Revised by
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Renal Function and GFR

We advise that you study the anatomy and histology of the kidney before studying these lectures; then quickly review them from here!

Red: very important.
Green: Doctor's notes.
Pink: formulas.
Yellow: numbers.
Gray: notes and explanation.

Physiology Team 436 – Renal Block Lectures 1 & 2

For further understanding please check our "Extra Notes" file which contains extra explanation for reference books.

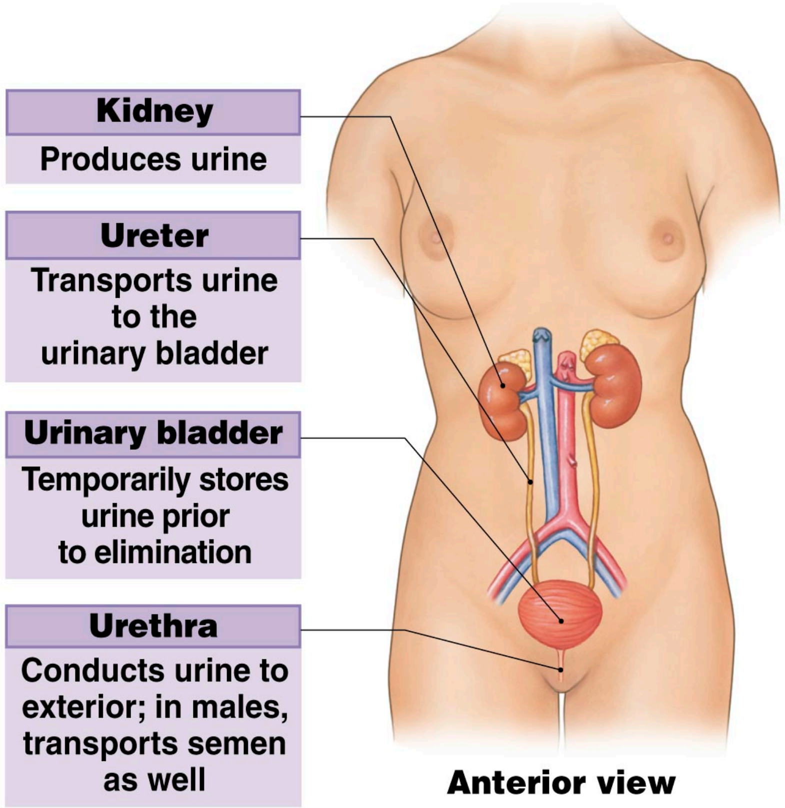
Objectives for Lectures 1 & 2

1. Enumerate general functions of the kidney
2. Identify and describe that the nephron is the structural and function unit of the kidney
3. Explain glomerular filtration membrane & filtration forces
4. Describe mechanism of filtration & composition of the glomerular filtrate
5. Calculate the net filtration pressure using parameters of Starling forces

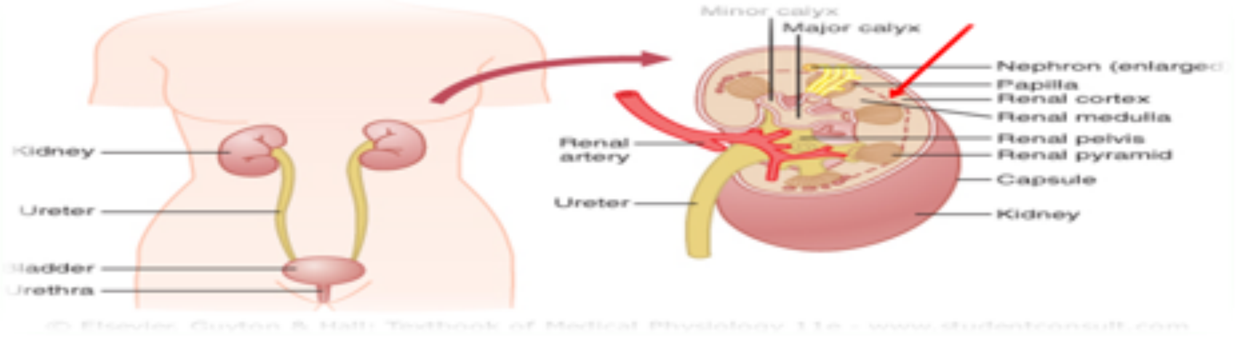
1. Describe that the mechanism of urine formation include three basic processes; glomerular filtration, tubular reabsorption and tubular secretion.
2. Define GFR and quote normal value.
3. Identify and describe the factors controlling GFR in terms of starling forces, permeability with respect to size, shape and electrical charges and ultra-filtration coefficient.
4. Describe Intrinsic and extrinsic mechanism that regulate GFR.
5. Describe autoregulation of GFR & tubuloglomerular feedback mechanism.

Urinary System Organs

- **Weight of Kidneys:** Each kidney of the adult human about 150 gram
- **Size of Kidneys:** as a clenched fist.



Kidney → Ureter → Urinary bladder → Urethra



Function of the Kidney

The kidneys serve many important homeostatic functions, including the following :

1. **Regulation of :**
   - Body fluid osmolality (including water) and electrolyte concentrations and balance (K,Na,Cl,.)
   - Arterial blood pressure (RAAS renin–angiotensin aldesterone system, excretion of excess salt and water)
   - Acid-base balance (H+ concentration along with lung).

2. **Excretion of :**

metabolic waste products and foreign chemicals (Nitrogenous Wastes) :

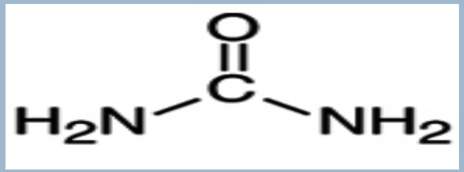
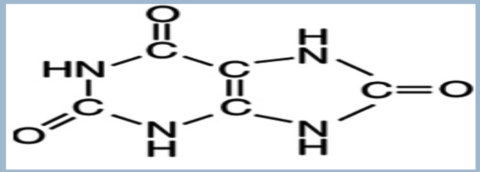
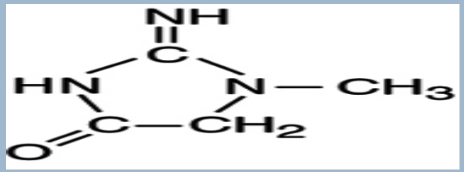
- UREA (proteins→amino acids →NH_2 removed →forms ammonia, liver converts to urea) , CREATININE , URIC ACID , Bilirubin
- Drug and Detoxification of pesticides

1. **Synthesizing/Activating functions :**
   - Erythropoietin production → RBC production by bone marrow
   - Renin formation
   - Gluconeogenesis: synthesis of glucose from amino acid during prolonged fasting (Glucose can be synthesized in the liver and kidneys during prolonged fasting)
   - 25, cholecalciferol will be activated in the kidneys to 1,25 dihydrocholecalciferol D3 (calcitrol)

Kidney Filter 200 liters of blood daily, allowing toxins, metabolic wastes, and excess ions to leave the body in urine,

The only hormone secreted from kidney is erythropoietin

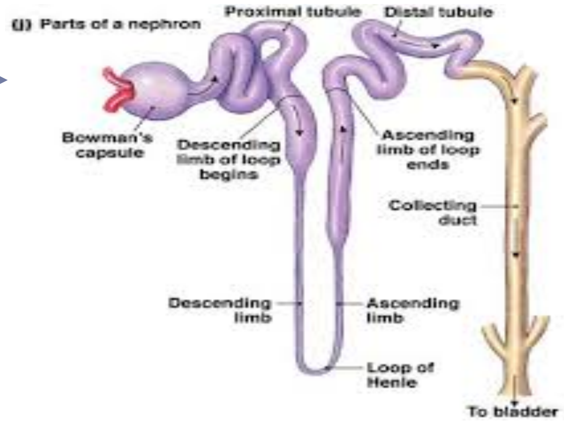
Nitrogenous Wates

1- Urea	2- Uric acid	3-Creatinine
		
Formation: from the metabolism of "amino acids" Proteins → amino acid → NH2 removed → forms ammonia → liver converts to urea.	from nucleic acids'	-from muscle creatine -Creatinine is the more specific than urea in diagnosing renal diseases. Why? Because unlike creatinine, urea is affected by the diet (E.g. urea is increased when protein consumption is increased).

- **Differences between secretion and excretion :**
  - **Secretion :** is excretion within the body,
  - **Excretion :** is excreting a substance out of the body.

Nephron: the functional unit of the kidney

- Nephron
  - Renal Corpuscle
    - Glomerulus
    - Bowman's Capsule
  - Renal tubules
    - Proximal convoluted tubules
    - Loop of Henle
    - Distal convoluted tubules
    - Connecting tubules
      - Intercalated cells
      - Principal cells



- **Nephron**: is the functional and structural unit of the kidney.
- Each kidney in the human body contains about 800,000 to 1,000,000 *"one million"* nephrons, **each** capable of **urine formation**.

Structure of Nephron

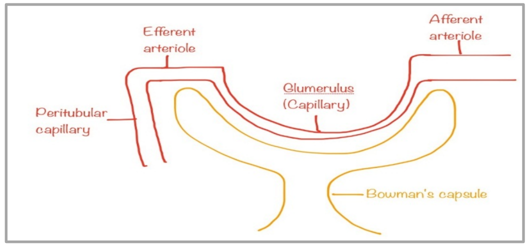
Nephrons

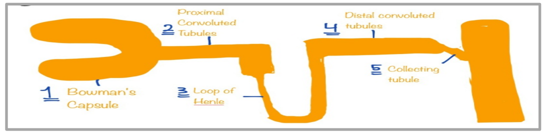
Vessels

- **Afferent arteriole** : delivers blood into the glomeruli
- **The Glomerulus** : capillary network or tuft in which large amount of fluid is filtered from blood (produces filtrate) it will be collected in capsular space then flows into urinary/renal tubule..
- **Efferent arterioles** : delivers blood from glomeruli to peritubular capillaries
- **Peritubular capillary** : vasa recta

Tubes (5) : in which filtered fluid eventually is converted into urine.

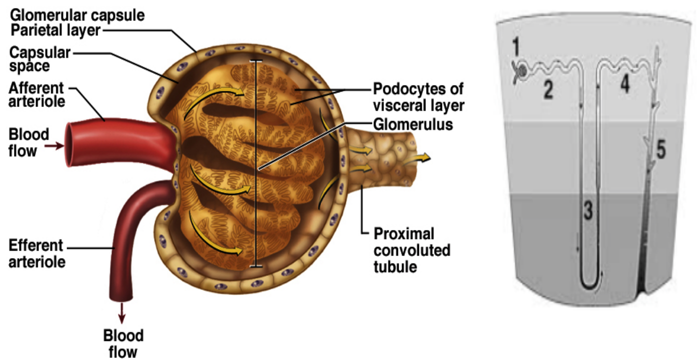
- **Bowman's capsule**: around the Glomerulus and receives the filtrate.
- **Proximal convoluted tubules** (in the cortex).
- **loop of Henle**
- **Distal convoluted tubules** (in the renal cortex).
- **Connecting tubule,** cortical collecting, and the cortical collecting ducts, which run downward in the medulla and become: Medullary collecting duct





These figures are similar to those drawn by Dr.manan in the lecture.

