GLOMERULAR FILTRATION

BY

Dr. Abdullah Kishawi

MMed Science in Nephrology.

ISN Fellowship, Sheffield, UK

Head Of Nephrology Department

Shifa Hospital

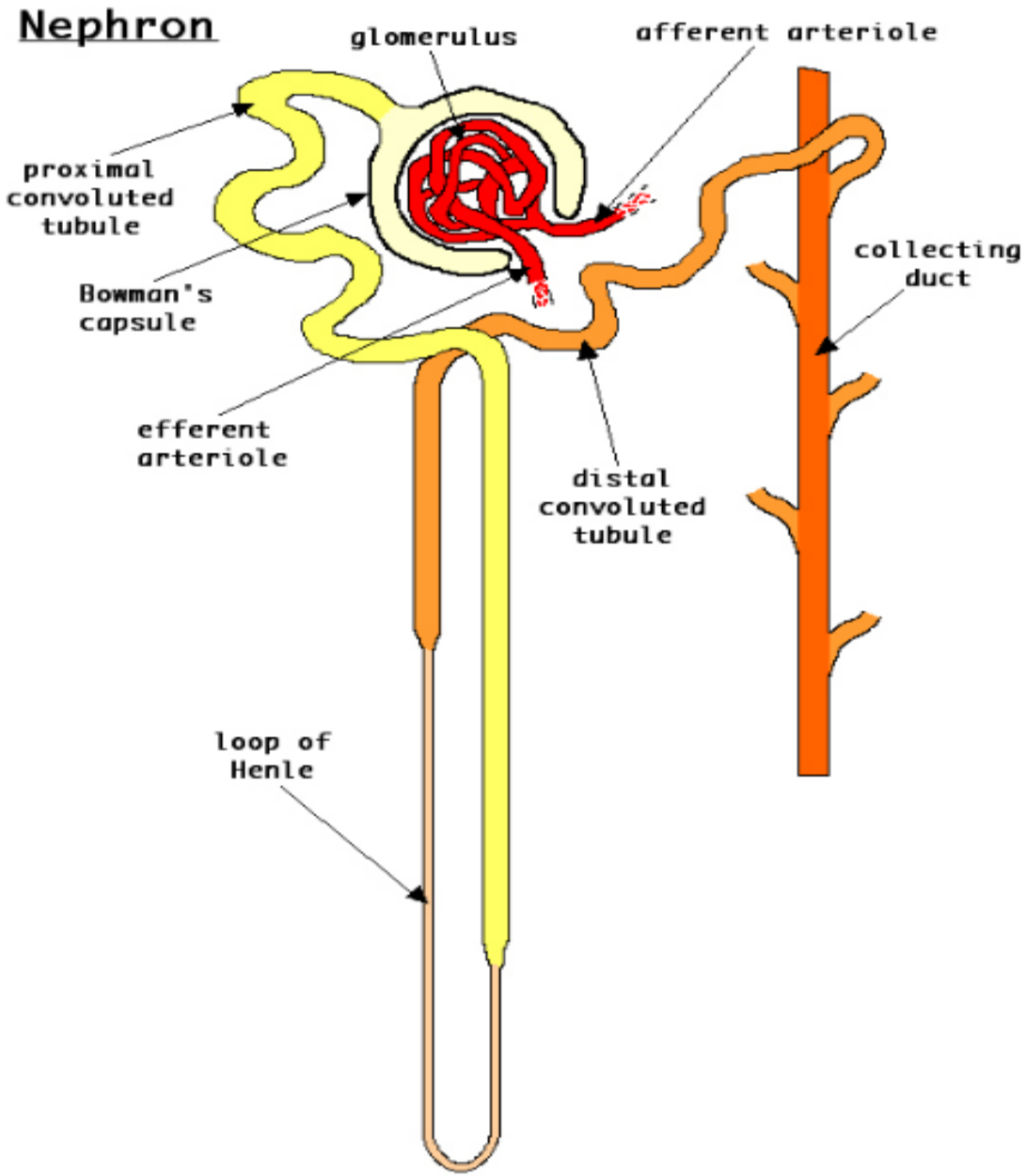
The Nephron

Is the functional unit (i.e capable of forming urine) of the kidney.

About **2.000.000** nephrons in Both kidneys.

Nephron parts:

1. **Glomerulus** : through which fluid is filtered from blood to
2. **Tubules** (PCT, Loop of henle, DCT , CT): fliltered fluid is converted into urine on its way to the pelvis.


Nephron
glomerulus
afferent arteriole
proximal convoluted tubule
Bowman's capsule
collecting duct
efferent arteriole
distal convoluted tubule
loop of Henle

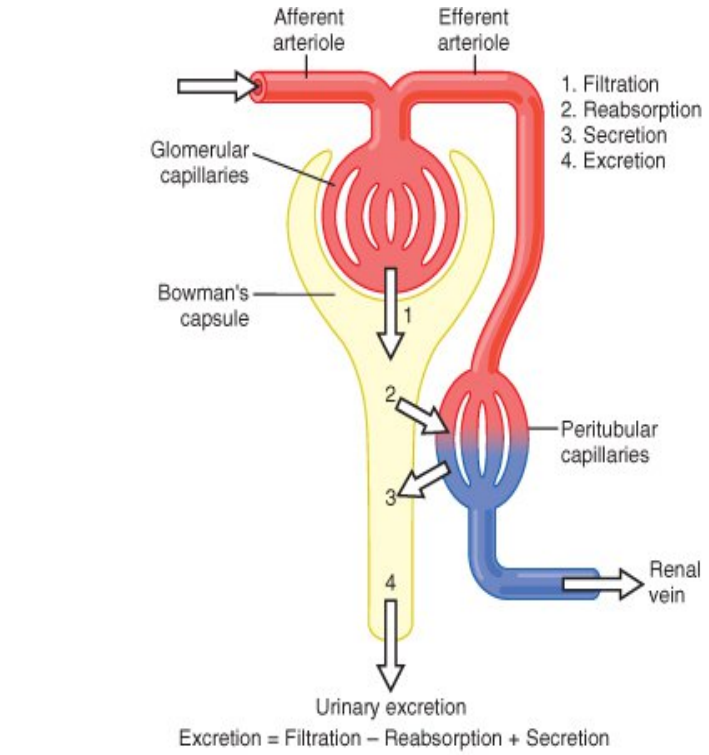
Urine formation

Urine formation results from:

1. Glomerular filtration.
2. Reabsorption of substances from renal tubules.
3. Secretion of substances from the blood into renal tubules.

Urine formation

Urinary excretion rate =
Filtration rate –
Reabsorbtion rate +
Secretion rate



Urine formation

Rate of filtration & reabsorbtion are extremely high relative to the rate of excretion.

Urine formation

Small changes of filtration or reabsorption rate can lead to large volume of urine when other is constant.

Urine formation

Reabsorbed substances:

Completely reabsorbed as Glucose and amino acids.

Highly reabsorbed as Na, Cl, HCO_3 ions.

Poorly reabsorbed as urea, creatinine, UA.

Urine formation

Advantages of high GFR:

1. Allow the kidneys to rapidly remove waste products.
2. All the body fluids to be filtered and processed by the kidney many times each day to control body fluids.

Urine formation

Each of the processes—glomerular filtration, tubular reabsorption, and tubular secretion is regulated according to the needs of the body.

Glomerular filtration

Considered the 1st step in urine formation.

The composition of most substances of glomerular filtrate in Bowman capsule is almost the same as in plasma, except proteins.

Few molecular-weight substances, such as Ca, fatty acids are not freely filtered because they are partially bound to the plasma proteins.

Glomerular capillary membrane

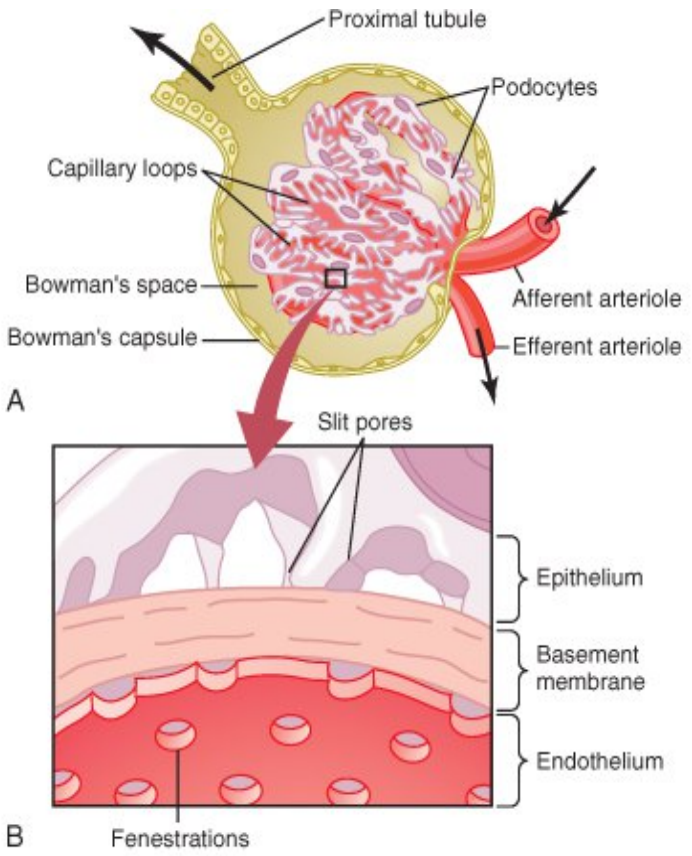
1- endothelium of the capillary

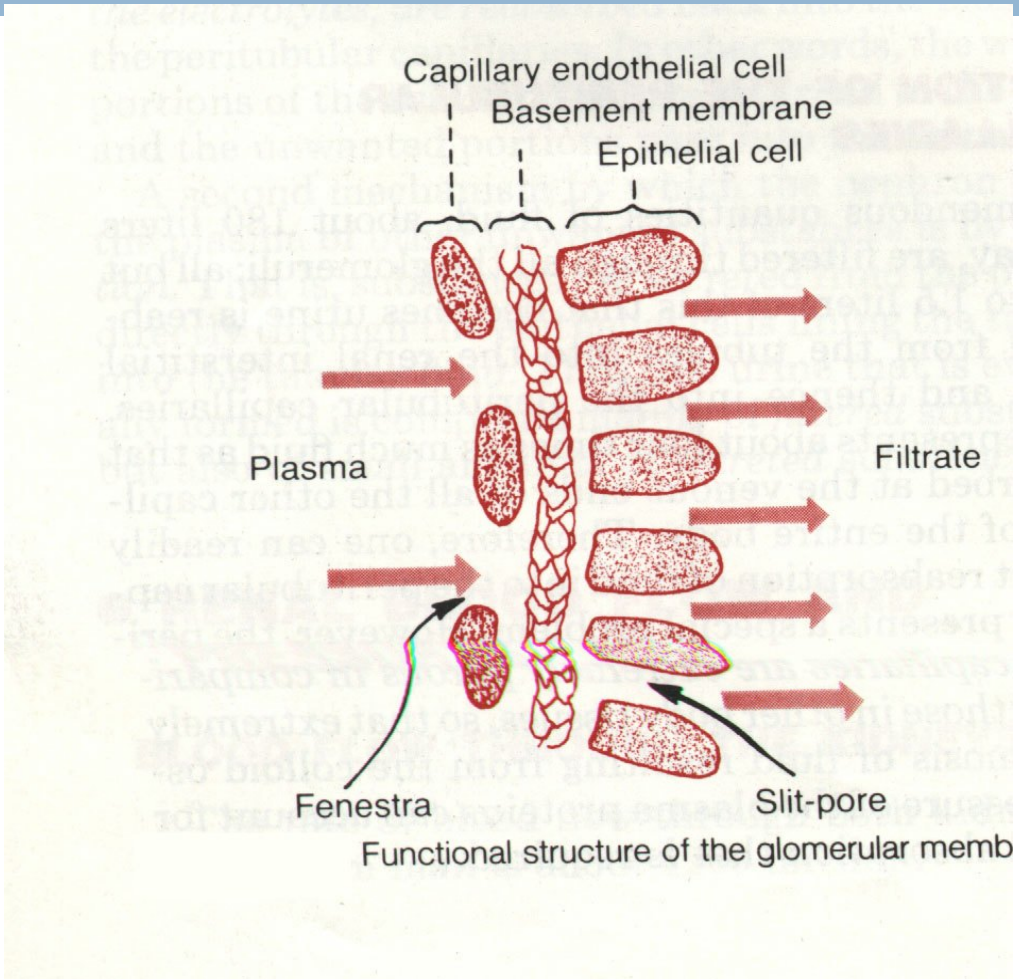
2- basement membrane:

3- epithelial cells:

Glomerular filtration barrier is selective, based on size & electrical charge of the molecules

Eg: Minimal change nephropathy: negative charge of the basement membrane are lost which lead to filtration of albumin (Albuminuria)





Functional structure of the glomerular memb

Characteristics of glomerulus basement membrane

1- High permeability (100-500 greater than capillaries)

2- Selectivity why : - pore size GM (8nanometer)

-basement membrane.....

(negative proctoglycan)

Molecules < 5,200 Mw : e.g inulin are filtered 100%

Molecules ~ 30,000 e.g protein only0.5% are filtered

Albumin (6 nanometer) 69.000 only 0.005 permeabihty .

G.M is almost impermeable to protien but almost always permeable to dissolved subs

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	5,500	1.0
Myoglobin	17,000	0.75
Albumin	69,000	0.005

Renal Blood flow

Rate : 1200 ml / min (in both kidney in 70 Kg man)

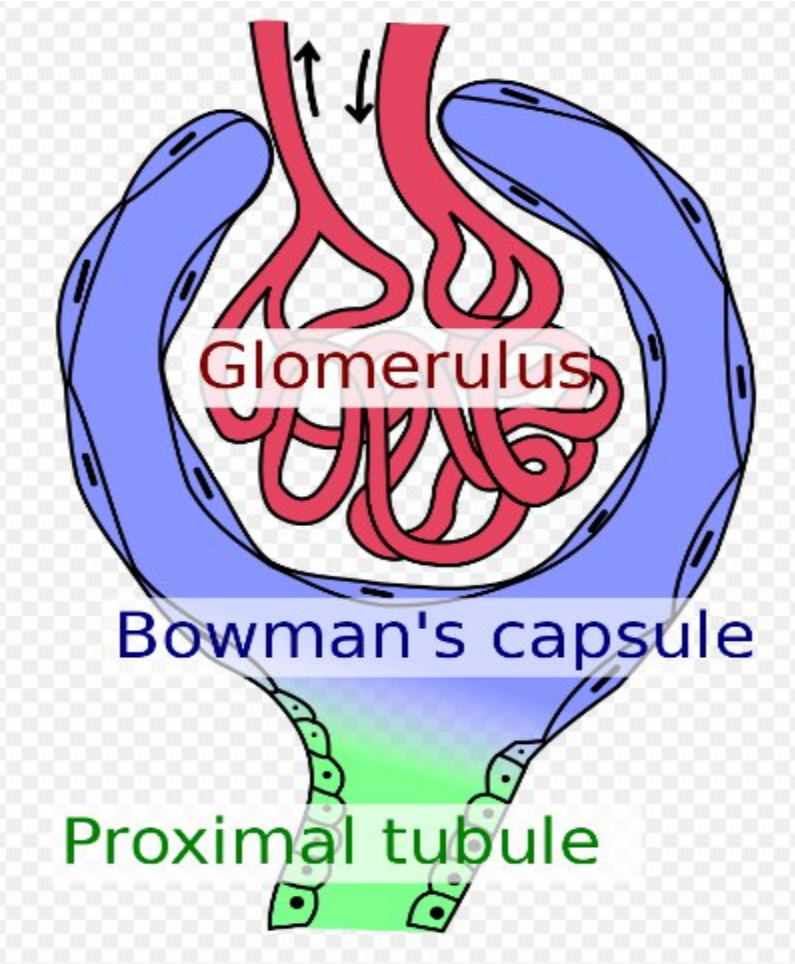
COP= 5600 ml/min

Range of renal fraction = 21% of COP.

