption, and Excretion Rates of Different Substances by the Kidneys

	Amount Filtered	Amount Reabsorbed	Amount Excreted	% of Filtered Load Reabsorbed
Glucose (g/day)	180	180	0	100
* Bicarbonate (mEq/day)	4320	4318	2	>99.9
* Sodium (mEq/day)	25,560	25,410	150	99.4
* Chloride (mEq/day)	19,440	19,260	180	99.1
* Potassium (mEq/day)	756	664	92	87.8
Urea (g/day)	46.8	23.4	23.4	50
Creatinine (g/day)	1.8	0	1.8	0

Changes in tubular reabsorption and glomerular filtration are closely coordinated to avoid large fluctuations in excretion

Tubular reabsorption

- Highly selective — according to the need of the body and the substance.
- Glucose and amino acids are completely reabsorbed
- Electrolytes are mostly reabsorbed but dependent on body needs
- Urea & creatinine poor absorption
- Tubular reabsorption includes passive and active mechanisms

passive → dose not need any energy and according to concentration gradient

active → need energy

Reabsorption of Water and Solutes

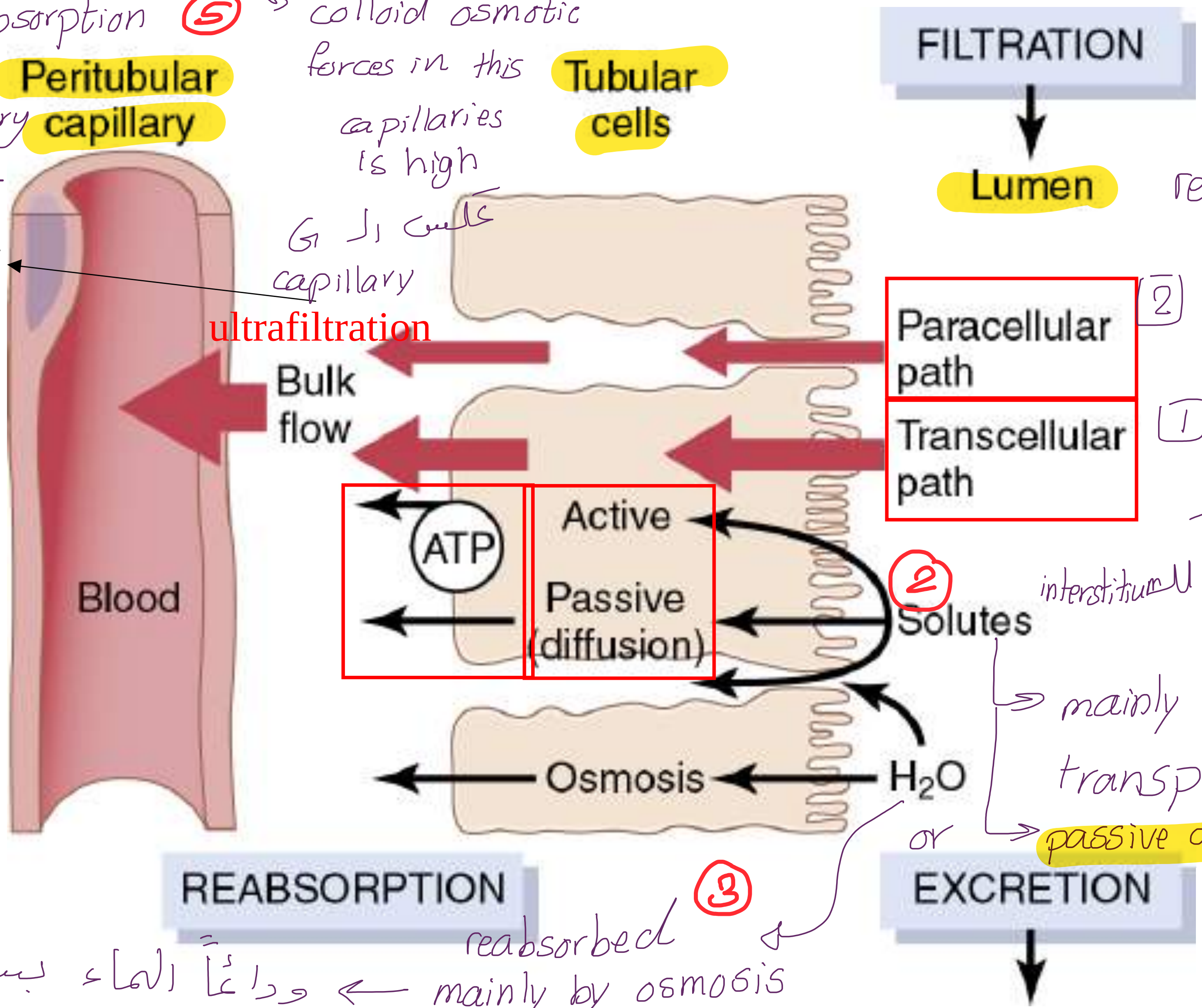
within this capillary is low → because the peritubular opposing the reabsorption while colloid osmotic forces in this capillaries is high

tight junction تدخل عن طريق ال [2] between the EC → تسمح بمرور ال water + substance

the final forces → reabsorption (5) on peritubular capillary H. P عشان هيك حكينا انو ال عكس ال G capillary

mediated by hydrostatic and colloid osmotic forces

مجرد ما دخلت ال substance (4) لل interstitial fluid ع تدخل على ال capillaries حسب ال hydrostatic and colloid osmotic forces.



(1) عملية ال reabsorption تتم إما عن طريق [2]

[1] إنو ال substance من ال lumen تدخل لل epithelial cells ويعبرن للinterstitium

(2) Solutes → mainly by active transport → على ال lumenal border أو على ال basal border

or → passive diffusion

(3) reabsorbed mainly by osmosis → وداغاً الماء بيسحب معه other substances

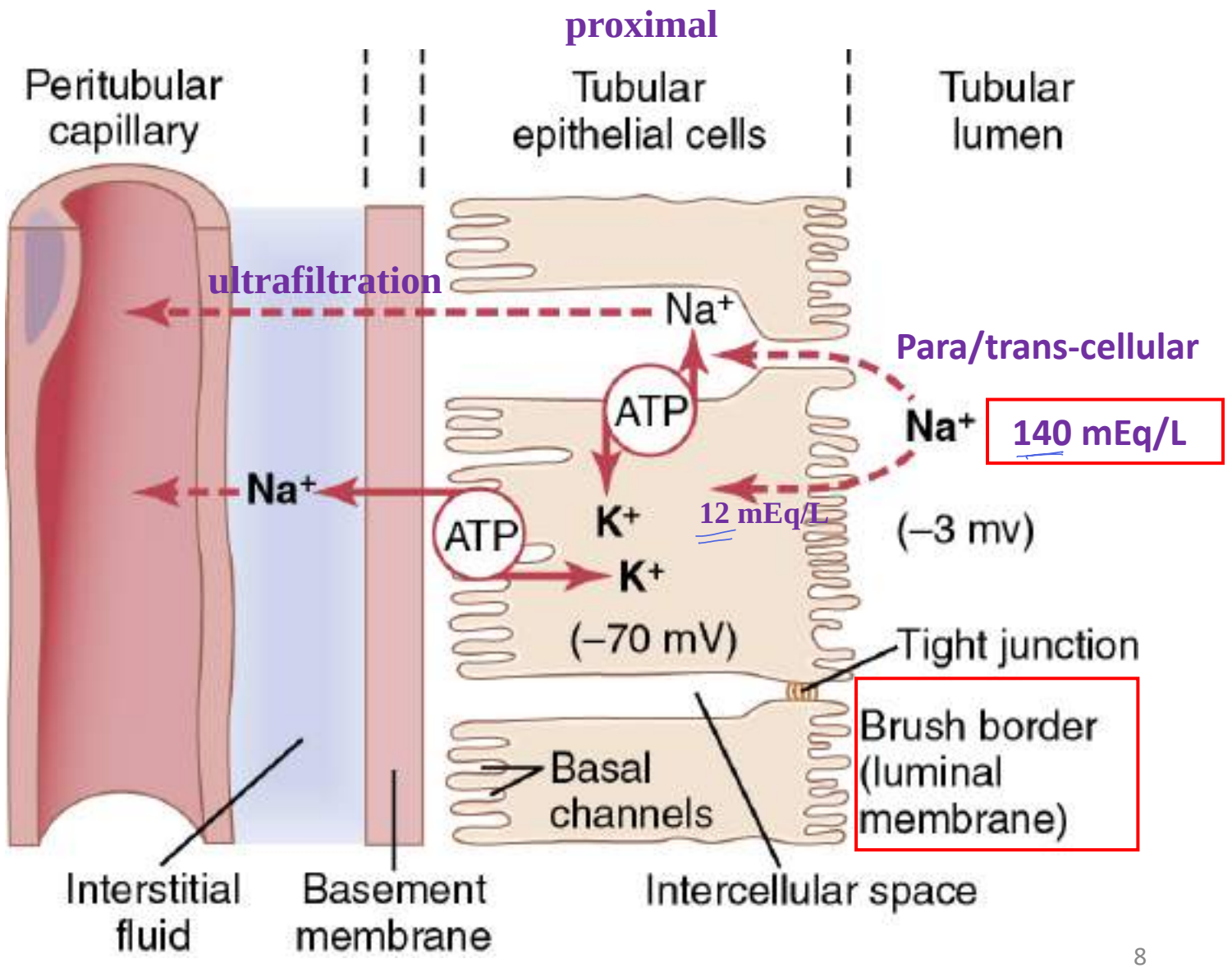
ACTIVE TRANSPORT

- Moved against electrochemical gradient
- ATP-dependent

- Primary active transporters in kidneys:
1. Na-K ATPase
2. H-ATPase
3. H-K ATPase
4. Ca ATPase

Primary Active Transport of Na^+

Passive diffusion of Na (Carrier proteins)
1-concentration gradient difference
2- -70 mV intracellular potential attracts positive Na



primary active transport of Na^+ → mainly on basolateral side of the epithelium
→ mainly happens in proximal tubular epithelial cells
↓ has brush border differ from one place to another within the tubules
on the lumenal membrane
also on basal membrane
→ increase the surface area of reabsorption on the both side of epithelium

---

* primary active transport on the basolateral side of the epithelium

we have Na^+/K^+ pump

this pump excrets Na into interstitial fluid
وبتدخل K ...

عملية ال excretion of Na outside of cells →

← بتخفف ال concentration of Na in tubular epithilial cell

بالتالي ع بدهم ب passive diffusion لل Na من ال lumen

فهاي ال pump بتضخ الصوديوم لبرا ① الخلية فبقل تركيز الصوديوم فبتعمل
② negative potential

1+2 → بسحبوا الصوديوم من ال tubular lumen عن طريق ال passive diffusion

Mechanisms of secondary active transport.

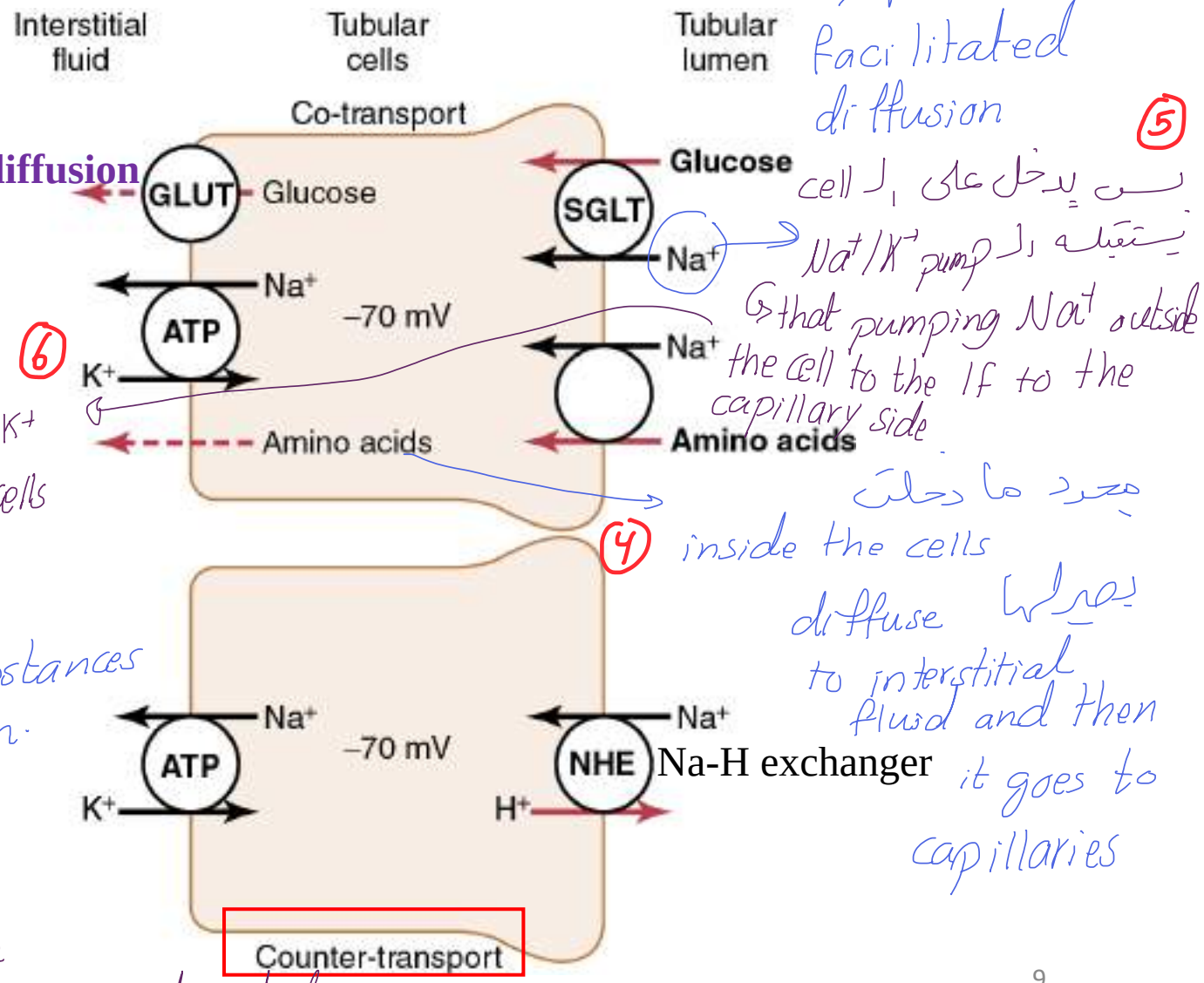
(1) Na^+ is used for the absorption of other substances by secondary active transport is also energy dependent which produced by substance to move other substances

(2) as examples

Na^+- Glucose co transporter

Na^+- aminoacids → transport of the substances in the same direction.

(3) reabsorption of Na^+, once its inside the cell, movement of glucose into the interstitial fluid by passive facilitated diffusion



passive facilitated diffusion

(5) ... cell ... Na^+/K^+ pump ... that pumping Na^+ outside the cell to the If to the capillary side

(6) and reabsorping K^+ inside the cells

(4) inside the cells diffuse to interstitial fluid and then it goes to capillaries

Na-H exchanger

a kind of active transport ← energy dependent

Pinocytosis

H+ ← pumping، بتدخل الصوديوم into tubular lumen by transporter called Na-H exchanger

its pumped outside the cell using the Na-Ka pump. ← وبمجرد ما دخل الصوديوم داخل الخلية

(1) • An **Active** Transport Mechanism for Reabsorption of Proteins

(2) • Inside the cell, protein is digested into amino acids→ reabsorbed through basolateral membrane into interstitial fluid. by passive diffusion.

pinocytosis ⟵ خلال الـ invaginations بصير عنا cell membrane بالون زي vesicals بتدخل فيها الـ proteins

and once the proteins inside the cells ⟵ بصير digestion ...

---- (2)

Transport Maximum

1. we have transporter protein on the either side of endothelium → they have capacity . معنية

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

4. max مجرد ما نوصل لـ filter load اي زيادة في reabsorption ما رح يصير لها وقت تنبلش في عملية الـ excretion

- Transport Maximum: Once the transport maximum is reached for all nephrons, further increases in tubular load are not reabsorbed and are excreted.

2. mainly used for actively transported substances لـ

- Threshold is the tubular load at which transport maximum is exceeded in some nephrons. This is not exactly the same as the transport maximum of the whole kidney because some nephrons have lower transport max's than others.

3. باي بوقف عملية الـ transport

maximum capacity الـ (عملت وصل لك

- Examples: glucose, amino acids, phosphate, sulphate

energy ما في (

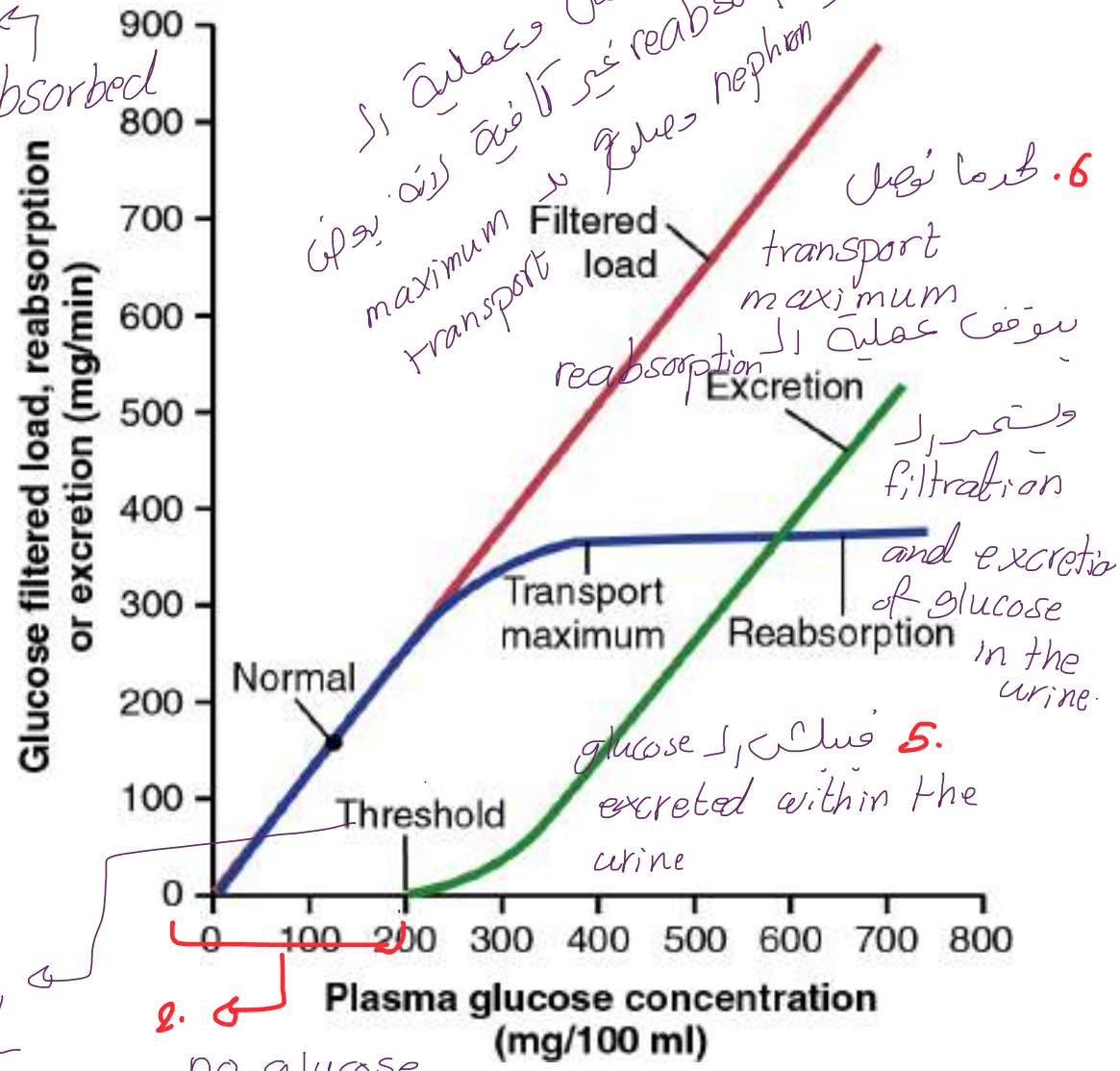
Glucose Transport Maximum

- Normally **No** glucose in the urine -all filtered and all reabsorbed
- glucose is reabsorbed in proximal tubule.

- 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 which is normally about **375 mg/min**, is reached when **all** nephrons have reached their maximal capacity to reabsorb glucose.



* ليه بيكشف بيبس الـ excretion قبل ما توصل لـ transport maximum ؟!

بالمختصر انه لسا شغالين الـ transport بتعت الـ nephrons اللي واصلت لـ capacity بتعتهم

other nephrons reached their transport maximum

وبالتالي عشان هيك بيكشف بيبس عندي في الـ glucose في الـ urine

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

- H_2O is absorbed by osmosis through tight junctions
- Proximal tubules are highly permeable to water
- H_2O osmosis drag other solutes (Na, Cl, K, Ca & Mg) mainly in proximal T. Distally less permeable membrane & less surface area→ less solvent drag & osmosis

2. always permeable to water

under control or not controlled. proximal tubules dont have control on permeability to water.