- Note that the pressures along the afferent arteriole, glomerulus and efferent arteriole are high. Why? to increase filtration.
- Note that the afferent arteriole is larger than the efferent arteriole.



Glomerular filtrate collects in capsular space then flows into renal tubule.

- Although blood circulation in the kidneys passes through two capillary beds (Glomeruli and peritubular capillaries), it is not considered a portal circulation. **Why**? Because glomeruli contain arterial capillaries only (There's no venous blood).
- In the blood supply of the kidney, the straight arterioles of kidney (or vasa recta renis) are a series of straight capillaries in the medulla (Latin: vasa, "vessels"; recta, "straight").

Video of (Nephron Structure and functions) Duration: (4:38) mins

Video of (A Journey Through the Nephron) Duration: (3:44)mins

The Nephron

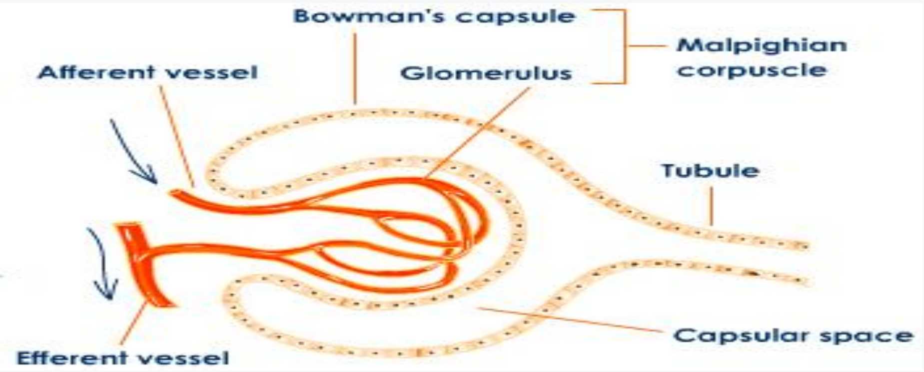
Nephrons are the structural and functional units of the kidneys that form urine, consisting of renal corpuscle and renal tubules . Each kidney has 1 million nephrons, each nephron is capable of urine formation.

- Renal corpuscle – the glomerulus and its Bowman's capsule
- Glomerulus – a tuft of capillaries associated with a renal tubule
- Glomerular (Bowman's) capsule – blind, cup-shaped end of a renal tubule that completely surrounds the glomerulus

Glomerular endothelium – fenestrated epithelium that allows solute-rich, virtually protein-free filtrate to pass from the blood into the glomerular capsule

Anatomy of the glomerular capsule:

- The external parietal layer is a structural layer
- The visceral layer consists of modified, branching epithelial **podocytes**
- Extensions of the octopus-like podocytes terminate in foot processes
- Filtration slits – openings between the foot processes that allow filtrate to pass into the capsular space



Renal Tubules

Proximal convoluted tubule:
Has microvilli and mitochondria.
Reabsorbs water and solutes from filtrate and secretes substances into it.

Distal convoluted tubule (DCT):
Without microvilli that function more in secretion than reabsorption.

Loop of Henle:

- a hairpin-shaped loop of the renal tubule
- Proximal part is similar to the proximal convoluted tubule.
- Proximal part is followed by the thin segment and the thick segment.

Connecting Tubules

Two important cell types are found here:

- **Intercalated cells**
  - Has a microvilli.
  - Function in maintaining the acid-base balance of the body.
- **Principal cells**
  - Without microvilli.
  - Help maintain the body's water and salt balance.

Capillary Beds of the Nephron

- Every nephron has two capillary beds
  - Glomerulus
  - Peritubular capillaries vasa recta

- Each glomerulus is:
  - Fed by an afferent arteriole
  - Drained by an efferent arteriole

- Blood pressure in the glomerulus is high because:
  - Arterioles are high-resistance vessels
  - Afferent arterioles have larger diameters than efferent arterioles

- Fluids and solutes are forced out of the blood throughout the entire length of the glomerulus

Capillary Beds

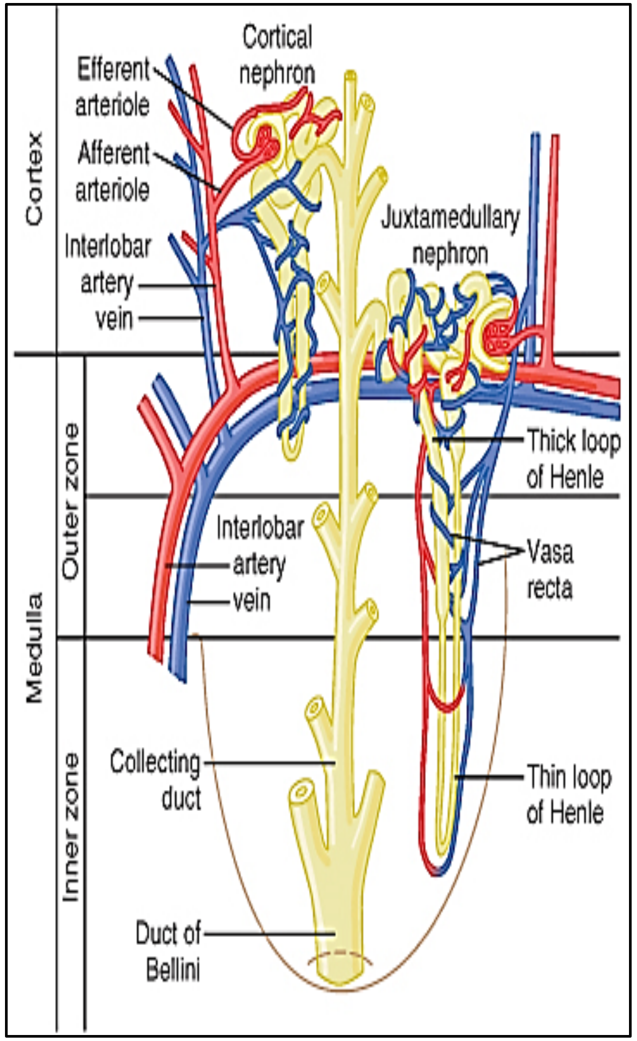
- **Peritubular beds** are low-pressure, porous capillaries adapted for absorption that:
  - Arise from efferent arterioles
  - adhere to adjacent renal tubules (because it takes electrolytes from Renal Tubules)
  - Empty into the renal venous system
  - In cortex

- **Vasa recta** – long, straight efferent arterioles of juxtamedullary nephrons

Types of Nephrons

Cortical nephrons: (85%)	Juxtamedullary nephrons: (15%) 1-2% of blood flows through them
Their glomeruli in the outer portion of cortex	located at the cortex-medulla junction They're located in the cortex with in the border of the the medulla only Henle's loop extend to the medulla)
-	Maintain salt gradient, helps conserve water (You'd expect camels to have abundant of these nephrons for more water reabsorption).
Have short loops of Henle	Have long loops extended into the medulla with extensive thin segments Are involved in the production of concentrated urine
Continues from efferent as : Peritubular capillaries	Continue from efferent as :Vasa recta

- Juxtamedullary nephrons are counter current in structure like this. , allowing more water reabsorption.
- Juxtamedullary nephrons work during prolong fasting



Originates in outer 2/3 of cortex.

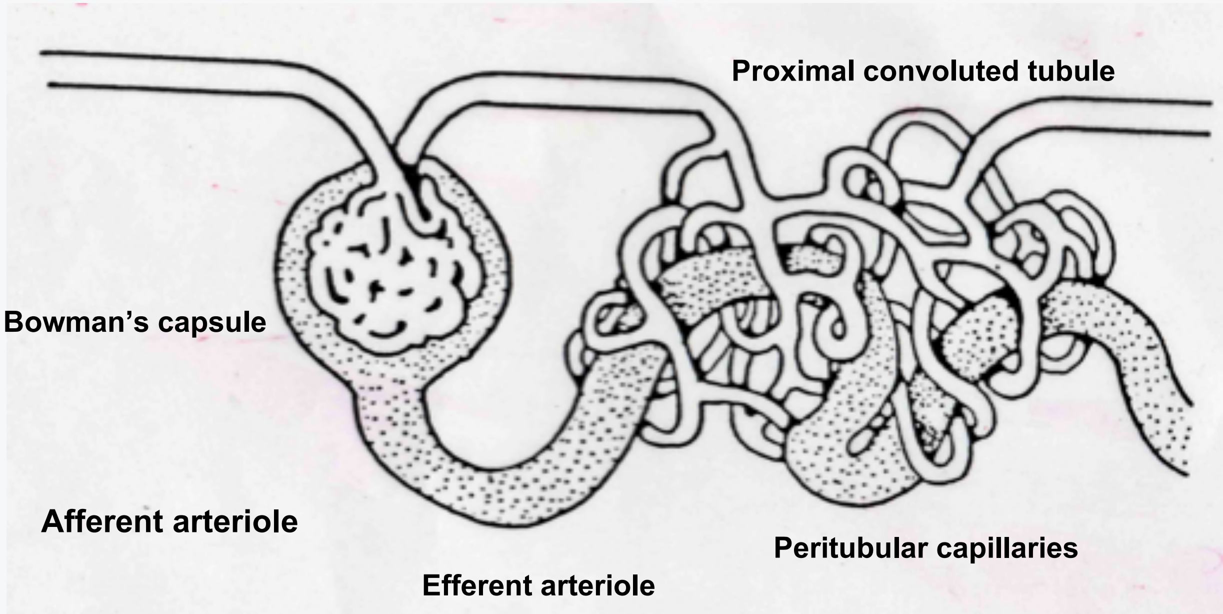
Originates in inner 1/3 of cortex.

ONLY IN MALES' SLIDES

Vascular Resistance in Microcirculation

- Afferent and efferent arterioles offer high resistance to blood flow
- Blood pressure declines from 95 mmHg in renal arteries to 8 mmHg in renal veins

Resistance in afferent arterioles:
    Protects glomeruli from fluctuations in systemic blood pressure
Resistance in efferent arterioles:
    Reinforces high glomerular pressure
    Reduces hydrostatic pressure in peritubular capillaries



Glomerular capillary bed
High pressure vascular bed, increasing oncotic pressure

Good for filtration

Peritubular capillary bed, Low pressure vascular bed, high oncotic pressure.