Glomerular filtrate

Glomerular filtrate is the fluid that is filtered into the bowman's capsule through the glomerular membrane .

Glomerular filtrate



Determination of GFR

GFR is determined by:

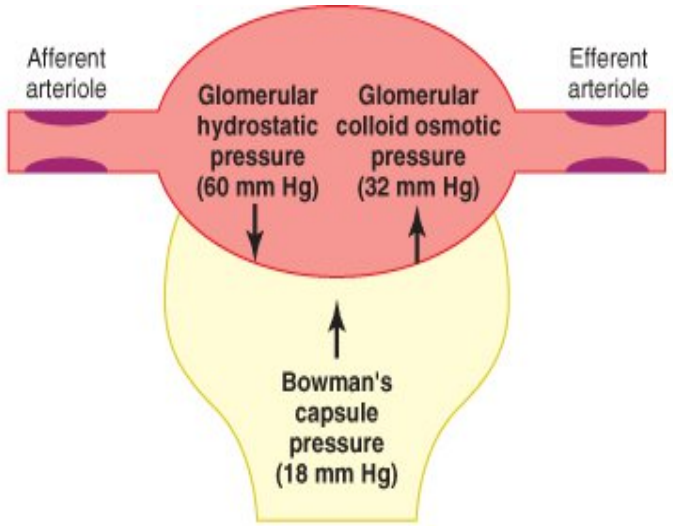
GFR= Kf x net filtration Pr.

Net filtration=Sum of hydrostatic pr. and colloid osmotic pr. across GBM .

(P_G-P_B-π_G+ π_B)

Kf= surface area of Glomerular capillaries. (filtering and permeability).

Kf=12.5 ml/min/mm Hg



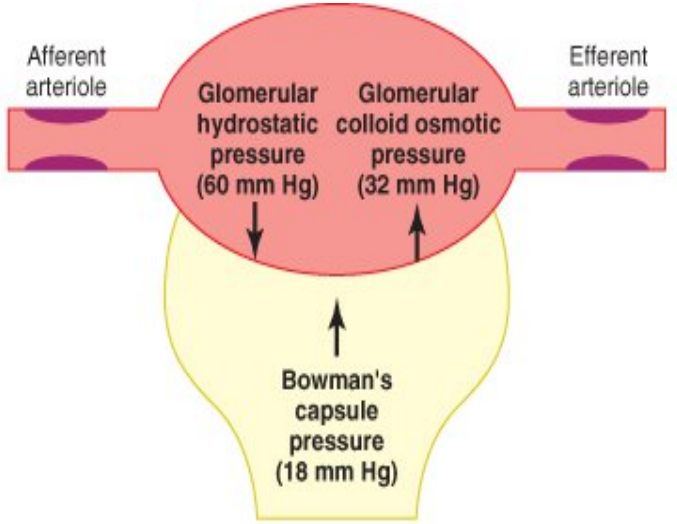
Determination of GFR

P_G=Hydrostatic pressure inside the glomerular capillaries which promotes filtration.

P_B=the hydrostatic pressure in Bowman's capsule outside the capillaries, which opposes filtration.

π_G =colloid osmotic pressure of the glomerular capillary plasma proteins , which opposes filtration.

π_B =the colloid osmotic pressure of the proteins in Bowman's capsule



Determination of GFR

GFR = 125 ml/min., 180 l/ day

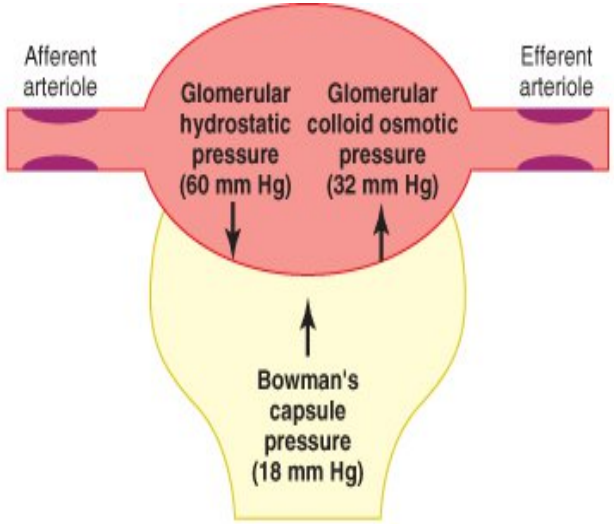
Glomerular capillary has higher filtration than other capillaries because of high P_G & large K_f

Filtration fraction= GFR/RBF

Net filtration pressure = $P_G-P_B-\pi_G+\pi_B$

=10 mmHg

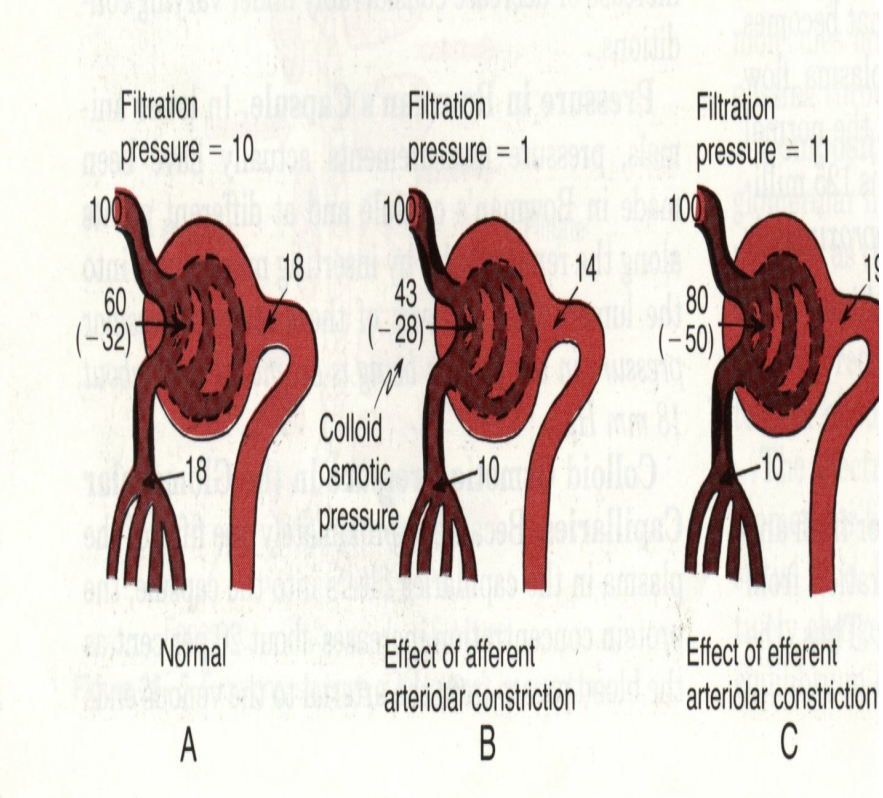
GFR= Kf x ($P_G-P_B-\pi_G+\pi_B$)



$GFR = Kf \times (P_G - P_B - \pi_G + \pi_B)$

$125 = Kf \times (60 - 18 - 32 + 0)$

$Kf = 12.5 ml/min/mmHg$



K_f

The Kf cannot be measured directly.

Estimated experimentally by:

K_f = GFR/net filtration pressure =12.5 ml/min/ mmHg

Pathophysiology: decreased number of functional glomerular capillary (surface area) or increased wall thickness→ ↓K_f→ ↓GFR

Like: HTN, DM, renal disease.

Changes in Kf don't provide a primary mechanism for the normal day to day regulation of GFR.

P_B

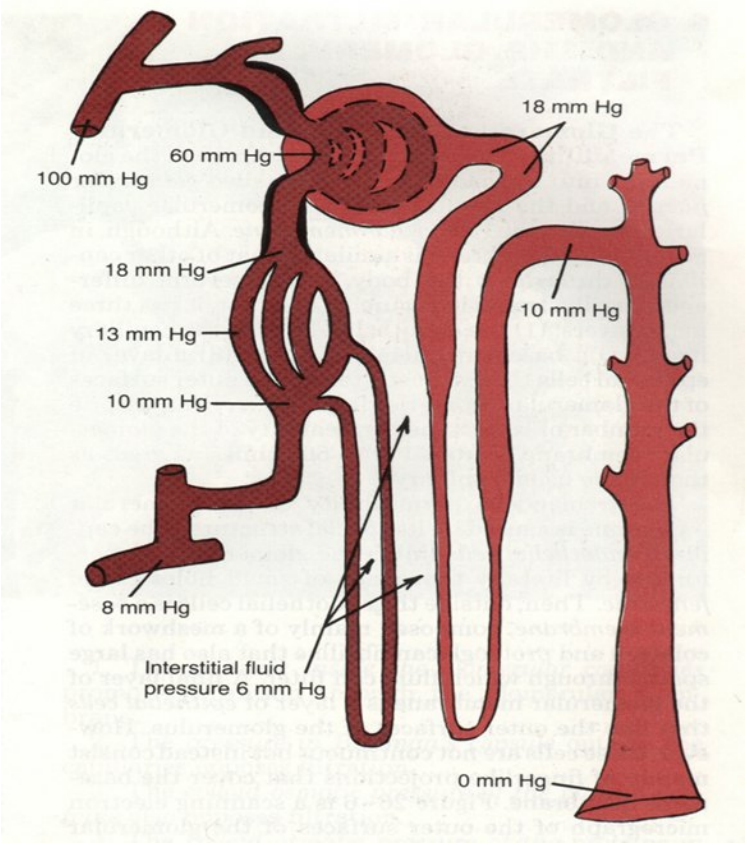
$\uparrow P_B \rightarrow \downarrow GFR$

$GFR = K_f \times (P_G - P_B - \pi_G + \pi_B)$

$GFR = 12.5 \times (60 - 18 - 32 + 0)$

Don't serve normally as a primary regulator of GFR

Pathophysiology: urinary tract obstruction (renal stones)



P_G

Primary mean for physiologic regulation of GFR

Determinants:

1- Arterial pressure:

↑Bp→ ↑P_G→ ↑GFR, has small effect due to autoregulation

2- Afferent arteriole resistance:

↑R_A → ↓P_G

Physiologic causes: increased sympathetic activity, vasoconstrictor hormones

3- Efferent arteriole resistance:

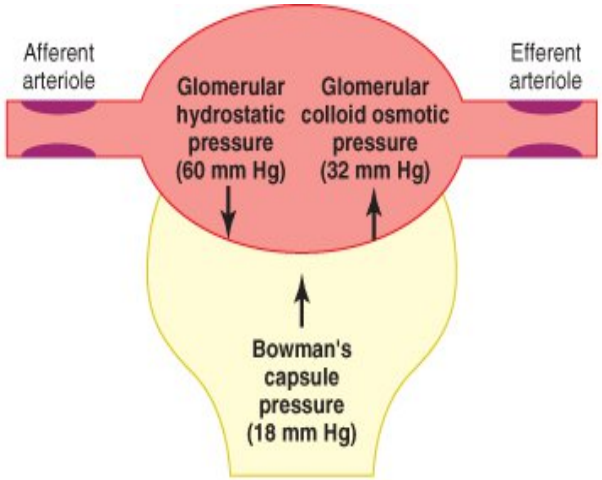
↓R_E → ↓P_G, patophysiology: angiotensin II blocker

Efferent arteriole constriction has biphasic effect

A- moderate level: ↑R_E→ ↑P_G → ↑GFR

B- severe constriction:

↓RBF → ↑π_G → ↓GFR, when the ↑of π_G > ↑of P_G



$$GFR = K_f \times (P_G - P_B - \pi_G + \pi_B)$$

↑P_G→ ↑GFR

π_G

π pressure =28 mmHg at afferent arteriole

π pressure=36 mmHg at efferent arteriole

Average= 32 mmHg, due to↑ 20% of plasma proteins concentration.

