JUXTAGLOMERULAR APPARATUS (JGA)

Definition:

It is a secretory structure present near the glomeruli at the region where the initial portion of the distal convoluted tubule (DCT) comes in contact with the glomerulus close to its afferent and efferent arterioles, actually passing the angle between them.

اللهم أخرجني من حولي إلى حولك ، ومن عزمي إلى عزمك ، ومن ضعفي إلى قوّتك ، ومن انكساري إلى عزّتك ، ومن ضيق اختياري إلى سعة إرادتك🌸✨.

اللهم إنّي أسألك أن تُعينني في دراستي، وأن تُسهّل عليّ مذاكرتي، وأن ترزقني قوّة الحفظ، وتجعله ميّسرًا علي ليس شاقًّا ولا صعبًا يا أرحم الراحمين 🤲💜.

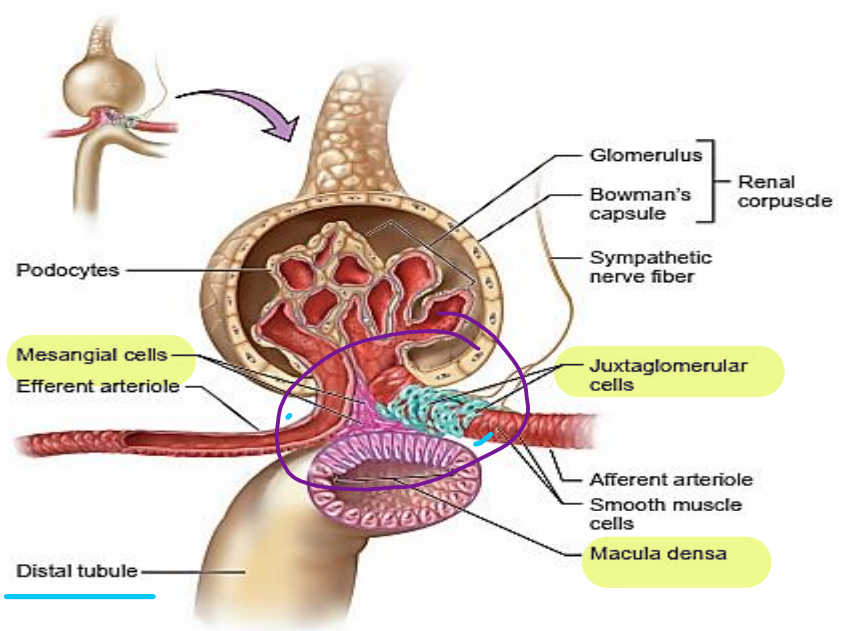


Figure 14.5 AP|R The juxtaglomerular apparatus.

It is formed of the following cells:

1. Juxtaglomerular cells:

Juxtaglomerular (JG) cells are **secretory cells** located in the **afferent arterioles**.

Function:

JG cells act as **intrarenal baroreceptors** (they sense afferent arteriole pressure), which enables them to efficiently monitor ABP and maintain normal GFR through the release of **renin**, the initial enzyme in the renin-angiotensin-aldosterone system (RAAS).

2. Macula Densa cells:

A specialized group of epithelial cells in the **initial part of DCT** that comes in close contact with the afferent and efferent arterioles.

Functions:

- Are important in sensing tubular fluid flow and sodium delivery to the distal nephron.
- Because of their proximity to the afferent arteriole, macula densa cells can regulate renal blood flow (RBF) and glomerular filtration rate (GFR) **(autoregulation)**.

high NaCl and reabsorption rate causes contraction of the afferent arteriole and a reduction in GFR

Function of JGA: Maintains the glomerular filtration rate (GFR) in response to blood pressure (BP) changes in the afferent arterioles (**autoregulation of GFR and RBF**).

RENAL BLOOD FLOW (RBF)

Normally, **RBF is about 1200 ml/minute**. The flow is much greater in the renal cortex, only about **2 % pass in the vasa recta**.

The renal fraction:

This is the portion of the cardiac output that passes through the kidneys. Normally, it averages about **20 %** of cardiac output (1200/5600 X100) ranging from (12 % - 30%).

RENAL PLASMA FLOW (RPF)

Renal plasma flow is the measure of the volume of plasma delivered to the kidney in a given time.

About **650 ml/minute**.

Mechanism of urine formation

- **Urine is formed as a result of:**

1) **Glomerular filtration:** Filtration of plasma from the glomerular capillaries into Bowman's space.

- Normally, glomerular capillary bed receives about 650 ml plasma/minute of which only about 1/5 **(125 ml)** is filtered into Bowman's capsules while the remaining 4/5 pass to the peritubular capillaries.

- Glomerular filtrate is called **primary urine** and it contains all plasma constituents except most plasma proteins (protein free fluid) which can't be filtered.

2) **Tubular reabsorption:**

Transport of substances (mainly essential substances) from the lumens of the renal tubules to blood in peritubular capillaries.

Normal values:

- GFR= 125 ml/minute (180 L/day).
- Tubular reabsorption: 124 ml/minute (99.2% of glomerular filtrate).
- Urine volume: 1 ml/minute (= 1.44 L/day = 0.8% of glomerular filtrate).

3) Tubular secretion:

Process by which substances are transported into the lumens of the renal tubules from the following sources:

- Blood of peritubular capillaries e.g. creatinine and K^+.
- Tubular epithelial cells e.g. H^+ and NH_3.

By these processes of reabsorption and secretion, the tubular fluid (= tubular urine) is changed into actual urine.

Excretion = Filtration – reabsorption + secretion.

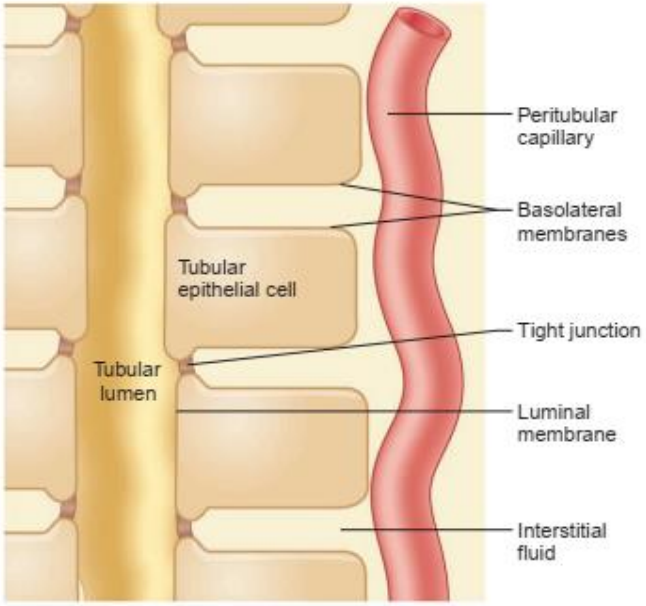
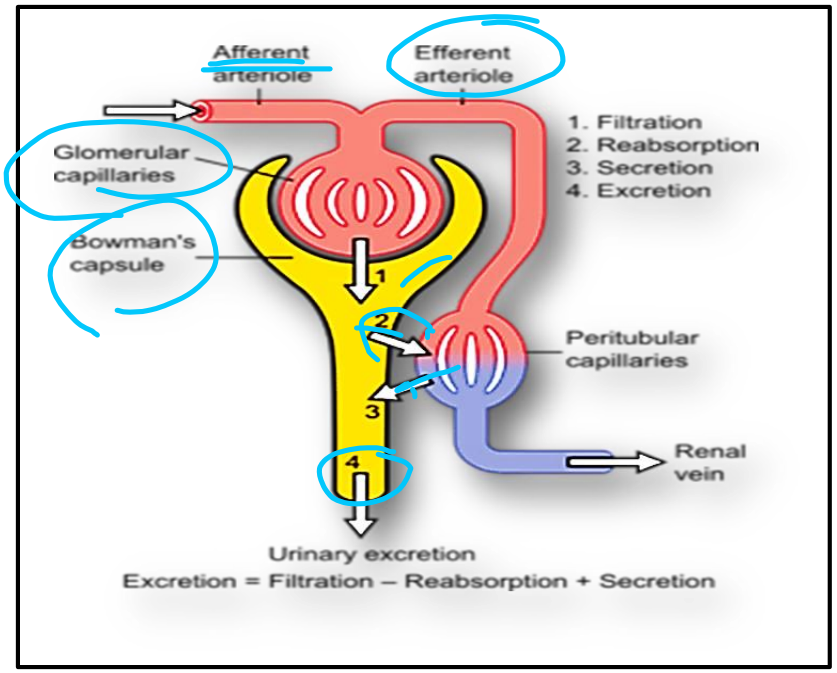
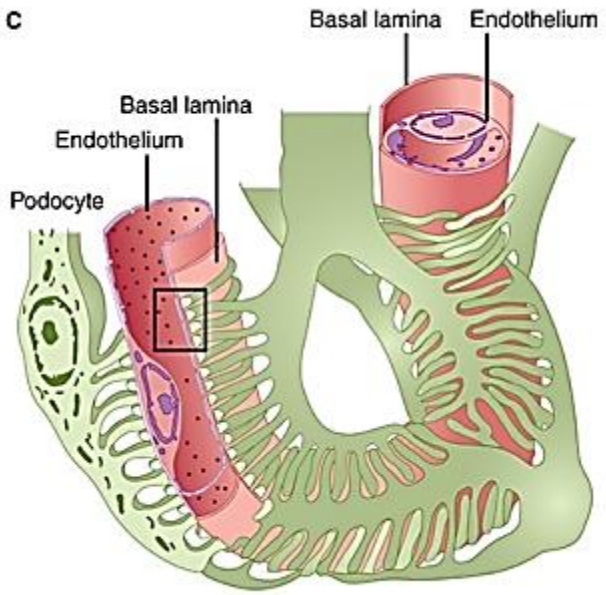


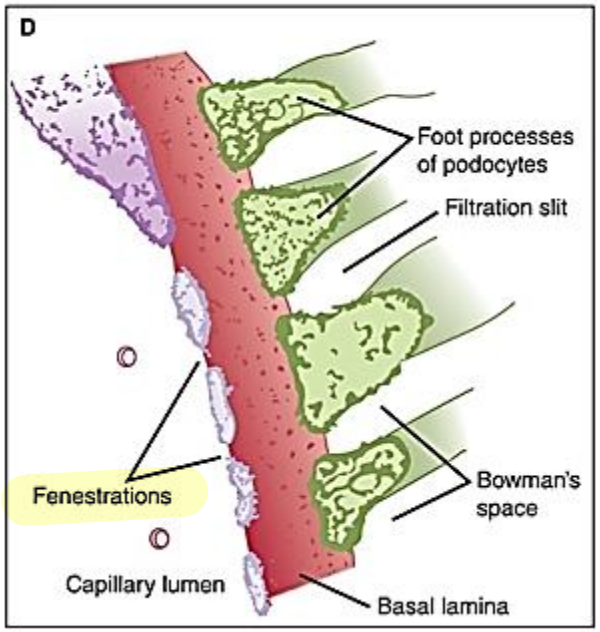
Figure 14.10 AP|R Diagrammatic representation of tubular epithelium. The luminal membrane is also called the apical membrane.