Good for re-absorption

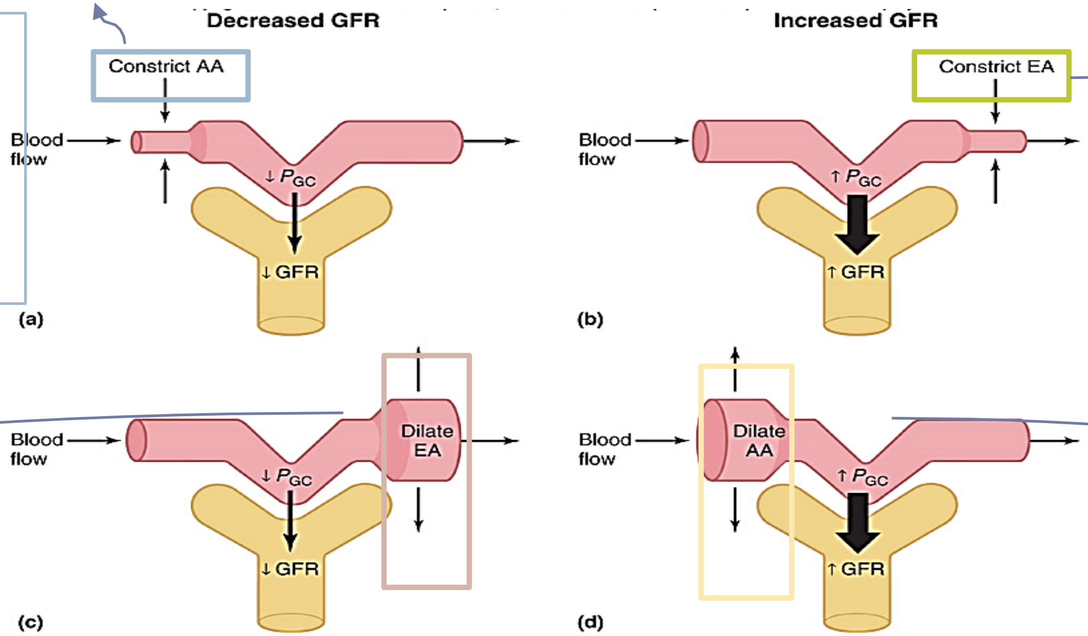
Afferent & Efferent Arteriolar Resistance Affect

As vasodilation and vasoconstriction of the afferent and efferent arterioles alter the blood flow through the glomerular capillaries, there are corresponding alterations in the glomerular filtration rate **(GFR).**

Constriction of Afferent
E.g.: Sympathetic stimulation (sever stimulation on shock (not affected on daily sympathetic stimulation) → Afferent artery constrict → decrease blood flow to glomerular → ↓PGC → ↓GFR

Constriction of Efferent E.g.: Angiotensin II
- Mild to moderate constriction → some fluid will be accumulated in the glomerular and the other will pass → ↑PGC → ↑GFR
- Sever constriction → fluid will be accumulated in the glomerular → have only one way leave by filtration → ↑GFR → ↑FF → ↑ πg → ↓GFR

Note that, as the afferent arteriole constricts in response to sympathetic stimulation, prostaglandins are released to cause vasodilation to prevent further damage and renal failure. This explains why NSAIDs should not be given at this point.

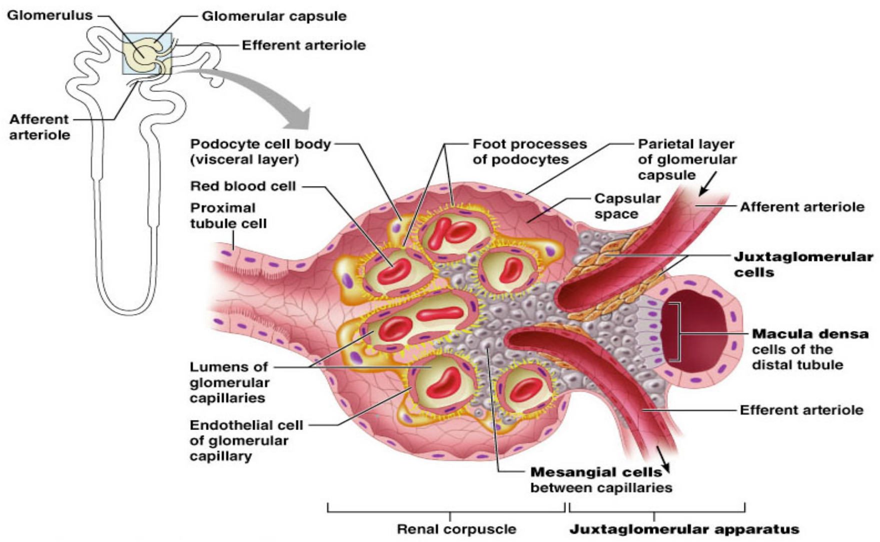


Dilation of Efferent ↓PGC →↓GFR

Dilation of Afferent by : NO ,PKs → ↑PGC →↑GFR

Juxtaglomerular Apparatus (JGA)

- Juxtaglomerular apparatus
  - JG cells
  - Macula densa
  - Mesangial cells



Mesangial cells have defense mechanisms (phagocytosis)

Juxtaglomerular Apparatus (JGA)

- JGA: here the distal tubule lies against the afferent (sometimes efferent) arteriole

Arteriole walls have juxtaglomerular (JG) cells

- Enlarged, smooth muscle cells
- Have secretory granules containing renin
- Act as mechanoreceptors

Macula densa

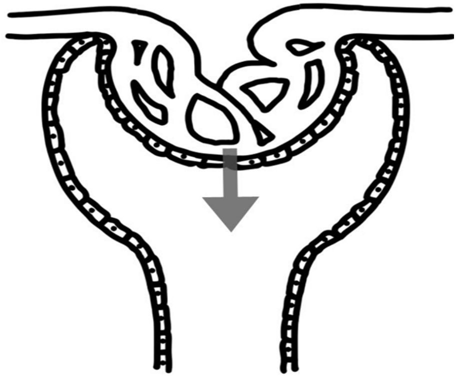
- Tall, closely packed distal tubule cells
- Lie adjacent to JG cells
- Function as chemoreceptors or osmoreceptors
- The cells of the macula densa are sensitive to the ionic content and water volume of the fluid in the tubule
- produce molecular signals that promote renin secretion by the juxtaglomerular cells

Mesangial cells

- Have phagocytic and contractile properties
- Influence capillary filtration

Intraglomerular mesangial cells provide structural support and regulate blood flow of the glomerular capillaries by their contractile activity

1- Glomerular filtration



- The FIRST step in urine formation is glomerular filtration.
- It is the filtration of fluid from the glomerular capillaries into the renal tubules.
- It contains all substances present in plasma except proteins.

we will know why on the next slides

- GFR is normally 125 ml/min = 20% renal plasma flow.
- Glomerular filtration rate (GFR) is the rate of production of filtrate at the glomeruli from plasma (ml/min) = 20% of renal plasma flow → means 1.25 L of the C.O. is being filtered

1.25 L x 60 min = 7,5L/h x 24h = 180L/day is filtered , if we excrete all of this we may die so the body try to compensate by: 99% of filtrate are **reabsorbed** so only 1 to 2 L urine excreted per day .

In order to know what molecules are filtered , we should know :

a) glomerular membrane layers

b) Factor controls passage of molecules through this membrane

c) Forces responsible for passage of fluid (filtrate) through this membrane

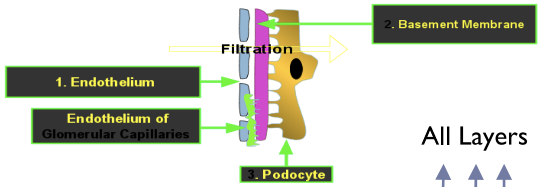
On next slides

Filtration Membrane

- Filter that lies between the blood and the interior of the glomerular capsule
- It is composed of three layers
  - Fenestrated endothelium of the glomerular capillaries (Pores are 50-100 nm in diameter)
  - Visceral membrane of the glomerular capsule (podocytes)
  - Basement membrane composed of fused basal laminae of the other layers.

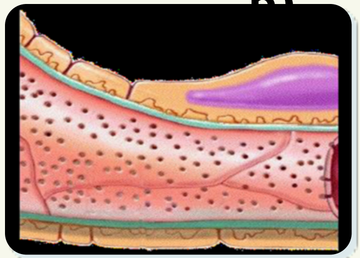
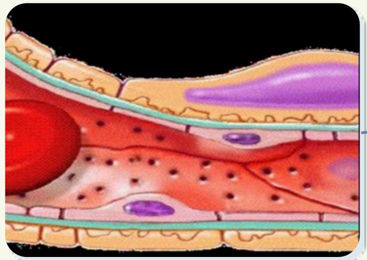
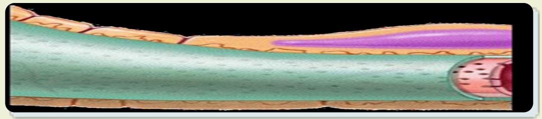
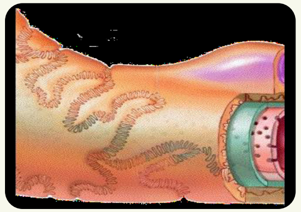
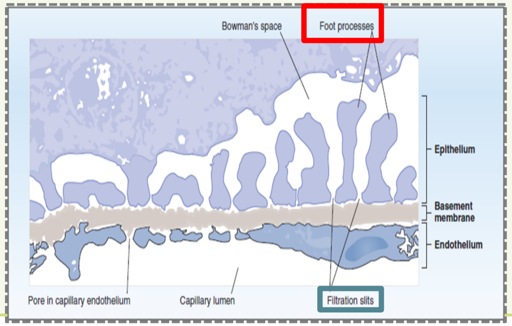
- Glomerular filtration membrane is highly permeable to water and small molecules (less than 10.000 MW)
- Large molecules (more than 70.000 MW especially proteins are not filtered due to their large size and negative electrical charge because their passage is repulsed by negatively charged glycoproteins present on endothelial pores, basement membrane and podocytes.

a)Glomerular membrane



All Layers

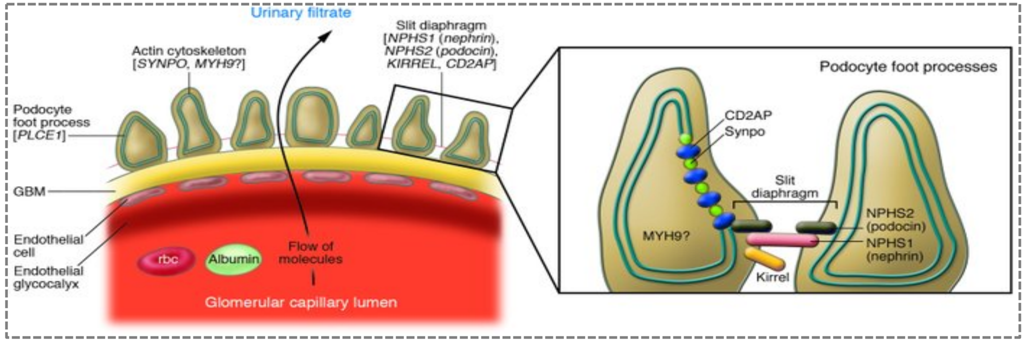
Blood in the glomerulus is separated from the fluid in the Bowman's space by a filtration barrier (glomerular membrane) consisting of three layers: (from glomerular toward bowman's capsule)

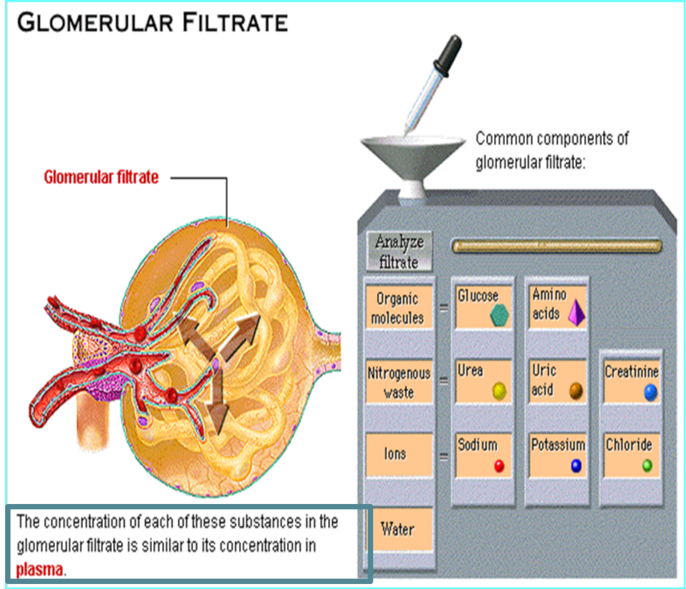
1- Single layer of **capillary endothelium** - picture "b" shows glomerular capillary in longitudinal section	a)  b) 
2- **Basement membrane** between endothelium and epithelium. (contain glycoprotein which is negative in charge)	
3- Single epithelial lining of Bowman's capsule **(Podocytes :** cell body with nucleus) - It consist of 2 layers : primary - Secondary : which contain foot processes , during filtration the fluid moves between their foot processes (pseudopodia). - Slits is the space between these foot processes	 

b) Factor controls passage of molecules through this membrane (Characteristics of glomerular membrane)

- Membrane allow passage of molecules up to 70,000 D
- Factors control passage of molecules through this membrane :
  1. Negative charge : **Albumin** does not normally pass as they are repelled by the negative charge of the glycoproteins material of basement membrane.
  2. Size :**Blood cells** do not normally pass through the membrane. Due to the big size , (that's why there is no Red color in the urine)

- Albumin is exactly the size of the fenestrae (i.e. it's size allows it to be filtered) but it is negatively charged and thus repelled by the negative basement membrane.
- Certain renal diseases neutralize the negative charge of the basement membrane and eventually causing albuminuria.