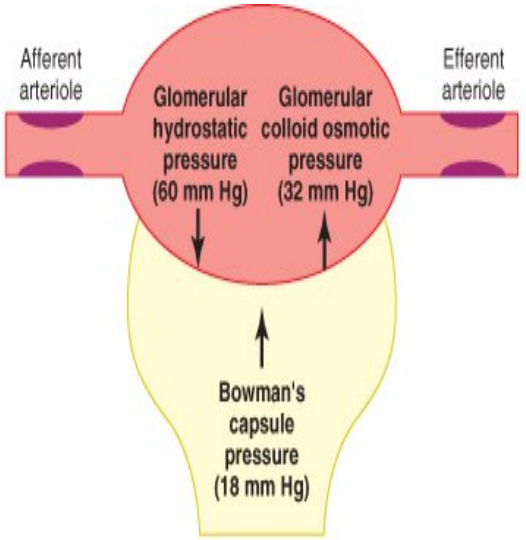
Factors affecting πG :

1-↑π pressure in arteries→↑π_G→↓GFR

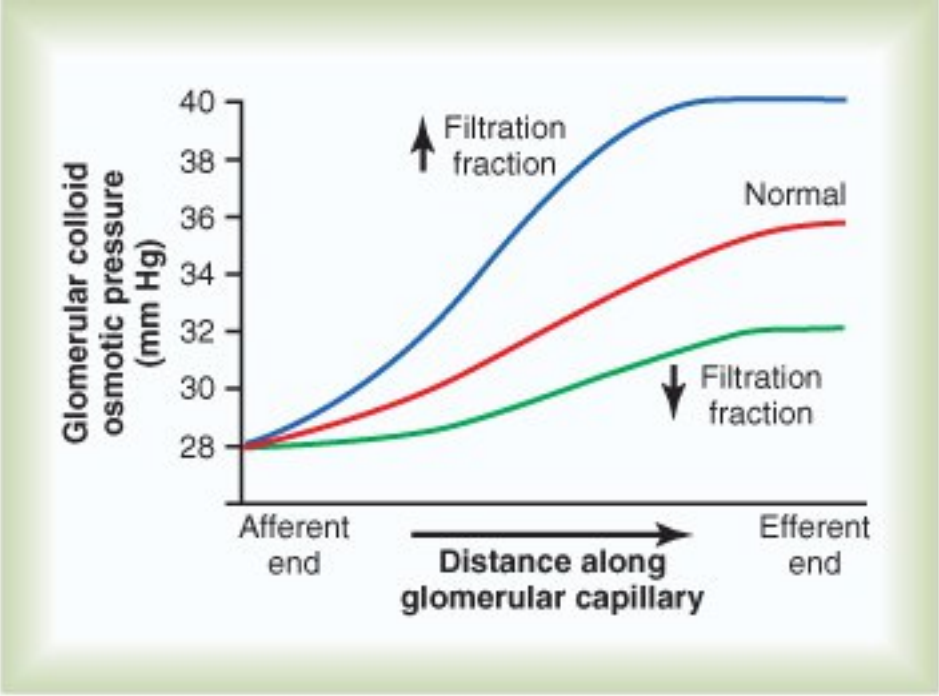
2-↑filtration fraction (GFR/RBF)→ concentrate proteins → ↑π_G →↓GFR

--↓RBF→↑ filtration fraction →↑π_G→↓GFR ,

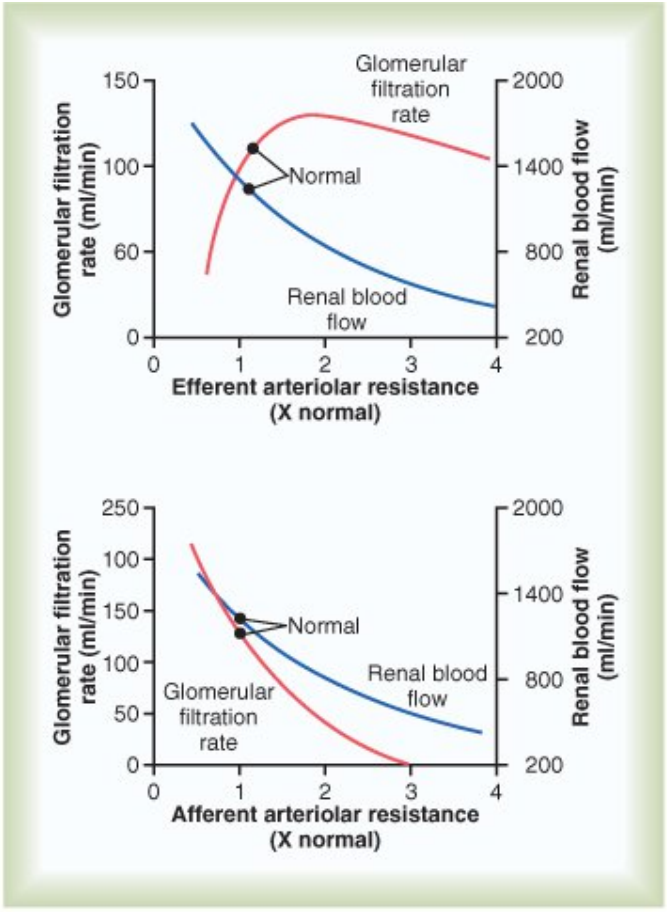
Pathophysiology:↓ RBF,↑plasm proteins.



π_G



P_G



Renal Blood Flow

Rate : 1200 ml / min (in both kidney in 70 Kg man)

COP= 5600 ml/min

Range of renal fraction:

21% of COP.

Renal Blood Flow

Advantages of high RBF:

Supply enough plasma for high GFR.

which regulate rapidly removal of waste products&

control body fluids.

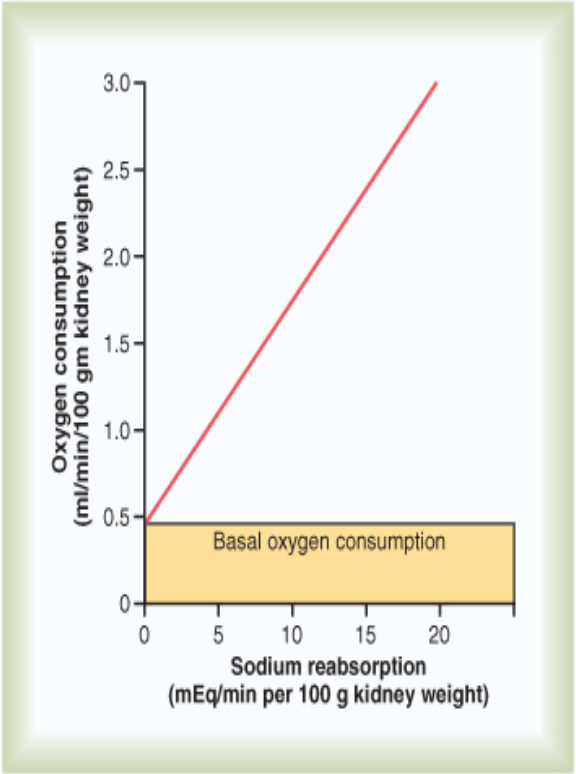
RBF

RBF is 7 times brain BF

Renal O2 consumption is twice that of brain.

Large fraction of O2 consumption is due to high rate of active Na reabsorption.

↑RBF→ ↑GFR→ ↑Na filtration→ ↑Na reabsorption→ ↑O2 consumption.



Determinants of RBF

$$\frac{\text{Renal artery pressure - Renal vein pressure}}{\text{Total renal vascular resistance}}$$

RA pressure= systemic BP.

RV pressure=3-4 mm/Hg

Interlobular A., afferent, efferent arterioles determine resistance.

Resistance of these vessels is controlled by the sympathetic nervous system, various hormones.

An increase in the resistance of any of the vascular segments of the kidneys tends to reduce the RBF, whereas a decrease in vascular resistance increases RBF if renal artery and renal vein pressures remain constant.

RBF, GFR relatively constant over arterial pressure change between 70 -170 mmHg (autoregulation)

The renal cortex, receives most of the kidney's blood flow.

Blood flow to renal medulla is very low =1-2% of RBF, supplied by vasa recta.

Physiologic control of GFR & RBF

The determinants of GFR that are most variable and subject to physiologic control include P_G & π_G

1- Sympathetic activation

2- hormones & autacoids

3- auto-regulation

Sympathetic activation

Strong activation→ constrict arterioles→ ↓RBF& GFR

Most important in ↓ GFR during severe, acute disturbance lasting for few min to few hours.

Such as: defense reaction, brain ischemia, severe hemorrhage

Mild & moderate→ little effect on GFR

Such as: sympathetic reflex resulting from ↓ in pressure at the carotid sinus baroreceptors

Hormonal & Autacoids

Autacoid: vasoactive substance released by the kidney & act locally

1-Norepinephrine & epinephrine:

Released by adrenal medulla

Little effect, except under extreme conditions (like severe hemorraghe)

2-Endothelin:

Released by damaged vascular endothelial cells

Minimize blood loss

↓GFR

↑ In diseases associated with vascular injury, like: toxemia of pregnancy, ARF, CRF.

Hormonal & Autacoids

3- Angiotensin II:

Circulating hormone & locally produced autacoid

Constrict efferent arterioles→↑ PG→ ↑GFR & ↓RBF

Realeased in hypotension , hypovolemia or hyponatremia to prevent ↓ of P_G & GFR.

↑ Tubular reabsorption of Na & water(autoregulation).

4- Endothelial- derived NO:

Released by vascular endotheluim

Vasodilator, ↑GFR.

5- PG_{E2} & PG_{I2} & Bradykinin:

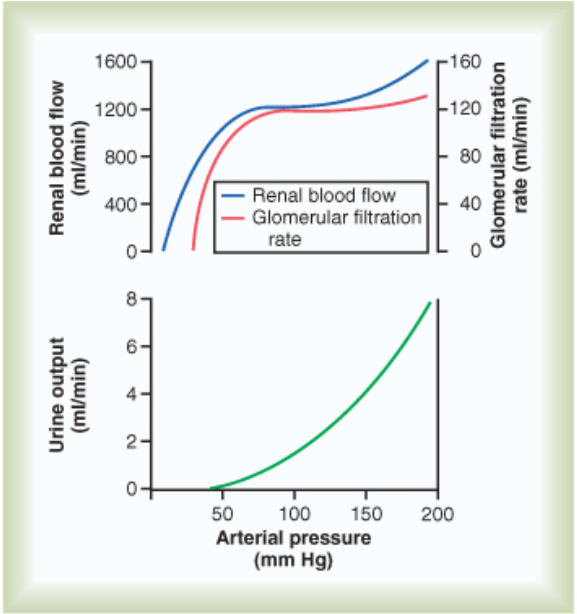
Vasodilator (not a major important of regulation).

After stressful conditions, administration of NSAIDs like Aspirin→ inhibit PG→ significant reduction of GFR.

Autoregulation

Feedback mechanisms intrinsic to the kidneys, keep RBF & GFR relatively constant, despite marked changes in arterial blood pressure.

The major function of autoregulation to maintain a relatively constant GFR and to control renal excretion of water and solutes.



Autoregulation

GFR= 180 L/day.

Tubular reabsorption= 178.5 L/day.

leaving 1.5 L/day of fluid to be excreted in the urine.

In the absence of autoregulation:

small increase in BP(from 100-125 mm Hg) (25%) cause increase in GFR (from 180 to 225 L/day).

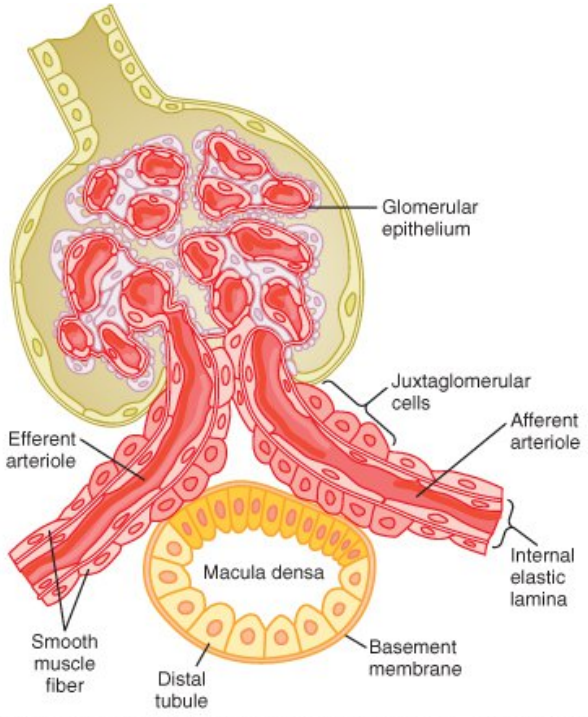
UOP= 46.5L/day.

A change in arterial pressure exerts much less of an effect on urine volume for:

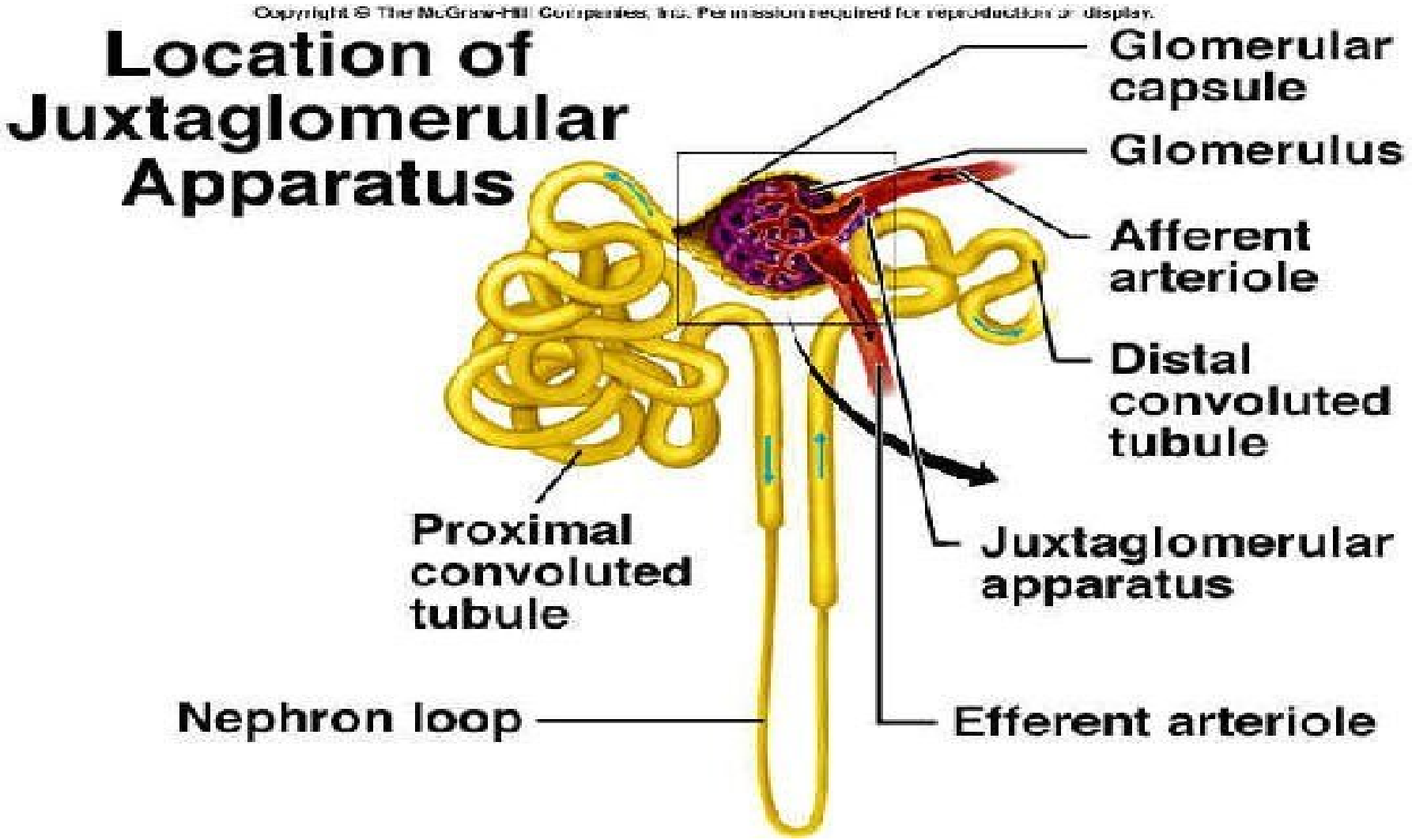
1. Renal autoregulation prevents large changes in GFR.
2. Glomerulotubular balance: adaptive mechanism that allow tubule to increase their reabsorption rate when GFR rises.