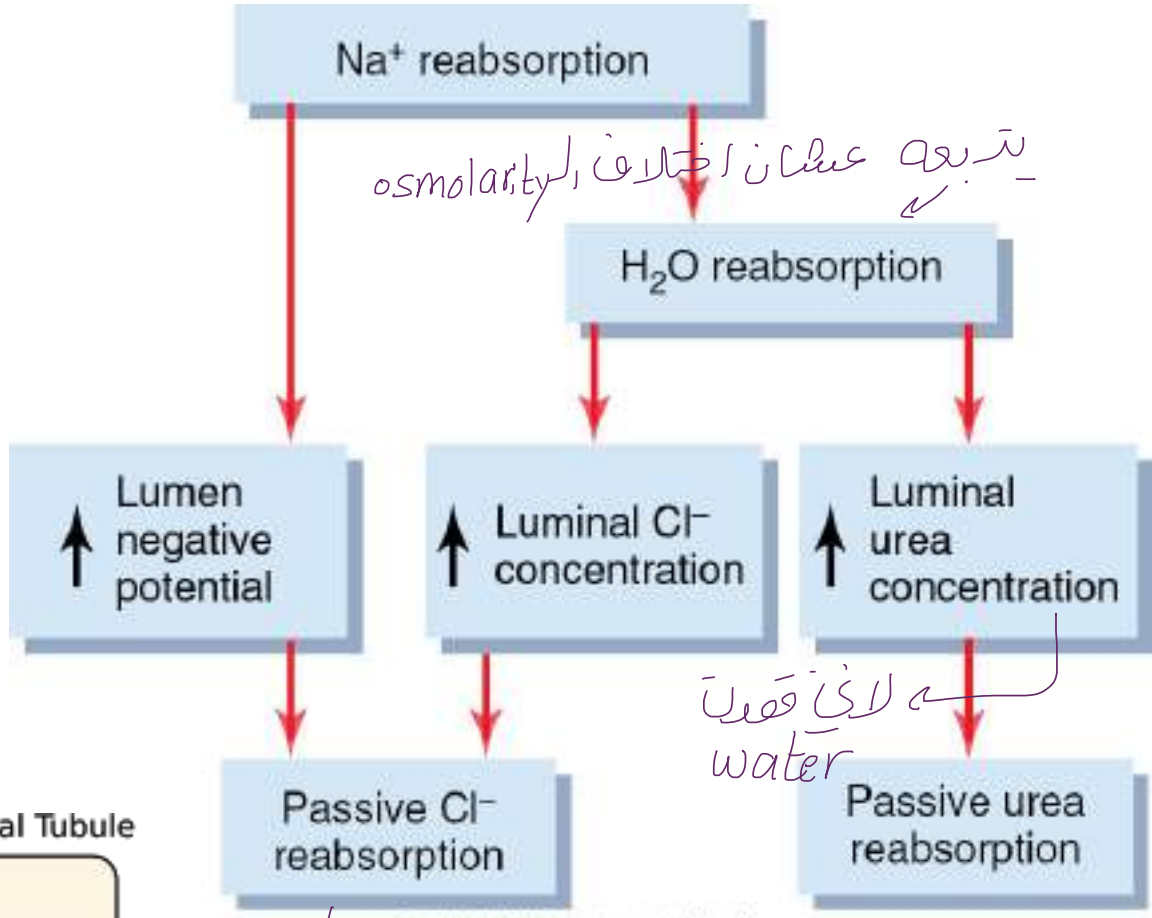
3. part of the tubule is always isoosmotic

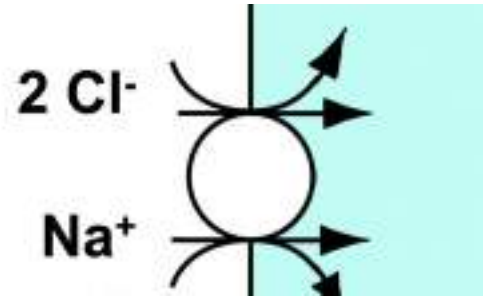
brush borders

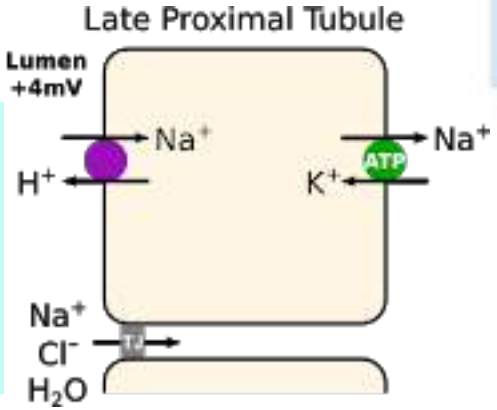
rate reabsorption of water and other solute

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

- Cl reabsorption (paracellular pathway) occurs via passive diffusion due to Na and water reabsorption
- Secondary active transport of chloride occurs a along with active transport of Na
- Urea is reabsorbed passively in the different segments of the nephron.
- Creatinine is large molecule and is essentially impermeant to the tubular membrane→almost none is reabsorbed





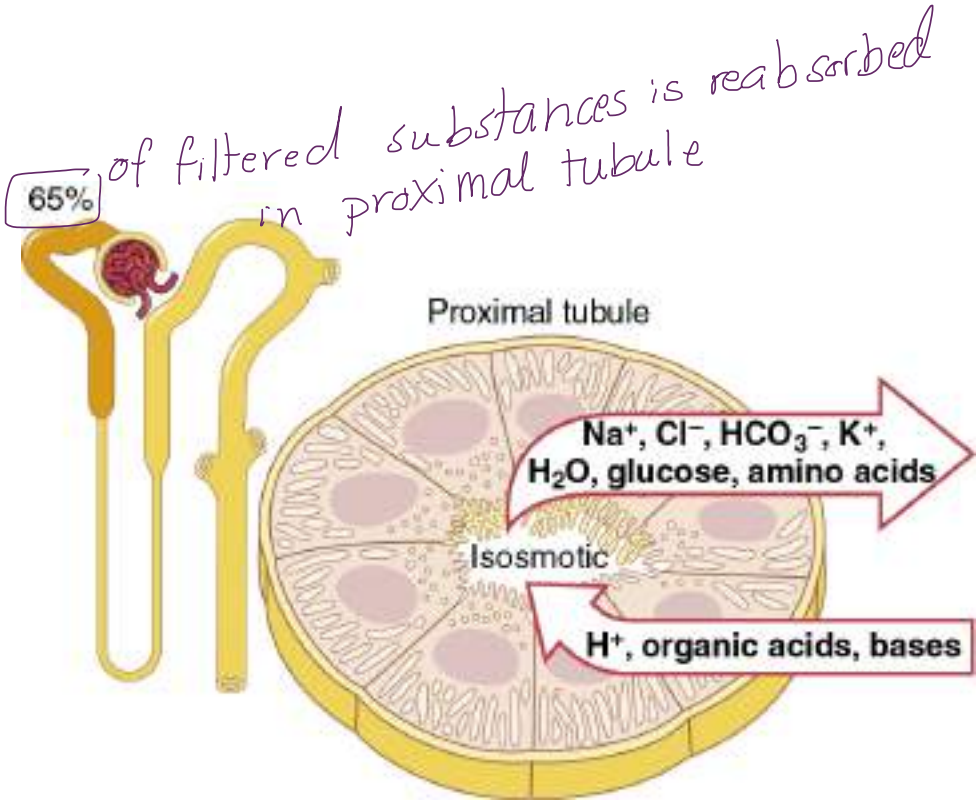


Transport Characteristics of Proximal Tubule (PT)

extensive active and passive transport

- Proximal tubules have a high capacity for active & passive reabsorption→↑ mitochondria & extensive brush border on luminal side, extensive basal channels →↑ SA

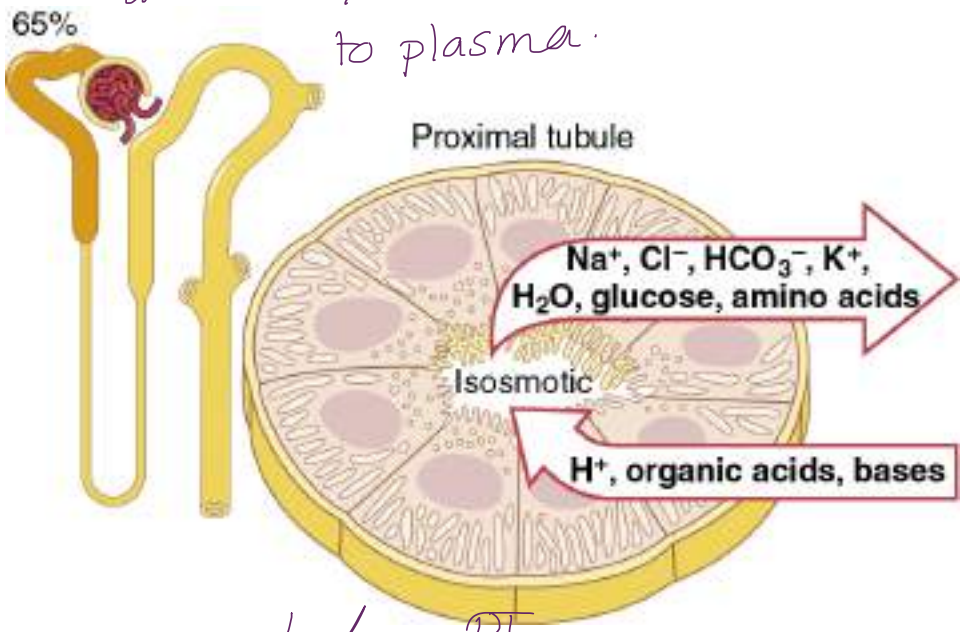
لحتى اوصل لأعلى rate of reabsorption



Transport Characteristics of Proximal Tubule (PT)

highly permeable to water → so the reabsorption of solutes and water is occuring in the same rate / so the tubular lumen is isoosmotic and mostly the same osmolarity to plasma.

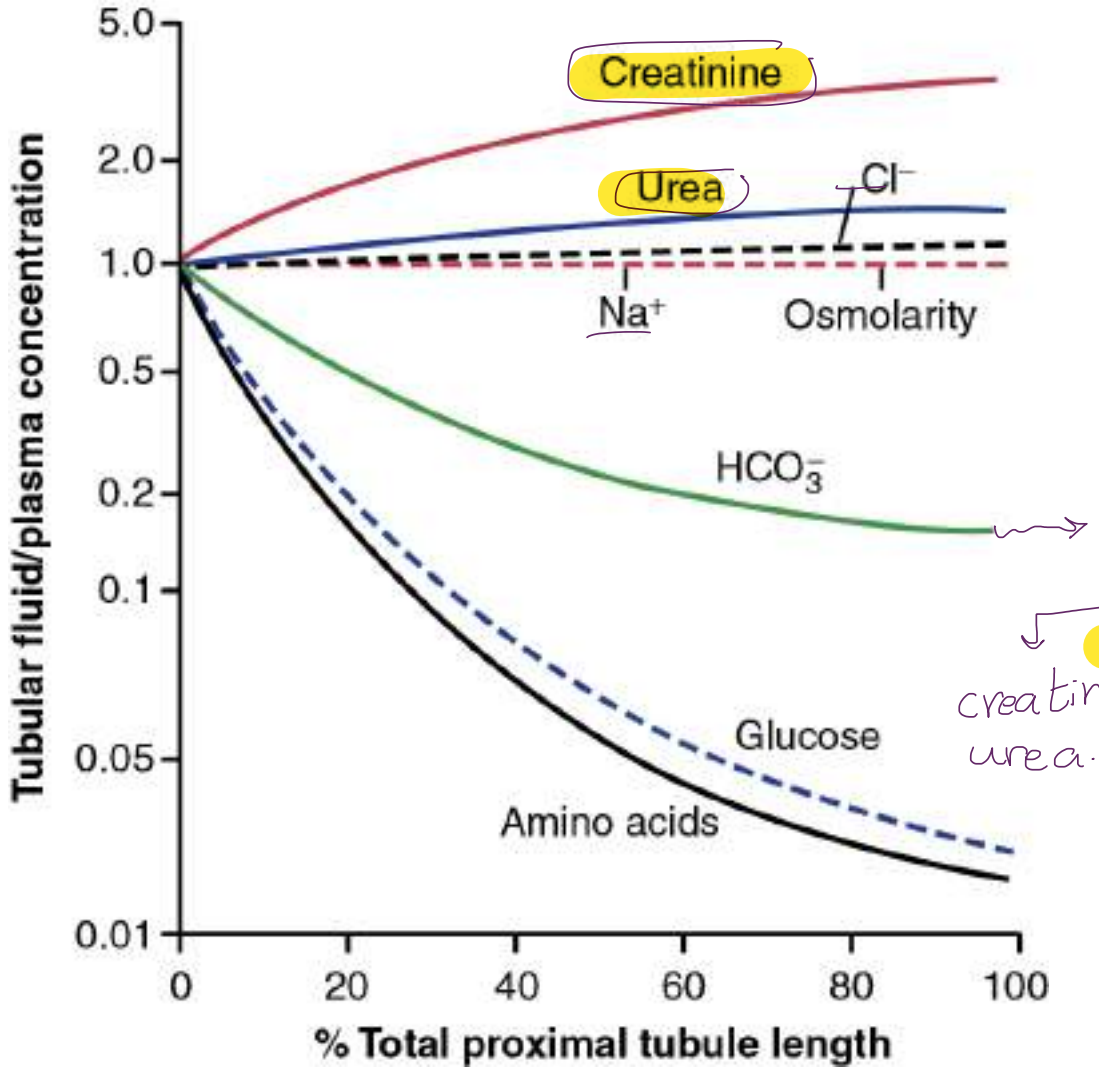
- PT reabsorb 65% of filtered Na, Cl, HCO3, & K
- Na is mainly reabsorbed by primary transport
- In 1st ½ of PT→ Na, GLU& AA → **COTRANSPORT**
- In 2nd ½ of PT → low GLU& AA & high Cl →mainly Cl reabsorption by diffusion through intercellular j.



- Reabsorb all filtered glucose and amino acids
- Secrete organic acids, bases, & H^+ into lumen.
- H^+ secretion binds HCO3 → H2CO3→H2O +CO2
- Secretion of drugs (penicillin and salicylates),toxins, bile salts , ureat oxlate and catcholamines are secreted by the proximal tubule.

are excreted in PT

Changes in Concentration in Proximal Tubule



Glucose + a.a → آلية في البداية [ ] أكثر toward the distal end of PT وتقل

=1.0 concentration of substance in tubular fluid = concentration in plasma→High H2O permeability

<1 substance is reabsorbed> H2O

>1.0substance is reabsorbed < H2O or is secreted into the tubules.

creatinine urea.

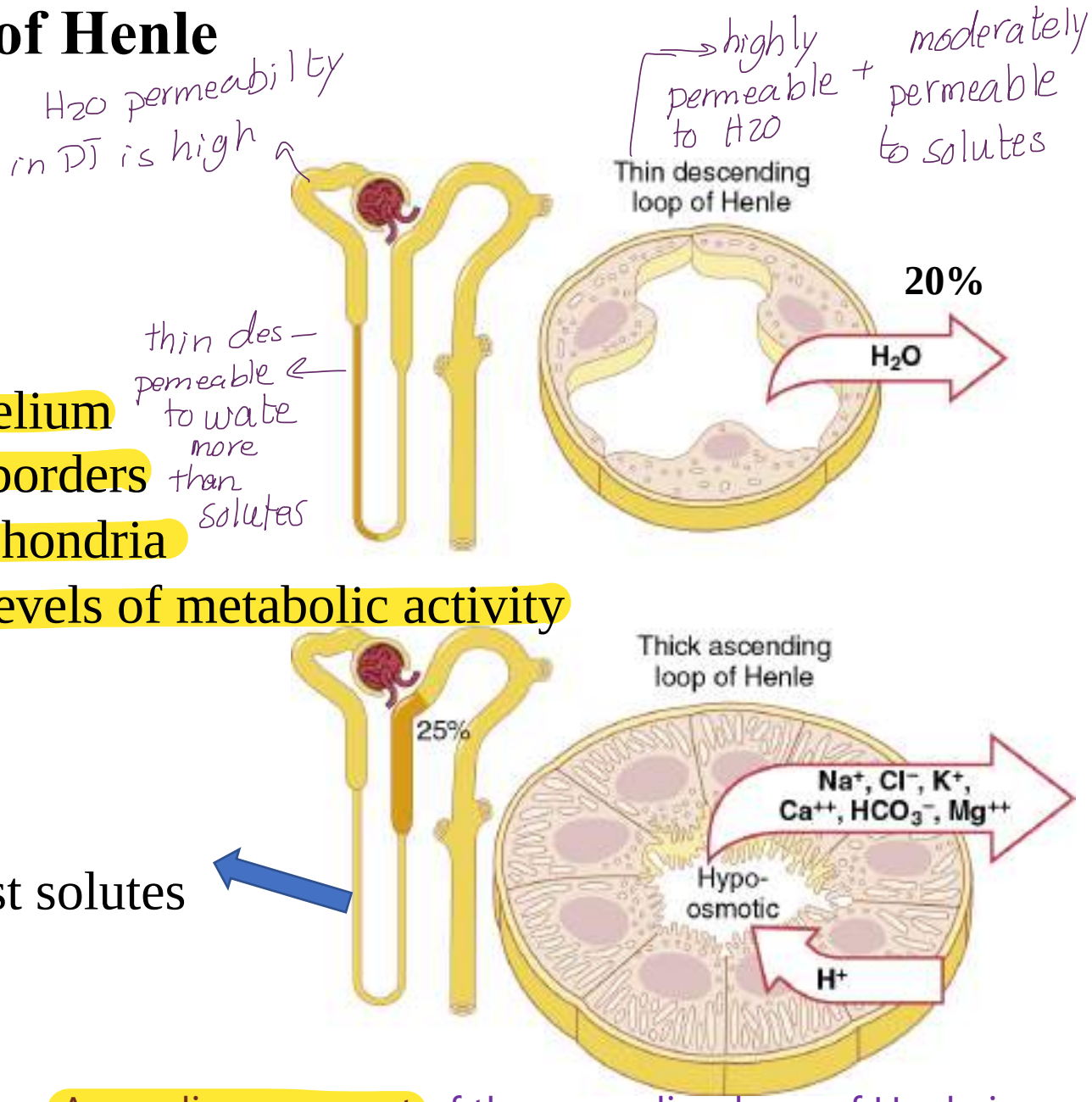
base line =1 → concentration of substance in tubule same as in plasma.

Transport characteristics of loop of Henle

3 functionally segments:

1- thin descending
2-thin ascending
3-thick ascending

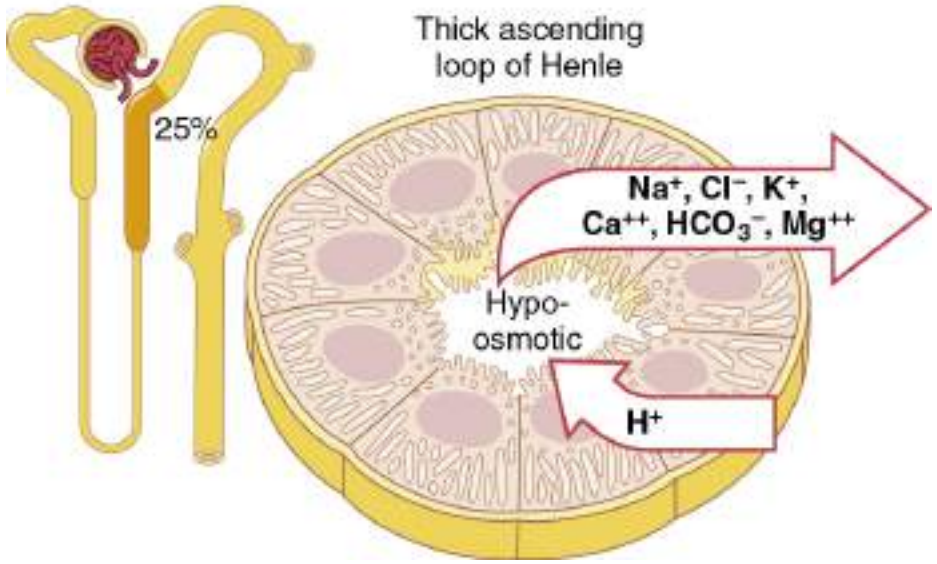
thin epithelium
no brush borders
few mitochondria
minimal levels of metabolic activity



highly permeable to H2O
moderately permeable to most solutes

Ascending segment of the ascending loop of Henle is virtually **impermeable** to water

Transport characteristics of loop of Henle



~ 25% of filtered load → reabsorbed in thick ascending loop of Henle.

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

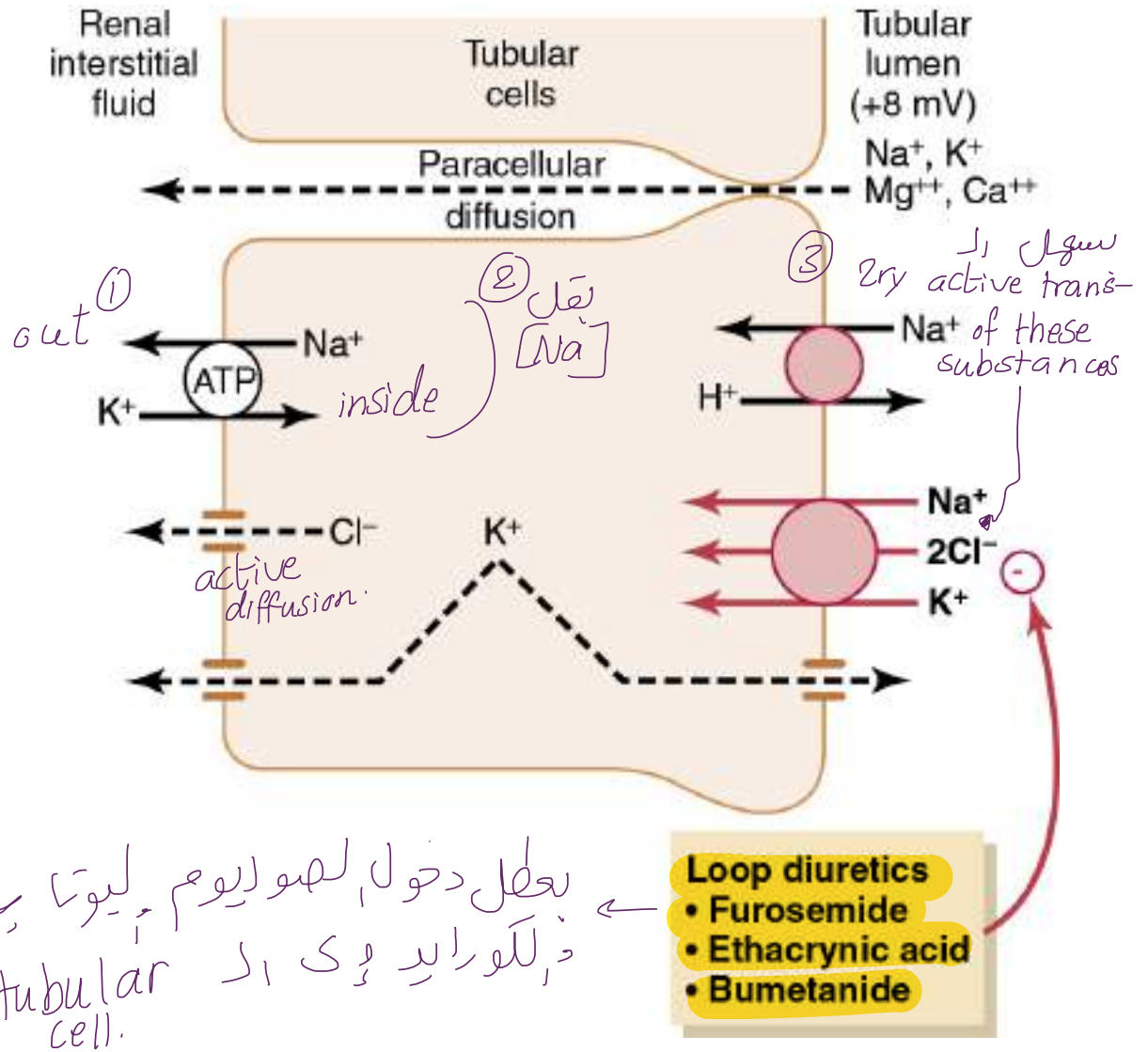
H_2O لا تخرج من الأنابيب ↵
inside the tubules
↵ تكون أعلى وبالتالي
the content is hypo osmotic.

Transport characteristics of loop of Henle

- NaCl & K transport in thick
- ascending loop of Henle depends on Na+-K+ATPase
- In the epithelial cell basolateral membranes
- Pump →↓ intracellular Na→ favorable gradient for movement of Na from tubular fluid into cell.