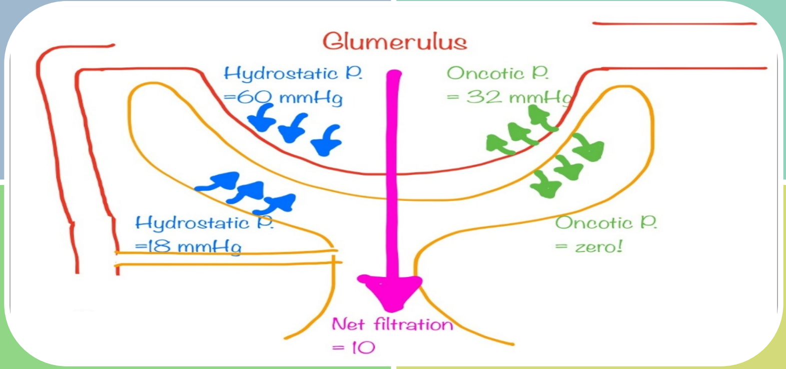




c) Forces responsible for passage of fluid (filtrate) through this membrane: Starling's forces

The net filtration pressure (NFP) is the sum of : The NFP formula is VERY IMPORTANT!!

	In Glomerular	***In bowman's capsule***
Hydrostatic pressure	• 1. glomerular hydrostatic pressure (Pg = 60 mmHg). It promotes filtration.	• 2. hydrostatic pressure in Bowman's capsule (Pb = 18 mmHg). It <u>opposes</u> filtration.
Colloid osmotic pressure	• 3. colloid osmotic pressure of glomerular plasma proteins • (**πg** = 32 mmHg). It <u>opposes</u> filtration.	Colloid Osmotic Pressure of Bowman's proteins **(Пb)** = **0** mmHg (**Promotes** filtration) As we knew filtration membrane doesn't allow proteins to pass therefore **bowman's space has NO proteins** which means oncotic pressure = 0 mmHg

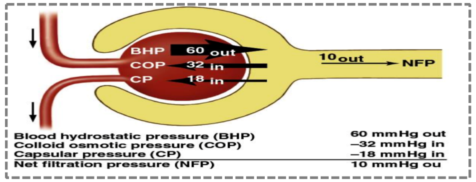


This figure is similar to that drawn by Dr.manan in the lecture. Thanks deema :). (Team435)

So, NFP = 60 – 32 – 18 = +10 mmHg

GFR = Kf x [(Pg – Pb) – (πg – πb)] → $GFR = K_f[(P_{GC} - P_{BS}) - \pi_{GC}]$

GFR = Kf x [(60 – 18) – (32 – 0)]

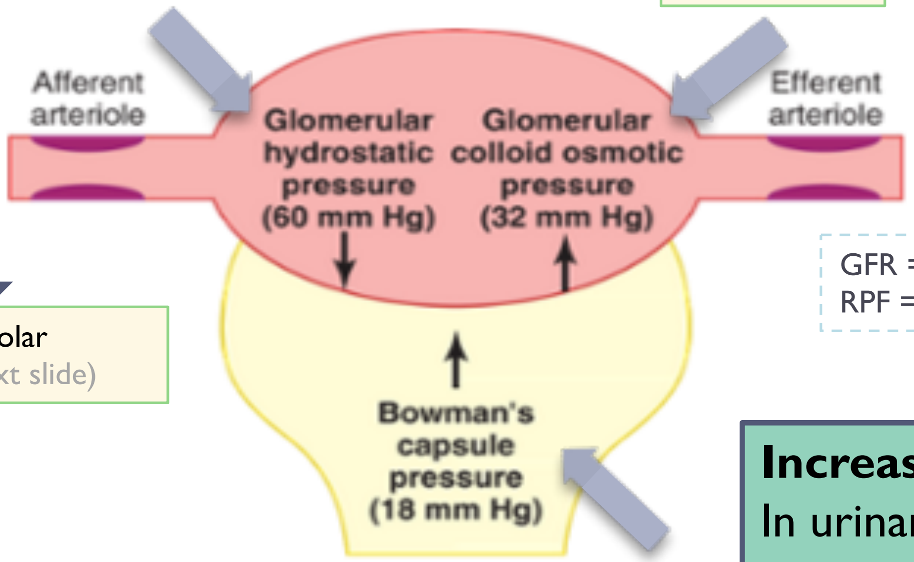


How changes in forces determining GFR affect GFR?

Physiological regulation of the GFR involves mechanisms that affect mainly the Pg.

Increased Pg Increases GFR.
This pressure is affected by:

- Arterial blood pressure (Explained on Regulation on GFR lecture)
- Afferent arteriolar resistance (next slide)
- Efferent arteriolar resistance (next slide)



Increased πg Decreases GFR By :

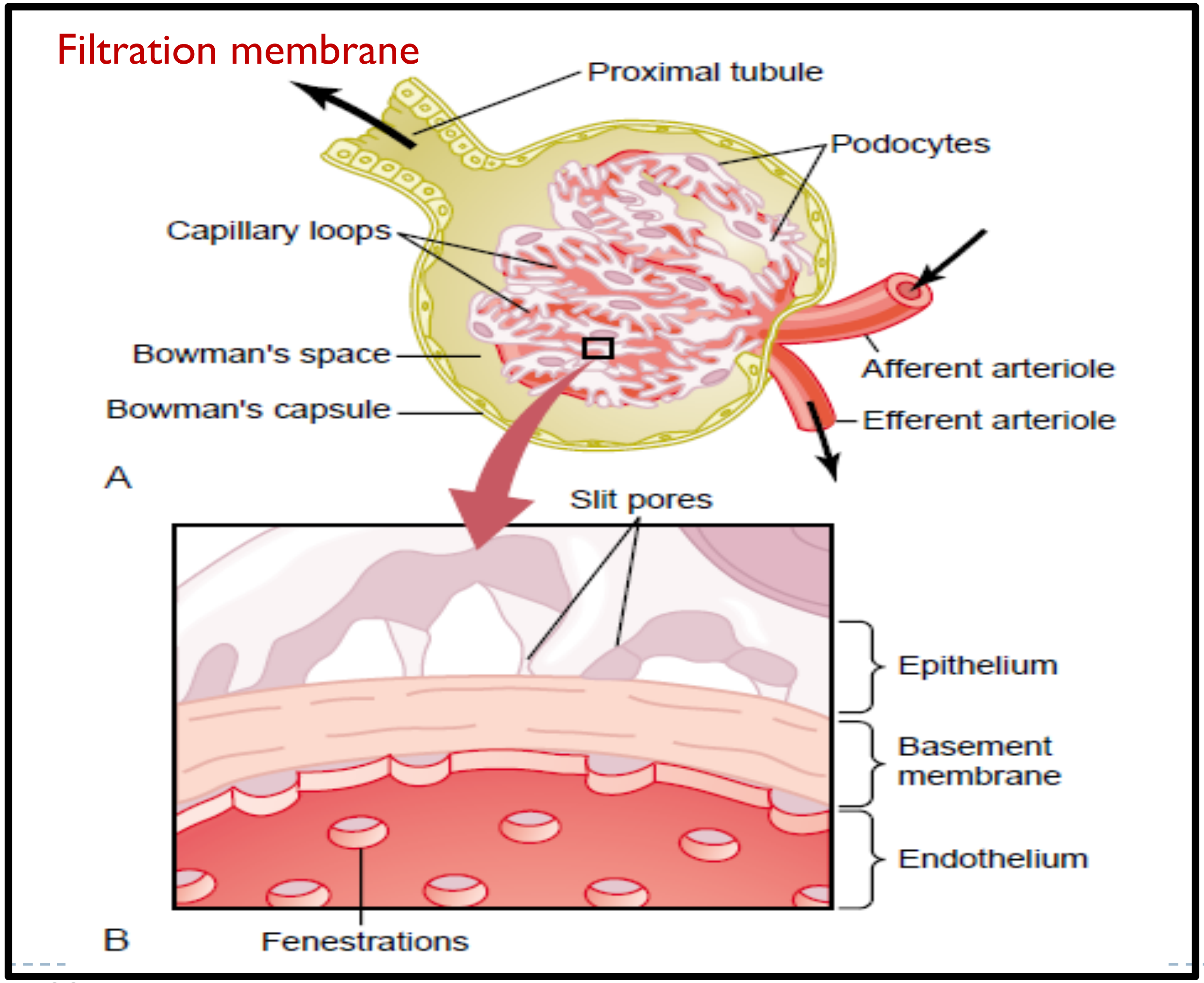
- Plasma pressure
- Filtration Fraction = GFR/RPF
  The normal = 125/600 = 20%
  If RPF increase → decrease FF → increase πg → decrease GFR

GFR = Glomerular Filtration Rate
RPF = Renal Plasma Flow

Increased Pb Decreases GFR
In urinary obstruction
e.g. stones or tumors.
Obstruction in tubule → plasma won't pass → increase in the pressure

Pg = Glomerular hydrostatic pressure
Pb = Bowman's hydrostatic pressure
π g = Colloid osmotic pressure of glomerular plasma proteins

Composition of Glomerular Filtration

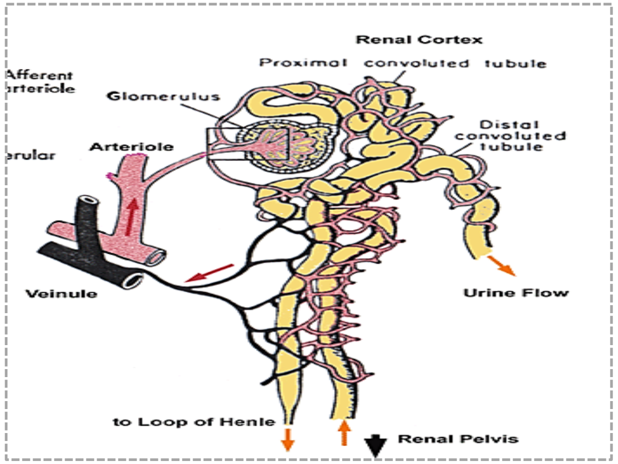


- Glomerular Filtrate has almost the same composition as that of plasma, except that it has no significant amount of proteins (it has about 0.003%)
- It is less than 1/2000 protein as compared with plasma.