Tubuloglomerular feedback

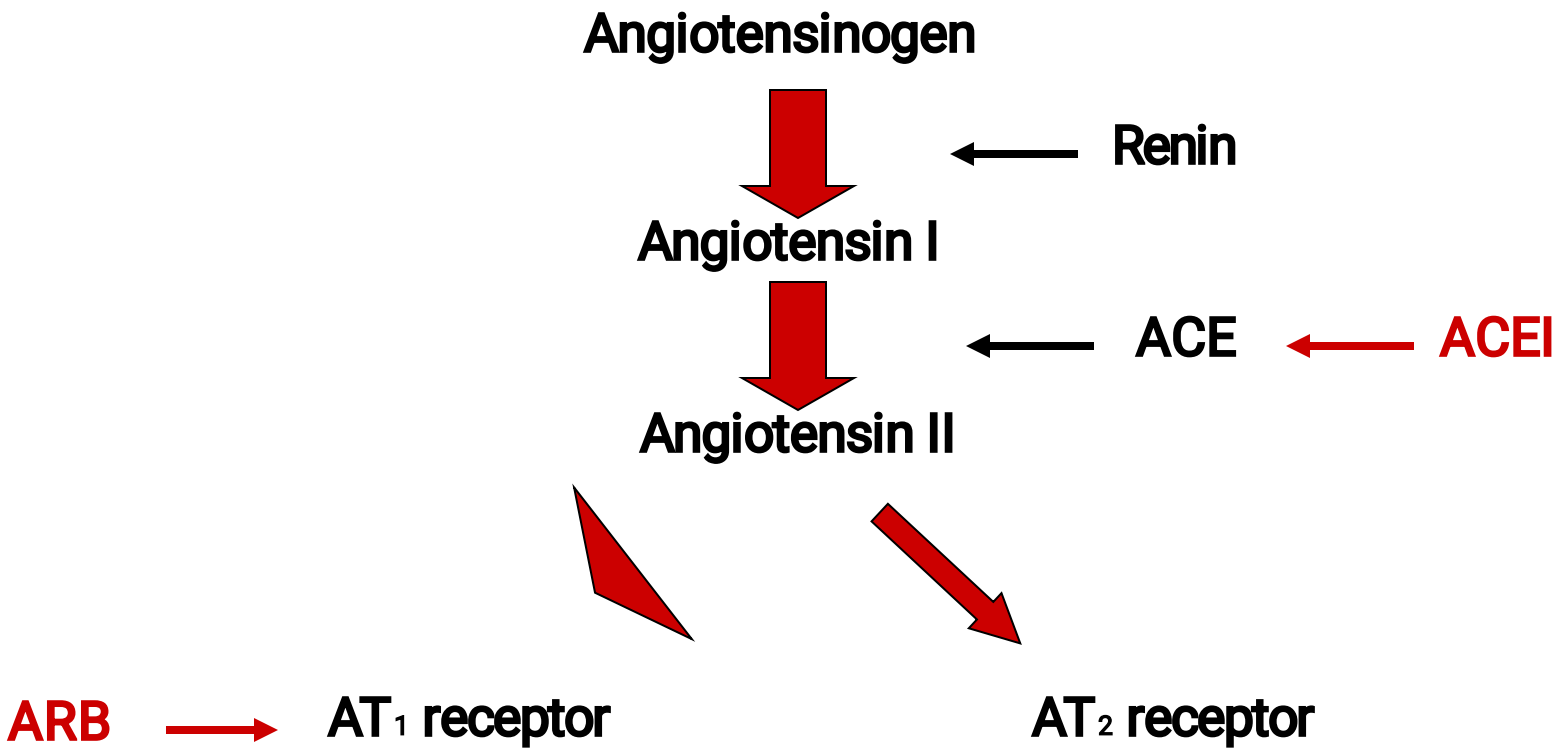
- 1st line of defense against change in GFR
- Ensure a relatively constant delivery of Nacl to the distal tubule & prevent fluctuation in renal excretion
- Juxtaglomerular complex



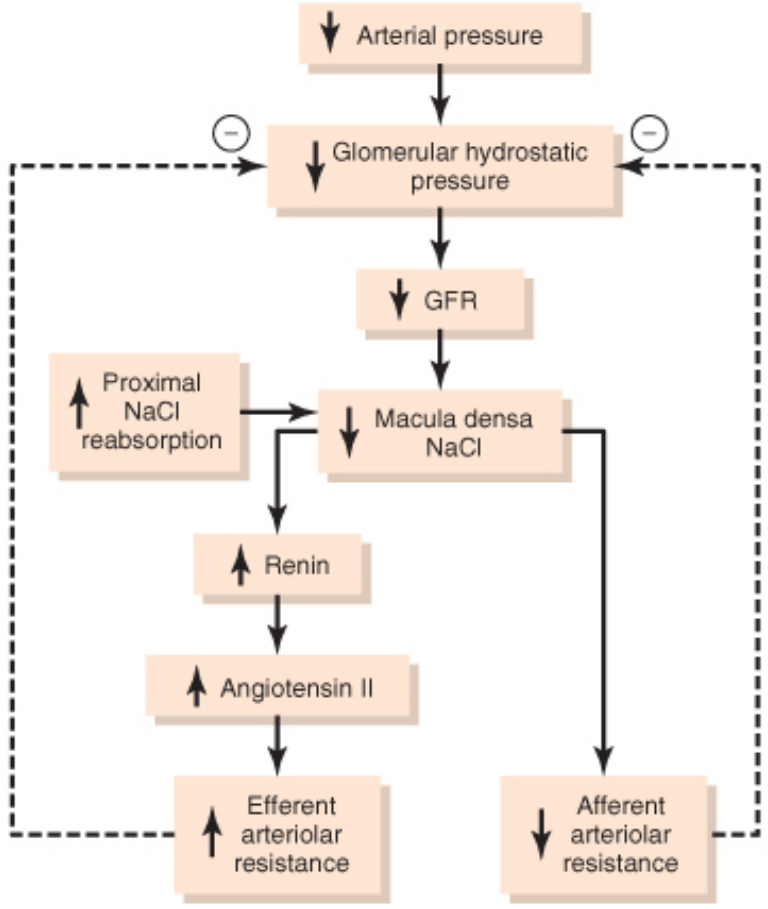
Tubuloglomerular feedback



Renin – Angiotensin Aldosterone System (RAAS)



Tubuloglomerular feedback



Clinical application

Blocking angiotensin II by ACEI in case of renal hypoperfusion due to decrease in renal arterial pressure→ further reduction of GFR

Its contraindicated in renal artery stenosis

Myogenic autoregulation of RBF&GFR

Ability of individual blood vessels to resist stretching during ↑ arterial pressure (myogenic mechanism)

↑Wall tension→ allow ↑ movement of Ca into cells→ vascular smooth muscles contraction (small arterioles) → prevent overdistension of vessels, helps prevent excessive increases of RBF and GFR when BP increases.

Other factors affect GFR as proteins & glucose.

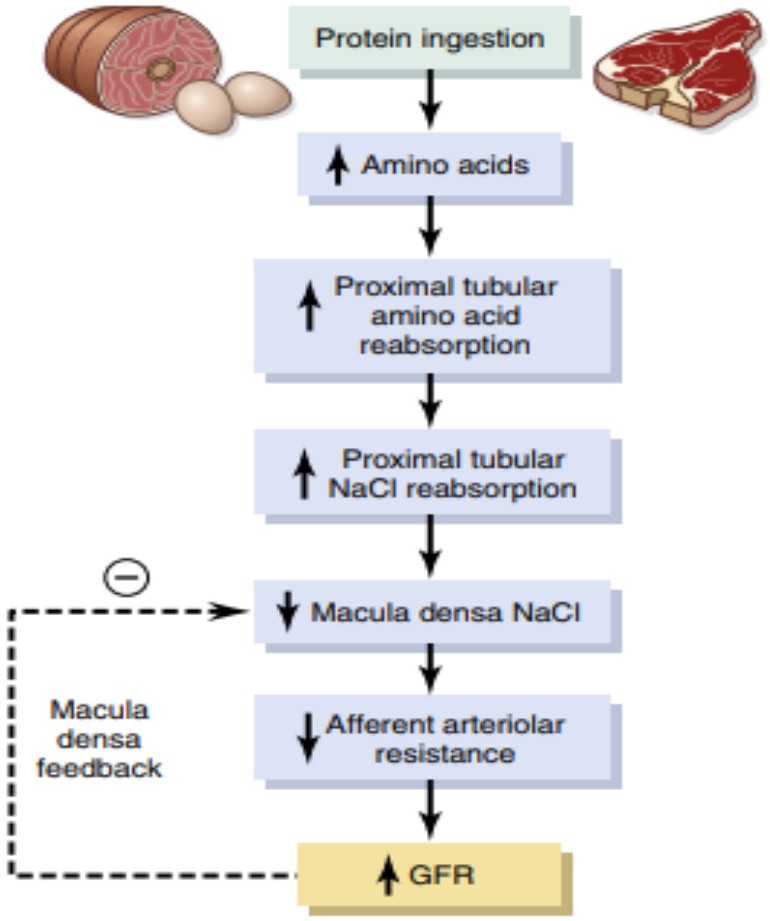
High protein meal→ ↑ filtration of a.a→ ↑reabsorption of a.a (& Na) by proximal tubules→ ↓Na delivery to macula densa→ tubuloglomerular feedback mechanism.

High blood glucose has same effect

Opposite effect occur when proximal tubular reapsorbtion reduced as damaged due to poisoning by heavy metals (Hg) or drugs (tetracycline)

Ability to reabsorb Na↓ → ↑NaCl amount delivered to Macula densa

Other factors affect GFR as proteins & glucose.



Thank you

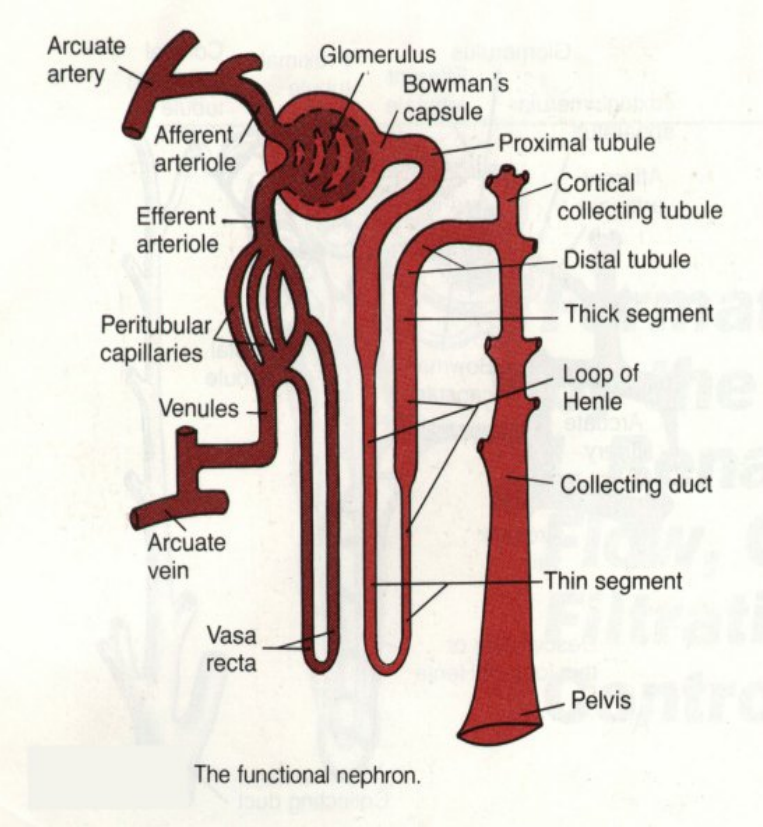
TUBULAR REABSORPTION

BY

Dr. Abdullah Kishawi

Tubular reabsorption

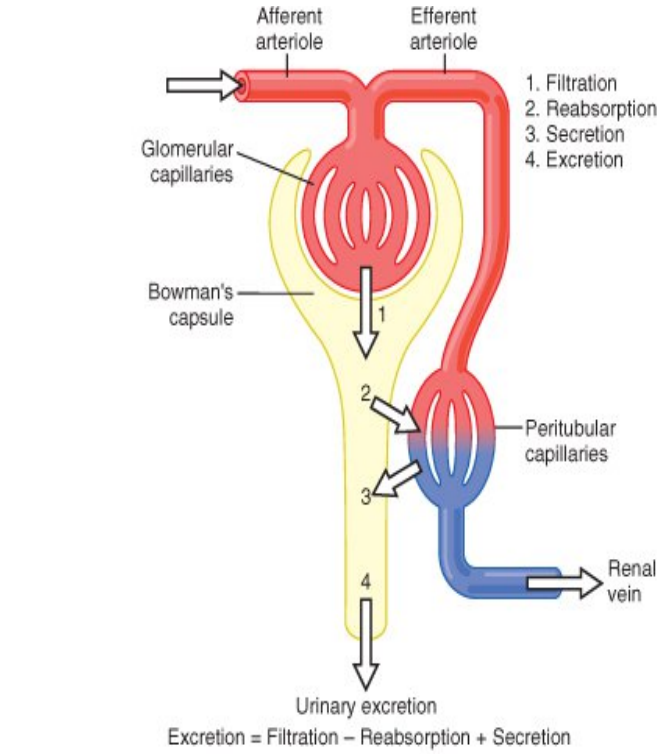
As the glomerular filtrate enters the renal tubules, it flows through the successive parts of the tubule, PCT, the loop of Henle, DCT, the CT, and finally, the collecting duct—before it is excreted as urine.



The functional nephron.

Tubular reabsorption

Urinary excretion =
Glomerular filtration –
T.reabsorbtion +
T.secretion



Tubular reabsorption

F. rate = GFR X Plasma concentration

F. G =180 L/d x 1g/L=180g/d

= 125ml/min x 1mg/ml =125mg/min

GF & tubular reabsorption are quantitatively large relative to urinary excretion

GF is non selective

Tubular reabsorption is highly selective

Reabsorption rate & urinary excretion are variable, depending on the body need.

Tubular reabsorption

Reabsorbed substances:

Completely reabsorbed as Glucose and amino acids.

Highly reabsorbed as Na, CI, HCO3 ions.