Glomerular Filtration

- **It is the first step in urine formation.**
- **Filtration occurs from the glomerular capillaries to Bowman's capsule through the glomerular filtration barrier (glomerular membrane).**





Mechanism and Forces mediating filtration

Glomerular filtration is a passive process (requiring no energy) that involves interaction between the following forces (Starling forces):

Filtering forces: اتجاه filtration الى

1-The glomerular hydrostatic capillary pressure (GCP): It is about **60 mmHg**. It is the highest capillary pressure in the body. It is due to the fact that the diameter of efferent arteriole is smaller than diameter of afferent arteriole.

2-The colloid osmotic pressure in Bowman's capsule: Normally, it is too low to be of any significance **(zero)** due to low protein concentration in the filtrate inside Bowman's capsule.

Opposing forces:

1-The glomerular colloid osmotic pressure (GOP): This is the force due to plasma proteins. It normally averages about **32 mmHg**.

2-Bowman's capsule pressure; capsular pressure (CP): this is the pressure of fluid in Bowman's capsule . It is normally about **18 mmHg**.

✓ The net filtration pressure (NFP):

This is the driving force for glomerular filtration.

NFP =

Filtering forces – Opposing forces

= (60+0) – (32+18) = 60-50 = 10 mmHg.

GFR is directly proportional to NFP.

✓ The glomerular filtration rate (GFR) :

GFR: The volume of glomerular filtrate /minute in both kidneys.

Volume: 125 ml/minute.

Composition: Deproteinized plasma (plasma free of proteins; **protein free fluid**).

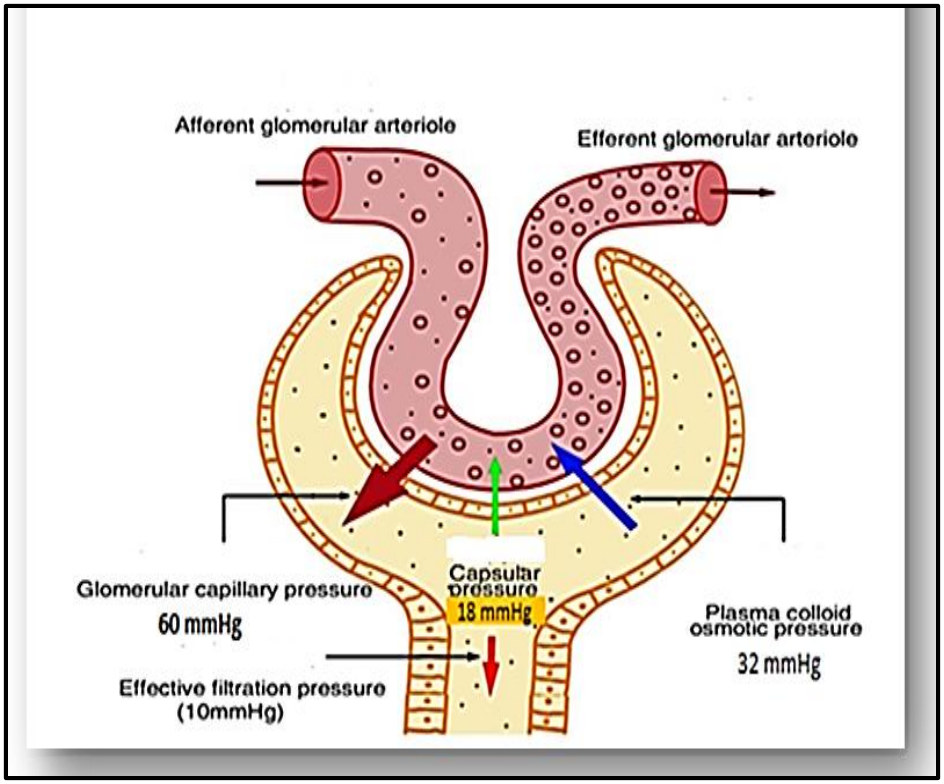
Measurement: This can be achieved by determination of **inulin clearance** or **creatinine clearance**.

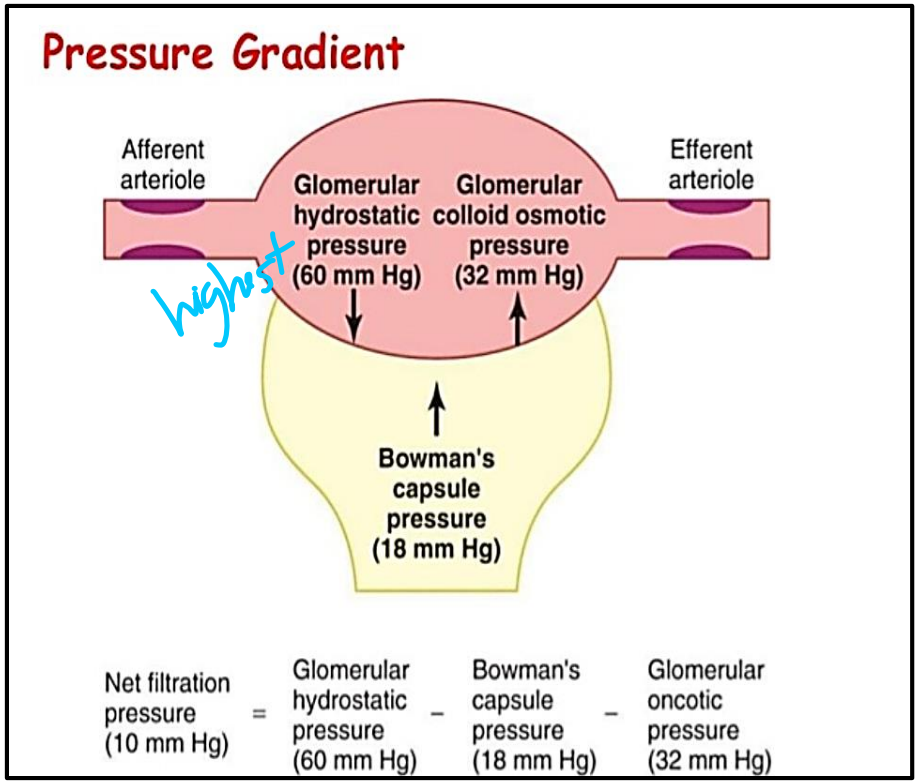
✓ The filtration coefficient (K_f):

125 – 10(net filtration(P)) →

This is the GFR/mmHg of net filtration pressure, and is normally about 125/10 = 12.5 ml/mmHg/minute.

Forces mediating filtration





Filtration Fraction

✓ **Definition:**

Filtration fraction (FF) is the fraction (in %) of renal arterial plasma filtered across the glomerular membrane.

✓ **It is the ratio of the GFR to the RPF**.

renal plasma flow

✓ It can be calculated if the GFR and the RPF are known:

✓ FF = GFR/RPF

✓ = **125/650 X 100 = about 20 % (about 1/5 RPF)**

✓ Therefore, about 20% of the RPF enters the renal tubules, while the remaining 80% leaves the glomerulus via the efferent arteriole and becomes the peritubular capillary circulation.

✓ When GFR is 125 ml/minute, the volume filtered 180 L/day. Since, the normal plasma volume is about 3 L, it is clear that plasma is filtered about 60 times daily.

Determinants of GFR

I) Renal blood flow (RBF):

The **GFR is generally directly proportional to the RBF**.

the blood pressure within the glomerular capillaries,

II) Glomerular capillary pressure (GCP):

The GFR is directly proportional to the GCP which is affected by the following factors:

A. Afferent arteriolar diameter:

- **VC decreases both RBF and GCP, so GFR is reduced.**
- **VD increases both RBF and GCP, so GFR is increased.**

B. Efferent arteriolar diameter:

- **VD decreases GCP, so GFR is reduced.**
- **VC increases GCP, so GFR is increased.**

C. ABP

Increased mean ABP (MAP) tends to raise glomerular capillary hydrostatic pressure and, therefore, to increase GFR. (However, this effect is buffered by autoregulatory mechanisms that maintain a relatively constant glomerular pressure as blood pressure fluctuates within a certain range.)