Renal blood flow

- Although blood circulation in the kidneys passes through two capillary beds (Glomeruli and peritubular capillaries), it is not considered a portal circulation. Why? Because glomeruli contain arterial capillaries only (There's no venous blood).
- In the blood supply of the kidney, the straight arterioles of kidney (or vasa recta renis) are a series of straight capillaries in the medulla (Latin: vasa, "vessels"; recta, "straight").

- The blood flows to each kidney through a renal artery.
- Renal blood flow to the kidney represents 20% - 22% of cardiac output.(C.O = 5L → 5x0.2=1L)



- **Features of renal circulation:**
  - Upon to the previous sentence it has a High blood flow rate (1200 ml/min). "Range: 1018-1200"
  - Presence of two capillary beds: ***glomerular*** *and* ***peritubular***.
  - major sites of renal resistance are : Efferent and afferent arterioles are

Urine Formation

- The primary function of the kidney is to 'clear' unneeded substances from the blood to be excreted in urine.
- **Steps of urine formation (basic renal processes) :**

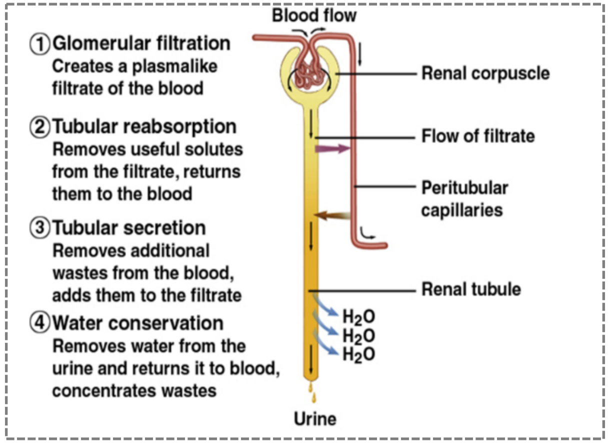
1- Glomerular filtration:

Filtration of fluid from glomerular capillaries <u>into</u> the renal tubules.

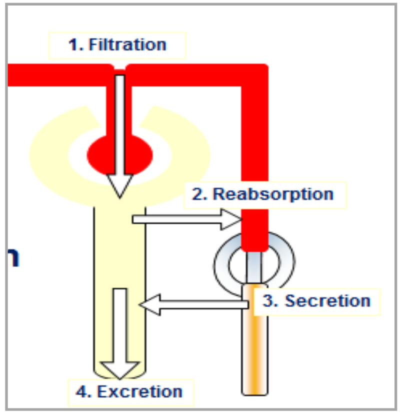
2- Tubular reabsorption

3- Tubular secretion.

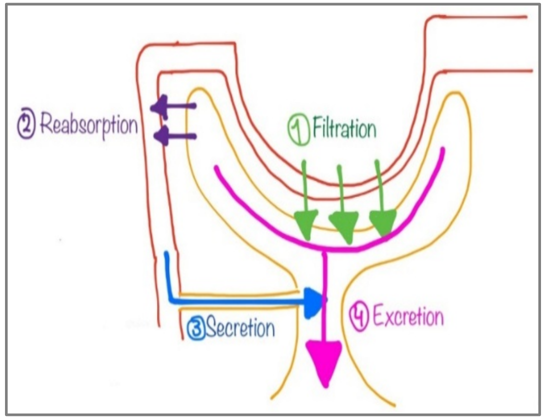
4- Excretion.



Urinary excretion rate = Filtration rate - reabsorption + secretion



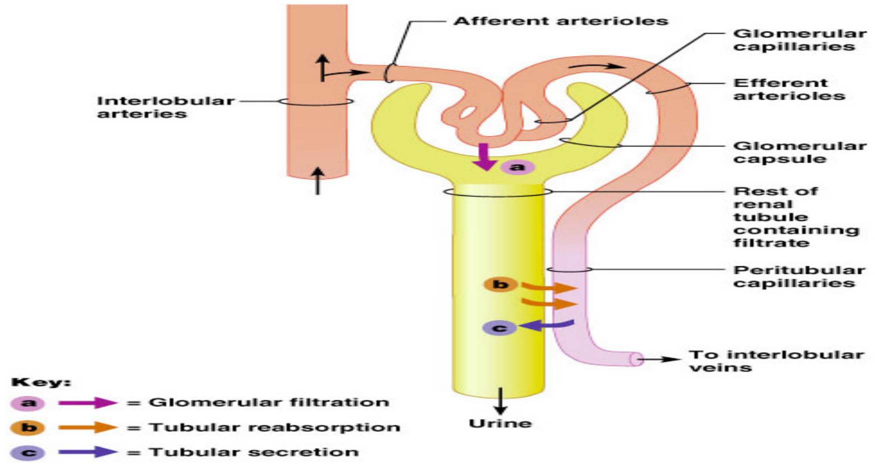
- More filtration, more urine production.
- More reabsorption, less urine production.
- Note that only plasma (excluding plasma proteins) is filtered into the capsule.
- Plasma proteins are not filtered. Why?
  - Because they're negatively charged, they repel the negative basement membrane of the glumerular barrier.
  - Because they're large in size.
- Filtrate = Plasma – Plasma proteinsC



This figure is similar to that drawn by Dr.manan in the lecture. Thanks deema :). (Team435)

Mechanisms of Urine Formation

- Urine formation and adjustment of blood composition involves three major processes
  - Glomerular filtration
  - Tubular reabsorption
  - Tubular Secretion
  - Excretion



- **Glomerular Filtration:**
  - The first step in urine formation
  - Filtered through the glomerular capillaries into the Bowman's capsule.
  - ~20% of plasma entering the glomerulus is filtered
  - 125 ml/min filtered fluid
  - Proteins do not cross filtration membrane

- **Tubular Reabsorption:**
  - Movement of substances from tubular lumen back into the blood.
  - Carried by the peri-tubular capillaries to the venous system.
  - Most of the filtered plasma is reabsorbed.

Mechanisms of Urine Formation (continue)

- **Tubular Secretion:**
  - The selective transfer of substances from the peritubular capillary into the tubular lumen.
  - Allows for rapid elimination of substances from the plasma via extraction of the 80% of unfiltered plasma in peritubular capillaries and adding it to the substances already in tubule as result of filtration.
- **Urine Excretion:**
  - The elimination of substances from the body in the urine
  - All plasma constituents filtered or secreted, but not reabsorbed remain in the tubules and pass into the renal pelvis to be excreted as urine and eliminated from the body

- Tubular Reabsorption "is nonselective (takes everything back) only toxins and wastes are excreted"
- Secretion is "selective"

Glomerular Filtration Rate (GFR)

- **Glomerular Filtration Rate (GFR) :**

The volume of filtrate produced by both kidneys per minute. ***(the rate of production of filtrate at the glomeruli from plasma)***(rate is imp in definition)

Averages : 125 ml/min (***Typically*** 80 – 140 ml/min)

Totals about : 180 L/day (45 gallons). " 125 ml/min x 60min (in 1hour) = 7500 ml/ h x 24 (in 1day) = 180000 ml/day =180L/day "

So most filtered water must be reabsorbed or death would ensue from water lost through urination!

ايش الحكمة من إن الفلتريشن يصير بهالكمية كل يوم مع إن كمية الدم بالجسم تقريبا ٥لتر ؟ نتخيل عندنا غرفة وتنظف مرة وحدة باليوم ، فرضا لو صارت تنظف مرتين أو ثلاث أو أربع مرات بكل الأحوال راح تكون نظيفة لكن كل ما زاد عدد المرات أو تكرار العملية راح نضمن نظافتها أكثر. بنفس الفكرة بالجسم معدل الفلتريشن باليوم تقريبا من ٤٠-٦٠ مرة يضمن لي إن الدم راح ينظف بشكل أفضل.

- **Glomerular Filtration Rate (GFR) is** directly proportional **to the net filtration pressure (NFP) :**

- When NFP increase → GFR increase
- When NFP decrease → GFR decrease

Changes in GFR normally result from changes in glomerular blood pressure.

Regulation of GFR

If the GFR is too high :
Fluid flows through tubules too rapidly to be absorbed.
↓
Urine output rises.
↓
Creates threat of **dehydration** and electrolyte depletion. **(It will lead to Hypo. Cases)**

If the GFR is too low :
Fluid flows sluggishly through tubules
↓
Tubules reabsorb wastes that should be eliminated
↓
Azotemia develops (high levels of nitrogen-containing substances in the blood)

Glomerular Filtration Rate (GFR)

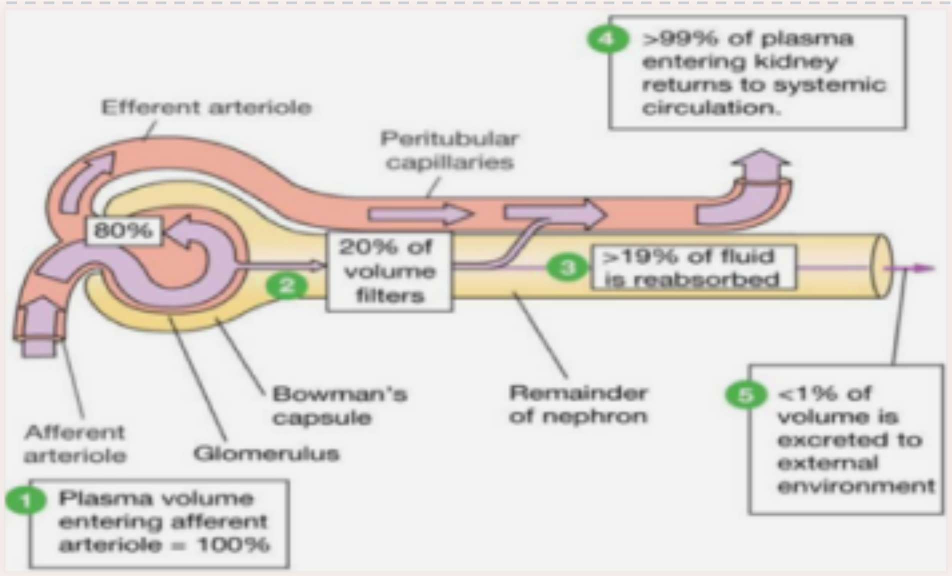
- Glomerular filtration rate (GFR) is the rate of production of filtrate at the glomeruli from plasma
  - Typically 80 – 140 ml/min depending on age, sex etc.
  - Sum of the filtration rates of all functioning nephrons
  - Index of kidney function

- Factors governing filtration rate at the capillary bed are:
  - Total surface area available for filtration (directly proportional to GFR)
  - Filtration membrane permeability (directly proportional to GFR)
  - Net filtration pressure (directly proportional to GFR)

Changes in GFR normally result from changes in glomerular blood pressure

- If the GFR is **too high**:
  - Needed substances cannot be reabsorbed quickly enough and are lost in the urine

- If the GFR is **too low**:
  - Everything is reabsorbed, including wastes that are normally disposed of



GFR = 125 ml/min

180 L /day , 1% excreted , 99% reabsorbed.

اللي يدخل ال glomerulus هذا اللي
يصيرله filtration كميته 20% من
البلازما وبعدين من ال 20 % يفضل 1%
والباقي يرجع للبلازما بس ال toxins و
ال waste products يصيرلها
excretion وممكن من كمية البلازما
اللي مرت وما صارلها filtrationيكون
فيه waste products يصيرلها
SECRETIONمرة ثاني في lumen
of the tubule

أتمنى فهمت ☺

<u>EXTRA EXPLANATION :</u>

- 20% of Plasma volume enters the glomerulus through the afferent arteriole will be filtered and 80% will go through the efferent arteriole to the peritubular capillary then to systemic circulation without filtration. 20% which is filtered 99% of it will be absorbed to the peritubular capillary and only very small amount 1% will be excreted to keep body fluid volume in balance.