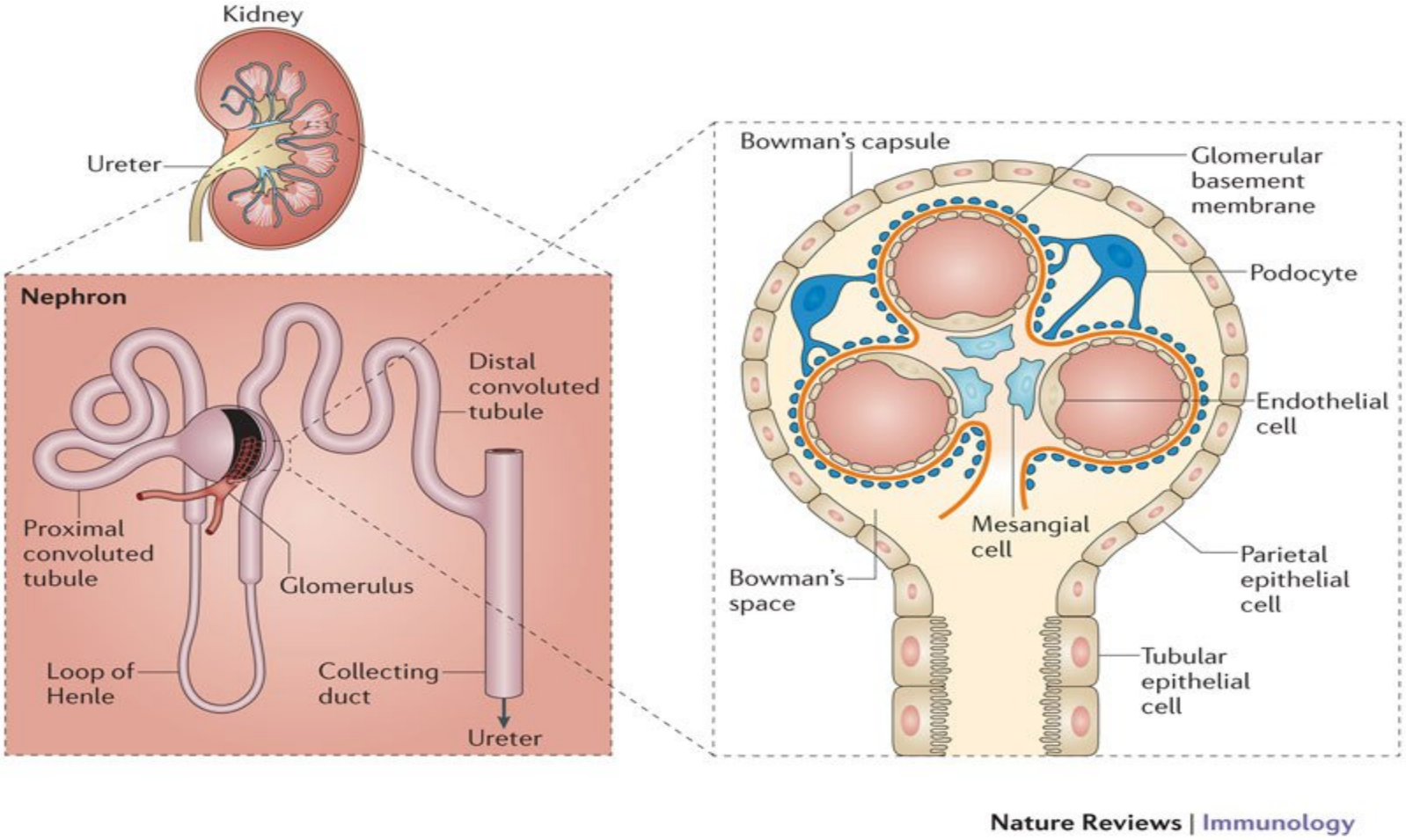
Poorly reabsorbed as Urea, Cr, UA.

Tubular reabsorption

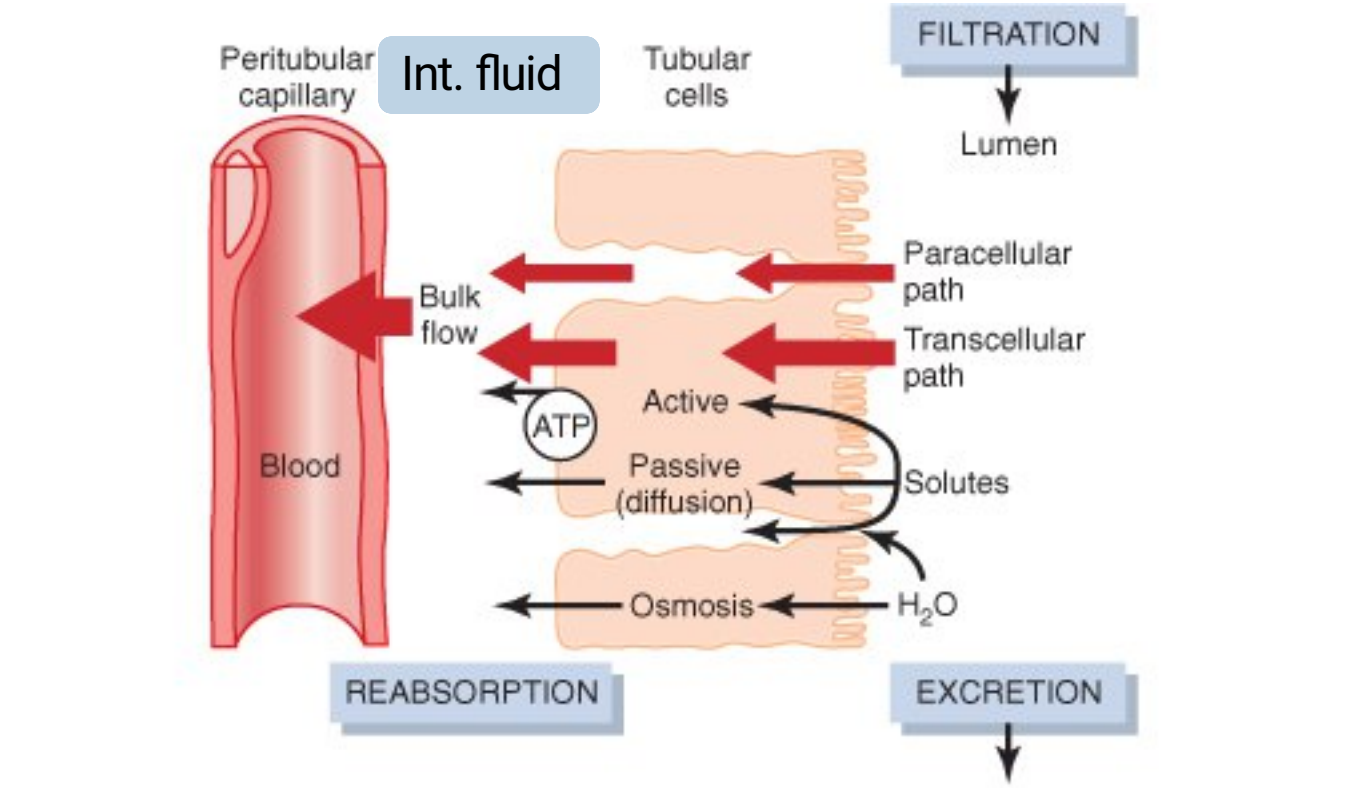
Filtration, Reabsorption, and Excretion Rates of Different Substances by the Kidneys

	Amount Filtered	Amount Reabsorbed	Amount Excreted	% of Filtered Load Reabsorbed
Glucose (g/d)	180	180	0	100
Bicarbonate (mEq/d)	4,320	4,318	2	> 99.9
Na (mEq/D)	25,560	25,410	150	99.4
Cl (mEq/d)	19,440	19,260	180	99.1
K (mEq/d)	756	664	92	87.8
Urea (g/d)	46.8	23.4	23.4	50
Creatinine (g/d)	1.8	0	1.8	0

Routes to cross tubular membrane

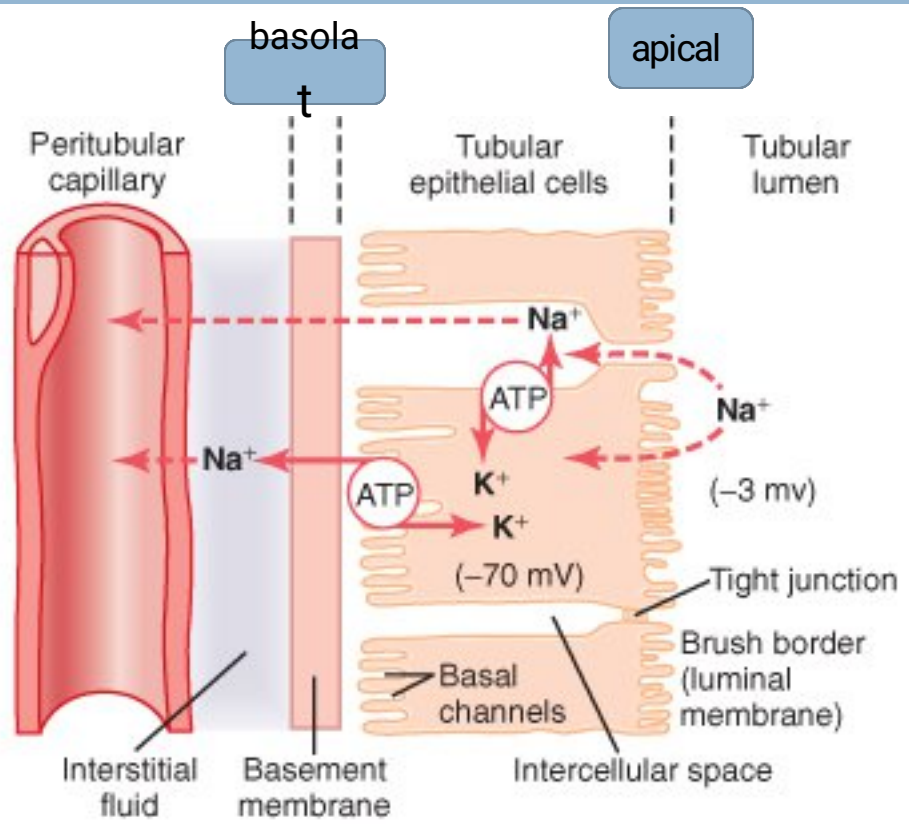


Routes to cross tubular membrane



Active transport of Na through tubular membrane (PCT).

1ry active trasport



Facilitated diffusion

Mechanism of secondary active transport (PCT).

Energy from ATPase pupm

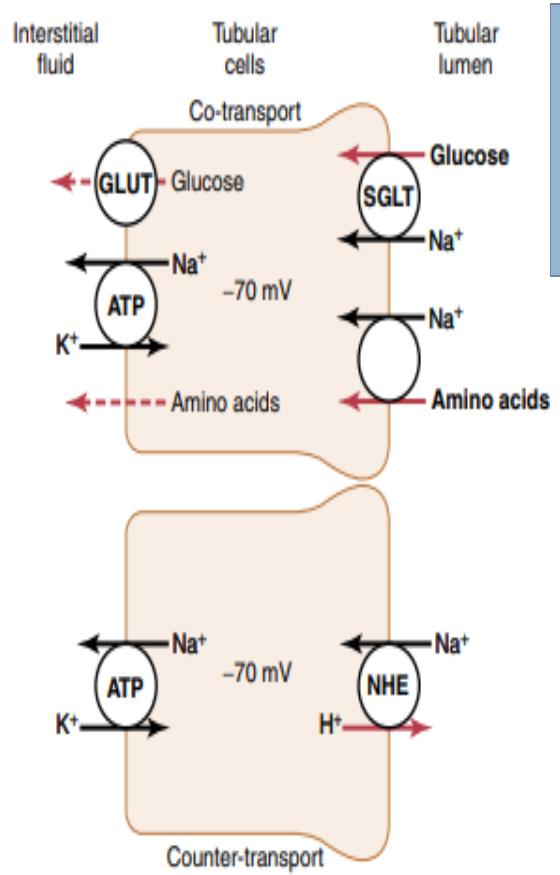
(indirectly).

By carrier proteins in the brush border of epithelial cells .

Specific protein for specific substances eg Na, glucose, amino acids.

After entry into the cell, glucose and amino acids exit across the basolateral membranes by facilitated diffusion, driven by the high glucose and amino acid concentrations in the cell.

Facilitated diffusion



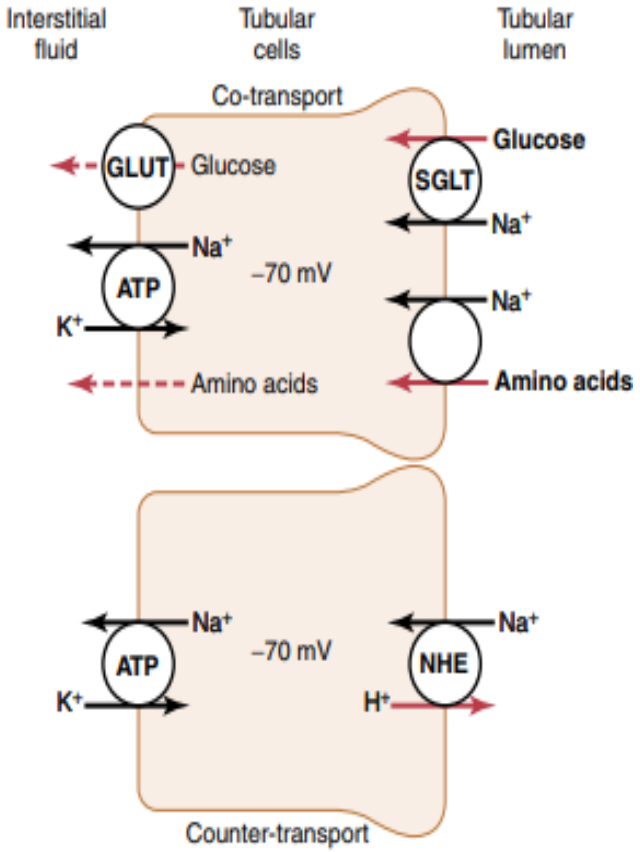
2ny actv. Trast.

Secondary active secretion into the Tubules.

It is a counter-transport of the substance with sodium ions.

active secretion of hydrogen ions coupled to sodium reabsorption in the luminal membrane of the PCT (H+)

mediated by a specific protein in the brush border (NHE)



Water reabsorption

When solutes are transported out of the tubule

their concentrations tend to decrease inside the tubule while increasing in the renal interstitium.