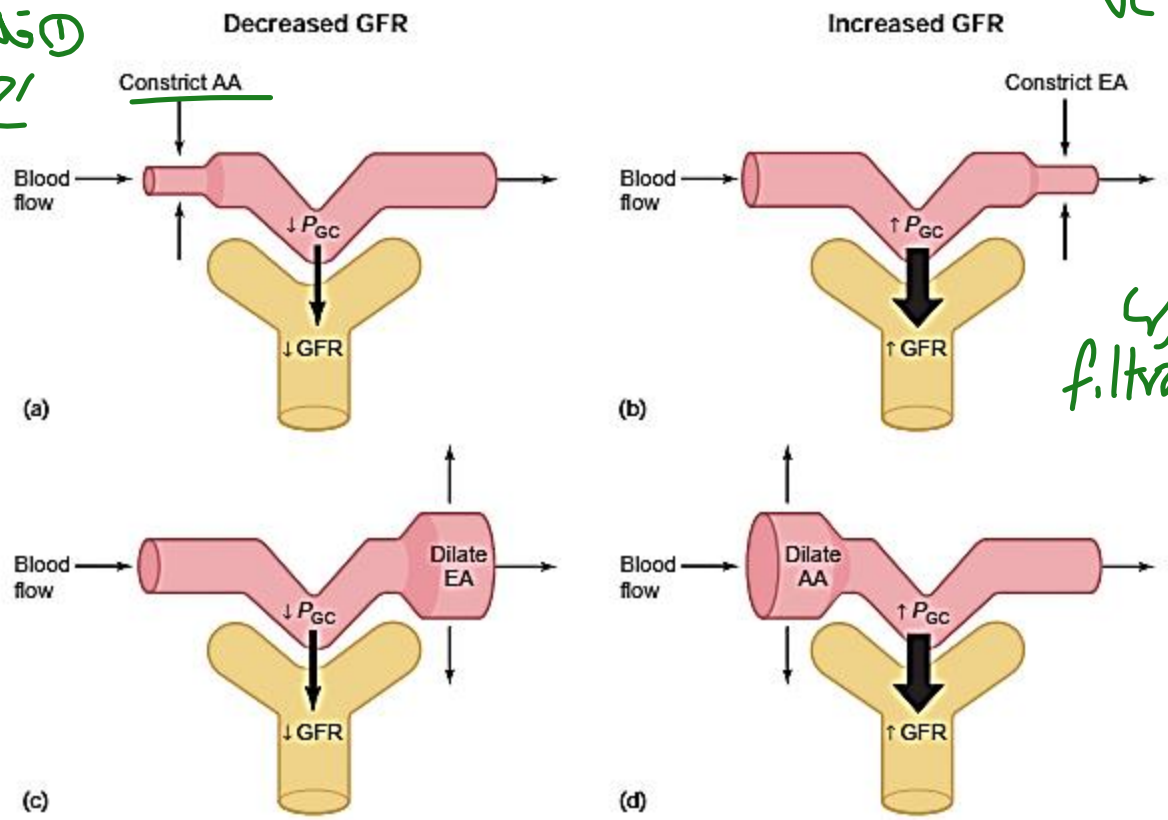


Figure 14.9 AP|R Control of GFR by constriction or dilation of afferent arterioles (AA) or efferent arterioles (EA). (a) Constriction of the afferent arteriole or (c) dilation of the efferent arteriole reduces P_{GC}, thus decreasing GFR. (b) Constriction of the efferent arteriole or (d) dilation of the afferent arteriole increases P_{GC}, thus increasing GFR.

III) The glomerular colloid osmotic pressure (GOP):

- **The GFR is inversely proportional to GOP.**
- As blood passes from the afferent arteriole through the glomerular capillaries to the efferent arterioles, the plasma protein concentration increases.
- **Thus an increase in GOP (as in dehydration) reduces GFR. While, a decrease in GOP (e.g. due to hypoproteinemia) increases the GFR.**

IV) Bowman's capsule pressure; capsular pressure (CP):

- **The GFR is inversely proportional to CP.**
- Thus **an increase in the CP due to stone in the ureter (obstructing outflow of urinary tract) reduces GFR.**

يعني حسب السوائل

V) Size of the glomerular capillary bed (the filtration surface area):

The **GFR is reduced if the glomerular surface area available for filtration is decreased (directly proportional)**.

This occurs due to either:

(a) **A decrease in functioning kidney mass** (i.e. number of nephrons) as in chronic renal failure and after nephrectomy.

(b) **Contraction of the mesangial cells** (stellate cells that surround the glomerular capillaries between the glomerular capillary endothelium and basal lamina). Contraction of these cells **reduces the surface area** of the capillaries, which causes **a decrease in GFR.**

VI) The glomerular capillary permeability:

- **The GFR is directly proportional to glomerular capillary permeability.**
- Glomerular capillary permeability is altered in renal diseases (e.g. it is increased in glomerulonephritis due to damage of capillary walls and reduction of their negative charges).

Regulation of GFR (Renal Hemodynamics)

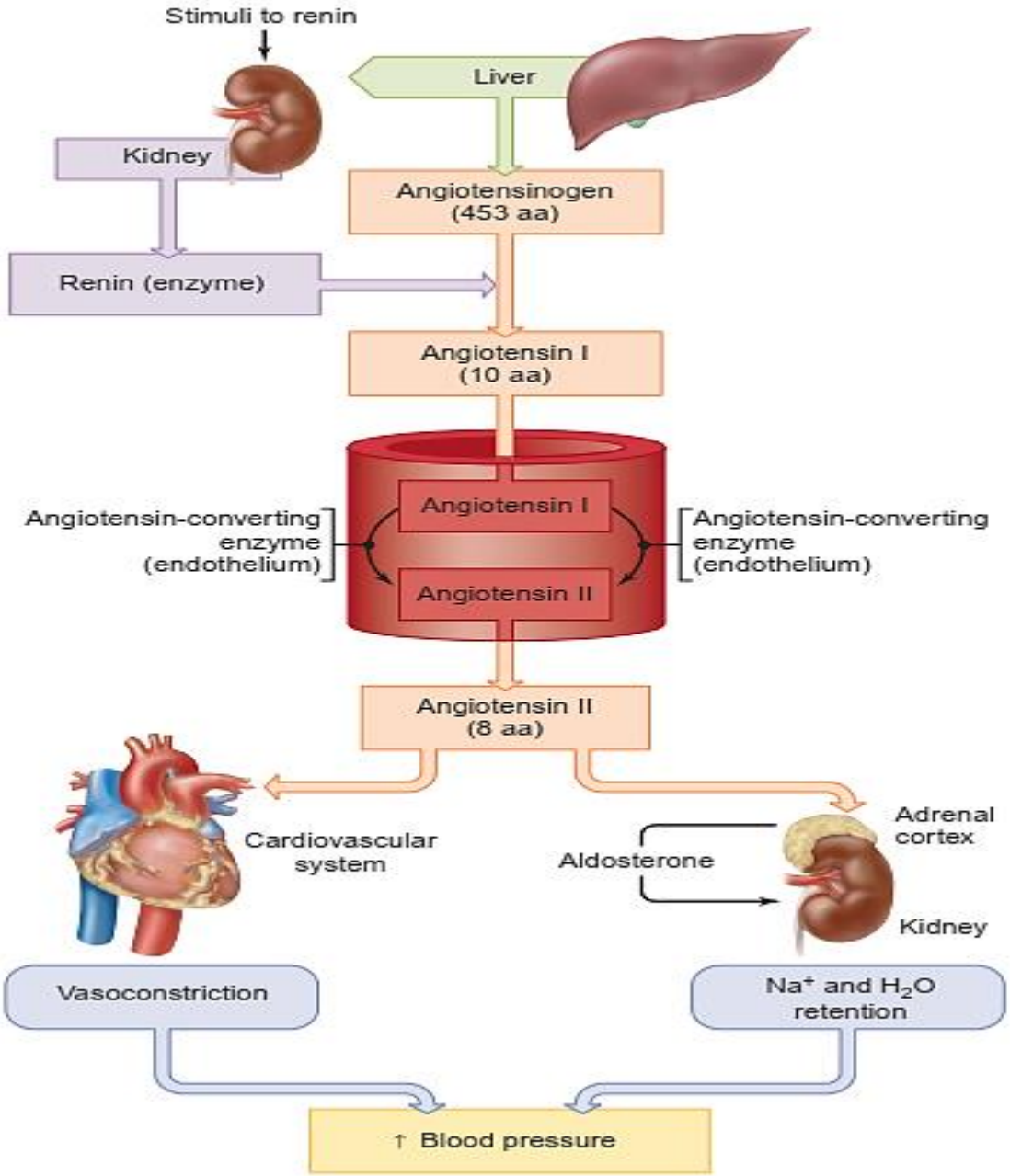
Control of renal hemodynamics occurs through the following mechanisms:

The renin-angiotensin-aldosterone system (RAAS):

- ✓ It is activated in response to **low renal vascular flow (renal ischemia)** which stimulates **renin** secretion by the **juxtaglomerular cells** at the ends of the **afferent arterioles**.
- ✓ This, in addition to the **modulation of renin secretion by the macula densa**, will **activate the RAAS**.
- ✓ **The renin will act on angiotensinogen to produce angiotensin I which is converted to angiotensin II by ACE and thus control GFR**.

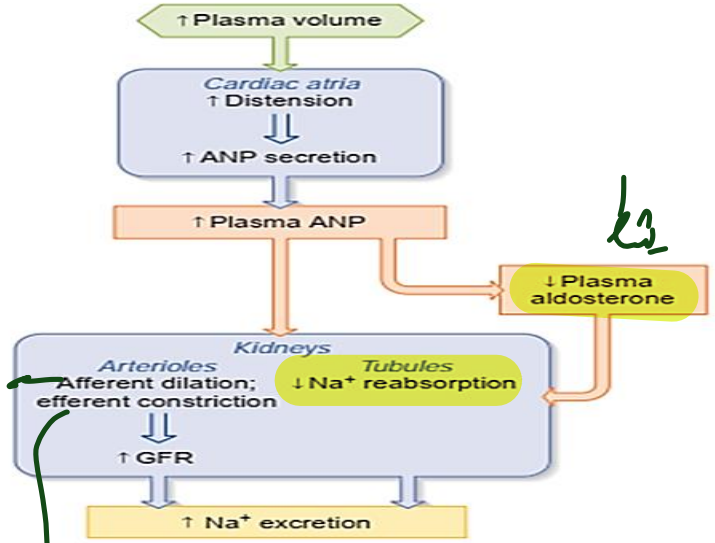
Angiotensin II:

- o It is a **vasoconstrictor**, and in the kidneys, it acts directly on the renal arteries, and to a greater extent at the **afferent and efferent arterioles**, increasing resistance.
- o **Angiotensin II actually has greater effect on the efferent arteriole than afferent arteriole.** Thus, increasing or **maintaining the glomerular capillary pressure in the glomerulus and GFR**.
- o **Angiotensin II maintains the GFR** even in the face of decreased overall RBF.