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

- Na-H counter-transport mechanism



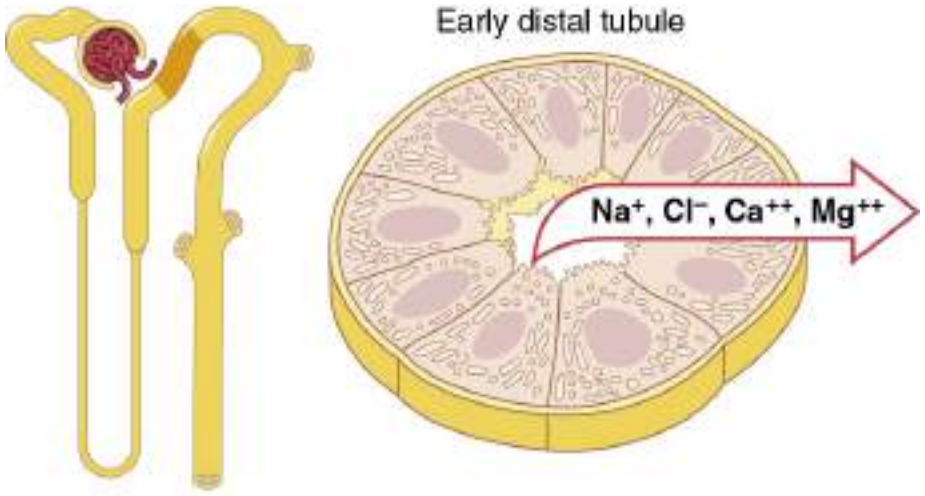
Early Distal Tubule

- Functionally similar to thick ascending loop
- Not permeable to water (called diluting segment)
- Active reabsorption of Na^+, Cl^-, K^+, Mg^{++}
- Early part contains macula densa (part of juxtaglomerular complex)& provides feedback control of GFR and RBF.
- The next part of the distal tubule is highly convoluted

→reabsorbs most of ions& impermeable to water and urea.

concentration ofurine

Early Distal Tubules

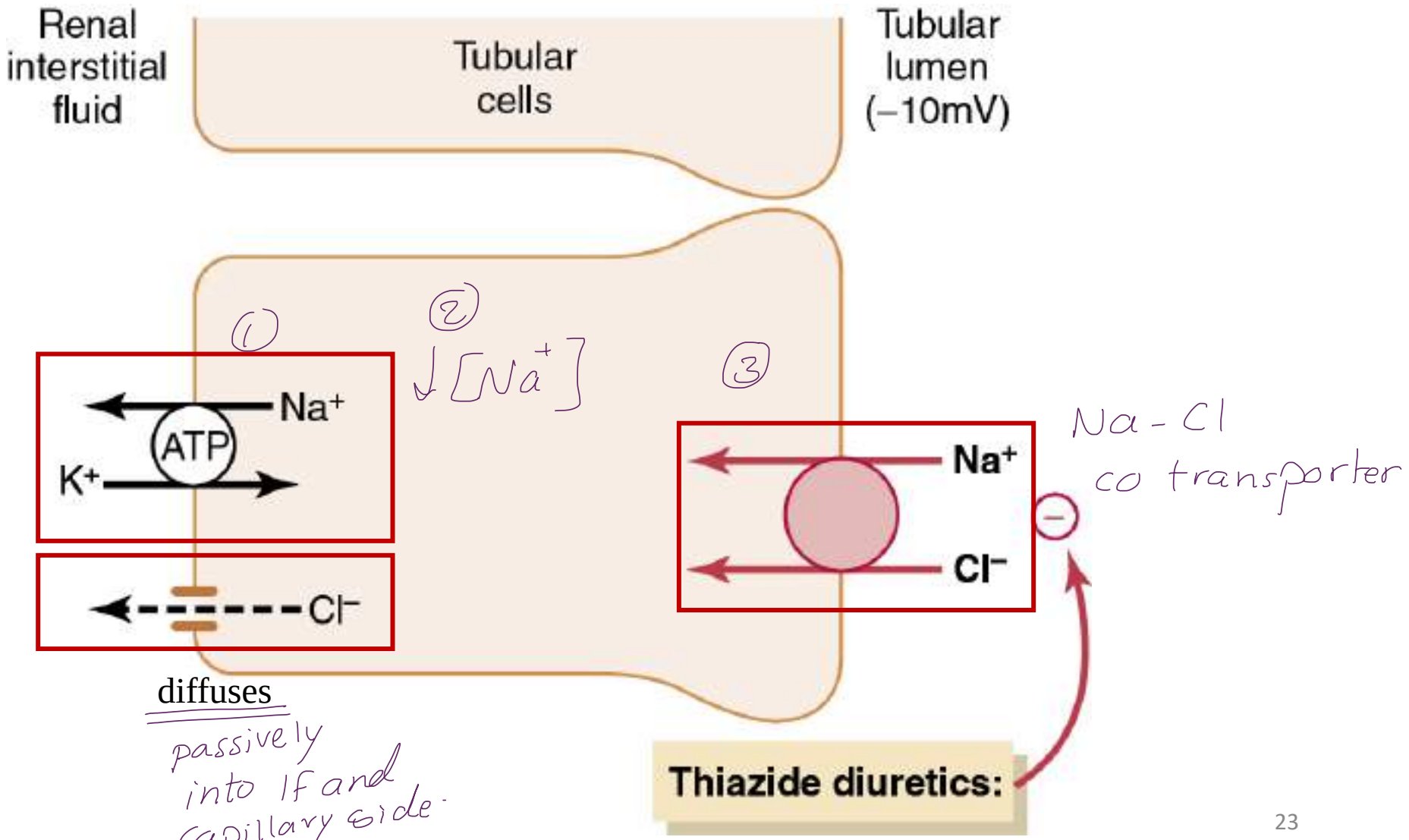


~ 5% of filtered load
NaCl reabsorbed

- not permeable to H_2O
- not very permeable to urea

Early Distal Tubule

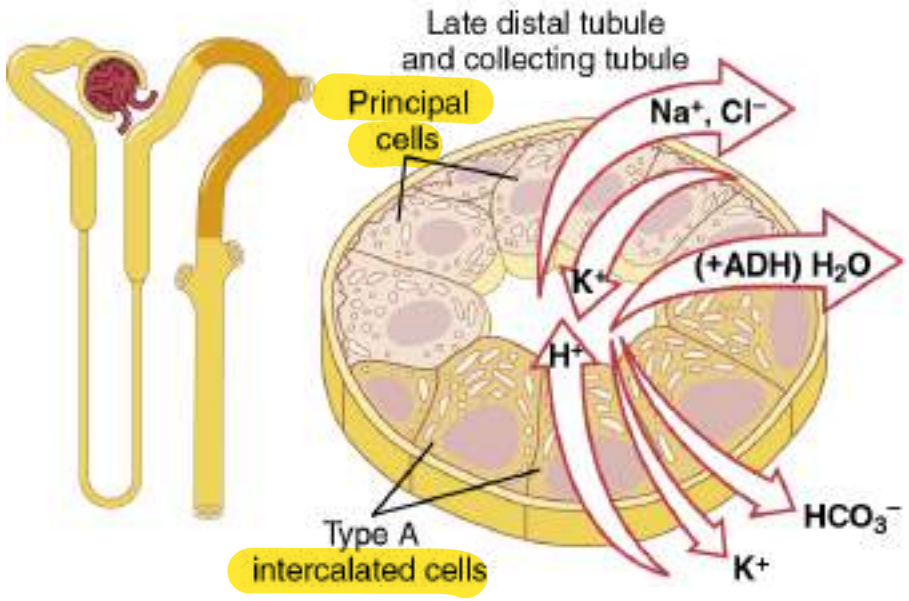
[2ry active transport]



Late Distal Tubules and Collecting Tubules.

early

Late Distal Tubules and Collecting Tubules have similar functional characteristics



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

anti diuretic hormone
ضد الادرار في البول

في مجرد ما انفرز مع يغير ال permeability of tubules

reabsorption يسهل ال of water

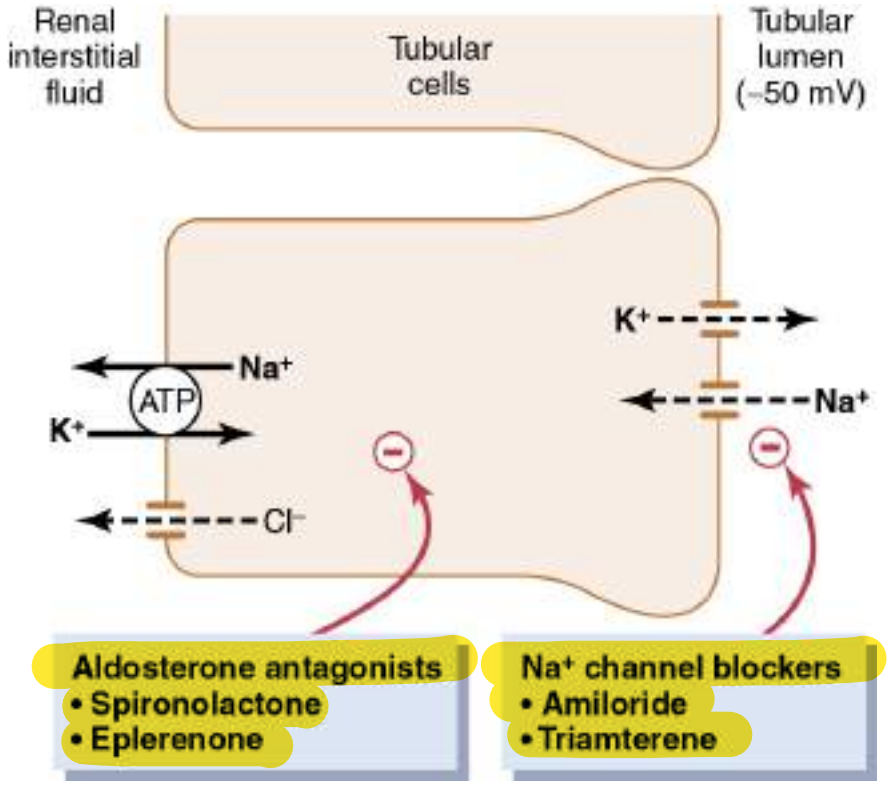
١. Principal Cells Reabsorb Na and Secrete K

Na-K ATPase activity تنشيط

- Depend on activity of Na+-K+ATPase pump basolateral membrane. Low intracellular Na→Na diffusion in+ high intracellular K →K diffusion OUT

- The principal cells are the primary sites of action of the K-sparing diuretics. → inhibit the excretion of K+
- Aldosterone antagonists inhibit stimulatory effects of aldosterone on Na reabsorption and K secretion.

- Na channel blockers inhibit the entry of Na into Na channels of →↓ Na that can be transported across the basolateral membranes by the Na+-K+ATPase pump.

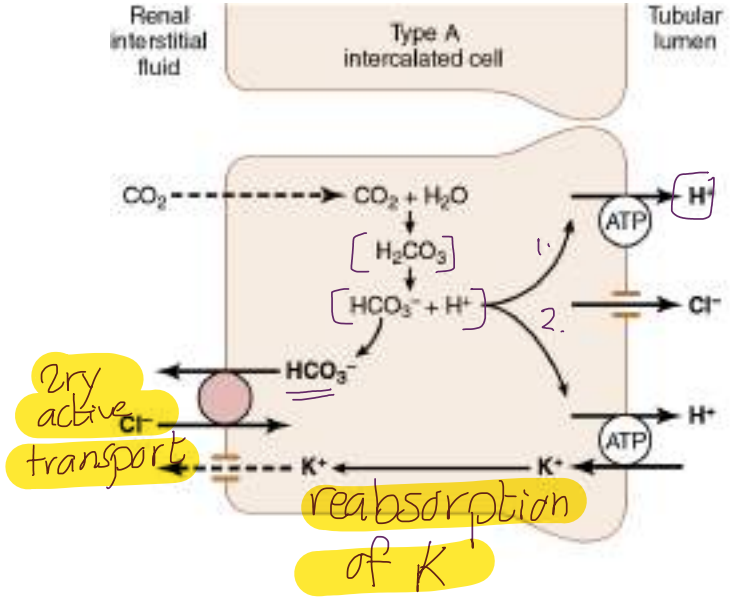


2. Intercalated Cells Secrete H and Reabsorb HCO3 & K

Type A intercalated cells

excrete H and reabsorb HCO_3

- H secretion is mediated by a H-ATPase
- H is generated in this cell by the action of CA on H2O and CO2 to form H2CO3→dissociates into H & HCO3.
- H secreted into the tubular lumen, and for each H secreted, HCO3 becomes available for reabsorption across the basolateral membrane.

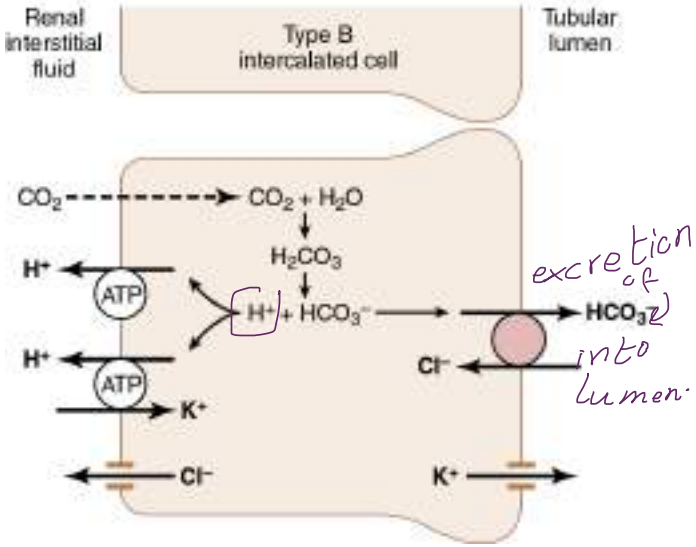


Type B intercalated cells

excretion of HCO_3

- Functions is opposite to those of type A cells (in alkalosis)
- HCO3 to lumen very important in metabolic distrpunce cases in alkalosis
- H reabsorption via H-ATPase

بنا نتخلص من HCO3 ال



Intercalated cells can also reabsorb or secrete K

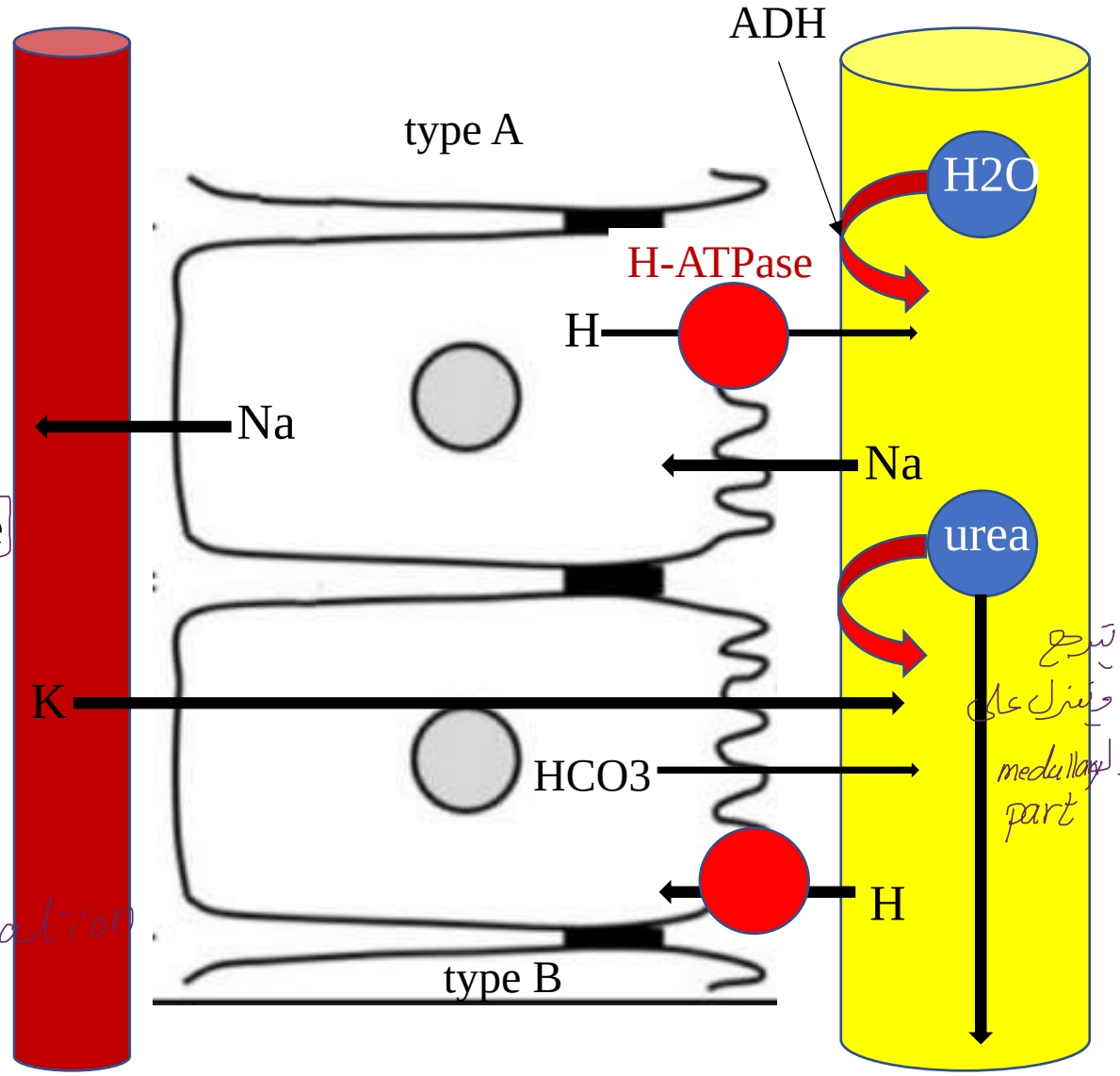
type ال و
and the function.

Late distal tubule & cortical collecting tubule

Functional characteristics:

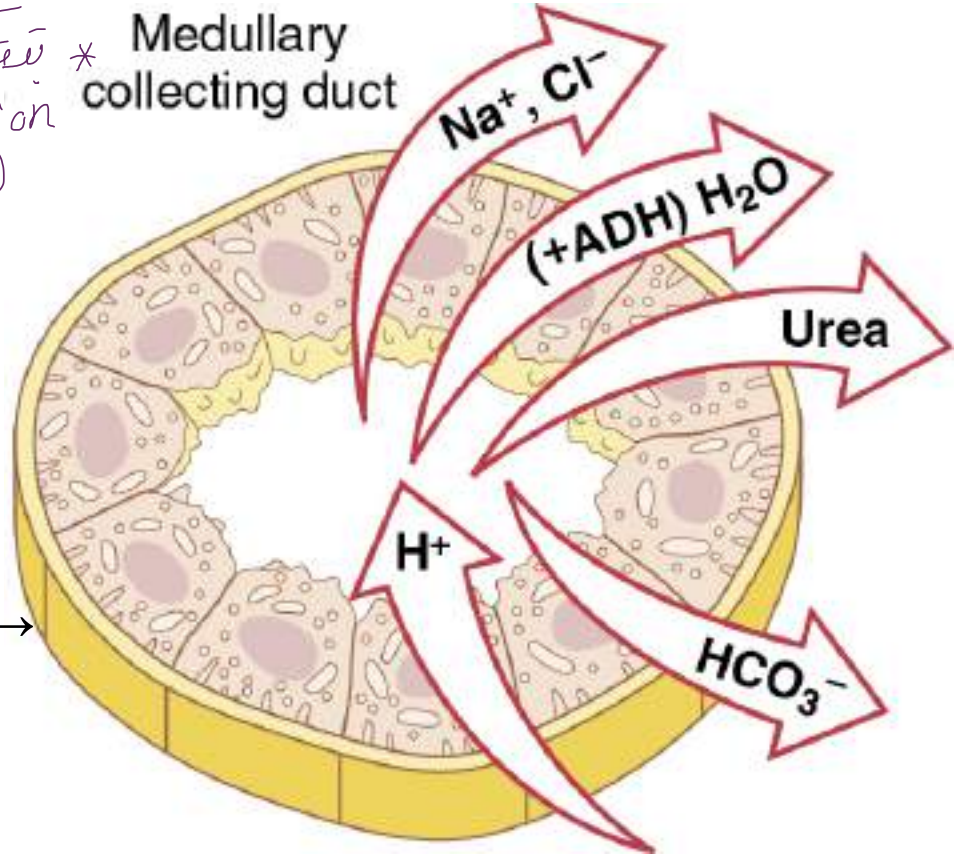
1. impermeable to urea, some reabsorption of urea occurs in the **medullary** collecting ducts.
2. reabsorb Na→ controlled by hormones, especially aldosterone.
3. secrete K from peritubular capillary to lumen controlled by **aldosterone**
4. play a key role in acid-base regulation
-type A intercalated cells → secrete H by active H-ATPase mechanism in **acidosis**.
-type B intercalated cells secrete HCO3 and actively reabsorb H In **alkalosis**
5. controlling the degree of dilution or concentration of the urine →permeability to water is controlled by concentration of ADH/vasopressin.

↑ ADH → ↑ permeability → ↑reabsorption → concentration of urine
↓ADH → ↓ permeability → water stays in the tubules → diluting the urine.



Transport characteristics of medullary collecting ducts

- Reabsorb <10% of filtered H2O & Na.
- The final site for processing the urine.
- Play an extremely important role in determining the final urine output of water and solutes.
- Its permeability to water is controlled by the level of 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.
- Secretes H against a large concentration gradient→ plays a key role in regulating acid-base balance.



concentrations of substances in the renal tubules

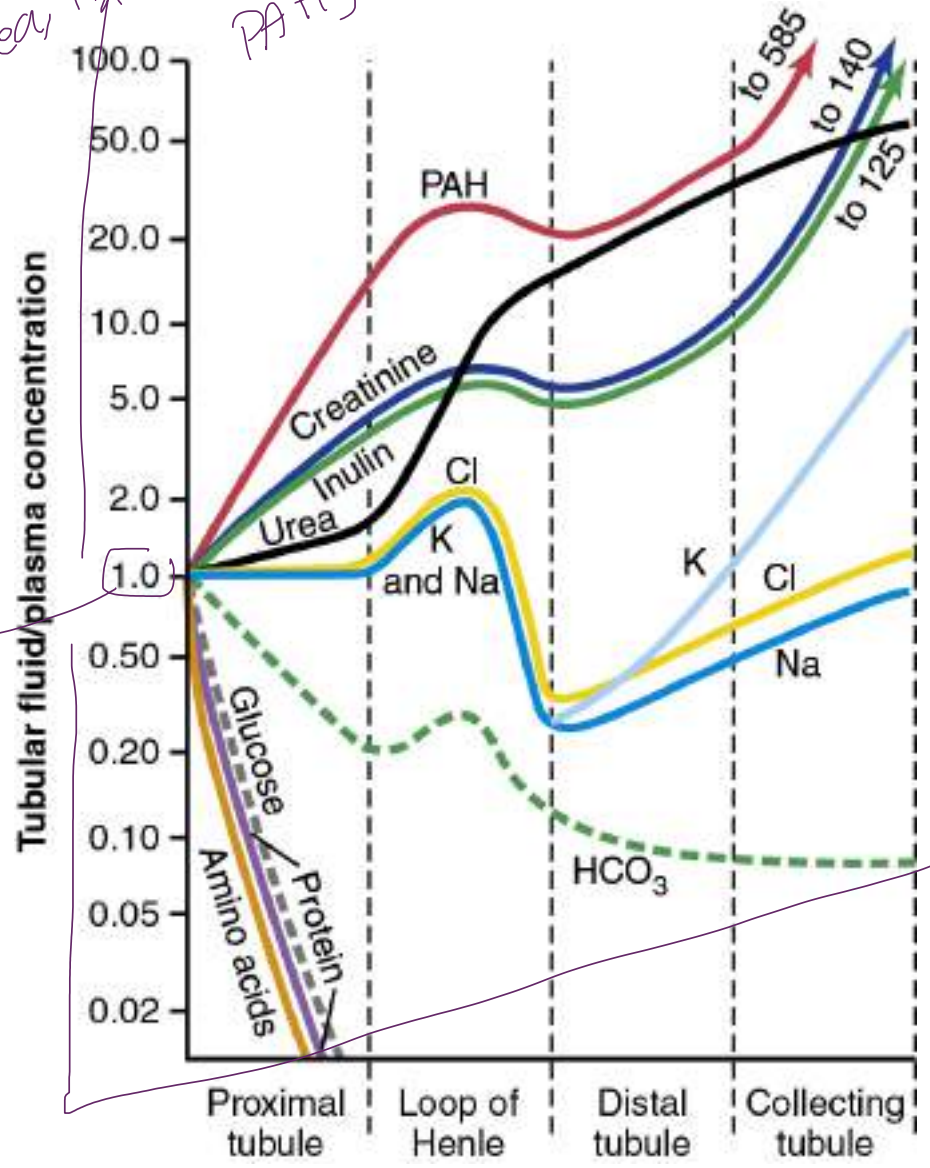
- Concentrations of solutes in different parts of the tubule depend on relative reabsorption of the solutes compared to water

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

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

↳ result in diluted filtrate.