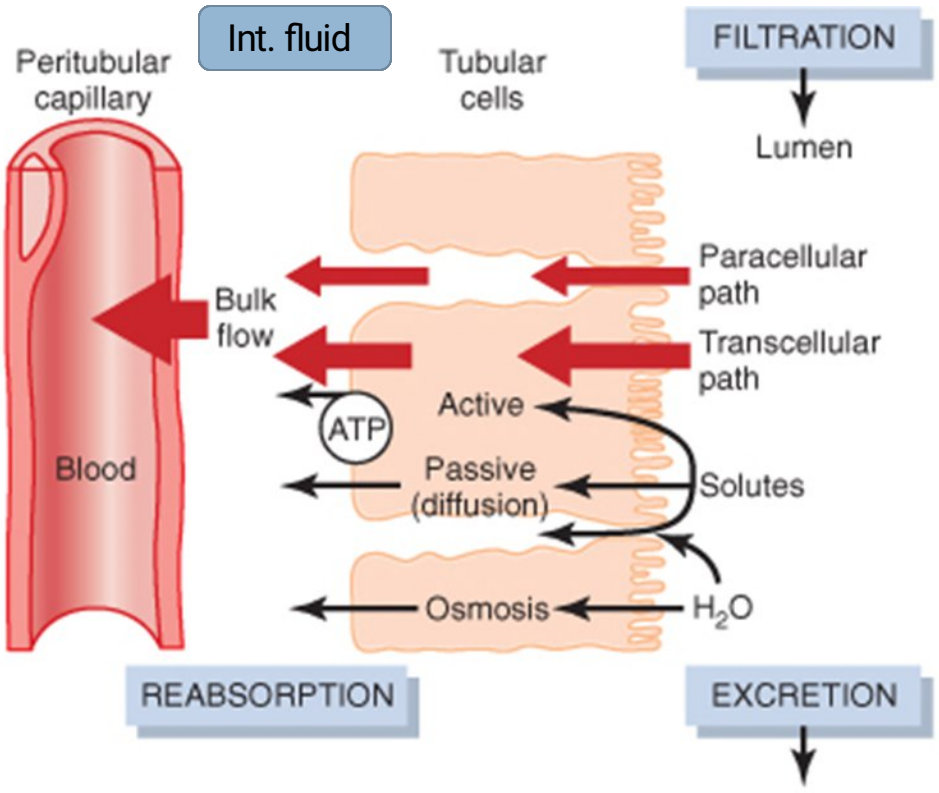
This creates a concentration difference that causes osmosis of water in the same direction that the solutes are transported.

Mainly through tight junctions (PCT).

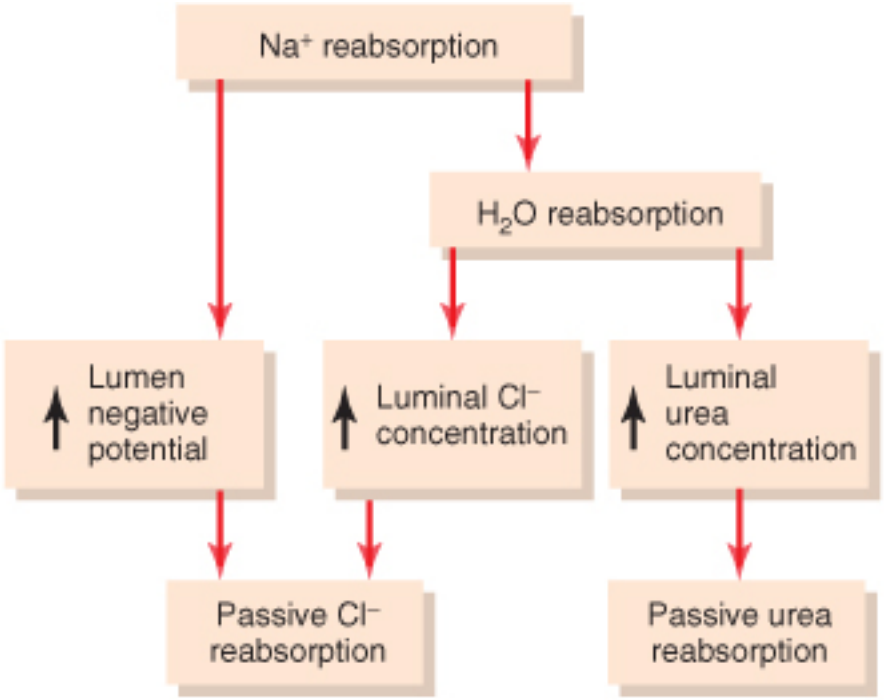
In loop of Henle and CT, the tight junctions become less permeable.

(ADH) regulates the water permeability in DCT &CT.

Water reabsorption

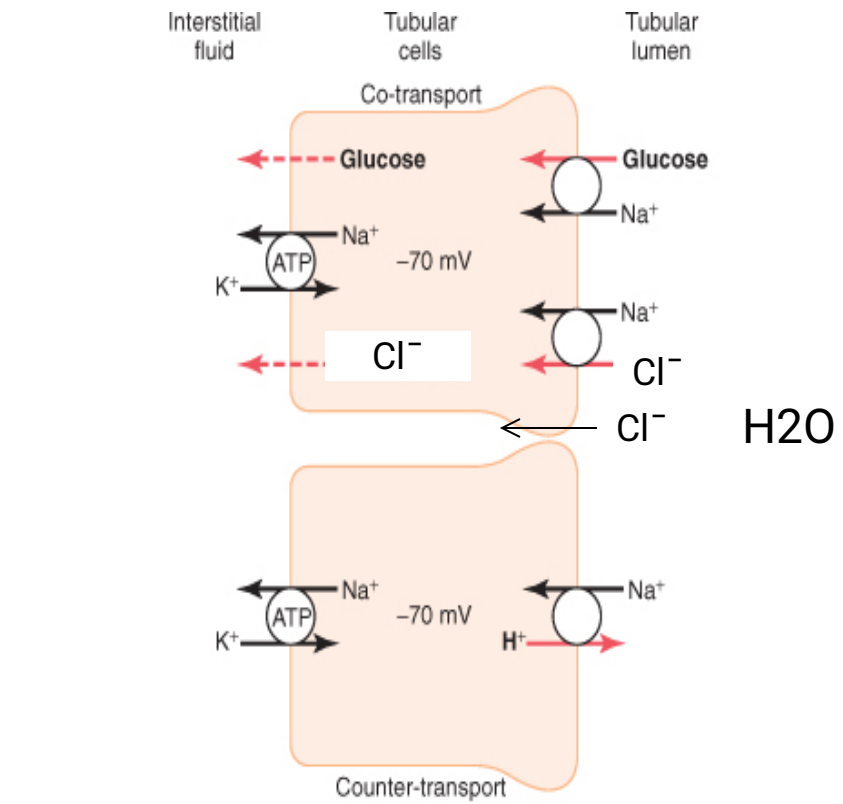


Cl & urea reabsorption



Chloride ion reabsorption (PCT)

- It occurs in the 2nd half of PCT.
- Na Cl cotransporter by 2nd active transport.
- Solvent drag.
- Diffusion of Cl from high conc. To low conc. through the paracellular pathway.



Urea & Creatinine reabsorption

Urea is also passively reabsorbed from the tubule,

As water is reabsorbed from the tubules (by osmosis), urea concentration in the tubular lumen increases

→ creates a concentration gradient favoring and reabsorption of urea.

Urea does not permeate the tubule as water.

So reabsorption is facilitated by specific urea transporters.

50% of filtered urea reabsorbed from tubules.

Creatinine has larger MW than urea.

All creatinine filtered by the glomerulus is not reabsorped and excreted in the urine.

Transport maximum

A limit at which the solute can be transported.

This limit is due to saturation of the specific transport systems involved when the amount of solute delivered to the tubule (referred to as tubular load) exceeds the capacity of the carrier proteins and specific enzymes involved in the transport process.

Threshold: the point where the substance start to appear in the urine before Tm is reached

The cause of threshold is not all nephrons have the same Tm for a substance.

Transport maximum

Substance that are passively reabsorbed, doesn't demonstrate Tm, their transport is determined by:

1- electrochemical gradient

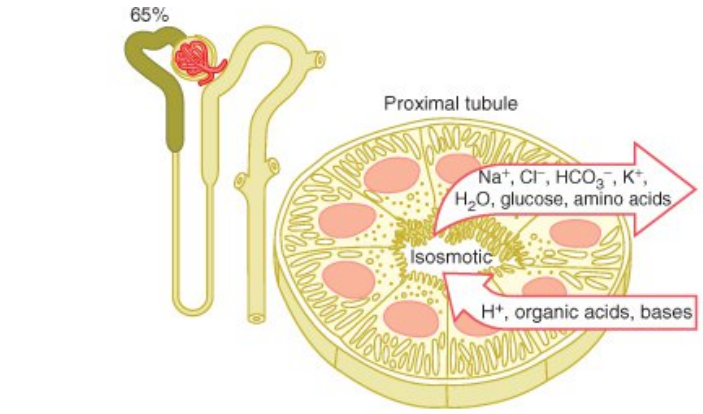
2- permeability of the membrane

3- the time that the fluid (containing substance) remain in the tubule - The transport of this type called gradient-time transport

- Some actively transported substances also have characteristics of gradient-time transport , Eg: Na

Proximal tubular reabsorption

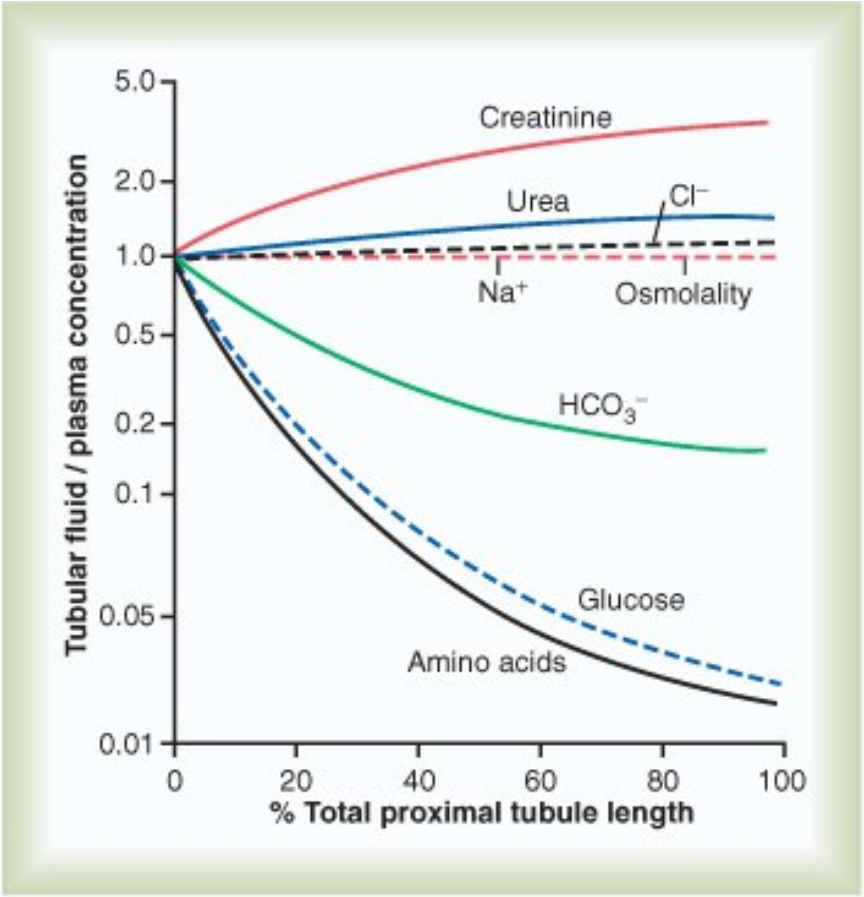
- Has high capacity for active & passive reabsorption
- Highly metabolic & have large numbers of mitochondria for active trasport processes.
- Have extensive brush border on the luminal membrane and basal channels in basolateral side which provide extensive surface area
- Brush border is loaded with protein carrier molecules
- 1st half: Co-transport of Na with glucose & a.as
- 2nd half: Na reabsorbed mainly with Cl



Proximal tubular secretion

The proximal tubule is also an important site for secretion of organic acids and bases such as bile salts, oxalate, urate, and catecholamines.

Solute concentration in the proximal tubules



Loop of Henle

Composed of thin descending, thin & thick ascending segments

1- thin descending segment:

thin epithelial membranes

with no brush borders,

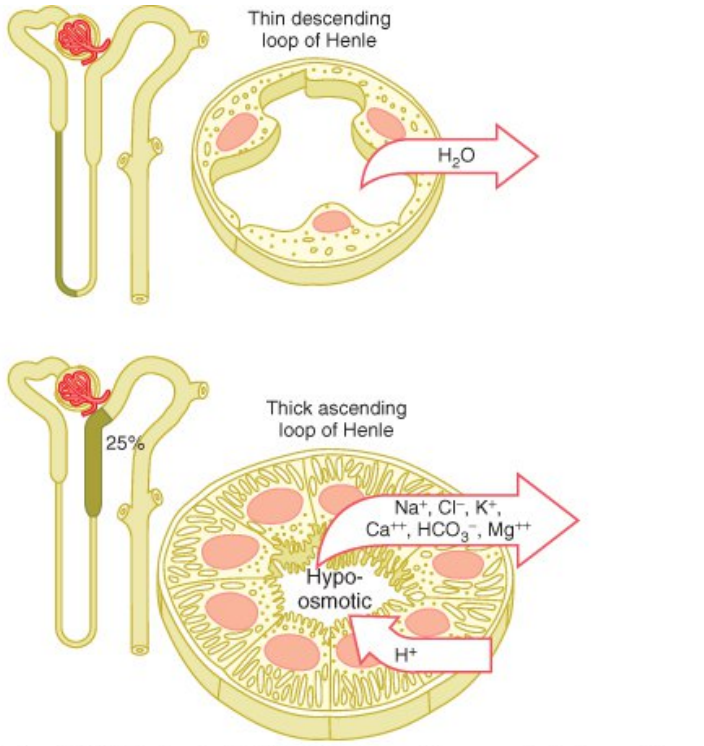
few mitochondria, and Minimal levels of metabolic activity.

Highly permeable to water

Moderately permeable to solutes

Allow simple diffusion.

20% reabsorption of water.



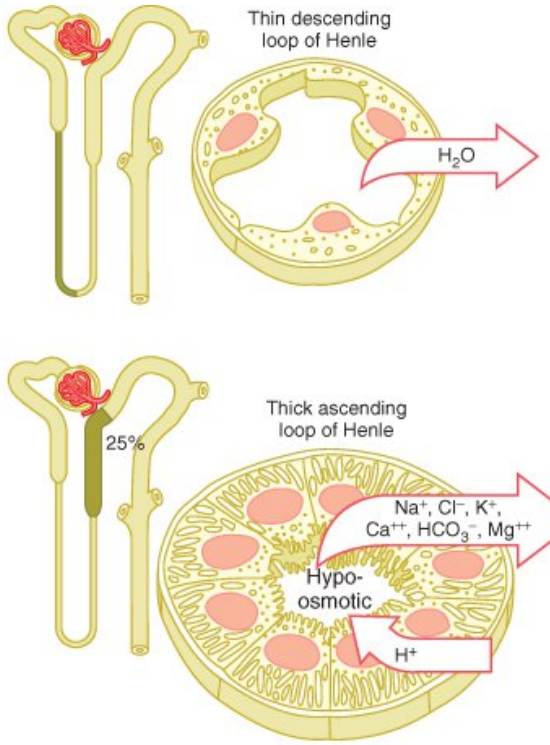
Loop of Henle

2- Ascending segment:

Thin segment

impermeable to water,

a characteristic that is important for concentrating or diluting urine.