Stimuli to renin
Liver
Kidney
Angiotensinogen
(453 aa)
Renin (enzyme)
Angiotensin I
(10 aa)
Angiotensin-converting
enzyme
(endothelium)
Angiotensin I
Angiotensin II
Angiotensin-converting
enzyme
(endothelium)
Angiotensin II
(8 aa)
Cardiovascular
system
Aldosterone
Adrenal
cortex
Kidney
Vasoconstriction
Na+ and H2O
retention
↑ Blood pressure

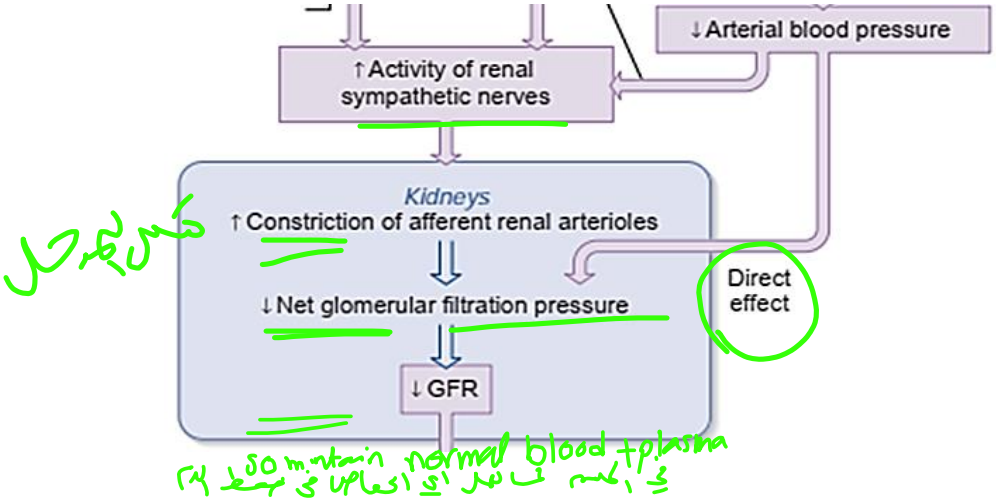
Atrial natriuretic peptide (ANP):

- Cells in the **cardiac atria synthesize and secrete ANP in response to stretch; atrial distension (at high blood volume)**.
- ANP acts on several tubular segments to inhibit Na^+ reabsorption.
- ANP also directly inhibits aldosterone secretion, which leads to an increase in Na^+ excretion.
- ANP causes natriuresis and diuresis, reducing ECF volume.
- **ANP also causes VD of renal afferent arteriole and VC of efferent arteriole increasing glomerular capillary pressure, and thus, GFR. The enhanced flow increases sodium and water excretion, reducing blood volume.**



Sympathetic nerves and catecholamines (NE and Epi):

- ✓ They are **stimulated in response to reductions in systemic blood pressure.**
- ✓ They cause **vasoconstriction of the renal arteries and arterioles (afferent > efferent).**
- ✓ **Mild stimulation of sympathetic nerve activity produces almost no effect, the intrarenal systems will counteract this effect, to ensure the kidney vasculature remains dilated, preserving GFR.**
- ✓ **During high sympathetic nerve activity** (severe hemorrhage), **sympathetic nerve activity overrides the intrarenal regulatory mechanisms and reduces RBF and GFR.**



Endothelial-Derived Nitric Oxide (NO):

endothelial cells

so more filtration

NO is an autacoid that decreases the renal vascular resistance and increases GFR.

Intrarenal prostaglandins: (PGE_2 and PGI_2)

- They are vasodilators, acting at the level of the arterioles and glomerular mesangial cells.
- They cause **dilation of afferent > efferent arterioles**, thereby **increasing RBF and GFR**.

the differances are:

NO → systemic ← out kidny

PG → act inside kidny

AUTOREGULATION OF GFR & RBF

- This is an **intrinsic mechanism** in the kidney that keeps GFR and RBF nearly constant despite changes in mean ABP (MAP) between 80 – 180 mmHg.
- **Intrinsic systems include the myogenic and tubuloglomerular feedback (TGF) mechanisms.**
- These systems allow regulation of GFR over a wide range of systemic blood pressure.

Mechanism of autoregulation of GFR and RBF

I. When the mean ABP rises to 180 mmHg:

In this condition, **constriction of afferent arterioles occurs, so both RBF and GFR are kept relatively constant (or increase slightly) in spite of the increased MAP.**

This is produced by either **myogenic mechanism or tubuloglomerular feedback mechanism**.

1. Myogenic mechanism:

↑ Mean ABP → stretch afferent arterioles→ entry of Ca^{2+} from extracellular fluid into cells→ vasoconstriction of the afferent arteriole → increasing vascular resistance to prevent excessive increases in RBF and GFR.

2. Tubuloglomerular feedback mechanism:

(**A feedback mechanism that links changes in sodium chloride concentration at the macula densa with the control of renal arteriolar resistance**)

- Rise of mean ABP increases glomerular filtration, so the rate of flow through the ascending limb of LH and first part of DCT also increases.

- This initiates a signal from **macula densa** (probably as a result of the **increase of Na^+ and Cl^- concentrations**) that produces **VC of the afferent arterioles** (which may be mediated by adenosine or ATP).

- The **afferent arteriole constricts, which reduces glomerular capillary pressure, and thus decreases the pressure for filtration, reducing GFR and tubular flow.**

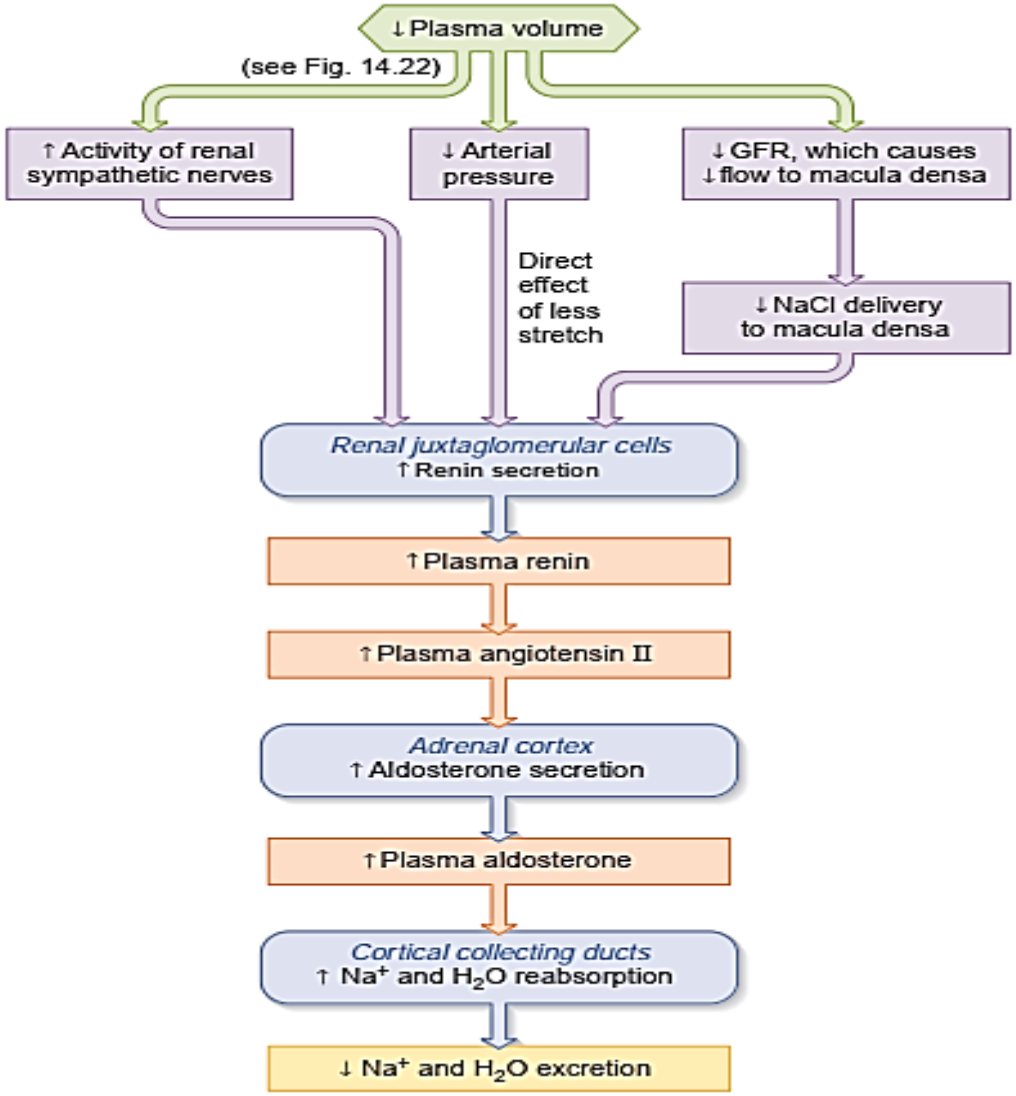
II. When the mean ABP falls to 80 mmHg:

- In this condition, **VC of efferent arterioles occurs.** So, the GFR is kept relatively constant (or decreases slightly) in spite of the decreased MAP.
- Such arteriolar response is produced by a **tubuloglomerular feedback mechanism** as follows:

✓ The fall of MAP decreases glomerular filtration, so the rate of flow through the ascending limb of LH and first part of DCT also decreases.

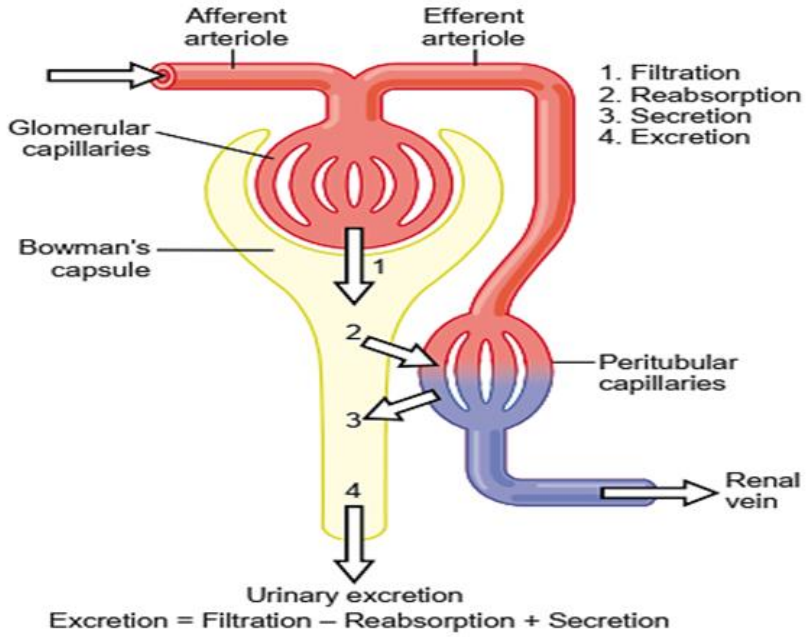
✓ This initiates a signal from **the macula densa (probably as a result of the decrease of Na^+ and Cl^- concentrations).**

✓ **Macula densa cells activate juxtaglomerular cells causing the release of renin** and this catalyzes formation of **angiotensin II, which specifically causes VC in the efferent arterioles**.