- The most important step in urine formation is filtration. When 1000 ml of blood enters the glomeruli through Afferent arterioles only 600 plasma is filtrated the rest RBC won't be filtrated. Also not all the 600 ml of plasma is filtrated only 20 % of it is filtrated which equal 125 ml.

Goals of Glomerular Filtration Rate (GFR)

الفائدة

- Index of kidney function
- Sum of the filtration rates of all functioning nephrons (***indicator for number of functioning nephrons***)

- **Factors governing filtration rate at the capillary bed are:**

Net filtration pressure (NFP)

Total surface area available for filtration

GFR

Filtration membrane permeability

Net filtration Pressure:

- The pressure responsible for filtrate formation
- NFP equals the glomerular hydrostatic pressure (HP_g) minus the oncotic pressure of glomerular blood (OP_g) combined with the capsular hydrostatic pressure (HP_c)

$$NFP = HP_g - (OP_g + HP_c)$$

Or

$$NFP = P_{GC} - P_{BS} - O_{GC}$$

Glomerular filtration rate (GFR)

Determined by:

NFP = 10 mmHg

1-the net filtration pressure across the glomerular capillaries.

×

Kf = 12.5

2-The glomerular capillary filtration coefficient

=

GFR=125 ml/min

It is determined by Starling's forces (next slide)

depend on:

- Surface area
  - Nephrectomy will decrease surface area → decrease Kf
- Permeability
  - Early in diabetes, GFR is high. It drops later due to membrane thickening. Diabetes and hypertension thicken the membrane, reducing permeability and filtration coefficient.

Hydrostatic, Colloid and Filtration Pressure

Filtration: **Hydrostatic Pressure**

- glomerular hydrostatic pressure (GHP)

→ pushes fluid out of vessels
- capsular hydrostatic pressure (CsHP)

→ pushes fluid back into vessels
- net hydrostatic pressure (NHP)

NHP = GHP – CsHP

35 = 50-15 mm Hg

Filtration: **Colloid Pressure**

- blood colloid osmotic pressure (BCOP)
- proteins in blood (hyperosmotic) draws water back into blood

~ 25 mm Hg

Oncotic = colloid = osmotic

importance of blood pressure
20% drop in blood pressure
50mmHg to 40mm Hg → filtration would stop

Filtration: **Filtration Pressure (FP)**

FP = NHP – BCOP
10 = 35 - 25 mmHg

الأرقام مب للحفظ ممكن يجي أي رقم

Filtration pressure Example

VERY IMPORTANT!!!

- Driven by **Starling** forces
- Pressure inside capillaries > Pressure outside

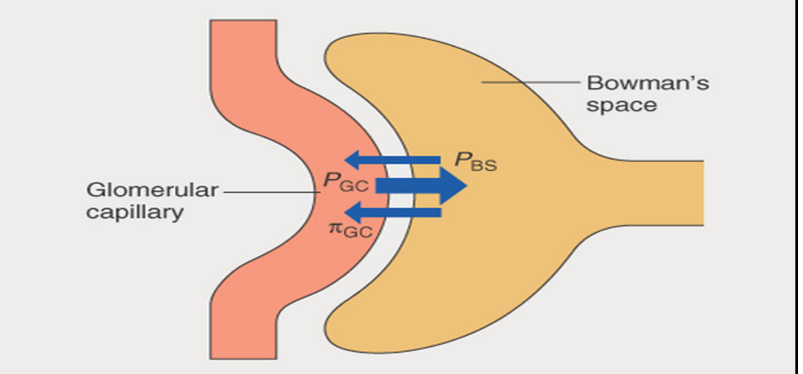
$\Rightarrow$ movement of fluid from blood

- Forces in capillaries: hydrostatic pressure P_{GC} = + 60mmHg
- oncotic pressure π_{GC} = - 29 mmHg

  $\therefore$ net outward pressure = 60 – 29 = 31mmHg

- Forces in capsule: hydrostatic pressure P_{BS} = -15 mmHg
- oncotic pressure π_{GBS} = 0 mmHg

- Overall: 31 – 15 = 16 mmHg outward



Forces	mmHg
Favoring filtration:	
Glomerular capillary blood pressure (P_{GC})	60
Opposing filtration:	
Fluid pressure in Bowman's space (P_{BS})	15
Osmotic force due to protein in plasma (π_{GC})	29
Net glomerular filtration pressure = $P_{GC} - P_{BS} - \pi_{GC}$	16

- Male adults GFR: ~ 90 – 140 ml/min
- Female: 80 – 125 ml/min
- 125 ml/min usually good average

الأرقام مب للحفظ ممكن يجي أي رقم

Glomerular Filtration Rate

$$GFR = \frac{[sub]_{urine} \text{ x urine flow rate}}{[sub]_{plasma}}$$

Sub urine = amount of substance in urine
Urine flow rate = Volume / time
Sub plasma = amount of substance in plasma

$$GFR = \frac{[creatinine]_{urine} \text{ x urine flow rate}}{[creatinine]_{plasma}}$$

- Measurement of creatinine concentration in a urine sample, urine flow rate and plasma creatinine concentration can be used to determine GFR.
- Only 15 – 20 % of plasma entering glomerulus filtered
- Composition of filtrate:

Similar to plasma BUT NO large proteins or cells

- From 435:
- د. أحمد قال عن الـ inulin انه افضل شيء لقياس الـ GFR ولكن ليس في البشر "موضع سؤال في الـ MCQs " فإذا لم يحدد في السؤال البشر : أنيولين, أما إذا حدد : كرياتينين.

Substances Used to Measure GFR

Details in the next lecture :)

Inulin

Inulin, a polymer of fructose, is used in research to precisely measure GFR

- Freely filtered into the Bowman's capsule
- Not reabsorbed, NOT secreted NOT metabolized by the nephron
- Non-endogenous, has to be infused intravenously (our bodies don't produce it)
- **Best marker.**
- **Not used in humans**

- **Assume**: (Don't memorize numbers)
  - $[Inulin]_{urine}$ = 30 mg/ml
  - $[Inulin]_{plasma}$ = 0.5 mg/ml
  - urine flow rate = 2 ml/min
- GFR = 120 ml/min or 172.3 L/day

Creatinine

- endogenously released into plasma by skeletal muscle
- Not as accurate as inulin as a small quantity is secreted into the proximal tubule
- amount excreted > amount filtered
- Reasonably accurate measurement of GFR
- **Clinically , Best marker**.

Explanation: next slide

- The usual analytical method for creatinine measurement (alkaline picrate method) also detects substances in the plasma other than true creatinine, leading to increase in plasma creatinine value.
- Thus, these two errors usually cancel each other and gives a correct estimate of GFR.

EXPLANATION

جهاز الي يحسب الكرياتينين في الدم يغلط ويحسب مواد ثانية على أساس انها كرياتينين (لأن تركيبها شبيه في الكرياتين)

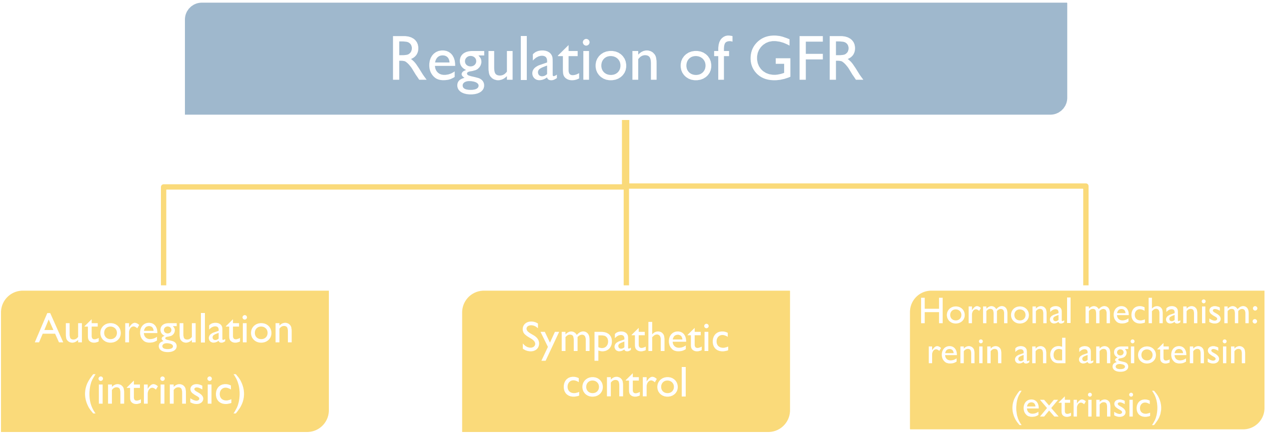
بس جسمنا ينتج كرياتين ويسويله سكريشن

عشان كذا تطلع القراءة دقيقة (الكمية الي حسبها الجهاز انها كرياتين = الكمية الي ينتجها جسمنا)

Regulation of GFR & RBF

- Changes in the GFR result primarily from changes in glomerular capillary blood pressure.

Because the net filtration pressure that accomplishes glomerular filtration is simply the result of an imbalance of opposing physical forces between the glomerular capillary plasma and bowman's capsule fluid, alteration in any of these physical forces affect the GFR.