Changes in concentrations of substances in the renal tubules



more water is reabsorbed than solute

more solute is reabsorbed than water

The End

Renal Tubular Reabsorption and Secretion-II

Unit V

Chapter 28

Dr Iman Aolymat

Regulation of Tubular Reabsorption

Regulation is required to maintain a precise balance between **tubular reabsorption** and **glomerular filtration**.

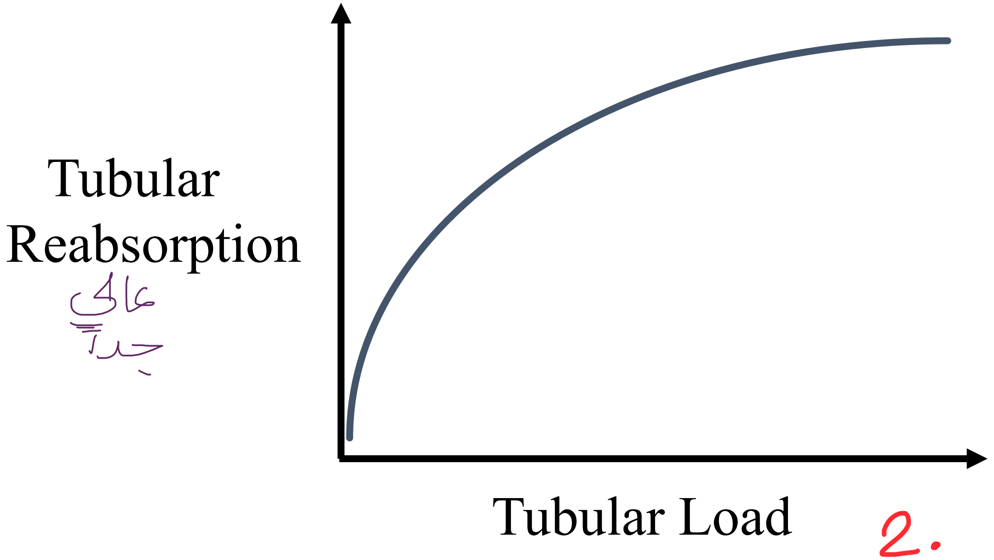
1. • Glomerulotubular Balance
2. • Peritubular Physical Forces
3. • Hormones
4. • Sympathetic Nervous System
5. • Arterial Pressure (pressure natriuresis)
6. • Osmotic factors.

reabsorption or filtration

defect or differences in the amount of the excretion

Glomerulotubular Balance

- Intrinsic ability of tubules to ↑ **reabsorption** rate in response to ↑ tubular load if GFR↑ to 150 ml/min.
- In **proximal tubule** reabsorption ↑ from 81 ml/min to 97.5 ml/min
- To less extent in Loop of Henle.
- The mechanisms for glomerulotubular balance can occur **independently** of hormones.
- It helps to prevent overloading of the distal tubular segments when GFR increases.



Peritubular Capillary Reabsorption

Peritubular reabsorption ال forces ال تنظم .1
G filtration هي مشابهة بشكل كبير لي في ال
3. the reabsorption on peritubular capillary depend on the differences between the pressure between the capillary and if

- Hydrostatic and colloid osmotic forces govern the rate of reabsorption across the peritubular capillaries
- Normal rate of peritubular capillary reabsorption is about 124 ml/min.

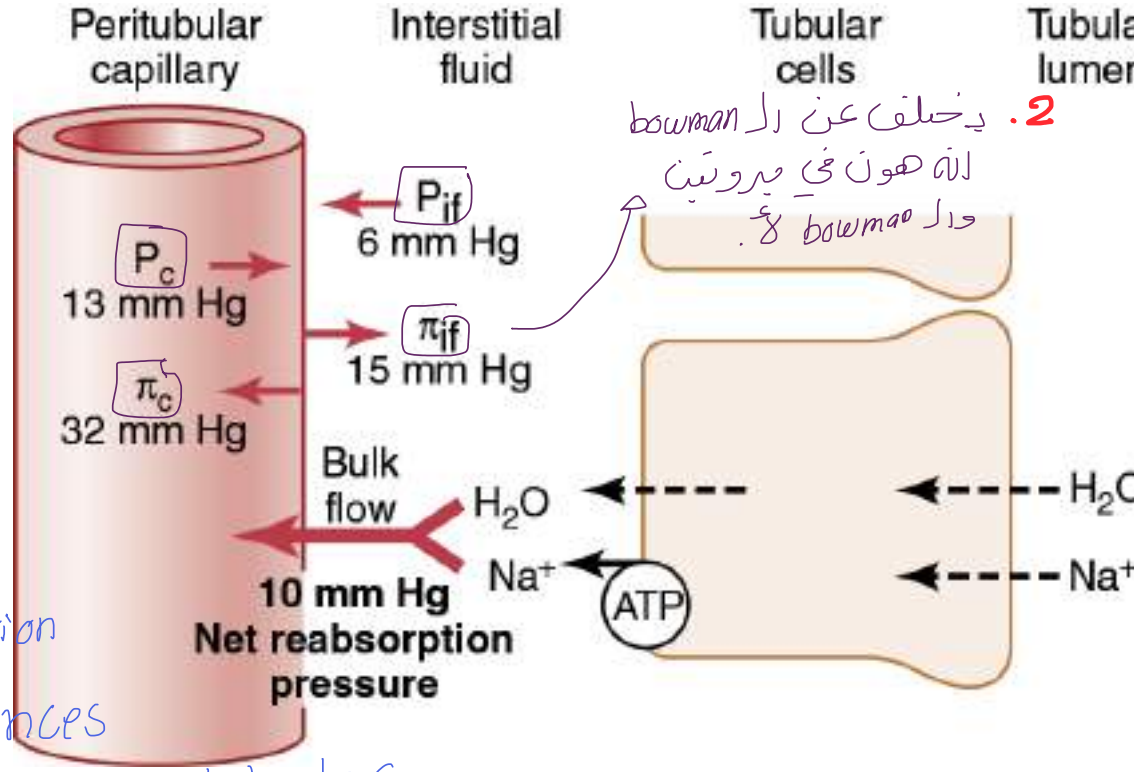
is low
a. Hydrostatic P. in capillary (Pc) **opposes** -13
b. Hydrostatic P In interstitium (Pif) **favors** 6
c. Colloid osmotic P in capillary (πc) **favors** 32
d. Colloid osmotic P in intrst. (πif) **opposes** -15

Net reab. P 10 mmHg

filtration coefficient

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

which favors the reabsorption of the substances from If into the peritubular capillary



.2 يختلف عن ال bowman
الله هون في بروتين
وال bowman لأ.

* hydrostatic P within the peritubular capillary is low ⟶ because it is opposing the reabsorption

H.P in G ← مقارنة بال

محاولة أنه يمنع ال reabsorption ← يخفض عملية ال peritubular hydrostatic P فأي شيء يزيد من ال

* on the other hand the colloid osmotic pressure ⟶ favors reabsorption

حكينا دلوقتي البروتين بتحاول تساعد/تمشي عملية ال reabsorption [in its direction]

↓

relatively high colloid osmotic pressure = 32

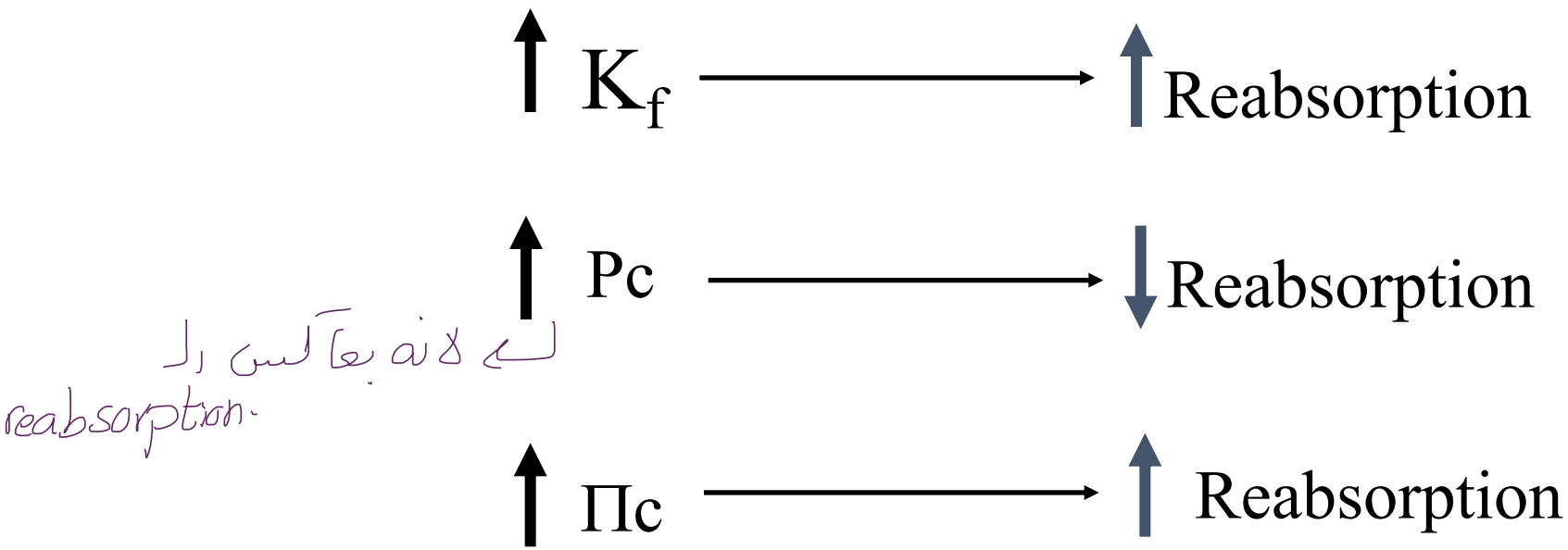
---

* in interstitium

1. the H. P within the If ⟶ is low and this favors the reabsorption
2. while colloid osmotic pressure ⟶ opposes the reabsorption = 15

Determinants of Peritubular Capillary Reabsorption

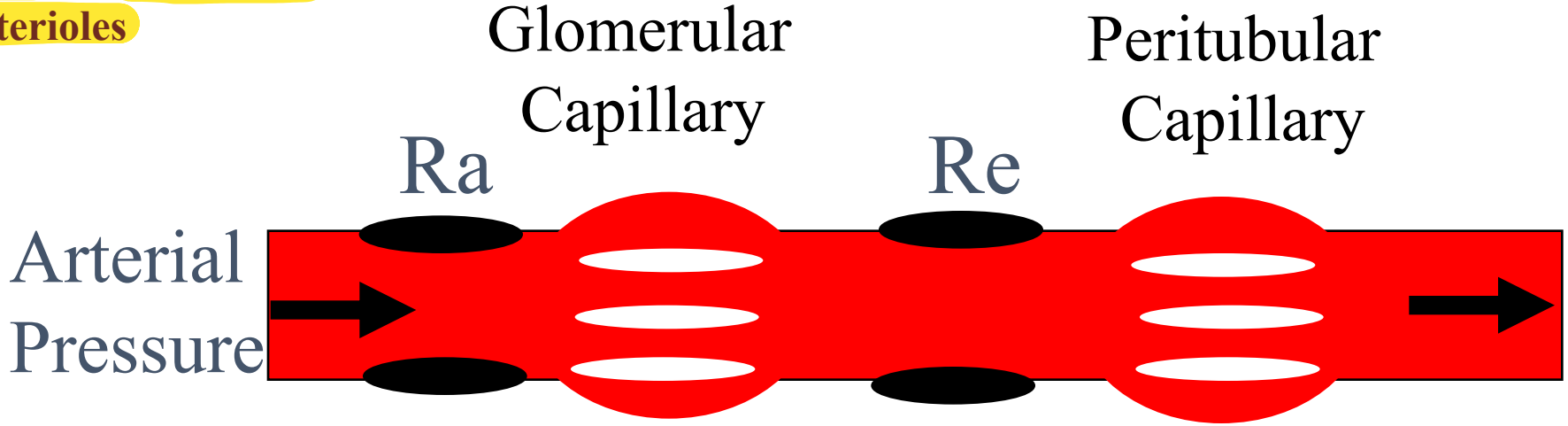
Reabsorption = Kf x Net reabsorptive P



reabsorption.

Determinants of Peritubular Capillary Hydrostatic Pressure

P_C depends on BP, and resistance of aff. & eff. Arterioles



↑ Arterial Pressure → ↑ Pc → ↓ Reabs.

↑ Ra → ↓ Pc → ↑ Reabs.

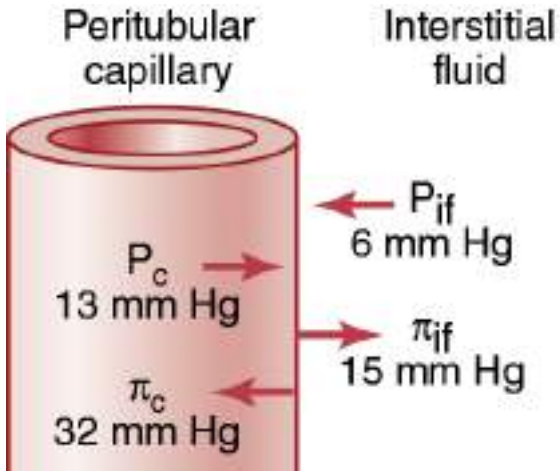
↑ Re → ↓ Pc → ↑ Reabs.

Determinants of Peritubular Capillary Colloid Osmotic Pressure

π_C depends: on [plasma protein] & filtration fraction

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

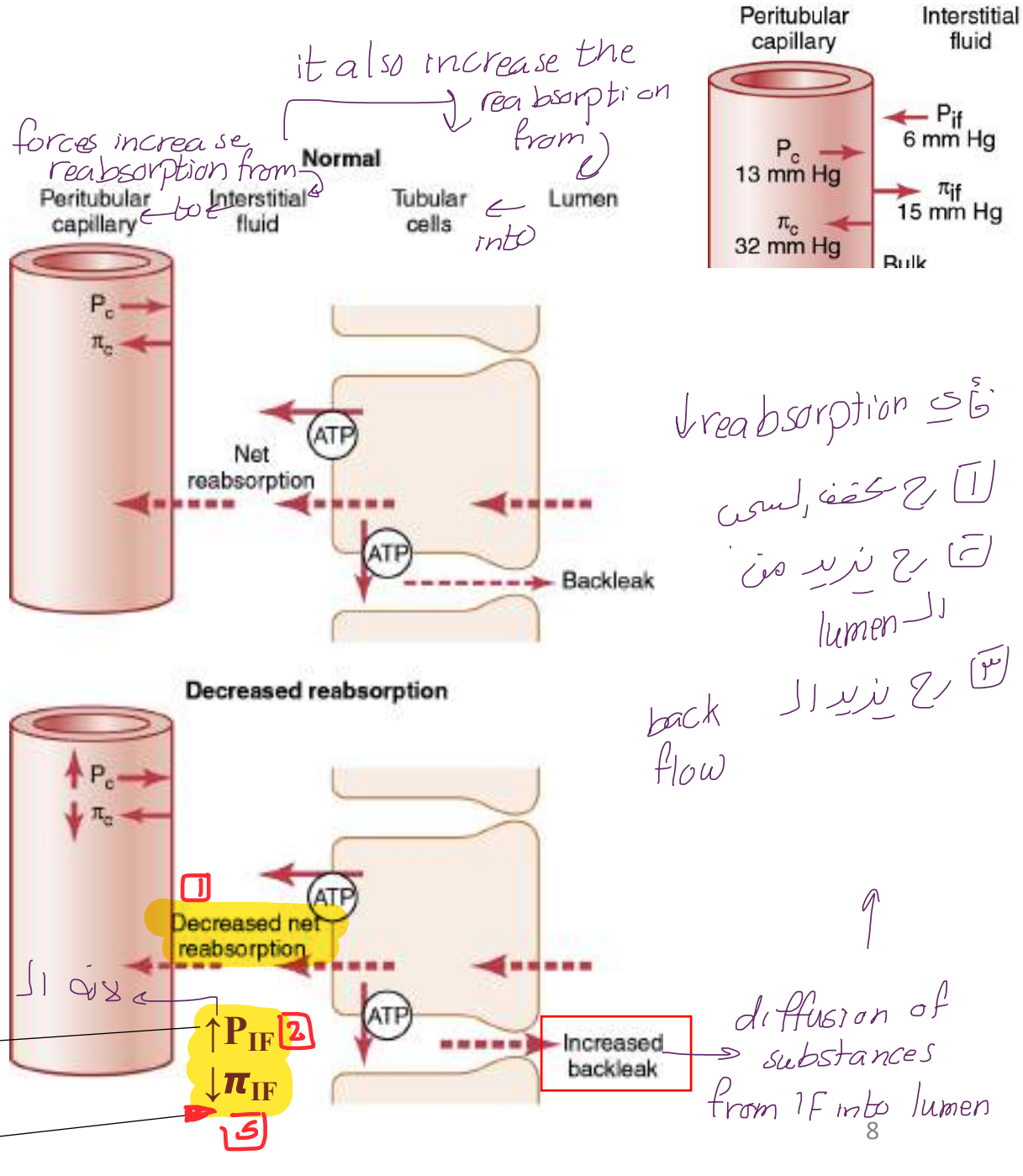
Filt. Fract. = GFR/RPF



In general, forces that increase peritubular capillary reabsorption also increase reabsorption from the renal tubules.

Conversely, hemodynamic changes that inhibit peritubular capillary reabsorption also inhibit tubular reabsorption of water and solutes

↳ such is ↑hydrostatic pressure
↓colloid osmotic pressure



Pressure diuresis and pressure natriuresis

↑ BP → kidneys excrete large amounts of H2O & Na,

Even a slight increase in blood pressure doubles the water excretion.

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

factor that contributes to the pressure natriuresis and pressure diuresis:

1-Impaired autoregulation & ↑ GFR

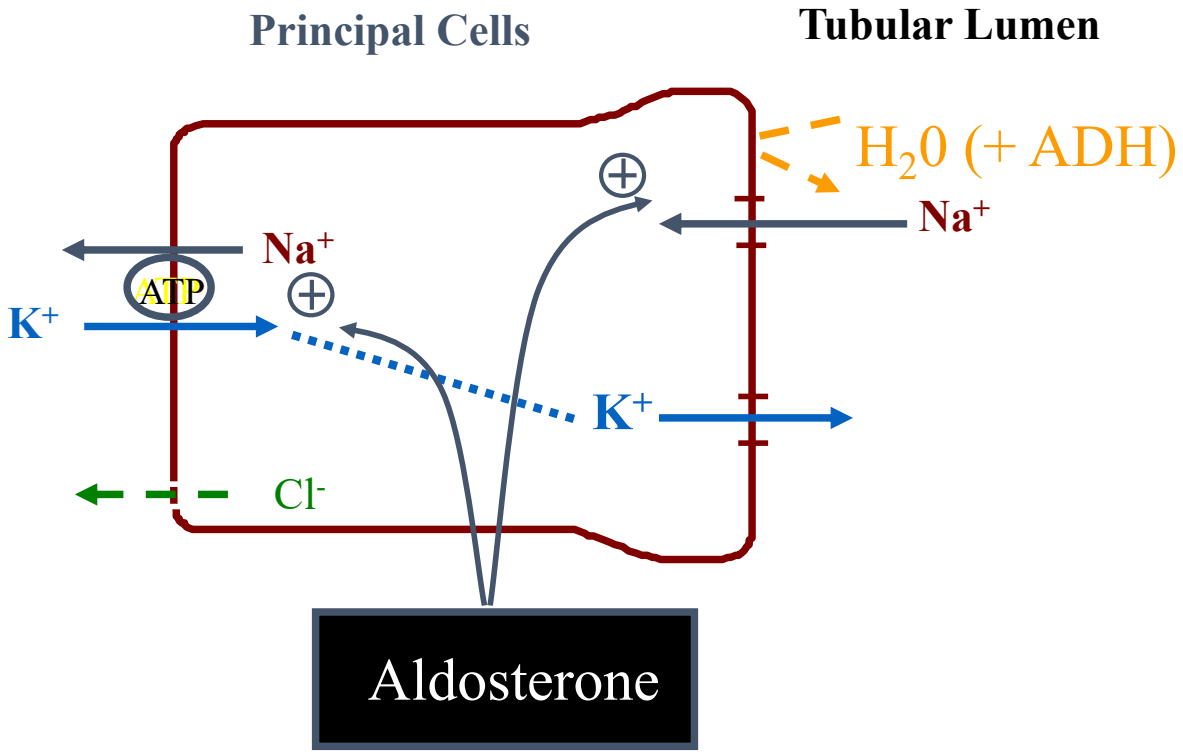
2- ↑ Pc in vasa recta→P_{if}→ prevent Na & H2O reabsorbtion+ backleak

3- ↓ Angiotensin II

Hormonal control of tubular reabsorption

Aldosterone actions on late distal, cortical and medullary collecting tubules

Aldosterone :
Secreted by adrenal cortex
Acts on the distal tubule and collecting ducts
↑Na Cl , H2O reabs.
Mainly acts on **principal calls** of cortical coll. tubule
increases K+ & H^+ secretion.