↓ Plasma volume
(see Fig. 14.22)
↑ Activity of renal sympathetic nerves
↓ Arterial pressure
↓ GFR, which causes ↓ flow to macula densa
Direct effect of less stretch
↓ NaCl delivery to macula densa
Renal juxtaglomerular cells
↑ Renin secretion
↑ Plasma renin
↑ Plasma angiotensin II
Adrenal cortex
↑ Aldosterone secretion
↑ Plasma aldosterone
Cortical collecting ducts
↑ Na+ and H2O reabsorption
↓ Na+ and H2O excretion

Renal Clearance

- **The renal clearance of any substance is the volume of plasma from which that substance is completely removed ("cleared") by the kidneys per unit time.**
- **Renal clearance is one of renal function tests that depends on combined blood and urine analysis.**



The clearance equation incorporates the urine and plasma concentrations of the substance, and the urine flow rate and is usually reported in ml/min.

Equation of clearance:

Clearance is calculated by using an equation that is determined as follows:

1. The amount of substance (x) cleared from the plasma/minute =the amount of this substance excreted in urine/minute.

2. The amount of substance (x) cleared from plasma/minute= C_x X P_x

C_x = volume of plasma cleared from substance (x) per minute = ml /min

P_x = concentration of substance per ml in plasma = mg /ml

3. The amount of substance (x) excreted in urine/minute= V X U_x, where

V is the volume of urine/minute (ml/minute).

U_x is the concentration of substance/ml urine (mg/ml).

4. Since both amounts are equal, then

$C_x \times P_x = V \times U_x$, therefore

$$C_x = \frac{V\,xUx}{P_x}$$

$$C = \frac{U_x \times V_x}{P_x} \Rightarrow \frac{50\ mg/mL \times 2\ mL/m}{1\ mg/m} = 100\ mL/m$$

This is **the equation of clearance (C) and it shows that the clearance value of any substance is obtained by finding its amount excreted in urine/minute (VxU), then dividing this amount by the concentration of this substance/ml plasma (P)**.

The clearance of various substances is not the same **depending on the mode of handling of each substances in the nephron** (i.e. what happens to the substance in the nephron).

Substances that are secreted in renal tubules have high clearance, while those reabsorbed have low clearance.

N.B. As the substance is freely filtrated so, its concentration in plasma(P_x) = its concentration in glomerular filtrate (GF_x).

When substance x passes through the renal tubule, the following possibilities can occur before being excreted in urine:

1. The substance is freely filtered in glomeruli and is neither reabsorbed nor secreted in the renal tubules, so;

The amount filtered/minute = the amount excreted/ minute

$GFR \times GF_x = V \times U_x$

$$\textbf{GFR} = \frac{V \times Ux}{GFx}$$

Since the substance is freely filtered

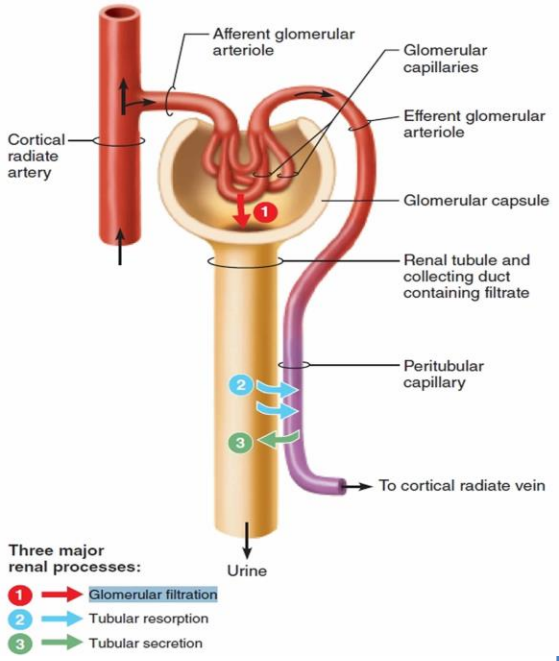
So, its concentration in plasma = its concentration in filtrate

$P_x = GF_x$

So, 125 = 125

$$\textbf{GFR} = \frac{V \times Ux}{Px} = C$$

e.g. inulin



Unfortunately, there is no endogenous substance that exactly meets these requirements (i.e., the substance is freely filtered, but neither reabsorbed nor secreted), Inulin does meet these criteria.

Inulin Clearance:

- Inulin is a polysaccharide. Its M.W is about 5200.
- Its mode of handling in the nephron is as follows:
  - **It is freely filtered in the glomeruli (i.e. its concentration in plasma= its concentration in glomerular filtrate).**
  - **It is neither reabsorbed nor secreted in the renal tubules, so the amount filtered/minute=the amount excreted in urine/minute.**
  - Accordingly, the **volume of plasma that is cleared from inulin/minute (inulin clearance) is that volume filtered in the glomeruli/minute i.e. the GFR**.

For this reason, **determination of inulin clearance is often used for measurement of GFR** as follows:

1. The amount of inulin filtered/minute= GFR X GF_{IN}

And since GFR=C_{IN} and GF_{IN}=P_{IN}

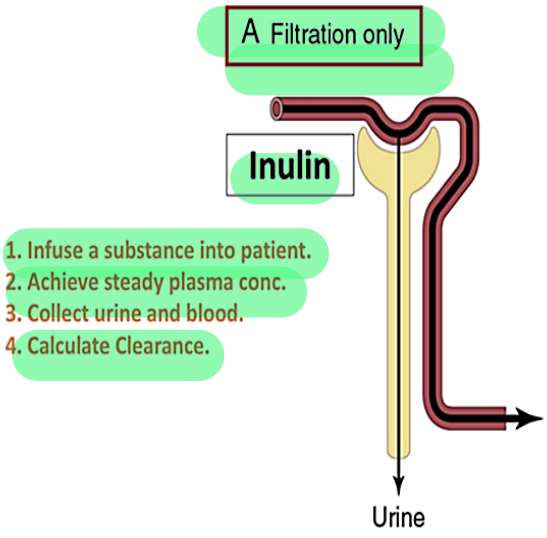
So, the filtered amount= C_{IN} X P_{IN}

2. The amount of inulin excreted/minute= V X U_{IN}

Since 1 and 2 are equal

C_{IN} X P_{IN} = V X U_{IN} and accordingly

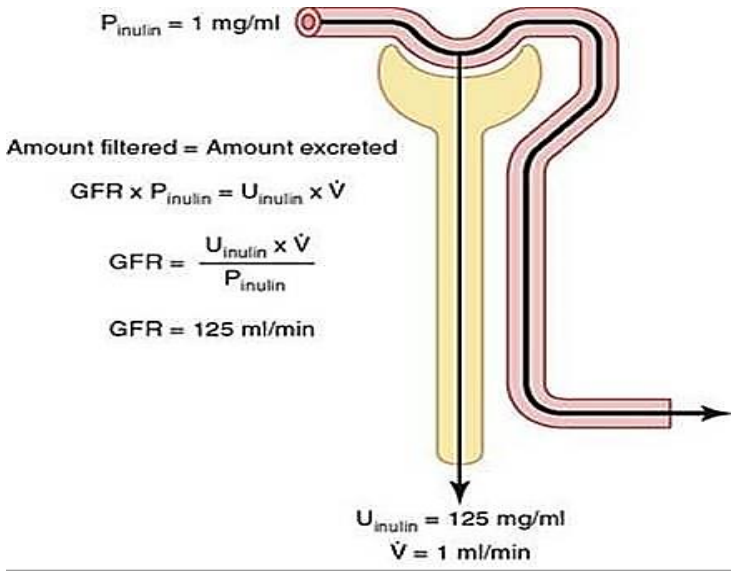
C_{IN} (GFR)= $\frac{V \; X \; UIN}{P_{IN}}$ = about 125 ml/minute.



- **Significance of inulin clearance:**

- **It measures GFR.**
- **It is used as a reference value:**

Substances having lower clearance than that of inulin (e.g. urea) means that they are reabsorbed in the renal tubules while those having higher clearances (e.g. creatinine) means they are secreted.



- Infusing inulin to determine clearance is not routinely used because of the invasive nature of the procedure.
- Instead, the renal clearance of the **endogenous substance creatinine is used to approximate GFR**.

Creatinine Clearance: موجود بشكل طبيعي في الجسم

- ✓ Creatinine is a by-product of muscle metabolism and is freely filtered by the kidneys.
- ✓ It is not reabsorbed, but there is about 10% secretion into the renal tubules from the peritubular capillaries, and thus, creatinine clearance overestimates GFR by about 10% but is close enough to be highly useful in most clinical situations.

inulin	creatinen
exogenus product (IV)	endogenous from end product of muscle meta
freely filtration	freely filtration
no absorbtion	no absorbtion
no secretion	secretion 10%
more accurat GFR = 125	less accurat ↑ GFR = 140 > 125
clinicaly not use	use clinicaly

2. If the substance is :

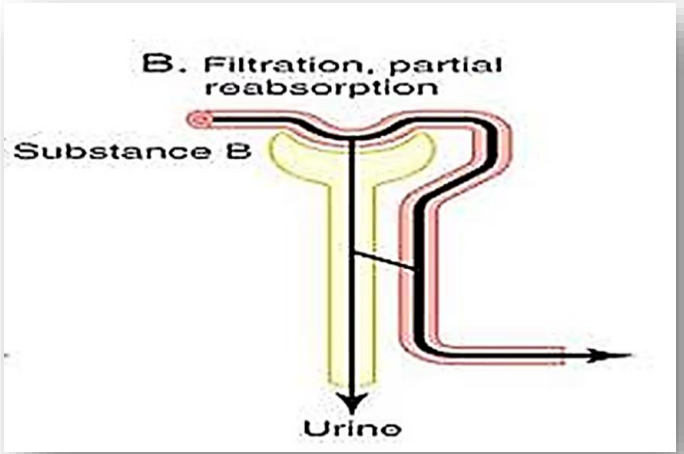
- **Freely filtered (in glomeruli)**
- **Partially reabsorbed and not secreted in the renal tubules:**

The amount excreted in urine/minute < the amount filtered/minute.

GFR > clearance of this substance.

e.g. urea.

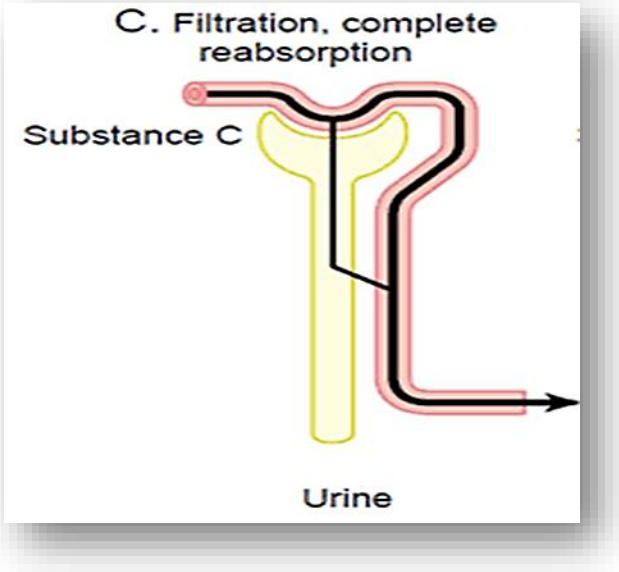
Urea clearance is normally about 70 ml/minute.