Loop of Henle

2- Ascending segment:

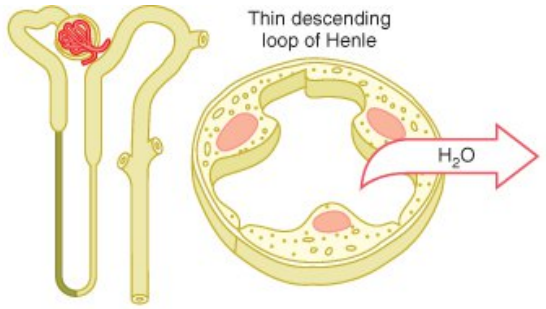
Thick segment

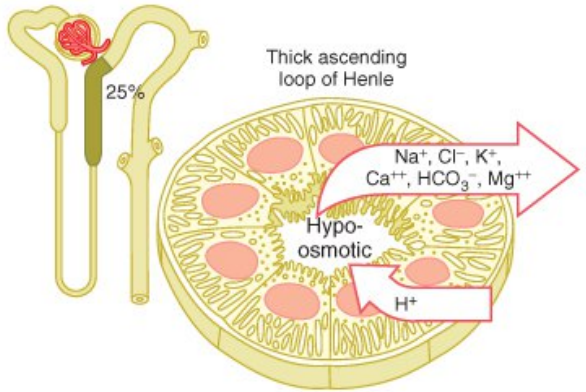
has thick epithelial cells that have high metabolic activity.

25% reabsorption of Na, Cl, K.

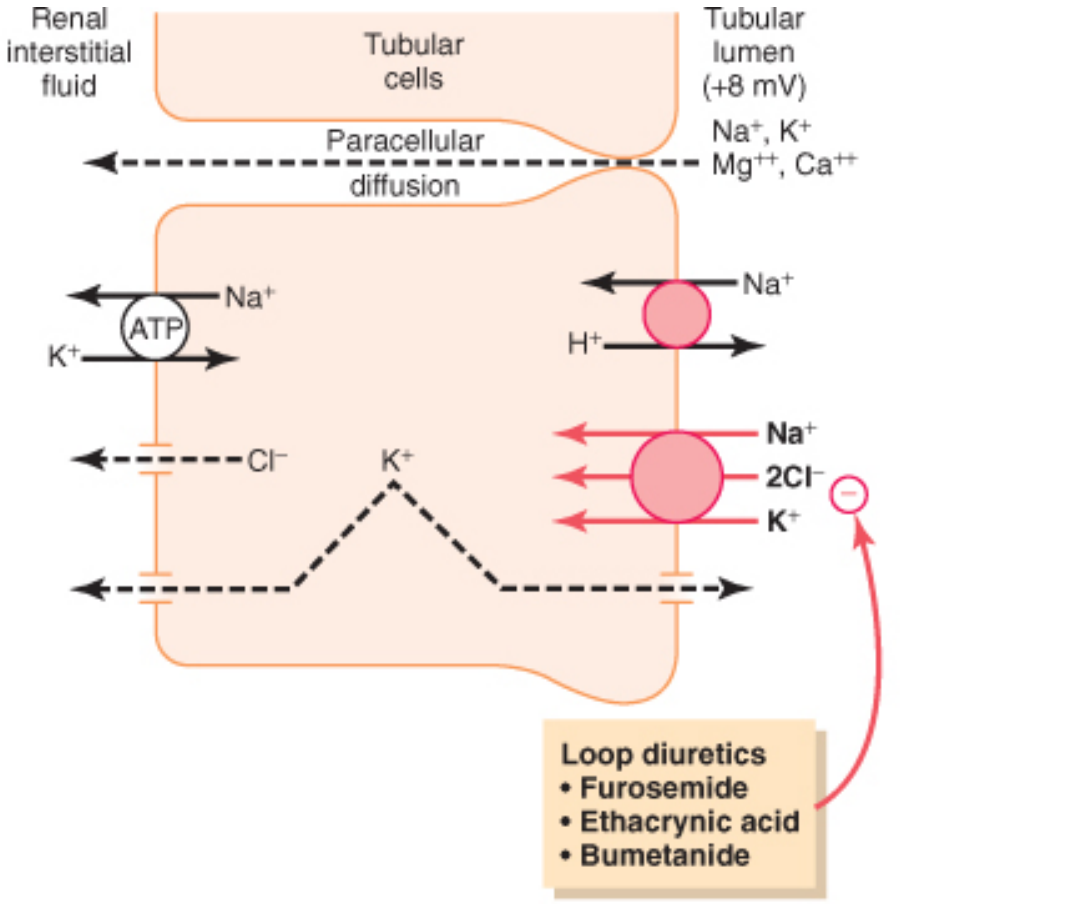
Reabsorption of Ca, HOC3, Mg.

Impermeable to water.





Reaborption in thick ascending segment



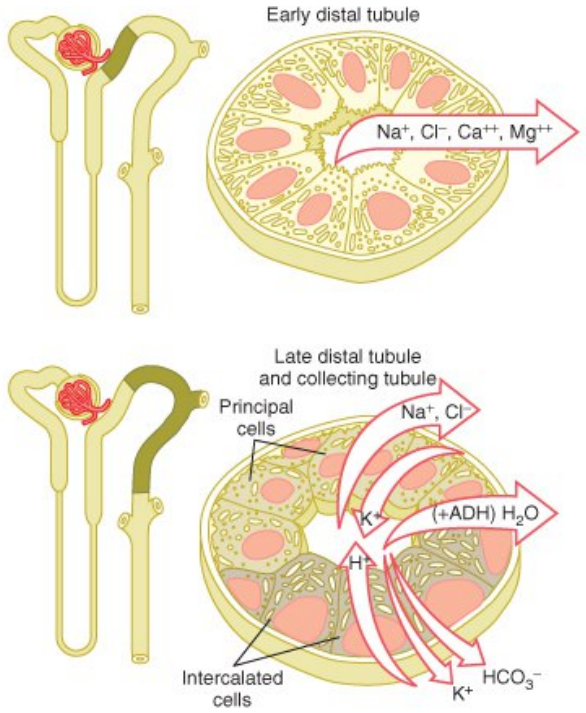
Distal tubules & cortical collecting duct

Early DT: impermeable to water (diluting segment)

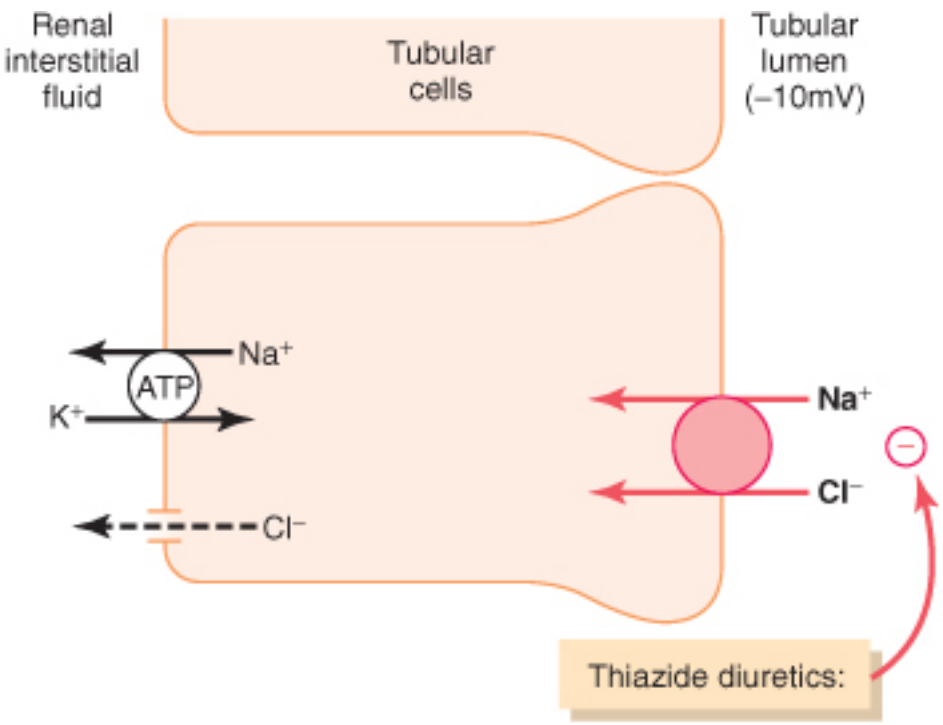
The very first portion of the distal tubule forms part of the juxtaglomerular complex that provides feedback control of GFR and blood flow in this same nephron.

Approximately 5 % of the filtered load of Nacl is reabsorbed in the early distal tubule.

Impermeable to water.

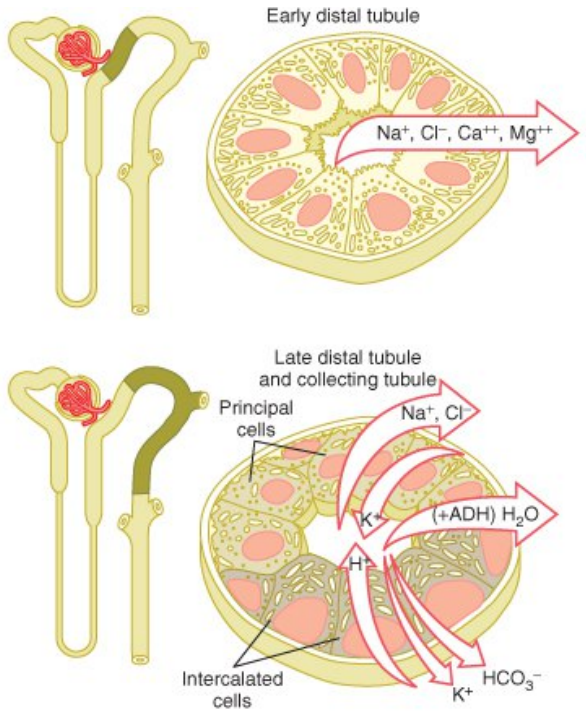


Na-Cl transport in early distal tubules



Distal tubules & cortical collecting duct

Late DT & collecting duct: permeability to water is ADH dependent



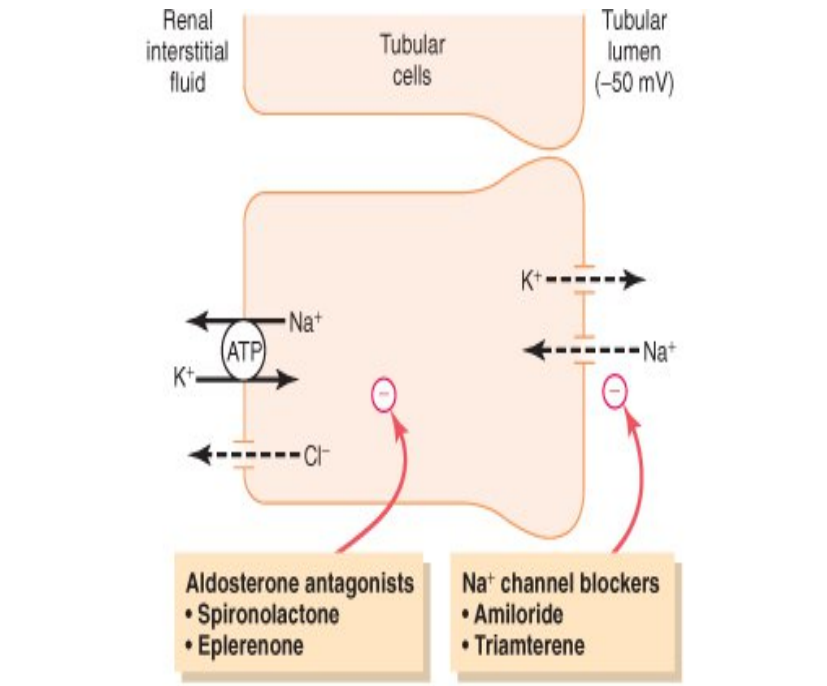
Cells of late distal tubules& CD

Principal cells

Intercalated cells :

play key role in acid-base regulation in the body by reabsorb K+ and secrete H+.

impermeable to urea

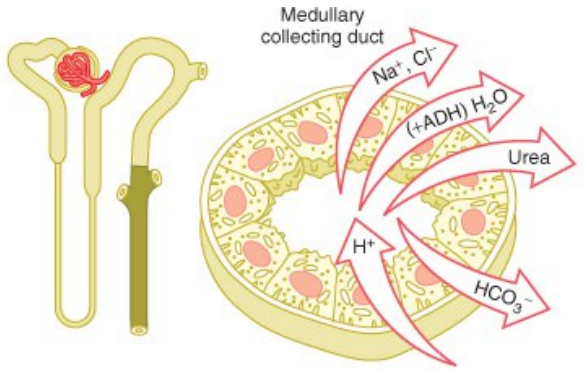


Medullary collecting duct

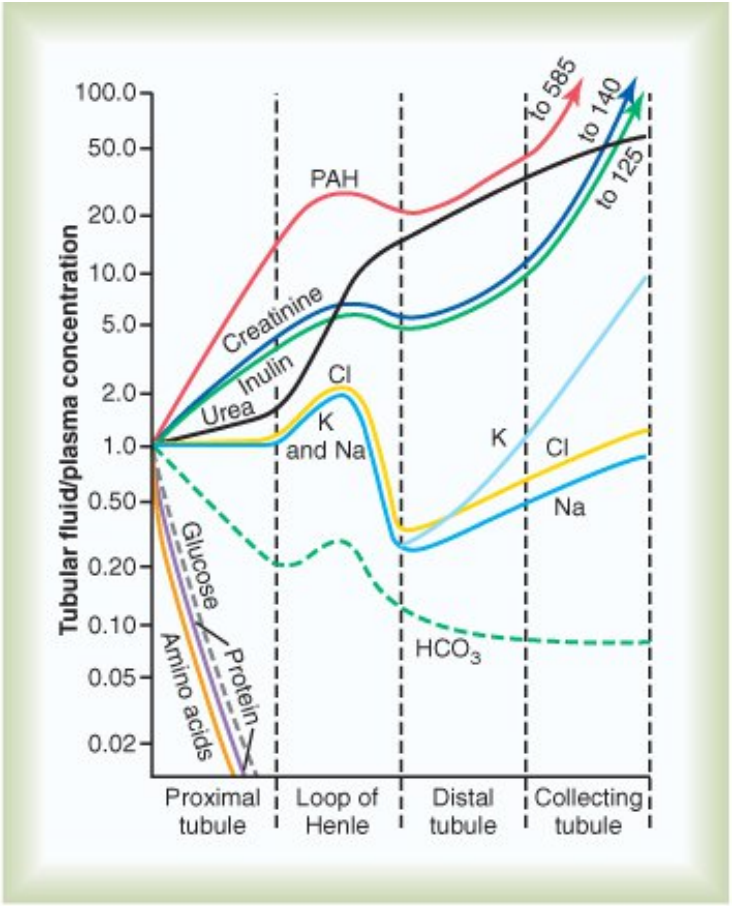
Permeability to water is ADH dependent

Permeable to urea

Secrete H by active transport.