Remember, GFR depends on

NFP, Surface area, Membrane permeability

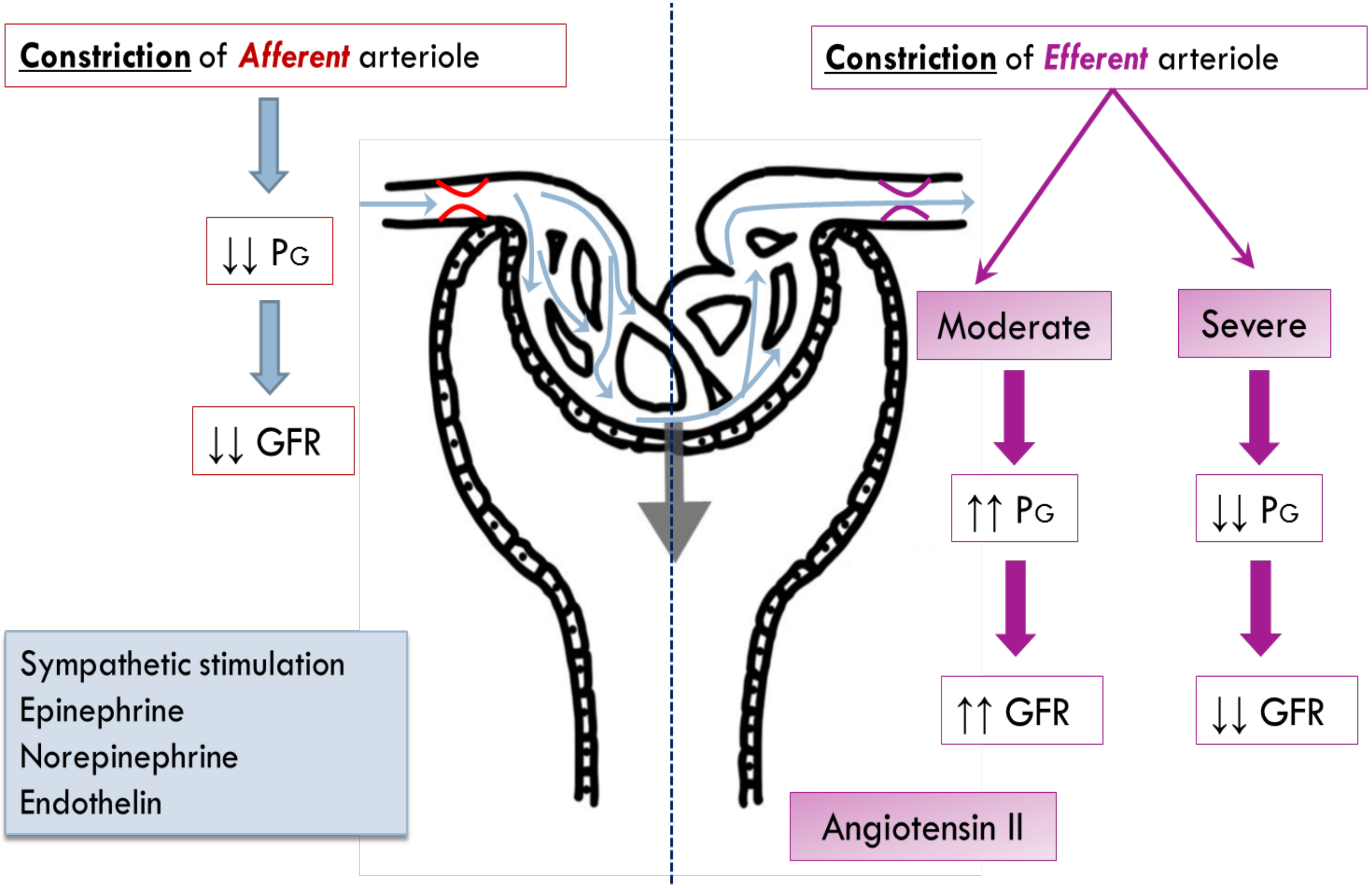
The Auto-regulatory mechanism is the most important one and it is intrinsic to the kidney itself. Let's imagine that you donate your kidney to someone, this mechanism will not change even within his body.

- **Intrinsic Autoregulation:**

  - Renal vasculature also exhibits a well developed **intrinsic** ability to adjust its resistance in response to changes in arterial BP and thus to keep BF and GFR essentially constant = **autoregulation.**

  - In man, effective over a range of MBP from 75-160mmHg. Below 75mmHg, filtration falls and ceases altogether when MBP = 50mmHg.

Physiologic Regulation of GFR



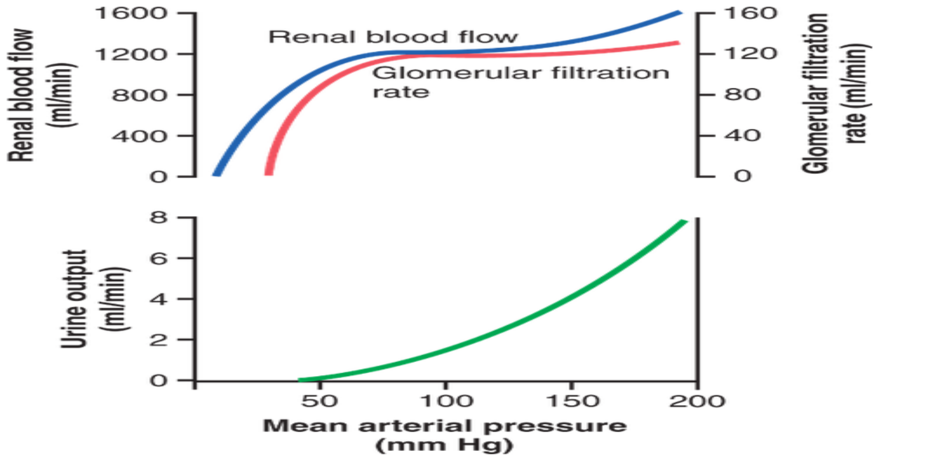
1- Autoregulation (intrinsic)

It is the relative constancy of GFR and renal blood flow in response to changes in blood pressure range from 75 to 160 mmHg

However, autoregulation is not perfect but it prevents potentially great changes in GFR , with changes in blood pressure, therefore, kidney continue to excrete waste

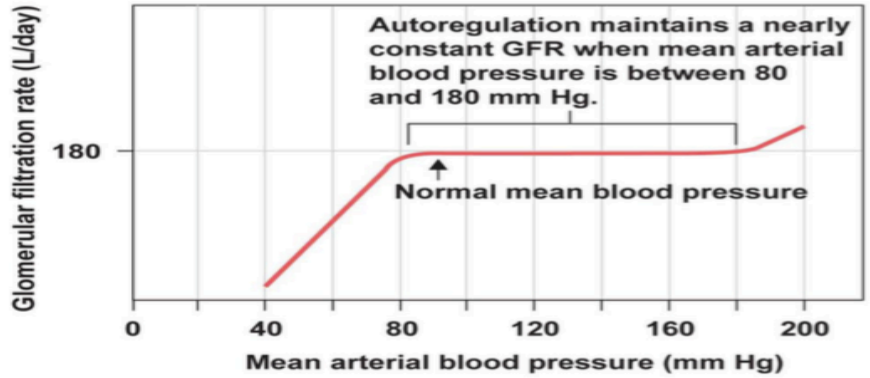
That means in a normal kidneys, a decrease in arterial blood pressure as low as 75 mmHg, or an increase as high as 160 mmHg causes a change in GFR by only a few percentage

if it drops below 75 the GFR keeps decreasing until the ABP become 50 then the filtration stops throw glomerulus



(Figure 26-17)

Autoregulation (intrinsic)



1- Autoregulation (intrinsic)

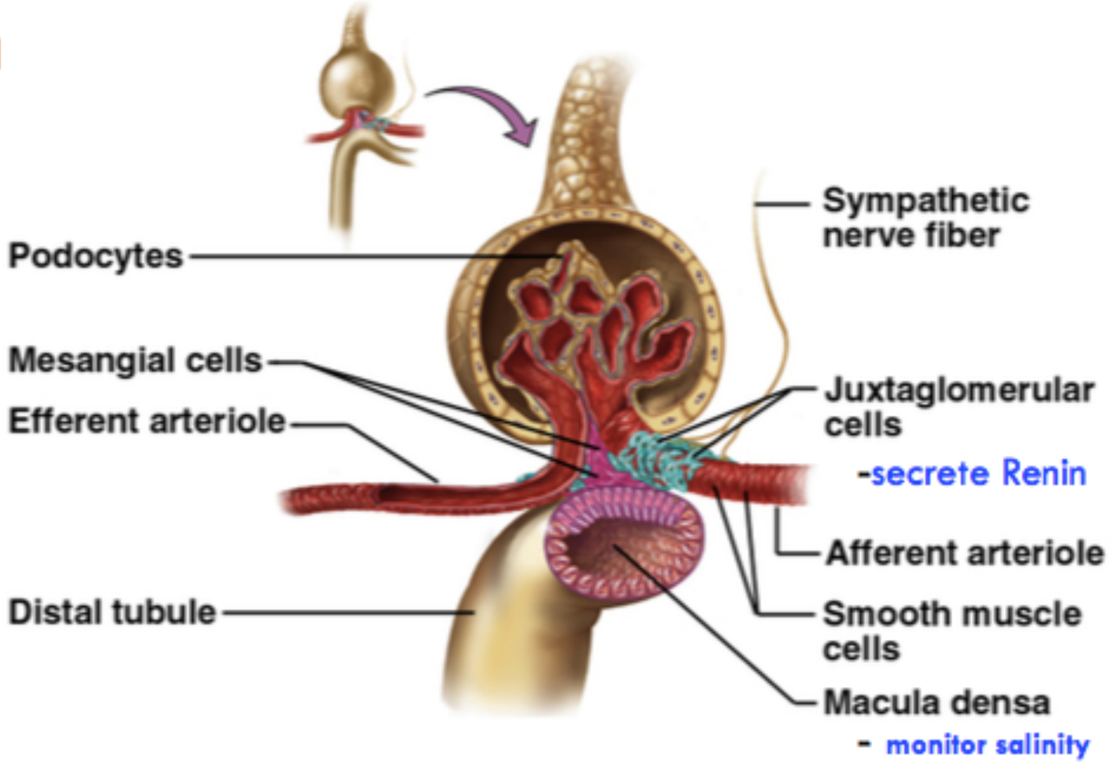
General information

- Refer to feedback mechanisms intrinsic to the kidney
- keep the renal blood flow and GFR relatively constant despite fluctuations in ABP
- These mechanisms operate over an ABP ranging between 75 -160 mmHg (systolic)

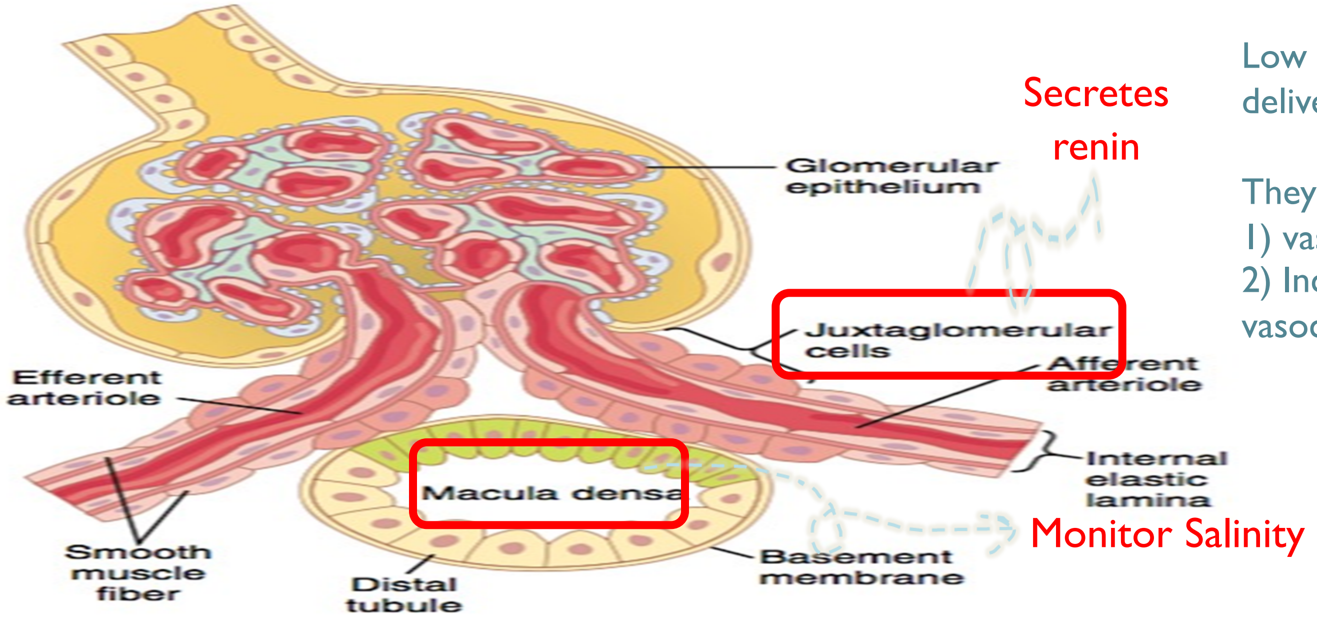
Achieved by 2 major mechanisms

1. Myogenic auto-regulation
2. Tubulo -glomerular feedback

Juxtaglomerular Apparatus



Juxtaglomerular complex



Low blood flow → low Hydrostatic pressure → low GFR → Decrease delivery of NaCl to the macula densa cells which are sensor for Na level.