3. If the substance is:

- ✓ **Freely filtered in glomeruli**
- ✓ **Completely reabsorbed and not secreted in the renal tubules :**

The amount of substance excreted in urine/minute =zero
So, the renal clearance of this substance **= zero**.
e.g. Glucose



Glucose Transport and Tm_G

type of transport?

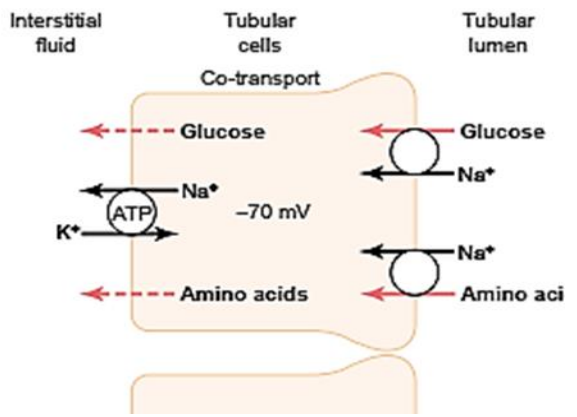
type of transporter?

- **Glucose reabsorption is an example of secondary active transport.**
- **For glucose transport, the rate-limiting step is the number of specific transporters (sodium-dependent glucose transporter (SGLT)-2) available in PCT.** site
- Glucose and Na^+ bind to the sodium-dependent glucose transporter (SGLT)-2 in the apical membrane, and glucose is carried into the cell as Na+ moves down its electrical and chemical gradient. The Na^+ is then pumped out of the cell into the interstitium, and the glucose exits by facilitated diffusion via glucose transporter (GLUT)-2 into the interstitial fluid.
- There is a **limit to the amounts of glucose that they can be transported per unit time known as the transport maximum (Tm). This is because the binding sites on the membrane transport proteins become saturated when the concentration of the transported substance increases to a certain level.**

maximum level to transport glucose due to

↑↑ glucose level lead to glucose urea

after saturation not reabsorbed and excretion in urine



- The **sodium-glucose carriers have a high transport maximum (Tm), and under normal conditions**, the filtered load of glucose is low enough that the transporters can carry all of the glucose back into the blood, leaving none in the tubular fluid and urine. Thus, **the renal clearance of glucose is normally zero**.
- However, if the filtered load (FL) of glucose is high, there may be too much glucose present in the tubular fluid and the carriers can become saturated.
- **The renal threshold for glucose: It is the plasma level at which glucose first appears in the urine. It is the point where the first nephrons exceed their Tm, resulting in glucose in the urine (glucosuria). It is about 200 mg/100 ml in arterial plasma**.
- When the plasma glucose concentration (and hence the filtered load of glucose) is under the renal threshold, all of the glucose in tubular fluid will be reabsorbed.
- However, when it exceeds the threshold, the transporters are saturated (Tm exceeded in some nephrons) and glucose appears in the urine.
- **The Tm_G is about 375 mg/min in men and 300 mg/min in women.**

transpor maximum of glucose

↑ more → lead to glucose in urin

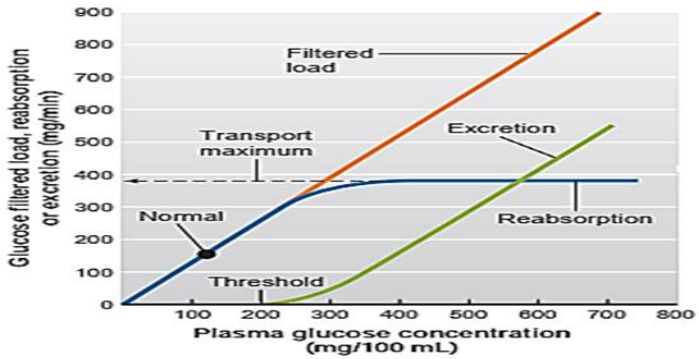


Figure 14.11 The relationship between plasma glucose concentration and the rate of glucose filtered (filtered load), reabsorbed, or excreted. The dotted line shows the transport maximum, which is the maximum rate at which glucose can be reabsorbed. Notice that as plasma glucose exceeds its threshold, glucose begins to appear in the urine.

(4) If the substance is

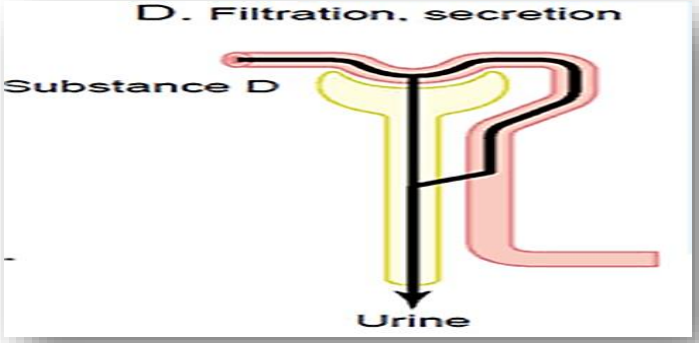
- ✓ **Freely filtered in glomeruli**
- ✓ **Partially secreted and not reabsorbed in the renal tubules**

then,

The amount excreted in urine/minute > amount filtered/minute.

The clearance of the substance > GFR.

e.g. Creatinine clearance (normally about 140 ml/minute).



(5) If the substance is

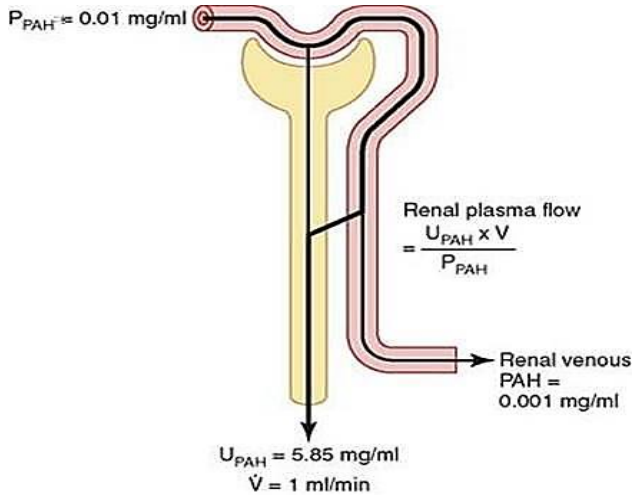
- **Freely filtered in glomeruli**
- **Completely secreted in the renal tubules and not reabsorbed.**

- So that the **renal venous blood is nearly free of the substance then,**
- **Consequently, all the plasma that enters the kidney per unit time is cleared of this substance.**
- **Therefore, the clearance of this substance = RPF (ml/minute).**
- **RPF** can be measured by infusing **p-aminohippuric acid (PAH)**.
- PAH is filtered by the glomeruli and secreted by the tubular cells,
- When PAH is infused, 90% of the PAH in arterial blood is removed in a single circulation through the kidney.
- So, the value obtained should be called the **effective renal plasma flow (ERPF)** to indicate that the level in renal venous plasma was not measured.
- **Extraction ratio** = Percentage of PAH removed from arterial plasma (90%).

- In humans, **ERPF** (= Clearance of PAH) averages about **585 ml/min**. Effective

So, 585 ml/minute represents 90 % of actual RPF.

- **Actual RPF= 585 X100/90= 650 ml/minute.**



Significance of renal clearance:

- **It is one of renal function tests.**
- **Measurement of GFR by inulin clearance.**
- **Measurement of RPF by PAH clearance.**
- **Estimation of filtration fraction (FF).**

$$\frac{GFR}{RPF} \times 100 = \frac{125}{650} \times 100 = 20\%$$

Urine Concentrating Mechanisms:
The Countercurrent Multiplier System

Renal Countercurrent Mechanism

Countercurrent system

- It is a system in which the **inflow** of a **current runs parallel, opposite (counter) and close to its outflow** for some distance.
- So, **LH (and vasa recta) acts as countercurrent system**.

Renal countercurrent mechanism:

- It is the **mechanism by which urine is concentrated in the kidney**.
- It **depends on the production and maintenance of a state of hyperosmolarity (hypertonicity) in the renal medullary interstitium (MI)** by the action of the structures that pass in the renal medulla which are:

1. **LH of juxtamedullary nephrons (countercurrent multiplier system)**. (production)
2. **Vasa Recta (countercurrent exchanger system)**. (maintenance)
3. **Medullary collecting ducts (MCDs).**

1. **LH of juxtamedullary nephrons:**

These constitute a **countercurrent multiplier system** that operates **actively** to **construct an osmotic stratification in the renal medulla (i.e. a progressively increasing hyperosmolarity in the renal medulla)**.

So that the osmolarity of the MI gradually increases from **300 mOsm/L in the renal cortex** to **1200-1400 mOsm/L** at the renal papillae.

2. **Vasa Recta (VR):**

These constitute a **countercurrent exchanger system** that operates **passively** to **maintain the hyperosmolarity of the MI**.