Control of Aldosterone Secretion

Factors that increase aldosterone secretion

1. • Angiotensin II
2. • Increased K^+ ← يدخل aldosteron لـ وظيفة عنده
3. • adrenocorticotrophic hormone (ACTH) صوديوم ويطلع K
   (permissive role) لأن لـ aldosteron ما رح يفرز إذا ما كان عنا ACTH

Factors that decrease aldosterone secretion

1. • Atrial natriuretic factor (ANF)
2. • Increased Na^+ concentration (osmolality)

Abnormal Aldosterone Production

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

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

Angiotensin II Increases Na^+ and Water Reabsorption

- low blood pressure and/or low ECFV

- Stimulates aldosterone secretion

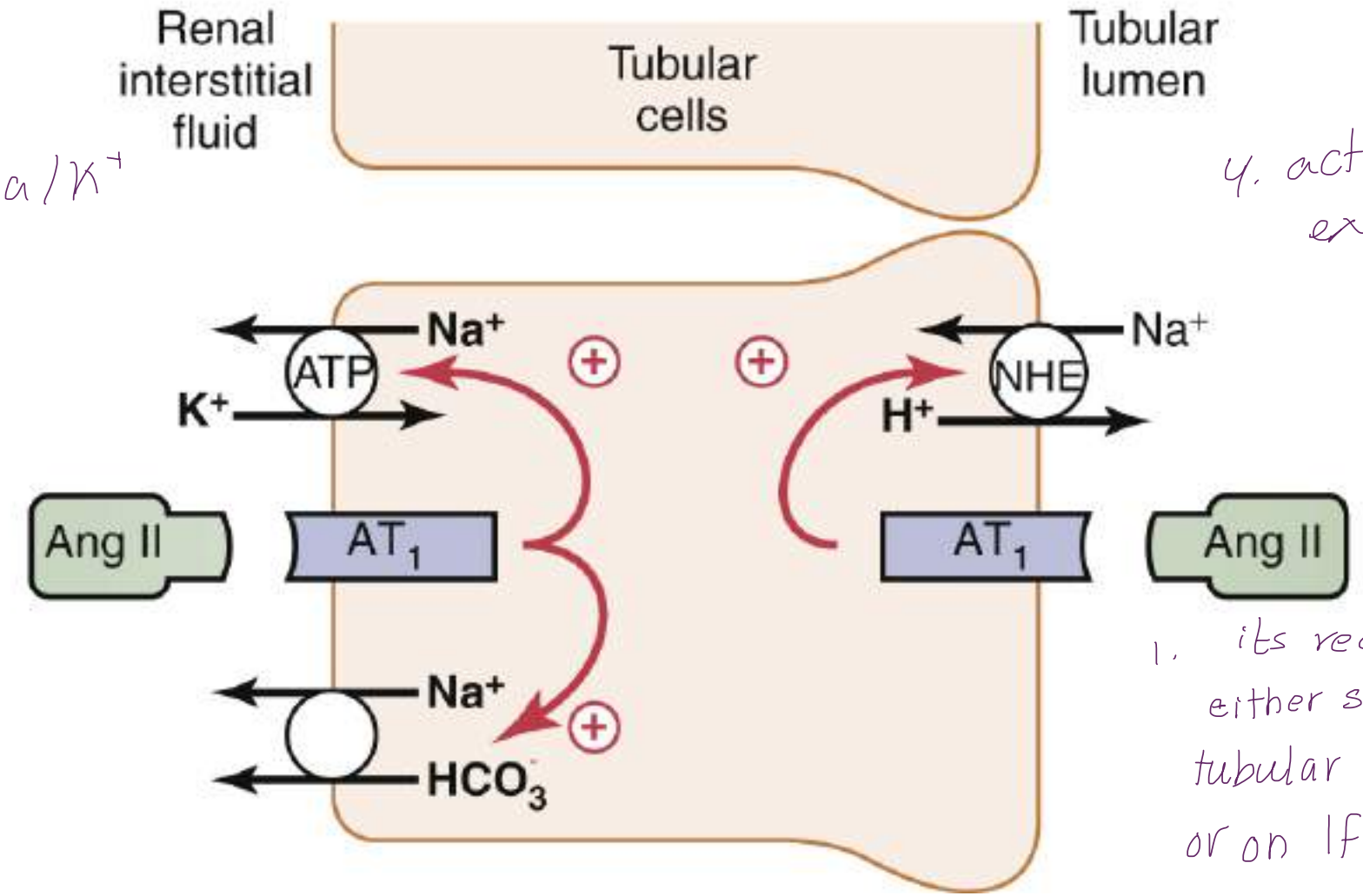
- Directly increases Na^+ reabsorption (proximal, loop, distal, collecting tubules)

act in most part of tubules

- Constricts efferent arterioles
  - **decreases** peritubular capillary **hydrostatic pressure**
  - increases **filtration fraction**, which increases peritubular colloid osmotic pressure)

↓ ↑ Na^+ reabsorption

Angiotensin II increases renal tubular sodium reabsorption



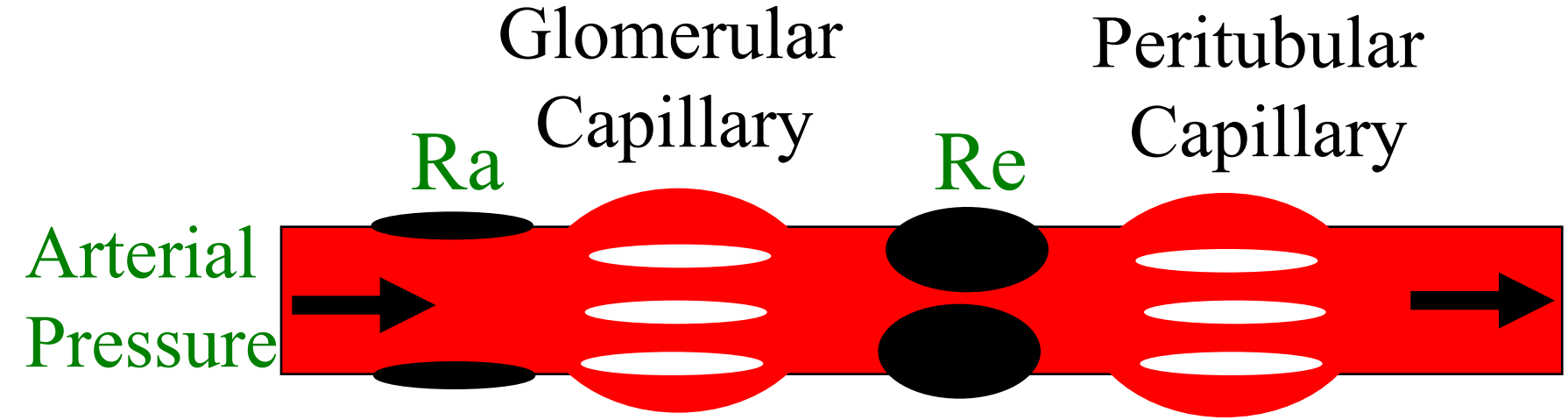
2. activate Na/K+ pump

4. activate Na-H exchanger.

3. activate Na-HCO3 co transporter

1. its receptor either sids on tubular lumer or on If part

Effect of Angiotensin II on Peritubular Capillary Dynamics

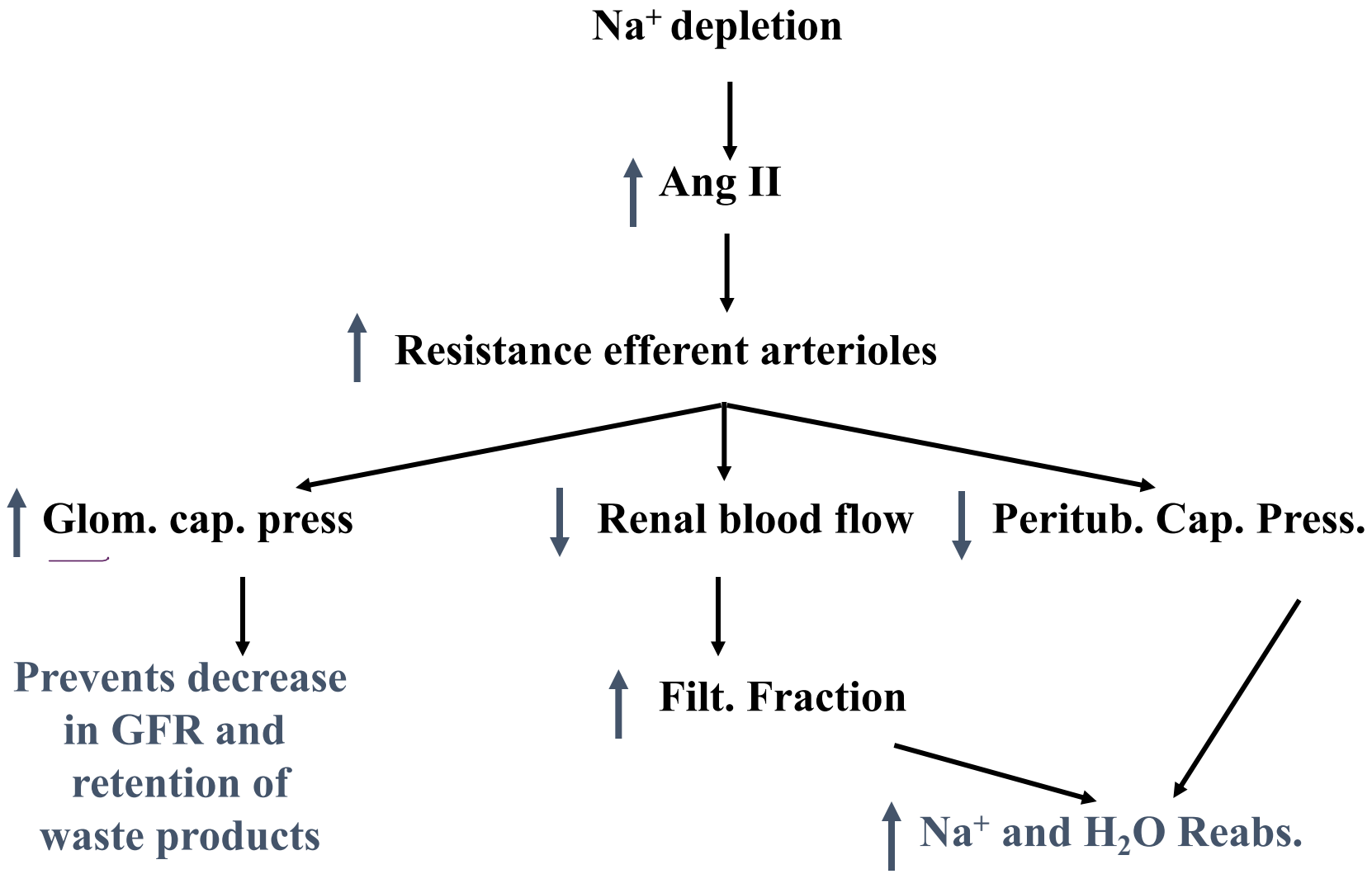


↑ Ang II → ↑ Re → ↓ Pc (peritubular cap. press.)

↓ renal blood flow → ↑ FF → ↑ Πc

→ وبالتالي بسهل عملية الـ reabsorption

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



Angiotensin II blockade decreases Na^+ reabsorption and blood pressure

ttt mainly used in hypertension

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

Natriuresis and Diuresis + ↓ Blood Pressure

Antidiuretic Hormone (ADH)

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

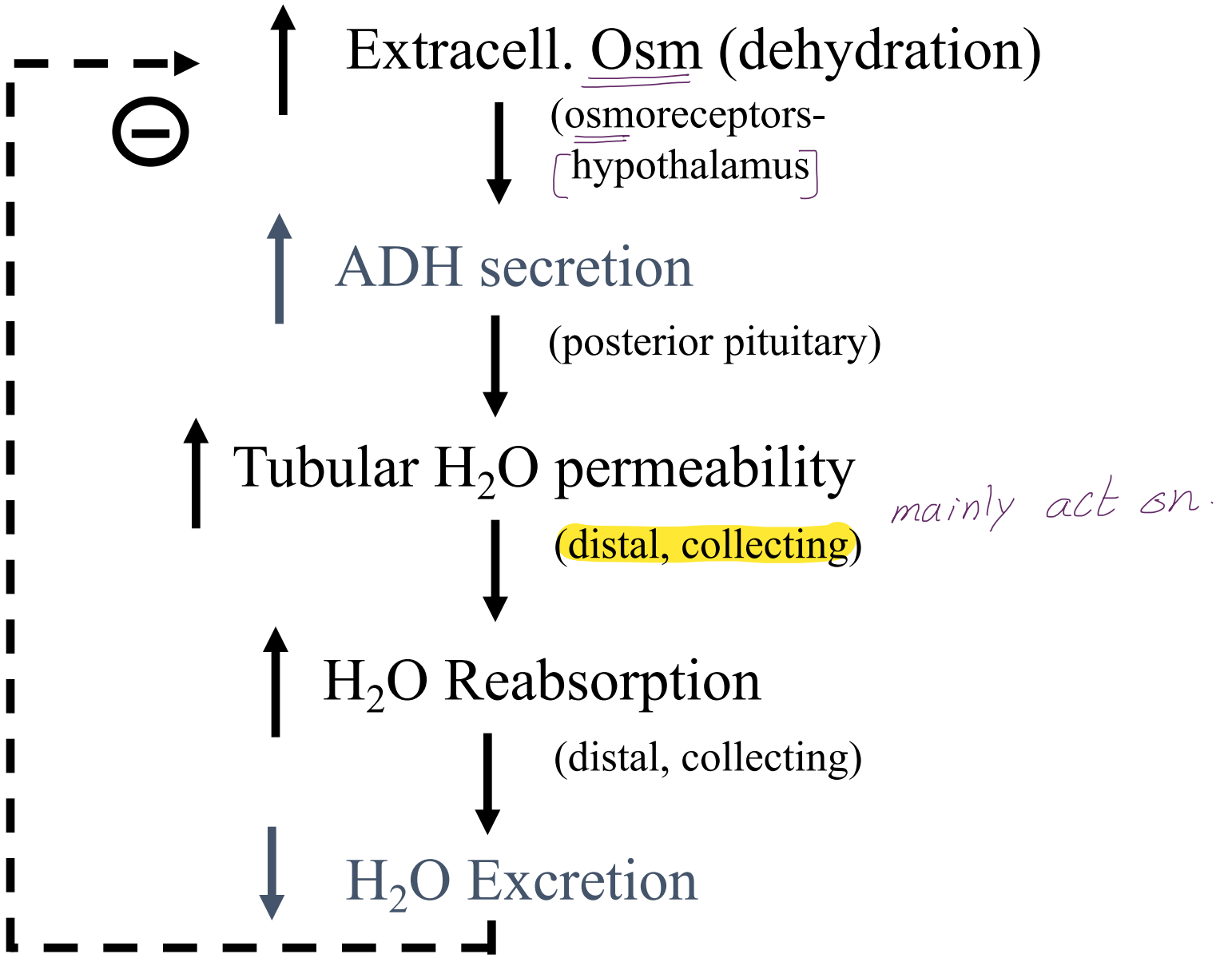
يزيد الـ H_2O لحال بدون الـ solutes reabsorption

في متى ما بدي اعمل urine لـ dilute / متى ما بدي urine لـ concentration

يقلل الـ ADH

يزيد الـ ADH

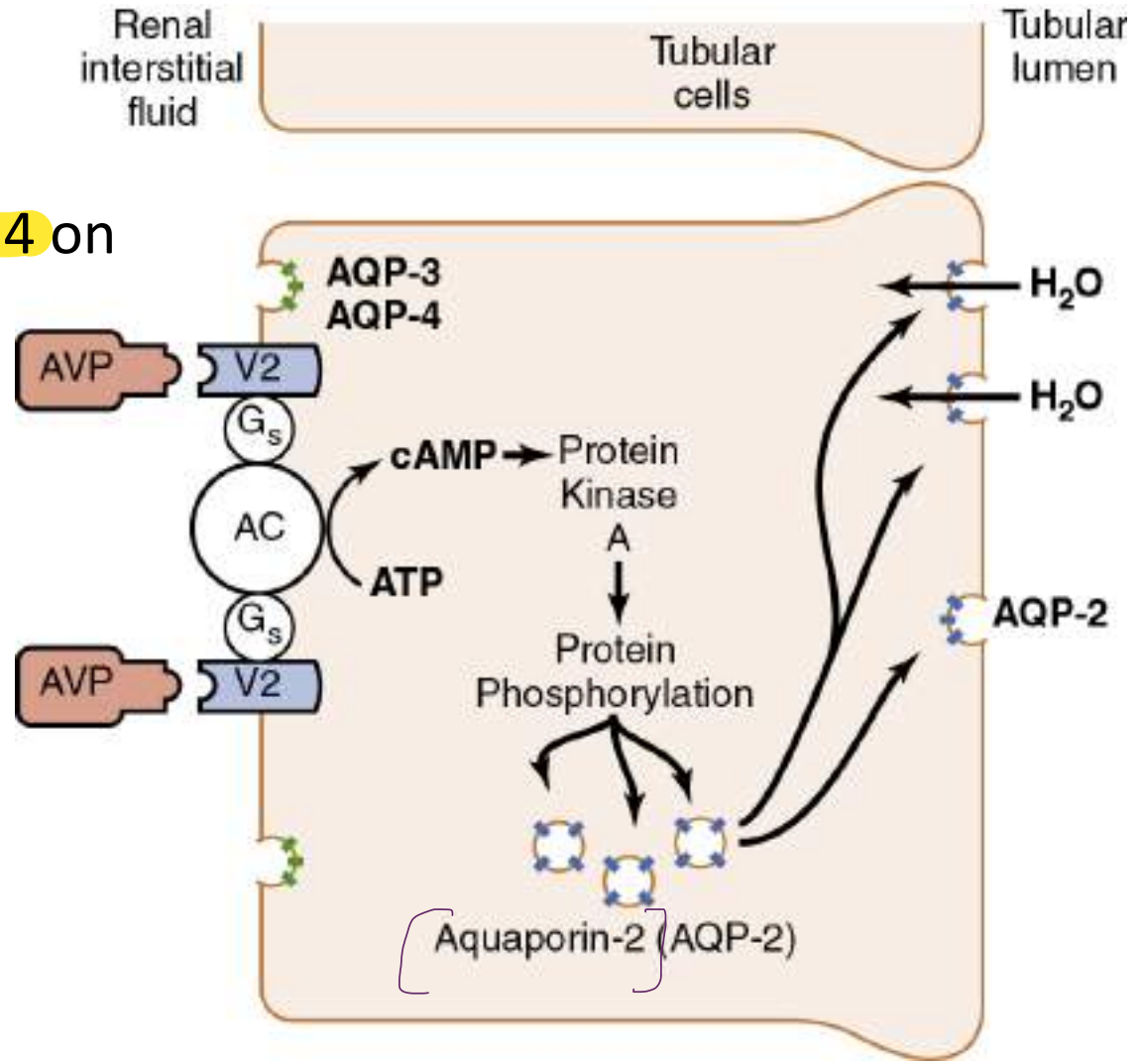
Feedback Control of Extracellular Fluid Osmolarity by ADH



Mechanism of action of ADH in distal and collecting tubules

Binds V2 receptors→form cyclic AMP
→increase aquaporin-2 on luminal, AQP3,4 on basolateral

- When ADH decreased→AQP back to cytoplasm



Abnormalities of ADH

- Inappropriate ADH syndrome (excess ADH)
  - decreased plasma osmolarity, hyponatremia
- "Central" Diabetes insipidus (insufficient ADH)
  - water loss (diluted urine), increased plasma osmolarity, hypernatremia, excess thirst

Desmopressin ttt

problem in the origin of production → posterior pituitary → defect in the production of ADH → we don't have ADH → water easily lossed → diluted urine

synthetic ADH

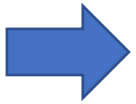
* المريض يعوض هاي المشكلة بشرب سوائل كثير

* كمان المشكلة انه عنده too much diluted urine.

Abnormalities of ADH

ADH clinically is high

- Failure of kidneys to respond to ADH: "nephrogenic" diabetes insipidus



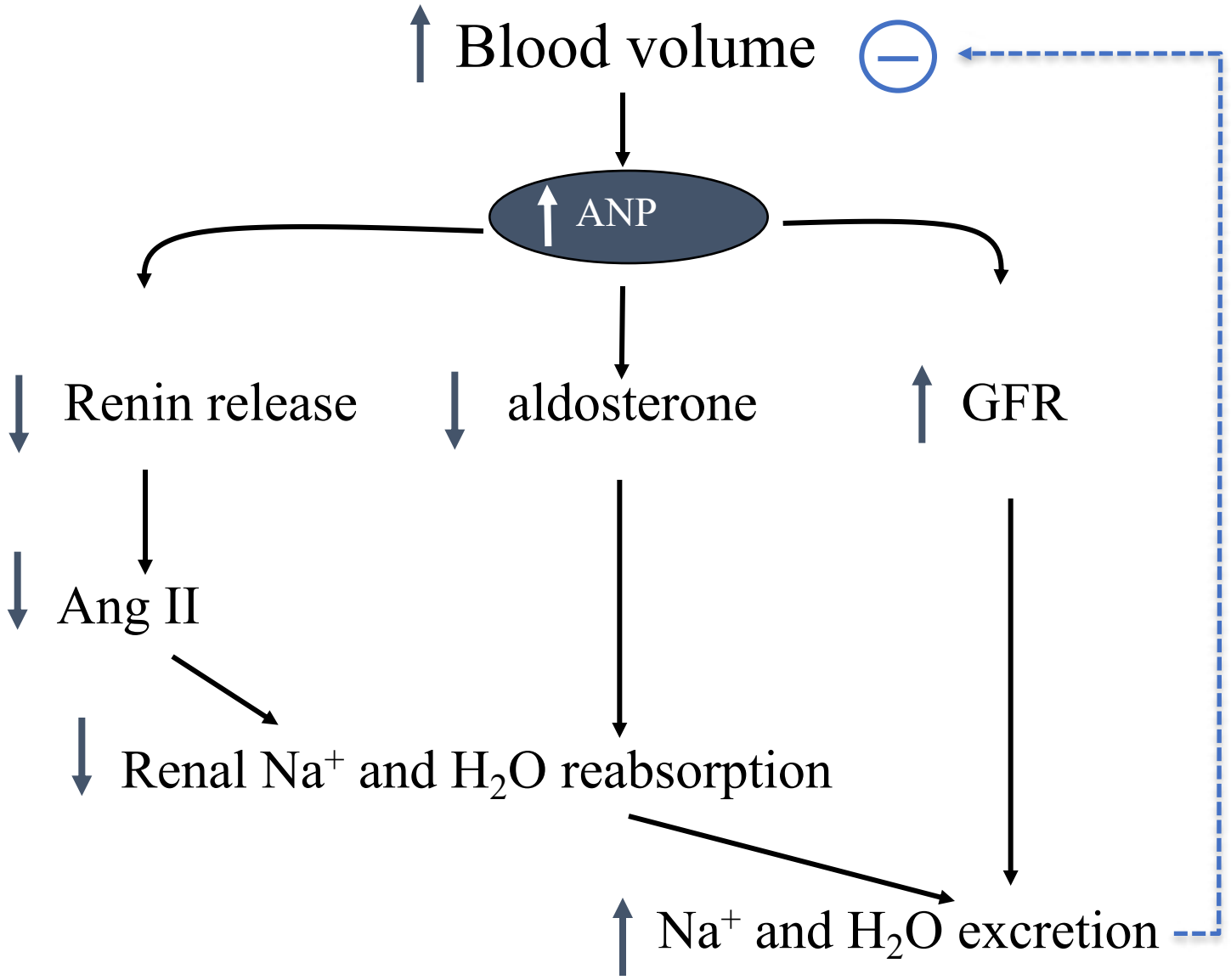
failure of countercurrent mechanism to form a hyperosmotic renal medullary interstitium/ failure of the distal and collecting tubules and collecting ducts to respond to ADH.