Changes in concentration of different substances in the tubular system



Regulation of tubular reabsorption
1- Glomerlotubular balance

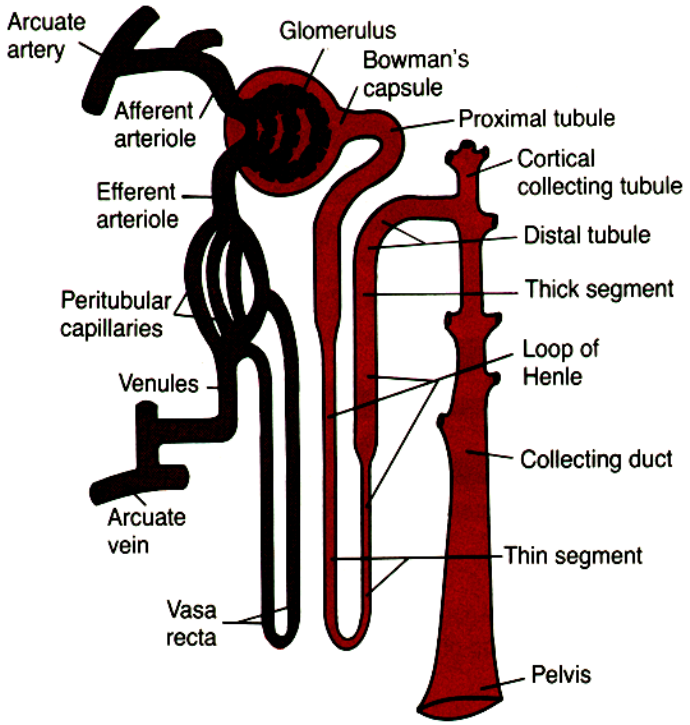
Intrinsic ability of the tubules to ↑ their reabsorption rate in response to ↑ tubular load (↑ tubular inflow).

In proximal tubules (mainly) & loop of henle

It occurs independently of hormones.

Prevent overload of the distal tubule when GFR↑.

2- Physical forces



The functional nephron.

2- Physical forces

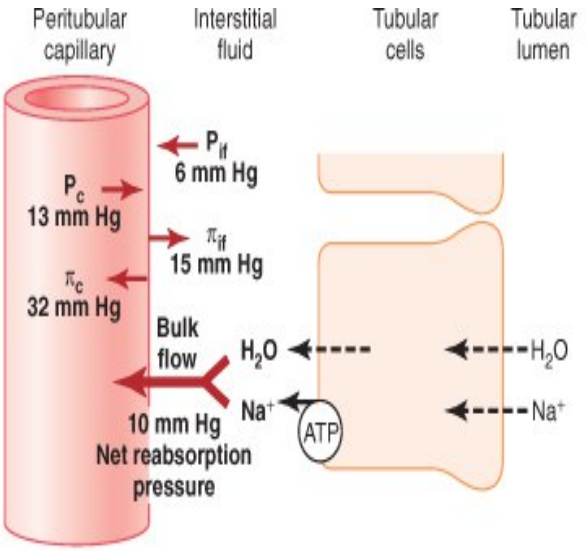
Reabsorption rate = 124 ml/ min

Reabsorption = K_f x net reabsorptive force

Net Re. force=$(\pi_c - \pi_{if}) - (P_c - P_{if})$

= (32-15) – (13-6)= 10mmHg

K_f = 124/10=12.4 ml/min/ mmHg



Regulation of peritubular capillary physical forces

1- ↑K_f→ ↑ Re.

Remain constant in most physiologic conditions.

2- ↑P_c→↓Re

- ↑R_A → ↓ P_c → ↑Re

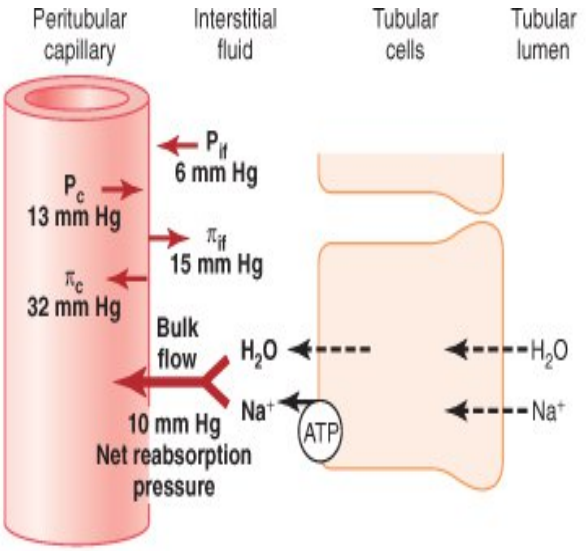
↑R_E→ ↓ P_c → ↑Re

↑Arterial pressure→↑ P_c→ ↓ Re

(buffered by Autoregulation)

3- ↑π_c→↑ Re

↑π_A→↑π_c



3- pressure natriuresis & diuresis (Effect of ABP on UOP)

Def: small increase in arterial pressure cause marked increase in urinary excretion of Na & water (autoregulation impaired)

Contributed factors:

1- ↑BP→↑ GFR→ ↑urinary excretion .

2- ↑BP→↑ P_c→↑ P_{if}→ ↓reabsorption → ↑ urinary excretion Na & water.

3- ↑BP→↓angiotensin II→↓ Na & water Re. →↑ urinary excretion

4- hormonal control
a- aldosterone

Secreted by zona glomerulosa.

Site of action: principal cells of collecting tubule

↑ Na Reabsorption, ↑ K secretion by stimulation Na K ATPase pump on basolateral side.

↑ Na permeability on luminal side.

Addison's disease→↓ aldosterone

Conn's disease→↑ aldosterone

b- angiotensin II

Most powerful Na retaining hormone.

Blood pressure & ECF volume are the main regulators for its secretion.

Site of action: proximal tubule, thick ascending loop of henle, DCT, collecting tubule

↑ Na, H2O reabsorption, ↑H secretion.

By main effects:

1- Stimulate aldosterone

2- Constrict the efferent arteriole.

3- Directly stimulate Na reabsorption (stimulation Na K ATPase pump).

4- stimulate Na H exchange the luminal membrane of PCT.

c- ADH

Secreted by Pos. Pit gland.

Site of action: distal tubules, collecting tubules.

↑H2O Re. by ↑the permeability

Bind V2 receptors→↑ cAMP→ stimulate the movement of IC protein (AQP-2)→ cluster together to form water channel in luminal border.

APQ-3, APQ-4 in the basolateral border.

d- ANP

Specific cells of the cardiac atria, secrete ANP when distended because of ↑ plasma volume.

Site of action: distal tubules, collecting ducts

↓ NaCl Reabsorption and increases urinary excretion.

e- PTH

↑Ca, reabsorption in the distal tubules and perhaps also in the loops of Henle.

↓PO4 reabsorption by the PCT.

5- sympathetic NS

Constrict arteriole→ ↓GFR→ ↓Na & water excretion.

↑ Na & water reabsorption in the proximal tubules , thick ascending segment of loop of henle

↑Renin release→↑ angiotensin II→ ↑Na & water reabsorption

Quantifying kidney function

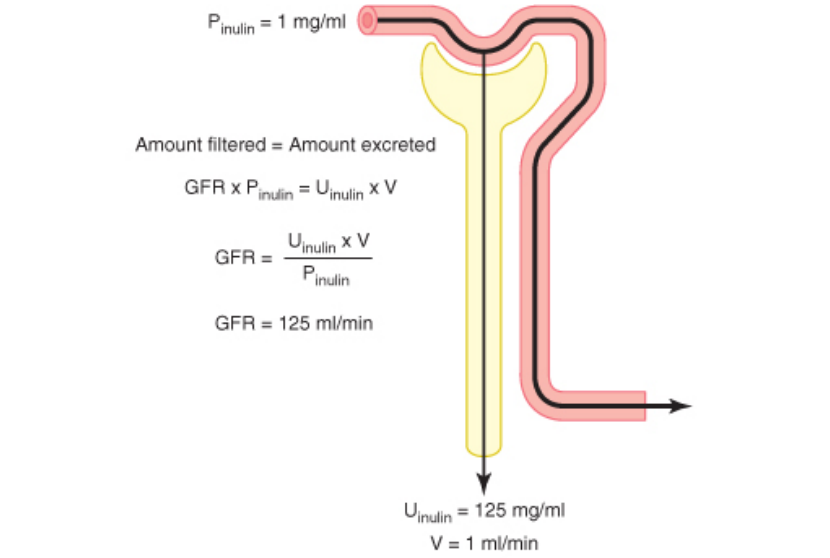
Renal clearance of a substance is the volume of plasma that is completely cleared of the substance by the kidneys per unit time

Excretion rate= Us * V

Clearance rate (Cs)= excretion rate /Ps, ml/min

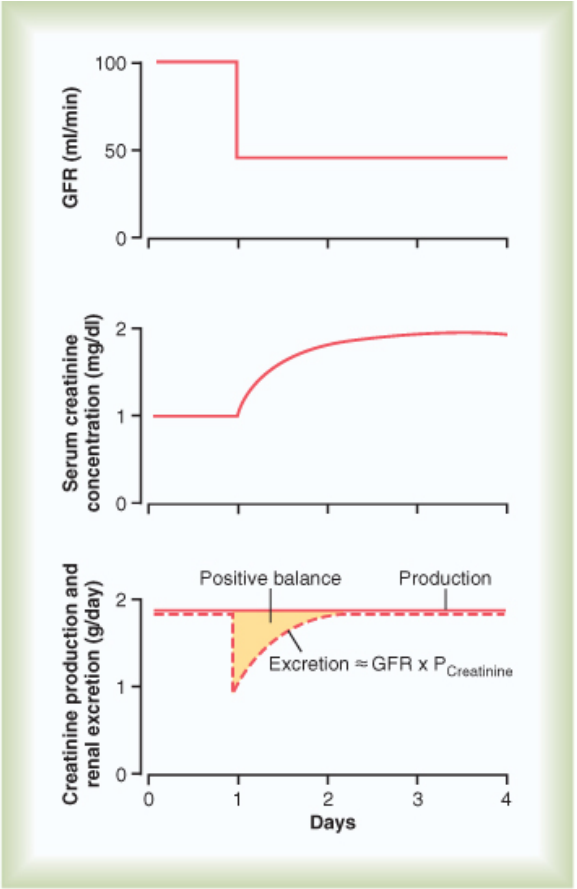
Inulin clearance

- Used to estimate GFR
- Freely filtered, not reabsorbed or secreted
- Excretion Rate = Filtration Rate
- Administered IV



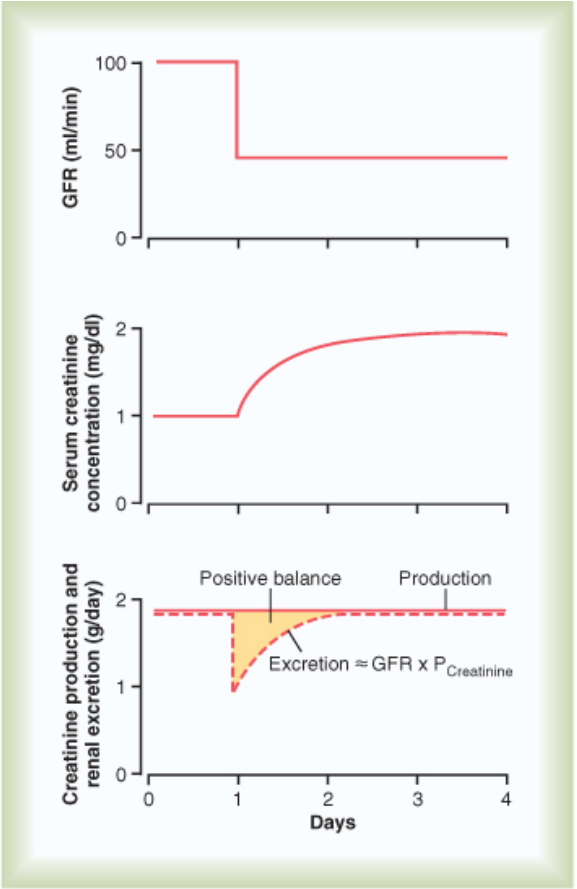
Creatinine clearance

- Used to estimate GFR
- Doesn't require IV administration, widely used clinically
- Crcl= Ucr x V/ Pcr
- Change in GFR obtained by simple measuring plasma [Cr] which is inversely proportional to GFR



Creatinine clearance

Creatinine clearance is not a perfect marker of GFR because a small amount of it is secreted by the tubules, so that the amount of creatinine excreted slightly exceeds the amount filtered.



PAH clearance

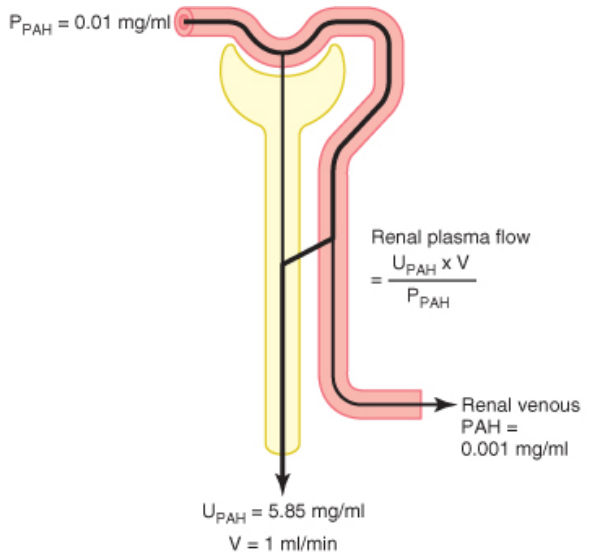
If a substance is completely cleared from the plasma, its clearance rate is equal to total RPF

RPF = Cs = Us * V/ Ps

GFR= 20% of total RPF, therefore, a substance to be completely cleared must be excreted by tubules as well as glomerular filtration

Percentage of PAH removed from the blood =90% (extraction ratio of PAH)

RPF = C pah /E pah



Filtration fraction

The fraction of plasma that filters through glomerular membrane

F.F = GFR / RPF

RBF = RPF/1-Htc

Reabsorption rate = filtered load – excretion rate

Secretion rate = excretion rate – filtered load