3. **Medullary collecting ducts (MCDs).**

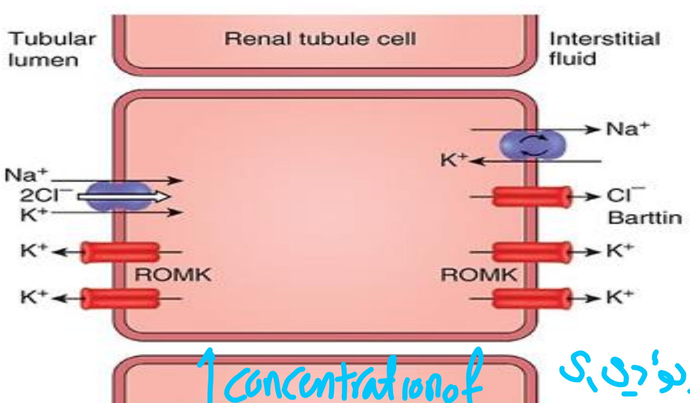
Countercurrent multiplier system

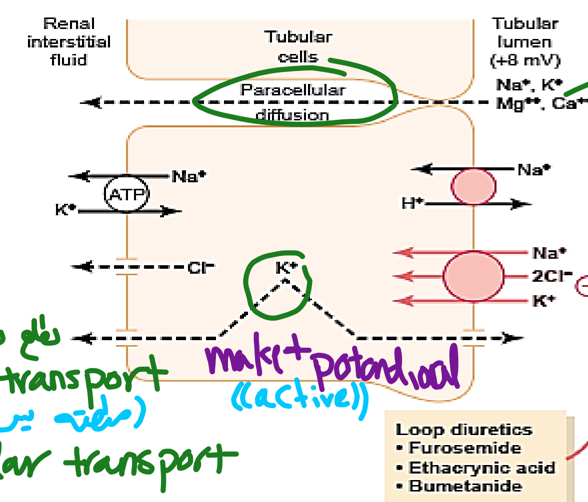
This system consists of **LH of juxtamedullary nephrons** which dip deeply in renal medulla, and is concerned with **production of graded hyperosmolarity in MI** by the following mechanism:

Steps involved in causing hyperosmotic renal medullary interstitium:

Step (1): First assume that the LH is filled with fluid with a concentration of 300mOsm/L, the same as that leaving PCT.

Step (2): There is **a carrier in thick ascending LH (TALH) which actively transported one Na^+, one K^+, and 2 Cl^- (Na^+- K^+ -2Cl^- Transporters) from the tubular lumen into the cells**. **Active transport of these solutes raises the interstitial concentration.**





Step (3): Osmosis of water out of the descending limb of LH raising osmolarity inside it gradually to about 1200 mOsm/L.

يسمح للماء بالخروج لكن مش للأملاح

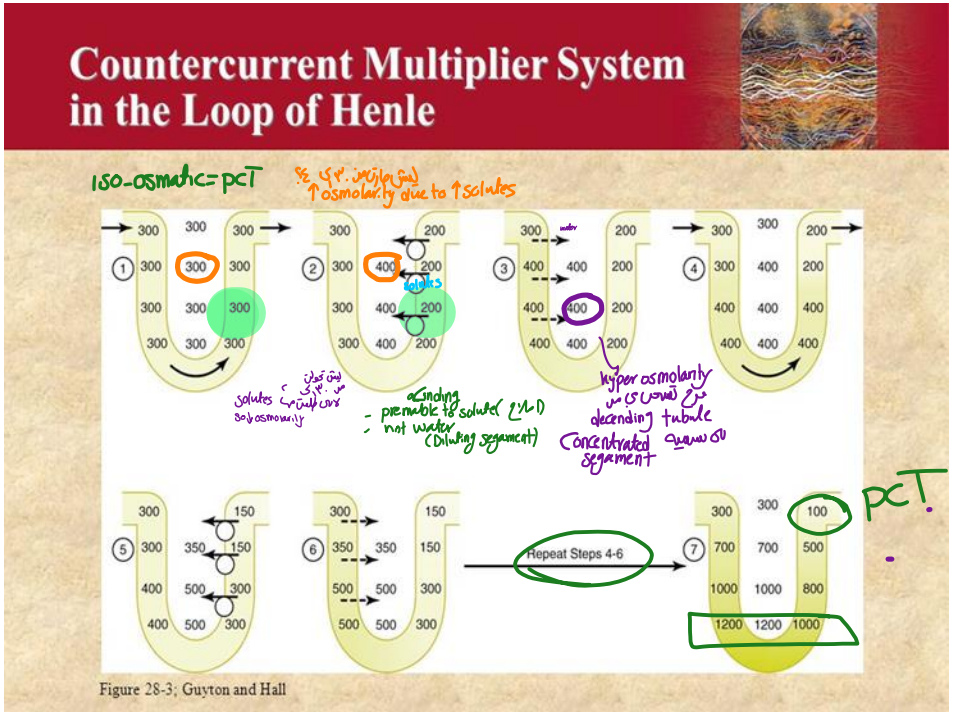
نسبة الأملاح إلى الماء جوه الأنبوب بتزيد = تركيز أعلى
وبيوصل تركيز السائل داخل الأنبوب بالتدريج لحوالي 1200

Step (4): Additional flow of fluid in LH from PCT, which causes the hyperosmotic fluid previously formed in the descending limb to flow into the ascending limb.

na k 2cl

Step (5): Active transport in the ascending limb repeated over and over with the net effect of adding more and more solutes to the medullary interstitium in excess of water.

نخلق بيئة تركيزها عالي عشان نقدر نسحب مي في
(Collecting ducts)



The ascending limbs of LH:

Are the segments responsible for creating graded hyperosmolality in MI.

✓ **The distal thick part (TALH):**

- It is **impermeable to water**.
- **Both Na^+ and Cl^-** are **actively transported** from the tubular lumen into the MI. This produces hyperosmolarity in the MI and at the same time, the tubular fluid becomes more **hypotonic (hypoosmotic)** with an osmolality about **100 mOsm/L when delivered to the DCTs**.
- The transport mechanism depends on **a carrier that transports one Na^+, one K^+ & 2 Cl^-** from the tubular lumen into the cells.

✓ **The initial thin part:**

- It is **impermeable to water but highly permeable to Na^+ and Cl^-**.
- **Na^+ and Cl^- diffuse passively (simple diffusion)** down their concentration gradients into MI.

Therefore, the tonicity of tubular fluid progressively decreases as it moves up while hyperosmolarity is developed in MI.

The descending limbs of LH:

- Receive **isotonic (iso-osmotic) fluid** from the **PCTs**.
- Their walls are:
- **Highly permeable to water.**
- **Impermeable to reabsorption of solutes (namely Na^+ and Cl^-).**
- Accordingly water passively diffuses outward down an osmotic gradient into the MI (which is hypertonic by the countercurrent multiplier effect of the ascending limb).
- As a result, the **tubular fluid becomes hypertonic, and its hypertonicity increases gradually as it flows downwards reaching 1200 (up to 1400) mOsm/L at the tips of the renal pyramids.**
- The **reabsorbed water in the LH is about 15% of the filtered water in the glomeruli, and it is also an obligatory reabsorption as that occurring in the PCTs.**

Causes of renal MI hyperosmolality:

1. **The thick ascending limb of LH (TALH):**
   - **Impermeable to water.**
   - **Active reabsorption of Na^+, K^+, and Cl^- (by common carrier protein that transports one Na^+, one K^+ & 2 Cl^-) with passive reabsorption of +ve ions.** para-cellular transport
   - There is a backleak of K^+ out of the cells into the lumen, creating a lumen-positive trans-epithelial potential difference (compared with interstitial fluid). This allows paracellular movement of cations (Ca^{2+}, Mg^{2+}, Na^+, K^+) out of the tubular lumen.

2. **The medullary collecting duct (MCD):**

ADH increases permeability to water → water reabsorption **(facultative water reabsorption)**→↑ concentration of **urea** in the tubular fluid→ diffuses to medullary interstitium **(urea recycling)**. excretion in urine 15% help in hyperosmolarity

3. **Transport** of additional Na^+ and Cl^- into the medullary interstitium from the **thin ascending limb of the LH.**

Countercurrent exchanger system of the vasa recta

Fortunately, the medullary blood flow has 2 characteristics:

1. It is **very sluggish representing 1-2% of the total RBF**. So, removal of solutes is minimized.
2. **The vasa recta function as a countercurrent exchanger** that **prevents wash out of solutes from the medulla. HOW?**

- Fluid flows through along U tubule, with its arms lying very close to each other so that fluid and solutes can exchange readily between the 2 arms (countercurrent exchanger).

- Thus, **as the blood flows down the descending limb, NaCl and urea diffuse into the blood from the highly concentrated interstitium while water diffuses outward into the interstitium**. Both effects cause the **blood osmotic concentration to raise progressively higher to a maximum of 1200 mOsm/L** at **the tips of vasa recta**.

- As the **blood flows back up the ascending limb, all the NaCl and urea diffuses back out the blood into the interstitium while water diffuses back into blood.**
- Therefore, **by the time the blood leaves the medulla with osmolarity slightly greater than that of the blood that had initially enter the vasa recta**. As a result, **blood flowing through the vasa recta carries only minute amounts of medullary interstitial solutes away from the medulla**.

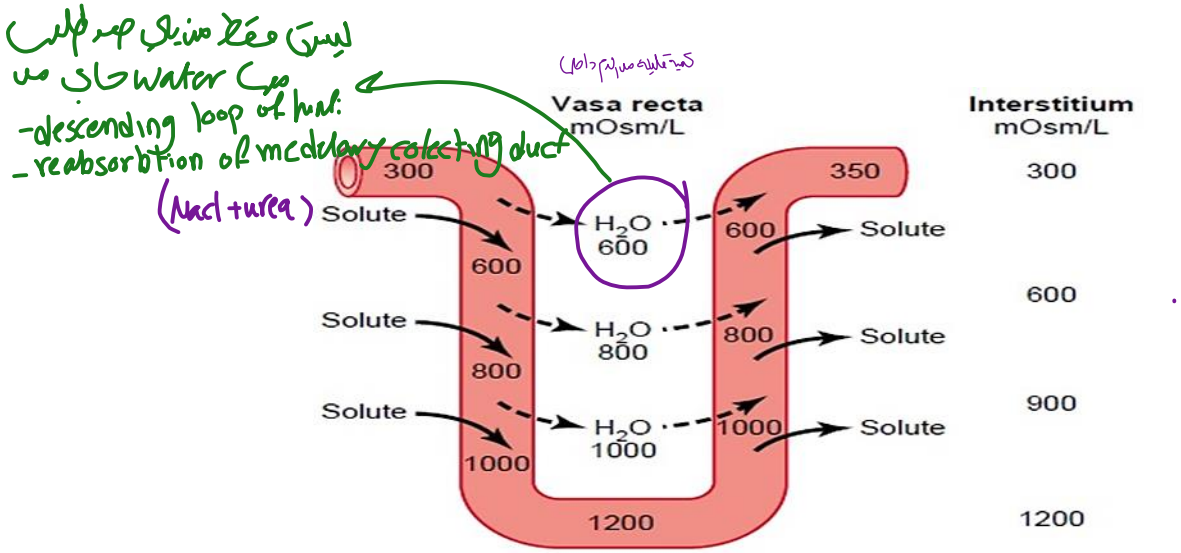


Figure 28–6

Countercurrent exchange in the vasa recta. 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. (Numerical values are in milliosmoles per liter.)