في ADH كلن كلية مش راضية تستجيب ... الخ

- impaired loop NaCl reabs. (loop diuretics)
- drug induced renal damage: lithium, analgesics
- malnutrition (decreased urea concentration)
- kidney disease: pyelonephritis, hydronephrosis, chronic renal failure

Atrial natriuretic peptide increases Na^+ excretion

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


Blood volume
ANP
Renin release
aldosterone
GFR
Ang II
Renal Na^+ and H_2O reabsorption
Na^+ and H_2O excretion

Parathyroid hormone increases renal Ca^{++} reabsorption

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

Table 28-3 Hormones That Regulate Tubular Reabsorption

Hormone	Site of Action	Effects
1. Aldosterone	Collecting tubule and duct	↑ NaCl, H_2O reabsorption, ↑ K^+ secretion, ↑ H^+ secretion
2. Angiotensin II	Proximal tubule, thick ascending loop of Henle/distal tubule, collecting tubule	↑ NaCl, H_2O reabsorption, ↑ H^+ secretion
3. Antidiuretic hormone	Distal tubule/collecting tubule and duct	↑ H_2O reabsorption
4. Atrial natriuretic peptide	Distal tubule/collecting tubule and duct	↓ NaCl reabsorption
5. Parathyroid hormone	Proximal tubule, thick ascending loop of Henle/distal tubule	↓ PO_4^- reabsorption, ↑ Ca^{++} reabsorption

Sympathetic nervous system increases Na^+ reabsorption

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

in hemorrhage shock

Questions?
The End

Urine Concentration and Dilution; Regulation of Extracellular Fluid Osmolarity and Sodium Concentration

Chapter 29

Unit V

Dr Iman Aolymat

Control of Extracellular Osmolarity (NaCl Concentration)

is mainly directed to the

Osmolarity is determined by amount of solute (mainly NaCl)/ ECFV

ای تغییرفیه و تأثرملی osmolarity

↓

ECF osmolarity & [NaCl] are regulated by **amount of extracellular water**

↓ regulated by

(1) fluid intake
(2) renal water excretion

regulated by ⊂

- ADH
- Thirst

] → ADH -Thirst Osmoreceptor System

Mechanism:

↑ extracellular osmolarity (NaCl) →stimulates ADH release→ ↑ H_2O reabsorption, and stimulates thirst

(intake of water)

act on renal tubules

[1] and ↑ H2O reabsorption from tubular lumen into epithelium

[2] and this result in stimulation of thirst center (stimulation the intake of water)

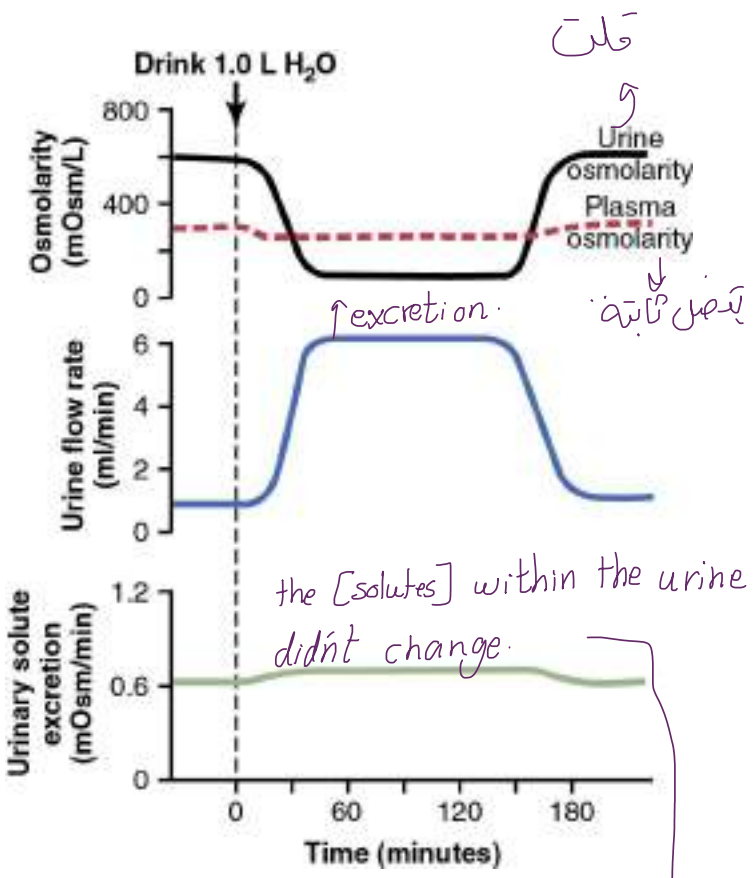
Concentration and Dilution of the Urine

- Kidneys excrete excess water by forming dilute urine

- Maximal urine concentration (H2O deficit)
  = 1200 - 1400 mOsm / L

- Minimal urine concentration (high H2O)
  = 50 - 70 mOsm / L

Water diuresis in a human after ingestion of 1 liter of water.



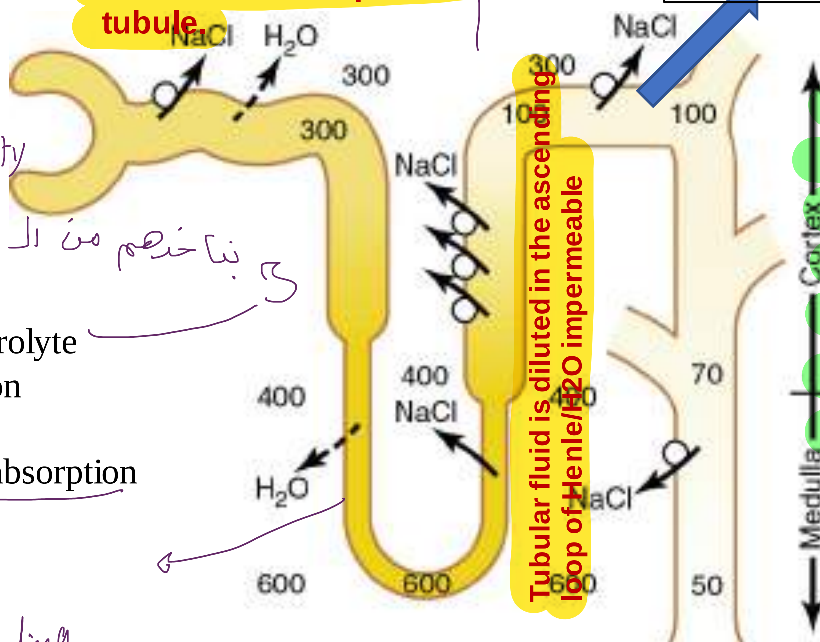
- kidneys can excrete diluted/concentrated urine without major changes in rates of excretion of solutes such as Na & K

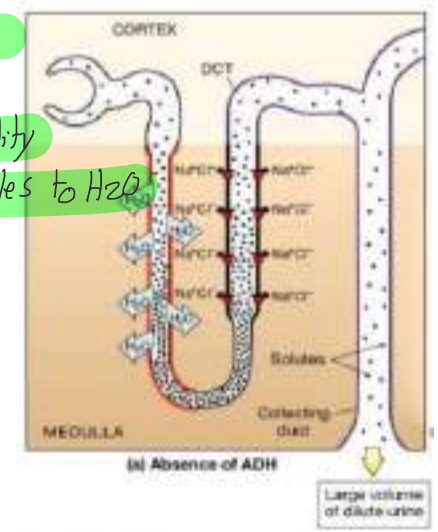
Formation of a dilute urine

late DCT, cortical collecting duct, and collecting duct, additional reabsorption of NaCl. (contribute more in dilution of urine)
In absence of ADH→ impermeable to H2O→ further dilution

Tubular fluid remains isosmotic in the proximal tubule

Tubular fluid is diluted in the ascending loop of Henle/H2O impermeable





1. • Continue electrolyte reabsorption (بناخذهم من ال lumen وبنخليهم على ال IF)

2. • Decrease water reabsorption

3. ← لأنه ال PT is permeable for both water and electrolytes فبالتالي ال [C] ما بتتغير ولذلك ما في تغيير على ال osmolarity لأنه بتفقد H2O + solutes.

4. thin descending is permeable to H2O more than electrolytes

5. in ascending there is more reabsorption of substances mainly by active transport in thick ascending part but it is not permeable to water

6. نزلك more H2O trapping within the lumen ← and this is the diluting segment

7. in late DT and collecting duct → the permeability of these tubules to H2O depend on the work of ADH

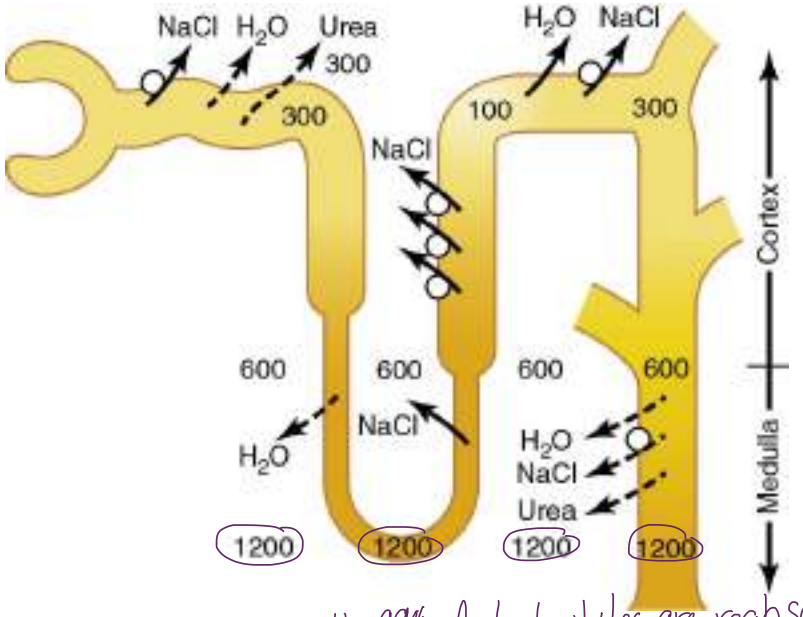
8. **The renal medullary interstitium surrounding the collecting ducts is normally hyperosmotic** → the osmolarity is very very high

Mechanism:

↓ADH release and ↓ H2O permeability in distal and collecting tubules

1. → too much solutes, too much electrolytes, too much salts, and less water

Formation of a Concentrated Urine when

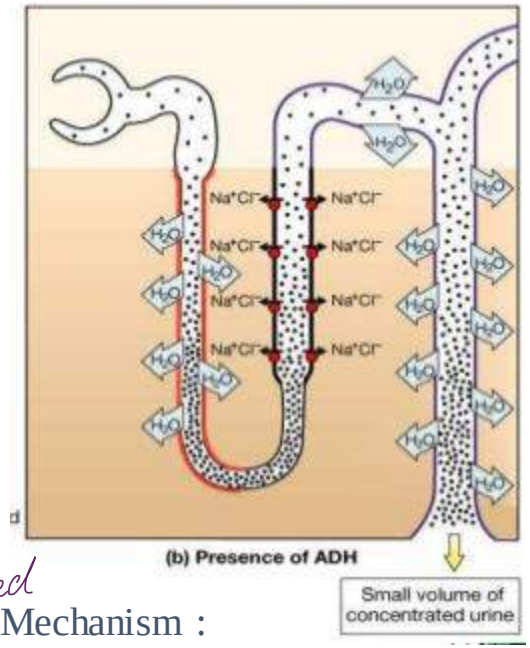


→ more the 99% of electrolytes are reabsorbed

2. • Continue electrolyte reabsorption

3. • Increase water reabsorption

↳ mainly by the work of ADH on the distal part of convulated tubule and collecting duct



Mechanism :

- Increased ADH release which increases water permeability in distal and collecting tubules → ↑water reabsorption so less water within the collecting duct ↓ so concentrated urine
- (2) • High osmolarity of renal medulla
- (3) • Countercurrent flow of tubular fluid

* الجسم بتخلص من الـ waste product عن طريق الـ urine
* في عنا كمية من الـ solutes اللي المفروض انتخلص منها لكن ما بتقدر تفرزها الكلية as dry
as a salt ← NaCl الـ بيضل ما بتقدر تطلع

Obligatory Urine Volume

minimum volume of water required to excrete the unwanted salts by dissolved these salts in water

* ففي عنا volume of water excreted لازم يكون موجود within tubules to disolve these unrequired substances

The minimum urine volume in which the excreted solute can be dissolved and excreted each day to maintain electrolyte balance, the obligatory urine volume is:

very concentrated urine

Example:

If the max. urine osmolarity is 1200 mOsm/L, and 600 mOsm of solute must be excreted

$$\frac{600\ \text{mOsm/d}}{1200\ \text{mOsm/L}} = 0.5\ \text{L/day}$$

هاد الكمية من الـ water بيتا إياها عشان تذوبي الـ salts

the average

obligatory urine volume $= \frac{\text{the amount of salts need to be excreted}}{\text{maximum urine osmolarity}} = \frac{600}{1200} = 0.5\ \text{L/day}$

3. poroportional relation ship between urin gravity and urine osmolarity (linear proportional)

1. تعطينا انطباع عن قديش فيه substances في ال urine
2. يعني كل ما زاد ال [salts] تزيد عنا ال gravity

Relationship between urine osmolarity and specific gravity

Estimation of [urine solute]
↑[urine solute]→ ↑Gravity

urine specific gravity increases linearly with increasing urine **osmolarity**

Urine specific gravity is a measure of **weight of solutes** in a given **volume** of urine (ranges from 1.002-1.028 g/ml)

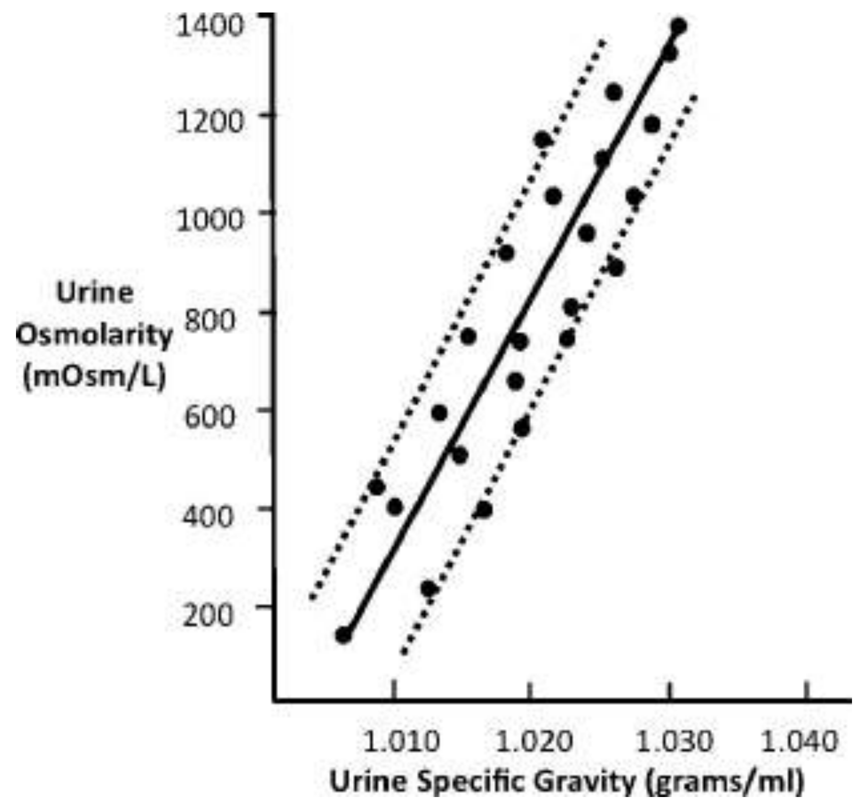
↓

Determined by **number** and **size** of solute

Osmolarity is determined by the **number of solute molecules** in a given volume. in the ECFV mainly

Relationship between specific gravity & osmolarity is altered when there are significant amounts of glucose, radiocontrast media & antibiotics. ← within the ECF

ع تتأثر هاي العلاقة



Hyperosmotic renal medulla is mediated by the special anatomical arrangement of the loops of Henle & the vasa recta.

شكل ال vasa recta وال loop of henle ← ال U-shape الانثنين

Factors That Contribute to Buildup of Solute in Renal Medulla - Countercurrent Multiplier

* this part is not permeable to H_2O

- Active transport of Na^+, Cl^-, K^+ and other ions from thick ascending loop of Henle into medullary interstitium
- Active transport of ions from medullary collecting ducts into interstitium
  ↳ does not need of energy
- Passive diffusion of urea from medullary collecting ducts into interstitium
  ↳ permeability to urea depends on ADH
- Diffusion of only small amounts of water into medullary interstitium

diffusion of urea ↑ permeability to urea.

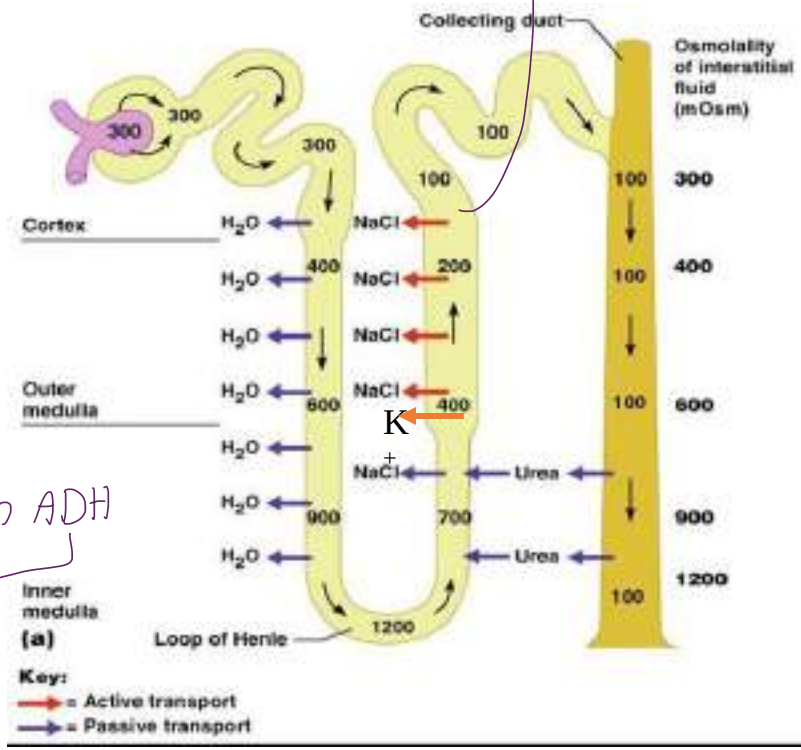
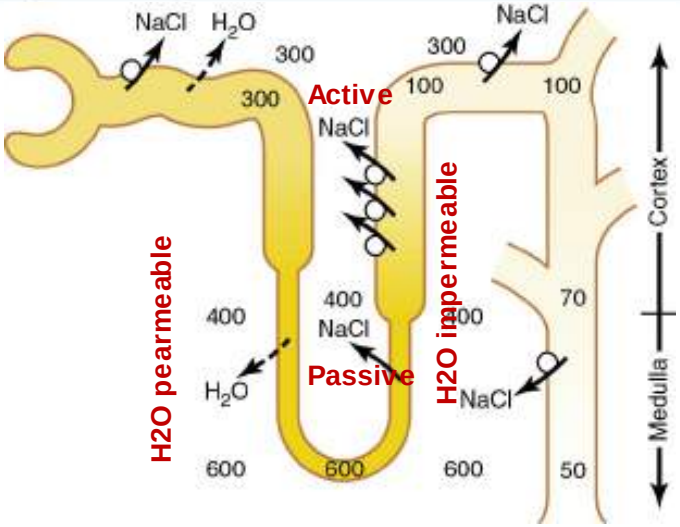


Table 29-1 Summary of Tubule Characteristics—Urine Concentration

		Permeability		
	Active NaCl Transport	H_2O	NaCl	Urea
Proximal tubule	++	++	+	+
Thin descending limb	0	++	+	+
Thin ascending limb	0	0	+	+
Thick ascending limb	++	0	0	0
Distal tubule	+	+ADH	0	0
Cortical collecting tubule	+	+ADH	0	0
Inner medullary collecting duct	+	+ADH	0	+ADH



4. الآن ال filtrate يدخل مكمل يجي من ال PCT إلى ال loop وبعدين يطلع لل distal

وهلأ اللي نازل من ال PT للـ descending part ← هاد permeable to water

فيما انه في عندي high asmolarity في in IF ← بيلاحظ ال H2O يطلع من ال tubule على ال lumen بالتالي ح يصير

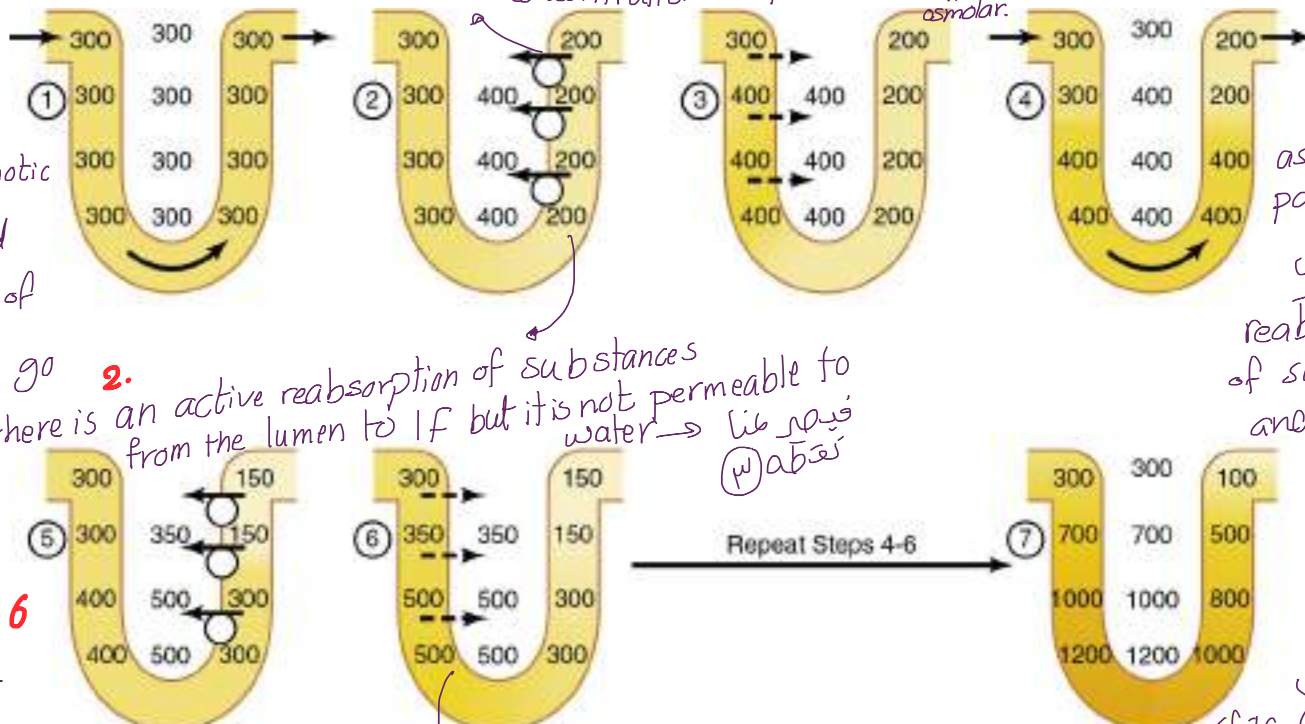
في concentration of substance inside the descending part

Countercurrent multiplier system in the loop of Henle.

5. وهاي ال concentrated substances ترجع ثاني تكمل في ال loop of henle وتوصل لل ascending part ونصير نعيد ال شي يصير عنا reabsorption of substances and solutes but it is not permeable to water so → dilution of substances وتكمل وتطلع لل distal tubule

1. مجرد ما اجا ال G filtrate يدخل على ال PCT in this part the filtrate is isoosmotic this substance descend down to the loop of Henle → and then go to ascending

3. - dilution inside the lumen
- concentration in IF → وهذا يحدث فرق تقريباً 200 ml osmolar.



2. there is an active reabsorption of substances from the lumen to IF but it is not permeable to water → فيصير عنا نقطة (٣)

6. حكينا ح يصير عنا secretion of these solutes

so more concentration to medulla ولفرق 200 mL osmolar بين ال lumen و ال IF

* no water permeability

7. ولو اللي تكون نازلة يدخل لها ضمن ال IF يصير عنا more concent of substances inside thin descending part of loop of Henle

وبالتالي انا حمل more concentrat substances to distal tubule ونعيد الكلة

multiplier وهاي العملية بتكرر لذلك تسمى

medullary interstitium حتى تستطيع انها تعمل osmolarity

1200 m1/osmolar.

are reabsorption of salts in distal part + diffusion of water in proximal part of loop of Henle

reabsorption في DT 8.