- In this way, **solutes are trapped in the MI while excess water is removed from it**, and both effects help **maintenance of MI hyperosmolarity**.
- **The excess water comes from 2 sources:**
  - **Water that diffuses from the descending limbs of both VR and LH.**
  - **Water that is reabsorbed from the MCDs.**
- **The countercurrent exchanger function of VR is helped by:**
  - **They are highly permeable to both solutes and water.**
  - **Blood flow is very sluggish (about 2% of total RBF).**
- **Thus, the main function of VR is to maintain the renal MI hyperosmolarity.**

Role of ADH in the Mechanism of Urine Concentration and Dilution

- ✓ Either **a small increase in plasma osmolarity (~1%) or a significant decrease (a greater than 10% loss) in plasma volume** (from, for example, hemorrhage or severe dehydration) will elicit release of antidiuretic hormone (ADH) from the posterior pituitary gland.
- ✓ **ADH binds to V2 receptors on principal cells of the renal collecting ducts.**
- ✓ The ADH increases apical water channels, or **aquaporins** (in the principal cells, **AQP-2**), In the presence of high concentrations of ADH, water reabsorption occurs from the **cortical collecting duct (about 10 %)** until the fluid in this segment becomes iso-osmotic to the interstitial fluid and peritubular plasma of the cortex—that is, until it is once again at 300 mOsm/L.
- ✓ The iso-osmotic tubular fluid then enters and flows through the medullary collecting ducts.
- ✓ In the presence of **high plasma concentrations of ADH**, **(about 4.7 %)** of water diffuses out of the medullary collecting ducts into the medullary interstitial fluid as a result of the high osmolarity that the loop countercurrent multiplier system and urea trapping establish there. Thus, leading to a **total water reabsorption of about 99.7% and a urine volume about 0.5 liter (obligatory urine volume) daily with an osmolarity of about 1400 mOsm/L (hypertonic urine)**.

- ✓ By this means, the **final urine is hyperosmotic**. By retaining as much water as possible, the kidneys minimize the rate at which dehydration occurs during water deprivation.
- ✓ **At the normal rate of ADH secretion, about 10 % of water is reabsorbed in the CCD and 4.2 % is reabsorbed in the MCDs, leading to a total water reabsorption of about 99.2% and a urine volume about 1.5 liters daily with an osmolarity about 400 mOsm/L.**

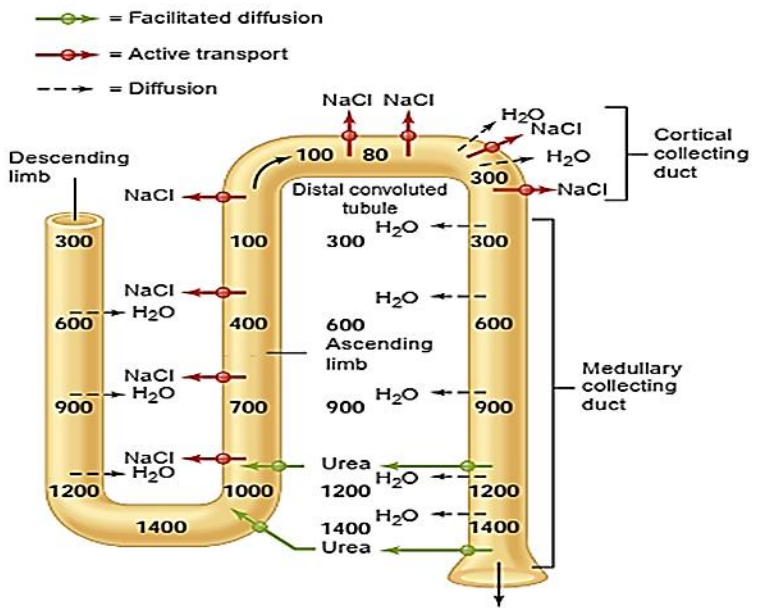
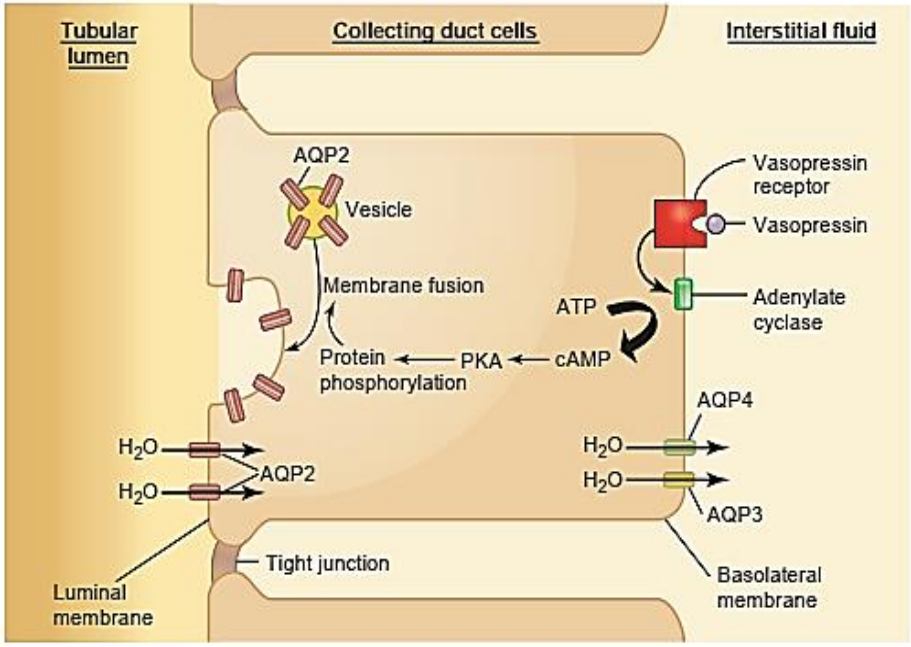


Figure 14.18 AP|R Simplified depiction of the generation of an interstitial fluid osmolarity gradient by the renal countercurrent multiplier system and its role in the formation of hyperosmotic urine in the presence of vasopressin. Notice that the hyperosmotic medulla depends on NaCl reabsorption and urea trapping (described in Figure 14.20).



- ✓ In contrast, **when plasma ADH concentration is low, both the cortical and medullary collecting ducts are relatively impermeable to water.**
- ✓ This occurs in cases of **hydration and after drinking large amounts of water.**
- ✓ It is produced secondary to **decreased secretion of ADH (as a result of both hypervolemia and blood hypotonicity)**.
- ✓ As a result, a **large volume of hypo-osmotic (dilute) urine is excreted, thereby eliminating an excess of water in the body**. When the excess fluid is excreted, the plasma osmolarity will increase.
- ✓ **In severe cases of diabetes insipidus**, the osmolarity of the tubular fluid in the CCDs decreases to about 90 mOsm/L and is further decreased in the MCDs, leading to excretion of a **large volume of dilute (hypo-osmotic) urine** with an osmolality less than 80 mOsm/L (about 50 mOsm/L).
- ✓ In cases of **complete absence of ADH, the urine osmolarity becomes about 30 mOsm/L, and its volume about 23.3 liters/day**.

تركيز الـ	حجم البول	حالة الـ ADH
mOsm/L 1400	0.5 لتر/يوم	عالي
mOsm/L 400	1.5 لتر/يوم	طبيعي
mOsm/L 90–50	15 لتر/يوم	منخفض
mOsm/L 30	23.3 لتر/يوم	غايب تماماً

Q22. Active reabsorption of glucose occurs in? Select one:

a. Proximal tubule
b. Loop of Henle
c. Distal tubule
d. Collecting duct
e. Bowman capsule

Answer: a. Proximal tubule

Q23. Glycosuria is most likely to occur with?

a. Increased GFR and increased blood glucose level
b. Decreased GFR and normal glucose level
c. Increased plasma protein level
d. Hypoglycemia and low GFR
e. Normal glucose with increased renal threshold

Answer: a. Increased GFR and increased blood glucose level

Q24. The following are the characteristic of substances suitable for measuring GFR, except?

a. Freely filtered
b. Stored in kidney
c. Not protein bound
d. Neither reabsorbed nor secreted
e. Metabolized by kidney

Answer: e. Metabolized by kidney

Q25. With respect to renal handling of glucose? Select one:

a. Normally, all glucose present in glomerular filtrate is partially reabsorbed during its passage in PCT.
b. Glucose reabsorption in PCT is a primary active transport mechanism not dependent on sodium transport.
c. Glucose and other sugars like galactose, mannose and fructose show competition on the same carrier.
d. Higher the plasma glucose level, the more its amount reabsorbed.
e. The kidney not the liver is the main site of glucose homeostasis.

Answer: d. Higher the plasma glucose level, the more its amount reabsorbed

21. Increase in GFR occurs with which of the following conditions?
a. Increased sympathetic stimulation
b. Decreased renal blood flow
c. Hypoproteinemia
d. Ureteric obstruction
e. Severe hemorrhage to get rid of waste products
Ans: C

22. Factor affecting GFR are? Select one:
a. Changes in renal blood flow
b. Changes in glomerular capillary hydrostatic pressure
c. Ureteric obstruction
d. Combined effects of Changes in renal blood flow, Changes in glomerular capillary hydrostatic pressure and Ureteric obstruction.
e. Changes in respiratory rate.
Ans: D

23. When GFR fall, the Na excretion well? Select one:
a. Fall
b. Increase
c. Fall followed by increase
d. No charge
e. Increase followed by sharp decrease
Ans: C

Answer: B

20. Which of the following statements regarding Bowman's capsule pressure (CP) is correct?

A) It is about 18 mmHg and results from plasma proteins.
B) It is about 32 mmHg and results from fluid in Bowman's capsule.
C) It is about 18 mmHg and results from fluid accumulation in Bowman's capsule.
D) It is about 10 mmHg and results from filtration of proteins.
E) It is about 32 mmHg and results from hydrostatic pressure in capillaries.

Answer: C

BLOOD FLOW (RBF)

ly, **RBF is about 1200 ml/minute**

21. Renal blood flow is? Select one:

a) 0.8 - 1.2 L/min
b) 1.2 - 1.3 L/min
c) 1.5 - 2 L/min
d) 2 - 2.5 L/min

RPF = 650

ماتخبط !!

e) 5 - 6 L/min

Answer: b

22. All of the following are true about the glomerular capillaries, EXCEPT? Select one:

a) Low pressure capillary bed.
b) Drain into efferent arteriole.
c) Highly permeable with wide fenestrae.
d) Provide wide surface area for filtration.
e) Engulfed with Bowman's capsule.

Answer: a