Net Effects of Countercurrent Multiplier

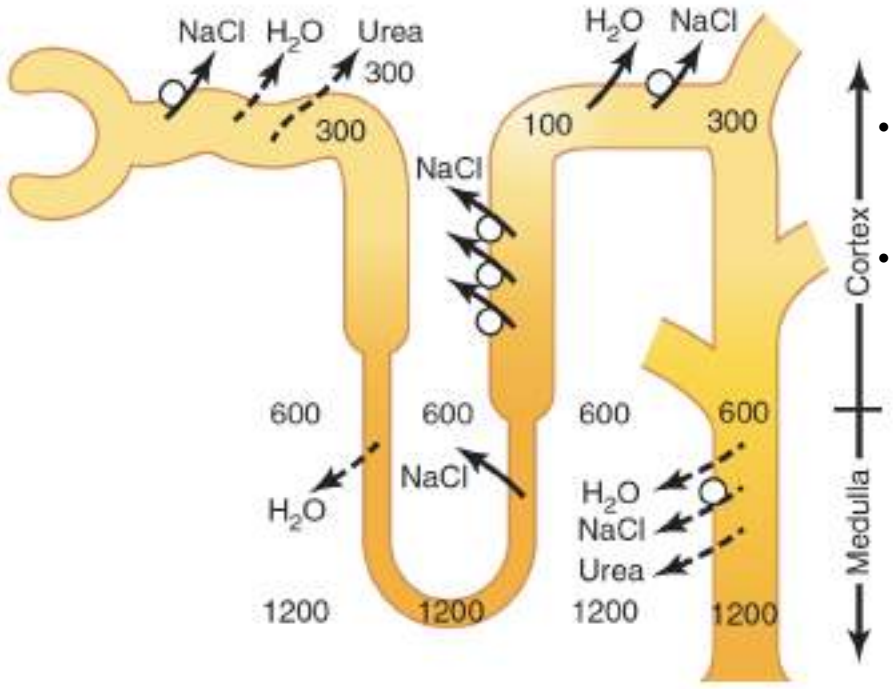
1. More solute than water is added to the renal medulla.
   i.e solutes are "trapped" in the renal medulla
2. Fluid in the ascending loop is diluted
3. Most of the water reabsorption occurs in the cortex (i.e. in the proximal tubule and in the distal convoluted tubule) rather than in the medulla

حتى ما يصير عنا dilution in medulla

4. Horizontal gradient of solute concentration established by the active pumping of NaCl is "multiplied" by countercurrent flow of fluid.

لـ حتى يصير عنا hyperosmolarity in medullary interstitial.

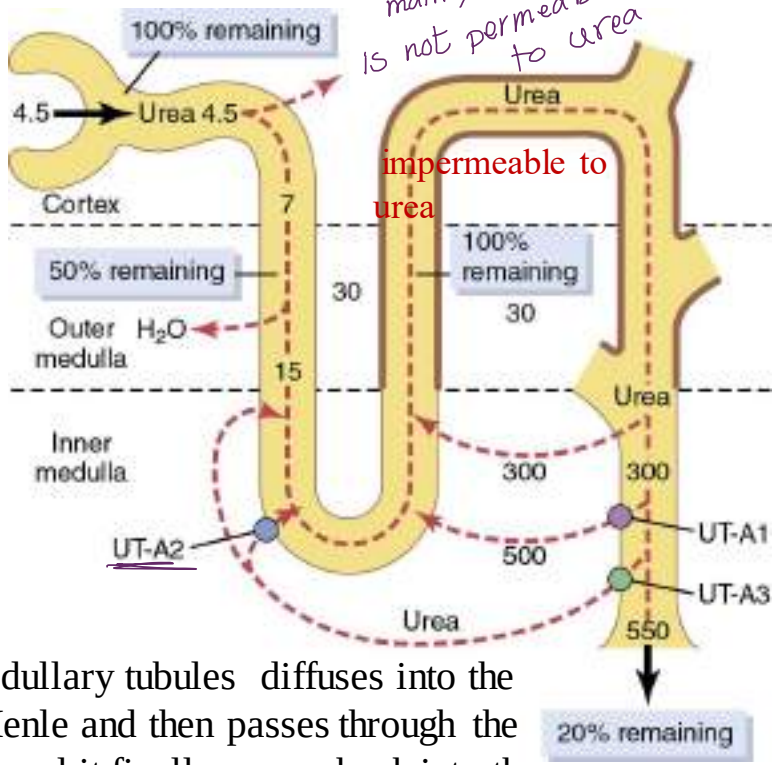
Hyperosmotic renal medulla



- large amounts of water are reabsorbed into the cortex (ADH action), rather than into the renal medulla, helps to preserve the
- Diffusion of only small amounts of water into medullary interstitium→ high medullary interstitial fluid osmolarity
- The reabsorbed water absorbed to medullary interstitium is carried away by the vasa recta into the venous blood.

Urea Recirculation

- Urea is passively reabsorbed in proximal tubule (~ 50% of filtered load is reabsorbed)
- In the presence of ADH, water is reabsorbed in distal and collecting tubules, concentrating urea in these parts of the nephron
- The inner medullary collecting tubule is highly permeable to urea, which diffuses into the medullary interstitium
- ADH increases urea permeability of medullary collecting tubule by activating urea transporters (UT-A)



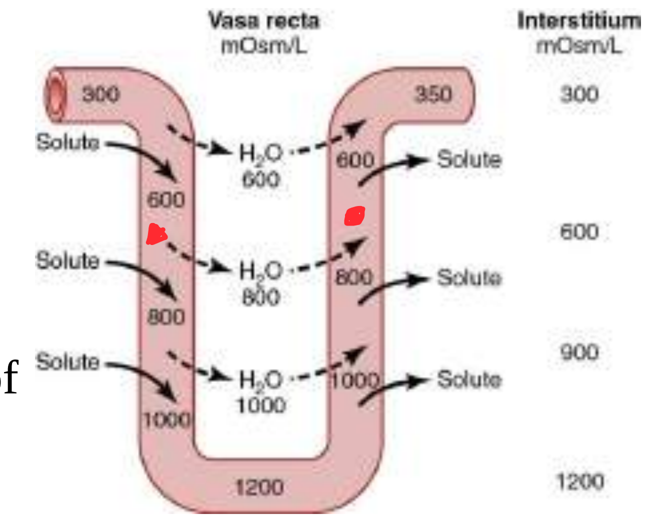
Urea from medullary tubules diffuses into the thin loop of Henle and then passes through the distal tubules, and it finally passes back into the collecting duct.

* حكينا انه بشكل ال vasa of recta وال loop of henle ← بسا عدوا على ال hyperosmolarity

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: Plasma flowing down the descending limb of the vasa recta becomes more hyperosmotic because of diffusion of water out of the blood and diffusion of solutes from the renal interstitial fluid into the blood.
In the ascending limb of the vasa recta, solutes diffuse back into the interstitial fluid and water diffuses back into the vasa recta.
Large amounts of solutes would be lost from the renal medulla without the U shape of the vasa recta capillaries.



* لما يجي ال blood flow في ال descending part of this limb يصير عنا تركيز ال substances inside ليه؟! لأنه بصير عندي reabsorption of solutes toward the lumen and at the same time we loss water from the lumen of capillary so → concentrated of substances in this part

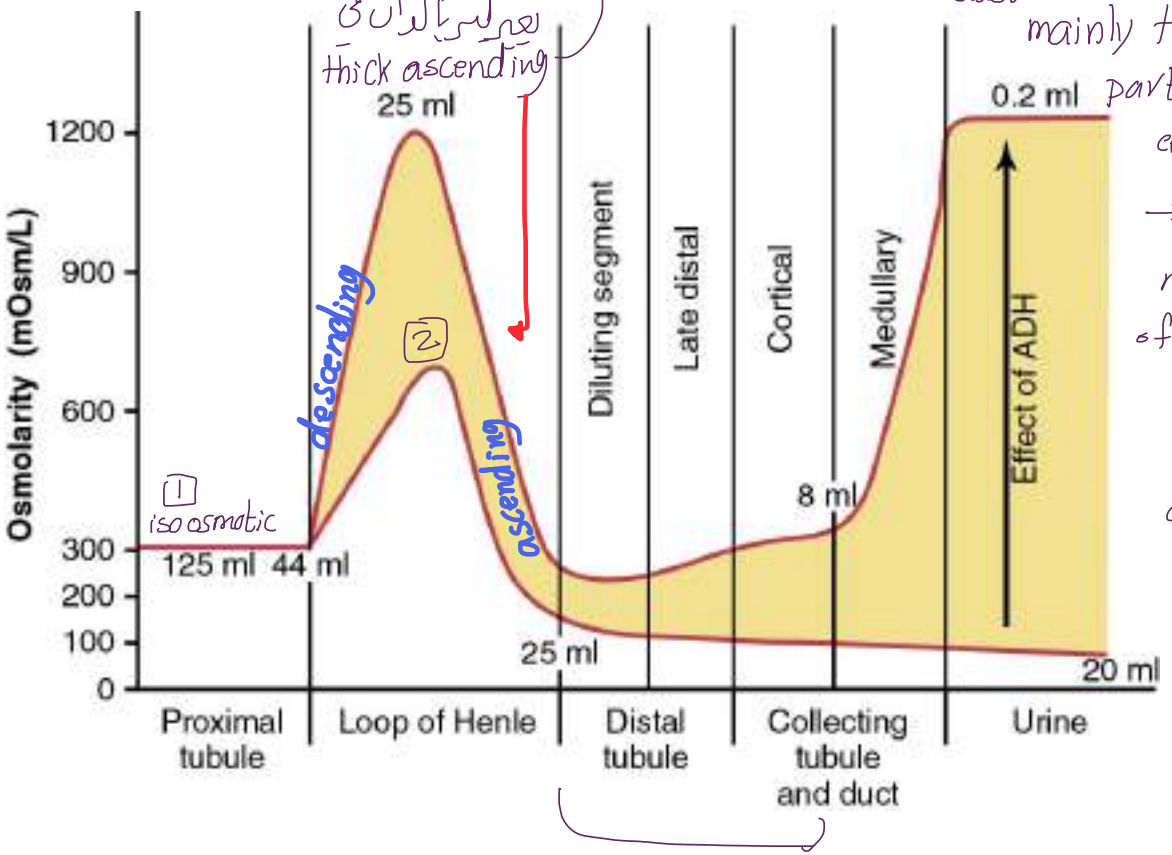
لما ينطلع في الجزء الأخر اللي هو ال ascending limb يصير عنا العكس ال solutes بتطلع برا ال interstitium لأنه ما بدي افقدها بدي اياها تظل في ال medullary interstitium و بدخل H_2O لحتى تصير dilution inside the vasa recta

Summary of water reabsorption and osmolarity in different parts of the tubule

Tubular part	H2O Reabsorption (%)	Osmolarity
Proximal Tubule	65 (water channel aquaporin 1 (AQP-1))	isosmotic
Desc. loop	15	increases
Asc. loop	0	decreases
Early distal	0	decreases
Late distal and coll. tubules	ADH dependent	ADH dependent
Medullary coll. ducts	ADH dependent	ADH dependent

Changes in osmolarity of the tubular fluid

1 both permeable to water and solutes



collecting duct لما بالنهاية ترجع للـ mainly the medullary part under the effect of ADH

→ يصير عنا more concentration of the urine

وبالتالي يزيد الـ osmolarity

Control of Extracellular Osmolarity (NaCl Concentration)

always regulated within tight range

[Plasma sodium] is normally regulated within close limits 140 - 145 mEq/L, Avg 142 mEq/L.
Osmolarity averages about 300 mOsm/L

plasma flow

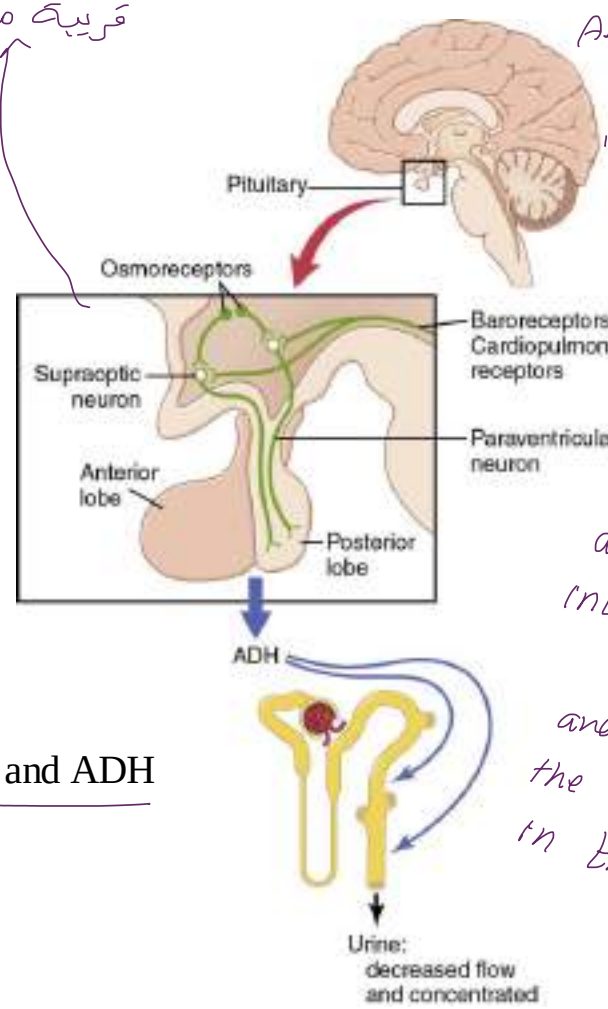
Plasma sodium concentration is used to estimate plasma osmolarity (most abundant ion)

$$P_{osm} = 2 \times [P_{Na^+}, mmol/L] + [P_{glucose}, mmol/L] + [P_{urea}, mmol/L]$$

Control of Extracellular Osmolarity (NaCl Concentration)

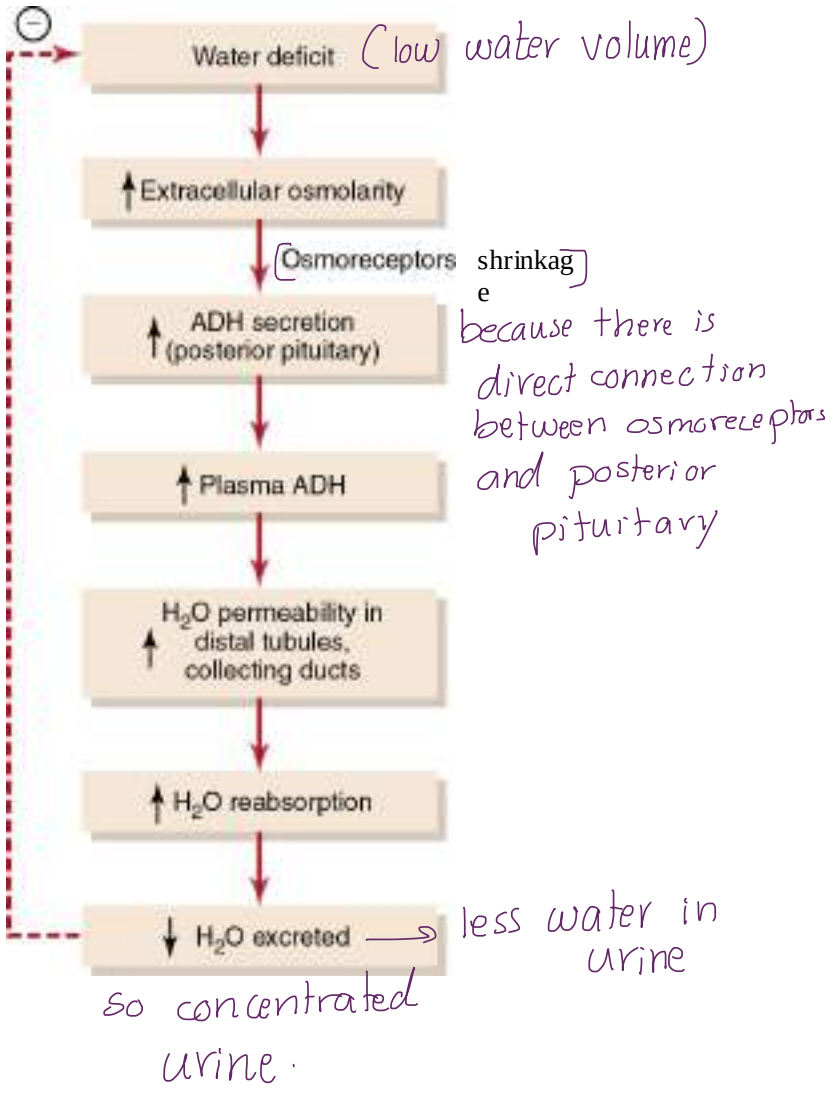
ADH -Thirst Osmoreceptor System

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



AV3V region also controls osmolarity and ADH secretion

Osmoreceptor–antidiuretic hormone (ADH) feedback mechanism for regulating extracellular fluid osmolarity.



ADH control of extracellular fluid sodium concentration and osmolarity

↓extracellular fluid osmolarity

↓

↓ ADH is formed

↓

↓ renal tubules permeability for water

↓

↓ water reabsorption

↓

↑volume of diluted urine

↓

concentrates body fluids and returns plasma osmolarity toward normal

Stimuli for ADH Secretion

- Increased osmolarity
- Decreased blood volume (cardiopulmonary reflexes)
- Decreased blood pressure (arterial baroreceptors)
- Other stimuli :
  - input from cerebral cortex (e.g. fear)
  - angiotensin II
  - nausea
  - nicotine
  - morphine

Factors That Decrease ADH Secretion

- Decreased osmolarity
- Increased blood volume (cardiopulmonary reflexes)
- Increased blood pressure (arterial baroreceptors)
- Other factors :
  - alcohol
  - clonidine (antihypertensive drug)
  - haloperidol (antipsychotic)

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

مثلاً - تغير الـ plasma osmolarity by 1% ← يحفز الـ ADH أكثر

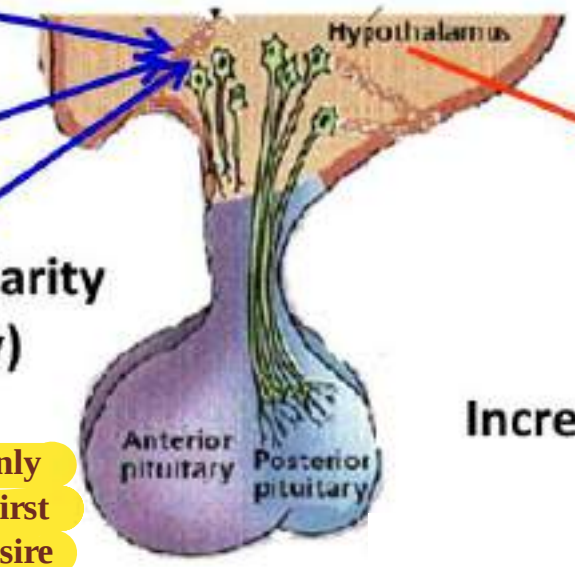
وتغير في الـ plasma volume by 1%

Thirst in controlling extracellular fluid osmolarity and sodium concentration

stimulate thirst center ↓ ↑intake of water.

1. * ↓ blood volume (Hypovolaemia)
2. * Angiotensin II
3. * ↑ plasma osmolarity (Hypertonicity)

Thirst Center → in hypothalamus



Thirst sensation

Increased water intake

dilute ECF & ↓ osmolarity

When Na concentration increases only about 2 mEq/L above normal, the thirst mechanism is activated, causing a desire to drink water. This is called the threshold for drinking.

Stimuli for Thirst

1. • Increased osmolarity
2. • Decreased blood volume
   (cardiopulmonary reflexes)
3. • Decreased blood pressure
   (arterial baroreceptors)
4. • Increased angiotensin II
5. • Other stimuli:
   - dryness of mouth & and mucous membranes of the esophagus

Factors That Decrease Thirst

1. • Decreased osmolarity
2. • Increased blood volume
   (cardiopulmonary reflexes)
3. • Increased blood pressure
   (arterial baroreceptors)
4. • Decreased angiotensin II
5. • Other stimuli:
   -Gastric distention

The end

Renal Clearence

Unit V

Chapter 28

Dr Iman Aolymat

Clearance

- "Clearance" describes the rate at which substances are removed (cleared) from the plasma.

- Renal clearance of a substance is the volume of plasma <u>completely</u> cleared of a substance per min by the kidneys.

volume of plasma تنظف كلياً في الدقيقة عن طريق الكلية

Clearance Technique

for one substance

= urine excretion rate.

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

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

Where : Cs = clearance of substance S

Ps = plasma conc. of substance S

Us = urine conc. of substance S

V = urine flow rate

Osmolar Clearance

total clearance of solutes

osmolar clearance (C_{osm})= total clearance of solutes from the **blood**
= Volume of plasma cleared of solutes each minute

$$C_{osm} = \frac{U_{osm} \times V}{P_{osm}}$$

where:

Uosm = urine osmolarity

V = urine flow rate

P = plasma osmolarity

example

If plasma osmolarity is 300 mOsm/L, urine osmolarity is 600 mOsm/L, and urine flow rate is 1 ml/min. Calculate the volume of plasma cleared of solutes each minute?

plasma osmolarity = 300 mOsm / L

urine osmolarity = 600 mOsm /L

urine flow rate = 1 ml/min

$$C_{osm} = \frac{U_{osm} \times V}{P_{osm}}$$

$$C_{osm} = \frac{600 \times 1/1000}{300}$$

$$= 0.002 \text{ L/min}$$

= 2 ml of plasma are being cleared of solute each minute

L → ml → L

$1 ml = \frac{1}{1000} L$

or calculate the osmolar Clearance (the same).

"Free" Water Clearance (C_{H_2O})

Free-water clearance (C_{H2O}) =rate of solute-free water excretion
is calculated as the difference between water excretion (urine flow rate) and osmolar clearance

$$C_{H_2O} = V - C_{osm} = V - \frac{(U_{osm} \times \dot{V})}{P_{osm}}$$

If: Uosm < Posm, C_{H2O} = + indicating water is being removed and excreted by the kidneys

If: Uosm > Posm, C_{H2O} = - indicating water conservation

الماء يحتفظ فيه جسمنا ما يطرحه

Question

Given the following data, calculate "free water" clearance :

urine flow rate = 6.0 ml/min

urine osmolarity = 150 mOsm /L

plasma osmolarity = 300 mOsm / L

→ Is free water clearance in this example positive or negative ?

$$CH_2O = V - \frac{Uosm \times V}{Posm} = 6.0 - \frac{(150 \times 6)}{300}$$

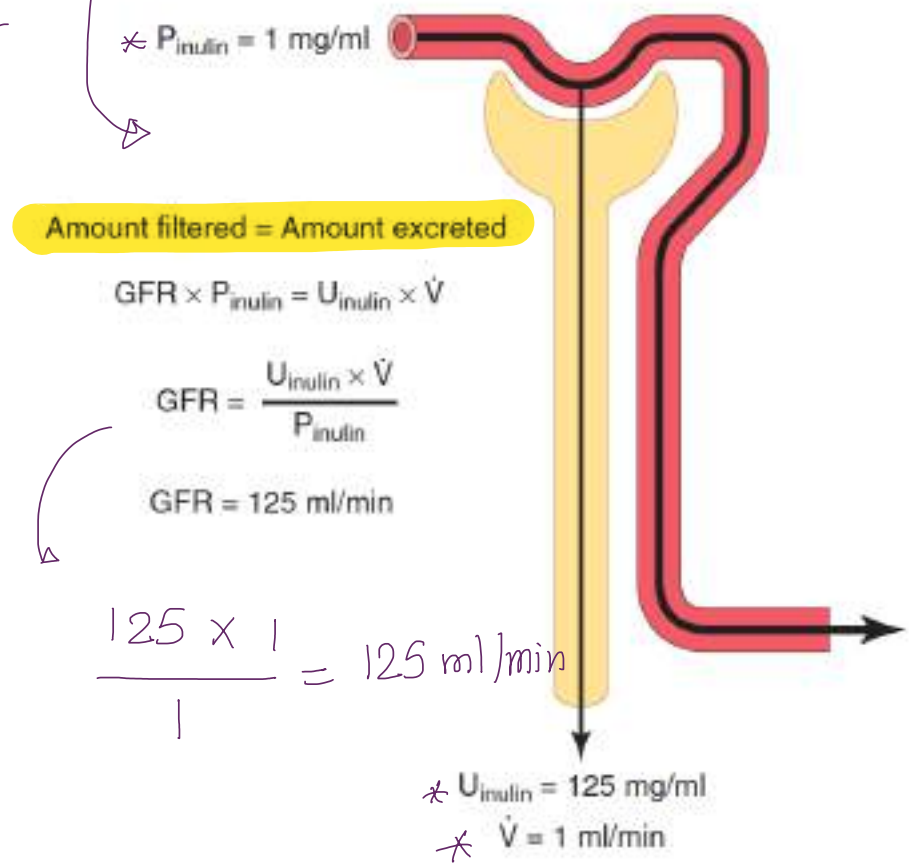
$$= 6.0 - 3.0$$

$$= +3.0 \text{ ml / min (positive)}$$

water is being cleared.

Use of Clearance to Measure GFR

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



Creatinine clearance and plasma creatinine concentration can be used to estimate GFR

produced by the body

فمافي داعي اعطيه IV زي ال inulin

- cleared from the body fluids almost entirely by glomerular filtration
- adv- not require intravenous infusion → so it is less invasive (because it is a normal product of metabolic process in the body)
- dis adv. is not a perfect marker of GFR because a small amount of it is **secreted** by the tubules → [amount of creatinine excreted > amount filtered]
- 2. a slight error in measuring plasma creatinine

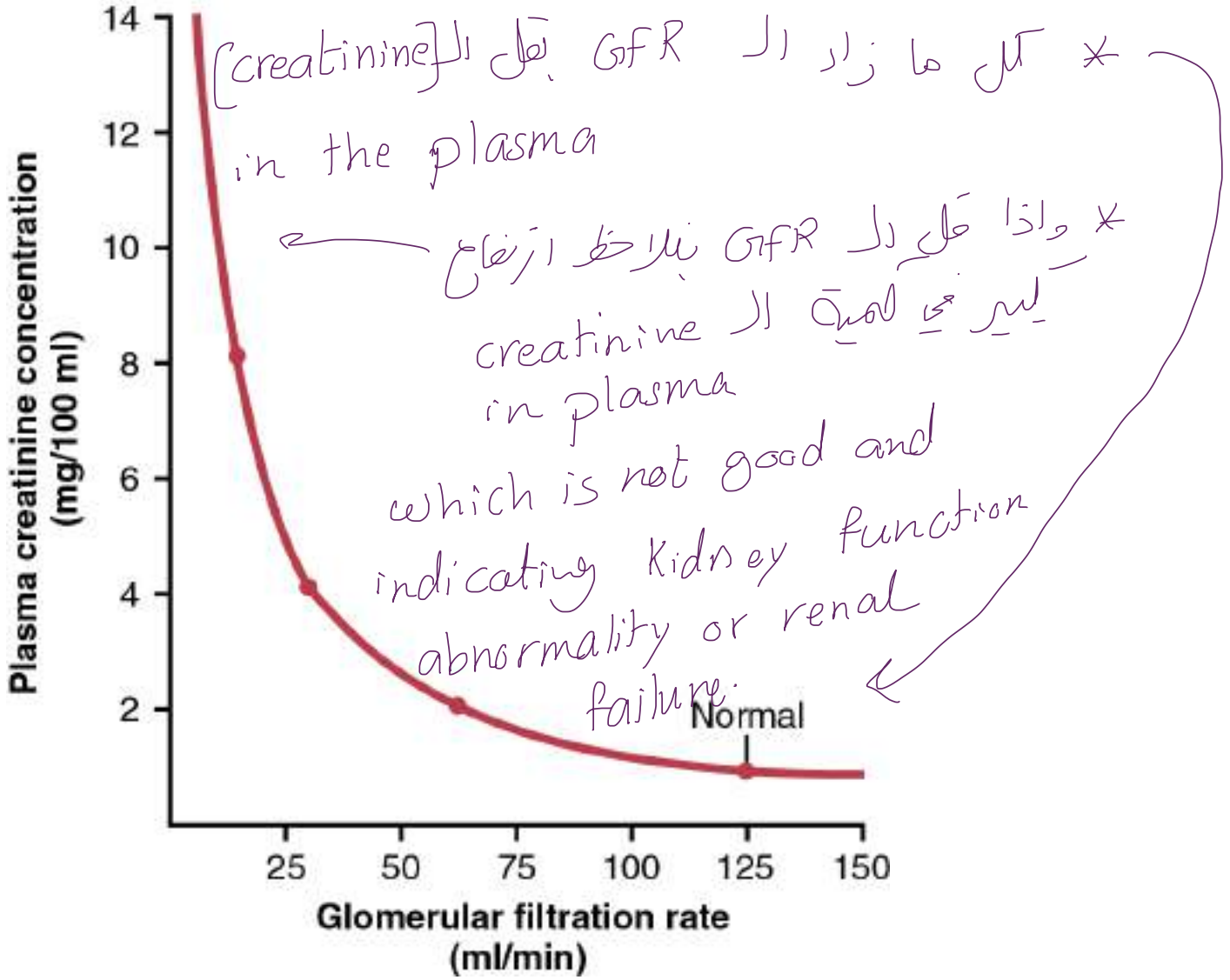
مش كل ال filtered is excreted.

في هنا load إضافي من ال tubules

يصيرله secretion وبالتالي كمية ال creatinine that excreted > amount filtered بجيه اشي اضافي على ال filteration, →

عشان هيك لما نيجي نحسب ال GFR لازم نعرف قديش فيه هنا creatinine secreted.

Plasma creatinine can be used to estimate changes in GFR



Use of Clearance to Estimate Renal Plasma Flow

Theoretically, if a substance is completely cleared from the plasma, its clearance rate would equal renal plasma flow (RPF)

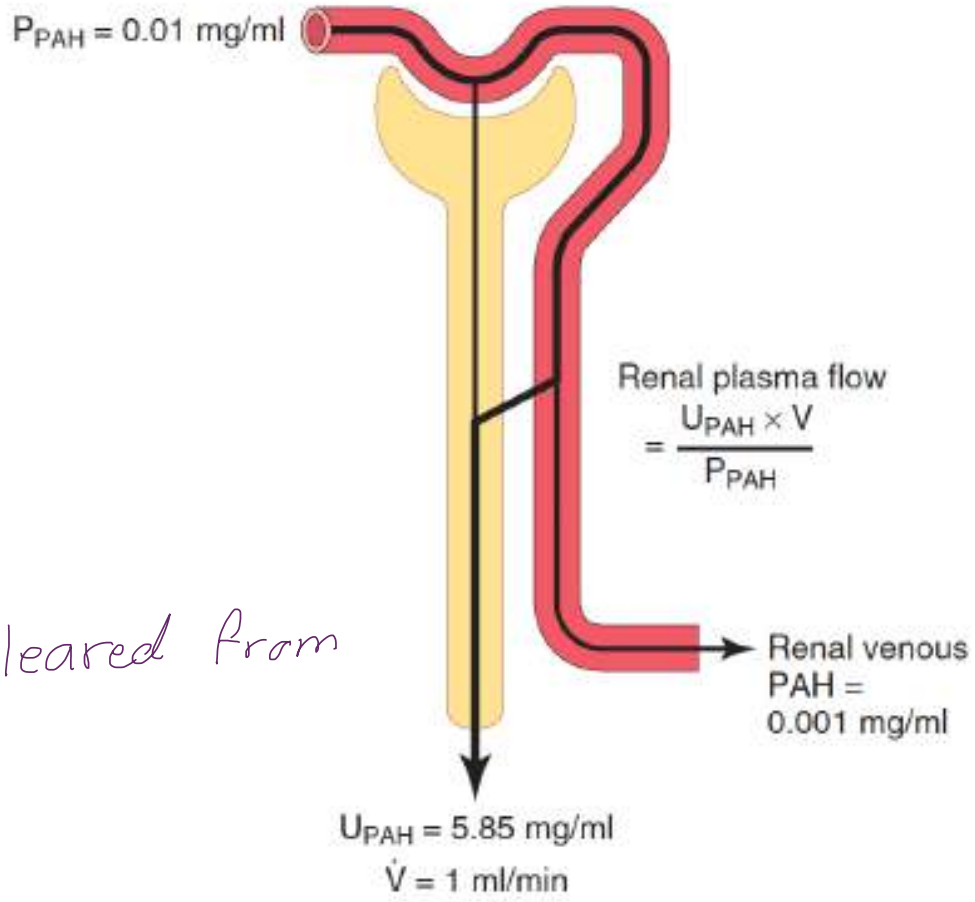
Paraminohippuric acid (PAH) is 90% filtered and secreted and is almost completely cleared from the renal plasma

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

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

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

Cx = renal plasma flow



To calculate actual RPF , one must correct for incomplete extraction of PAH

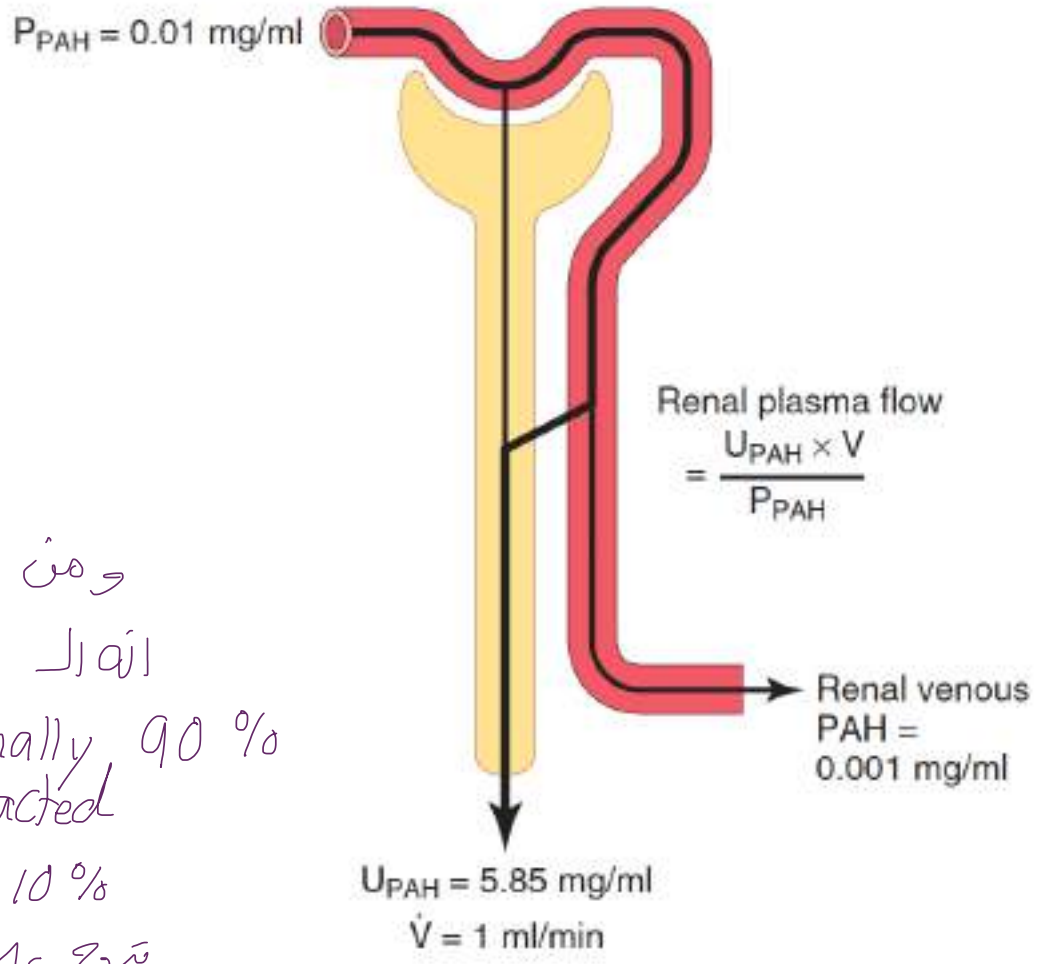
arterial venous

$$E_{PAH} = \frac{A_{PAH} - V_{PAH}}{A_{PAH}}$$

$$= \frac{0.01 - 0.001}{0.01} = 0.9$$

normally, $E_{PAH} = 0.9$

i.e., PAH is 90% extracted



ومن هون عرفنا انو الـ PAH normally 90 % extracted and 10 % بترجع على الـ venous circulation-

Filtration fraction is calculated from GFR divided by RPF

RPF =PAH clearance
GFR =inulin clearance

If the RPF is 650 ml/min and the GFR is 125 ml/min, the filtration fraction (FF) is calculated as

FF = GFR/RPF = 125/650 = 0.19

Calculation of Tubular Reabsorption

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.**

Calculation of Tubular Reabsorption

Reabsorption = Filtration - Excretion

$$\text{Filt}_s = GFR \times P_s$$

$$\text{Excret}_s = U_s \times V$$

Urine flow rate = 1 ml/min
Urine concentration of sodium (U_{Na}) = 70 mEq/L
= 70 µ Eq/ml
Plasma sodium concentration = 140 mEq/L
= 140 µ Eq/ml
GFR (inulin clearance) = 100 ml/min
Calculate
1-Filtered sodium load
2- Urinary sodium excretion
3- Tubular reabsorption

Answer
1-filtered sodium load= GFR x P_{Na}
=100 ml/min x 140 µ Eq/ml = 14,000 µ Eq/min.

2-Urinary sodium excretion =U_{Na} x urine flow rate=70 x1 =70 µ Eq/min.

3- tubular reabsorption of Na= filtered load - urinary excretion
14,000 µ Eq/min – 70 µ Eq/min = 13,930 µ Eq/min.

Acid-Base Regulation

Chapter 31
Unit V

Dr Iman Aolymat

Introduction

Multiple acid-base buffering mechanisms are nvolved in maintaining normal H+ concentrations in both the extracellular and intracellular fluid:

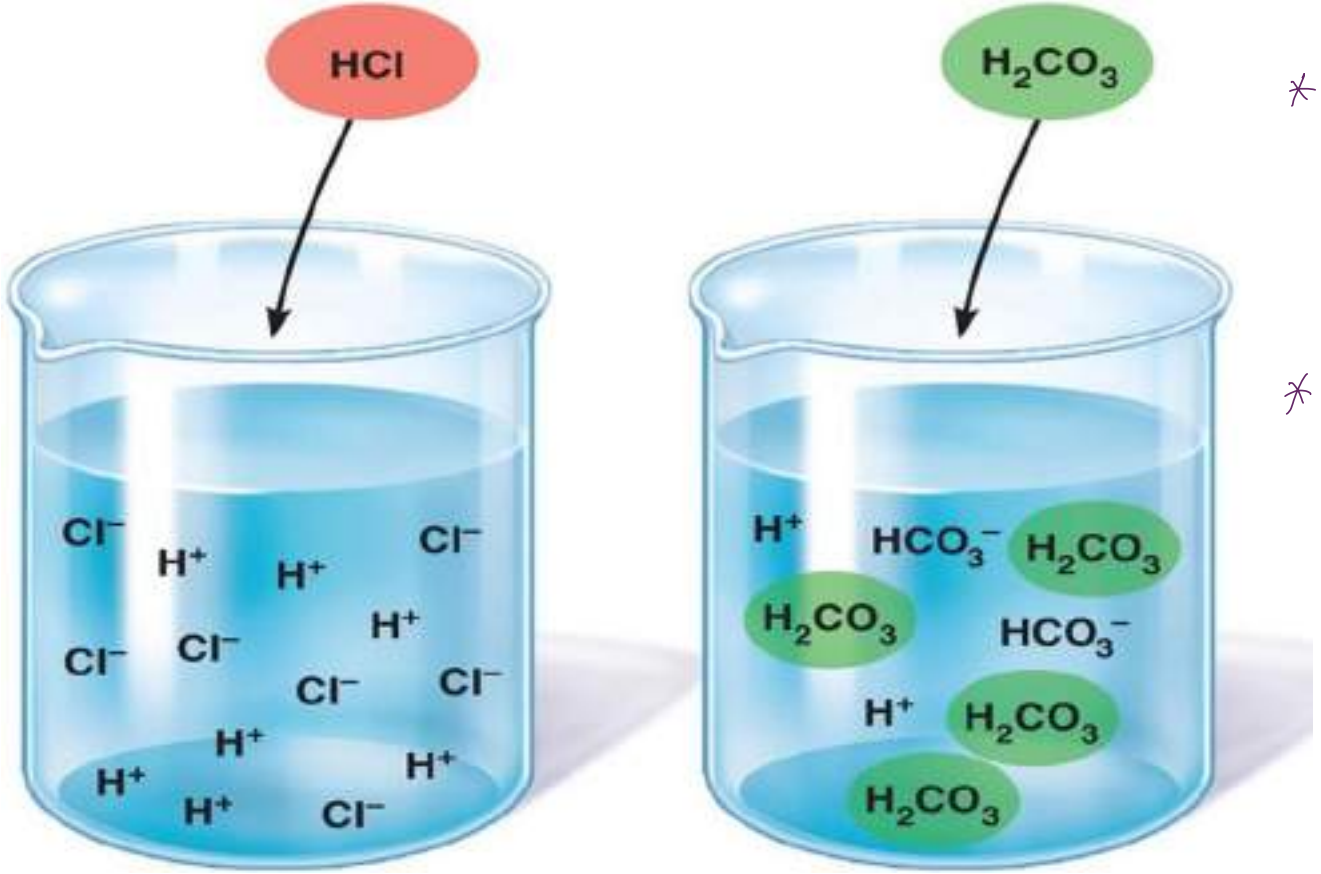
1- blood
2- cells
3- lungs
4- kidneys

Acid-Base Fundamentals

- ***An Acid*** = a molecule that can release H^+ in a solution.
  - H_2CO_3 (carbonic acid) → weak acid
  - HCl (hydrochloric acid) → strong acid

- ***A base*** = a molecule that accepts H^+ in a solution.
  - Bicarbonate ions (HCO_3^-).
  - Hydrogen phosphate (HPO_4^{-2})
  - Proteins in body function as bases because some of amino acids that make up proteins have net negative charges that readily accept H+.

Strong vs weak Acid/Base



* A strong base is one that reacts **rapidly** and strongly with H+ → quickly removing H+ from a solution.
  Example is OH– + H+ → H2O

* weak base e.g HCO3– because it binds with H+ much more weakly than does OH–.

Most acids and bases in ECF that are involved in normal acid-base regulation are **weak** acids and bases

Strong acids **dissociate rapidly and release large amounts of H⁺ in solution**

Weak acids **dissociate incompletely and less strongly releasing small amounts of H⁺ in solution**

→ ionization جزء يصير
وبعطيني H^+ مع ال HCO_3^-
وجزء ما بنفصل

* **Alkalosis= excess removal of H+ from the body fluids**

* **Acidosis= excess addition of H+**

build up of H^+ within the body fluid

is tightly regulated

[H+] & the 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= 7.2-7.44

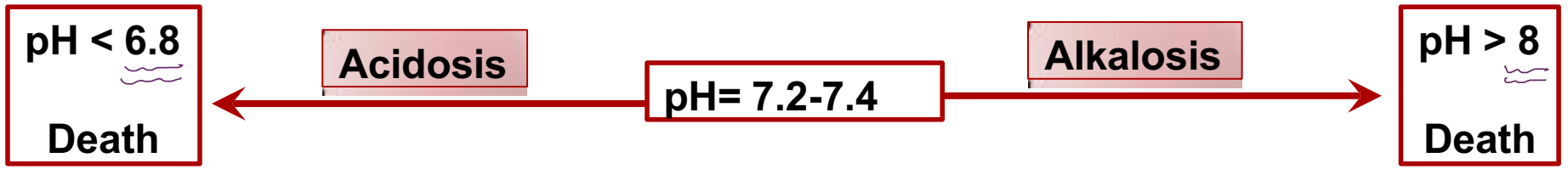


Table 31-1 pH and H^+ Concentration of Body Fluids

	H^+ Concentration (mEq/L)	pH
Extracellular fluid		
Arterial blood	4.0×10^{-5}	7.40
Venous blood	4.5×10^{-5}	7.35
Interstitial fluid	4.5×10^{-5}	7.35
Intracellular fluid	1×10^{-3} to 4×10^{-5}	6.0-7.4
Urine	3×10^{-2} to 1×10^{-5}	4.5-8.0
Gastric HCl	160	0.8

a little bit more acidic → because of metabolic waste mainly CO_2

metabolic active and produce acids as waste product

Intracellular pH usually is< plasma because the metabolism of the cells produces acid especially (H_2CO_3).

Hypoxia of and poor blood flow to tissues → acid accumulation and ↓intracellular pH.

and any defict in blood supply ↑

component is up and body demand

very very acidic.

Acid Production by the Body

- The body produces large amounts of acids on daily basis as by products of metabolism.
  - Metabolism of dietary proteins.
  - Anaerobic metabolism of carbs and fat.

- Acids in the body are of two kinds:
  1. Volatile (CO_2) which converts to carbonic acid
  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).

2. ***Lungs***

   Works within minutes (eliminate CO2).

3. ***Kidneys***

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

   The most powerful of the three.

Strong acid → weaker acid

Strong base → weaker base

change in the acidity or basic componant

excrete CO2.

most effiecient and important one

according to the need of the body

Chemical Buffer Systems in the Body

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

1. The Bicarbonate buffer system.
2. The phosphate buffer system.
3. Proteins.

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

↳ like bicarbonate

- Some are more powerful extracellularly and others are more powerful intracellularly.

↳ like proteins

The Bicarbonate Buffer System

- The main ECF buffer system
- Composed of: 2 components :-
  - A weak acid (H_2CO_3).
  - Its conjugated base ($NaHCO_3$).

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

$$CO_2 + H_2O \underset{}{\overset{\text{Carbonic anhydrase}}{\rightleftharpoons}} H_2CO_3$$

secreted from lungs alveoli

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

weak acid

partial

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

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

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

The Bicarbonate Buffer System

Putting it all together;

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

weak acid

HCO_3^- + Na^+

Adding ACID (HCl)

very strong

$$(HCl \rightarrow H^+ + Cl^-)$$

$$+HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$$

Weak acid

lung

Adding base (NaOH)

strong base.

$$CO_2 + H_2O \longrightarrow H_2CO_3 \longrightarrow \uparrow HCO_3^- + H^+$$

H_2CO_3 + NaOH

HCO_3^- + Na

sodium bicarbonate weaker than Sodium Hydroxide.

The Henderson-Hasselbalch Equation

What is the HHE?

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

What is it?

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

K = dissociation constant, pK = 6.1

0.03 = solubility of CO_2

The Henderson-Hasselbalch Equation

$$CO_2 + H_2O \xrightleftharpoons{CA} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

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

pK = dissociation constant= 6.1

0.03 = solubility of CO_2

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

1. pH α $\frac{HCO3-}{PCO2}$ **Regulated by kidneys** / **Regulated by lungs**

Each element of the buffer system is regulated

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

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 mainly in intracellular compartments.

- Contributes to buffering inside cells→ H+ /HCO3- diffusion to the cell.
- E.g. Hb. very efficient buffer within blood circulation

فلازم ال HCO_3^- / H^+ تدخل لـ داخل الخلية حتى يصير balance

Summary of Body's Buffering Systems

- Buffer systems do not work independently in body fluids but actually work together.
- A change in the balance in one buffer system, changes the balance of the other systems.
- Buffers do not reverse the pH change, they only limit it.
- Buffers do not correct changes in $[H^+]$ or $[HCO_3^-]$, they only limit the effect of change on body pH until their concentration is properly adjusted by either the lungs or the kidney.