They have two main mechanism to return to normal level
1) vasodilatation of AFFERENT arterioles (Direct)
2) Increase in Renin release from the juxtaglomerular cells → Ang II → cause vasoconstriction of EFFERNT Arteriole.(indirect)

باختصار رح تحس انه في نقص صوديوم
وتقوم تحفز افراز هرمون renin

- Juxtaglomerular apparatus composed of : macula densa cells , Juxtaglomerular cells , Afferent and efferent arterioles
- juxtaglomerular cells : the site where the renin is released

1- Autoregulation (intrinsic)

Renal Autoregulation of GFR		
Blood pressure	Afferent arteriole	Efferent arteriole
↑ BP	**Constriction**	**Dilation**
↓ BP	**Dilation**	**Constriction** (mild to moderate)

- If mean arterial P ↑, there is an automatic ↑ in afferent arteriolar constriction, preventing a rise in glomerular pressure . Dilatation occurs if P falls.
- Autoregulation is independent of nerves or hormones, occurs in denervated and in isolated perfused kidneys.

- **Can not** compensate for extreme BP changes.
- Stable for BP range of 75 to 160 mmHg (systolic).

When BP increases → Afferent and Efferent arterioles CONSTRICT (mainly afferent)

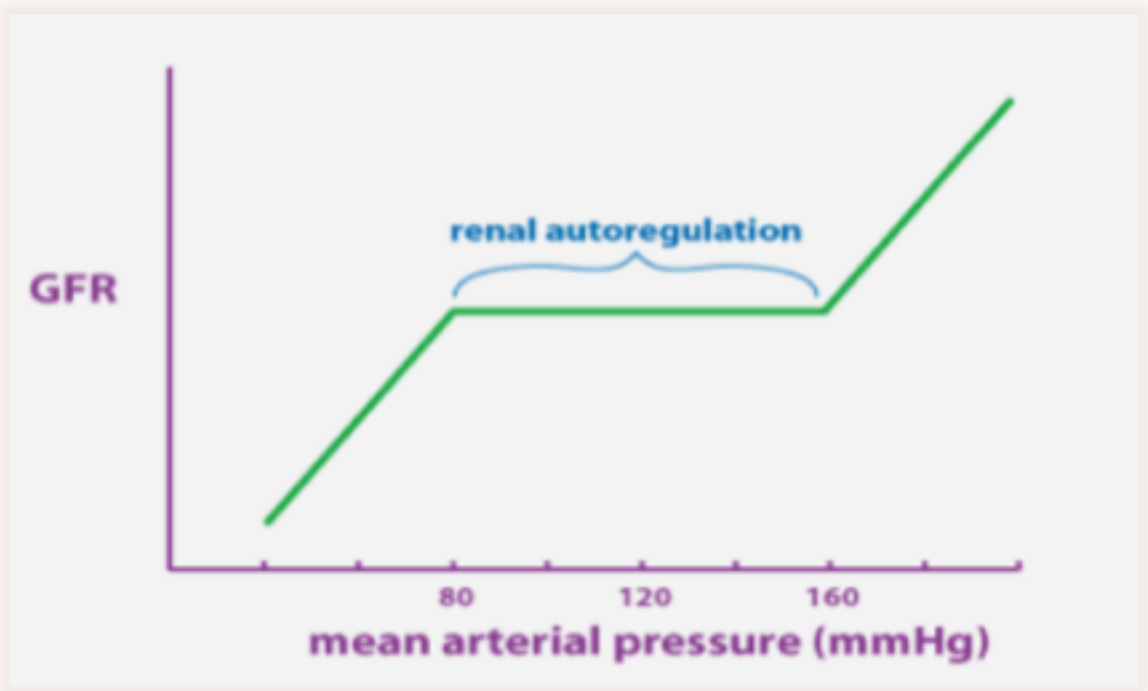
When BP decreases → arterioles dilate

Autoregulation is effective 75 – 160

Below 75 filtration decreases and stops at 40-50 mmHg

Video of (control of GFR)
Duration: (4:13)mins

Effect of arterial blood pressure on GFR



Normally when ABP increase → GFR increase

But, because of the auto-regulation the body maintains constant GFR over an ABP range of 75-160 mmHg.

Filtration stops when > 50 mmHg.

Explanation of autoregulation in next slide

General notes about autoregulation of GFR

- If we are in stressful condition our blood pressure increases ☾ the blood flow increase which result in increased hydrostatic pressure ☾ NFP increase ☾ GFR increase. But even though we don't urinate, why? Because kidney has mechanism to regulate by itself (auto regulation) within certain blood pressure range .

- If the BP within 75-160 the kidney is auto regulated which mean GFR is constant . And its auto regulated by 2 mechanism THE 1ST one is myogenic mechanism : if the BP increases the renal blood flow increases which will stretch the A.A this will stimulate Ca+2 channels to open ☾ Ca+2 influx to smooth muscle cells in the wall of A.A leading to vasoconstriction ☾ decreased blood flow ☾ decreased Pg ☾ decreased NFP ☾ decreased GFR .

- Remember :GFR in addition to renal plasma flow are constant ☾ due to autoregulation

- At the beginning of distal convoluted tubules (between A.A & E.A) there are cells called macula densa cells. The cells opposite to macula densa are called juxtaglomerular cells. Macula densa is sensitive to NaCl (salt). Let's say BP is increased, fluid going to A.A increases therefore increased GFR, and the filtrated fluid in proximal convoluted tubules increases and moves very fast which make no time for reabsorption in PCT. When this fluid reach to macula densa in DCT it will sense high sodium chloride and send signals that stimulate vasoconstriction of A.A . In addition, it prevents release of renin by juxtaglomerular cells and prevent production of Ang II, no vasoconstriction of E.A.

- Low BP ☾ Low blood flow ☾ low Pg ☾ low GFR ☾ Fluids enter the proximal convoluted tubule are low and move slowly which make them reabsorbed ☾ Decrease delivery of NaCl to the macula densa cells ☾ vasodilatation of Afferent arterioles ☾ Increase in Renin release from the juxtaglomerular cells to → Ang II → cause vasoconstriction of EFFERNT Arteriole. In addition , it stimulates juxtaglomerular cells to release renin ☾ produce Ang II ☾ causing vasoconstriction of E.A.

1- Autoregulation : Tubuloglomerular Feedback Mechanism

Increase in ABP

Increase blood flow in renal tubules
→ increase GFR

Decrease reabsorption by renal tubules (caused by the rapid flow)

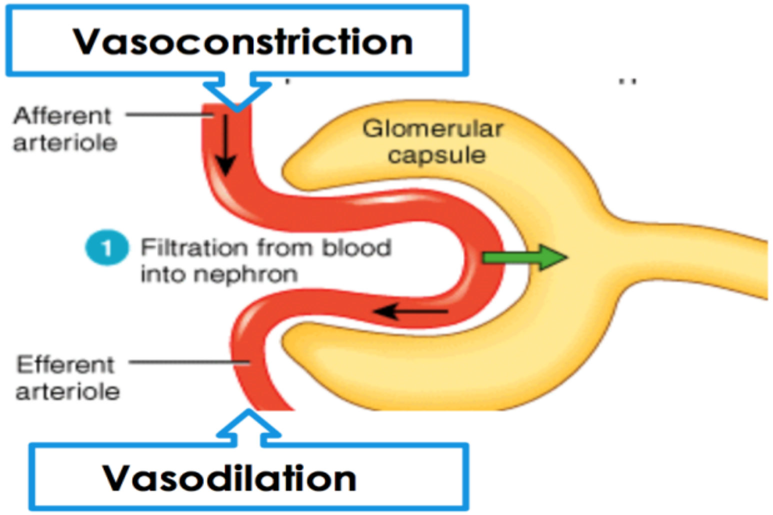
Increase delivery of NaCl to the macula densa cells, which are capable of sensing this change

Macula densa releases signals which will cause vasoconstriction of Afferent arterioles.

Inhibit the release of Renin from the juxtaglomerular cells leading to vasodilation of EFFERNT arterioles.

- Net result :

1. Decrease glomerular hydrostatic Pressure.
2. GFR back to its normal rate.



1- Autoregulation : Tubuloglomerular Feedback Mechanism

Decrease in ABP

↓

Decrease blood flow in renal tubules

→ Decrease GFR

↓

Increase reabsorption by renal tubules

↓

Decrease delivery of NaCl to the macula densa cells, which are capable of sensing this change

↓

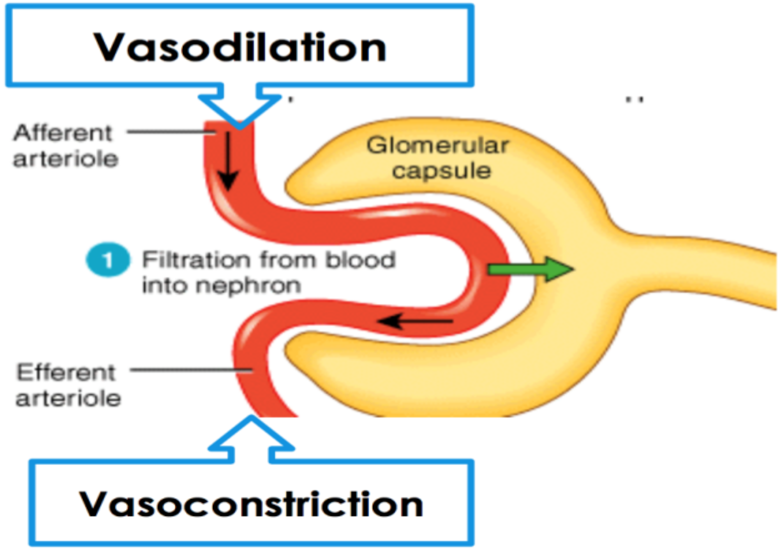
Macula densa releases signals which will cause vasodilatation of Afferent arterioles.

↓

Increase in Renin release from the juxtaglomerular cells to → Angiotensin II → cause vasoconstriction of EFFERNT Arteriole.

- Net result :

1. Increase glomerular hydrostatic Pressure.
2. GFR back to its normal rate.



1- Autoregulation : Myogenic auto-regulation Mechanism

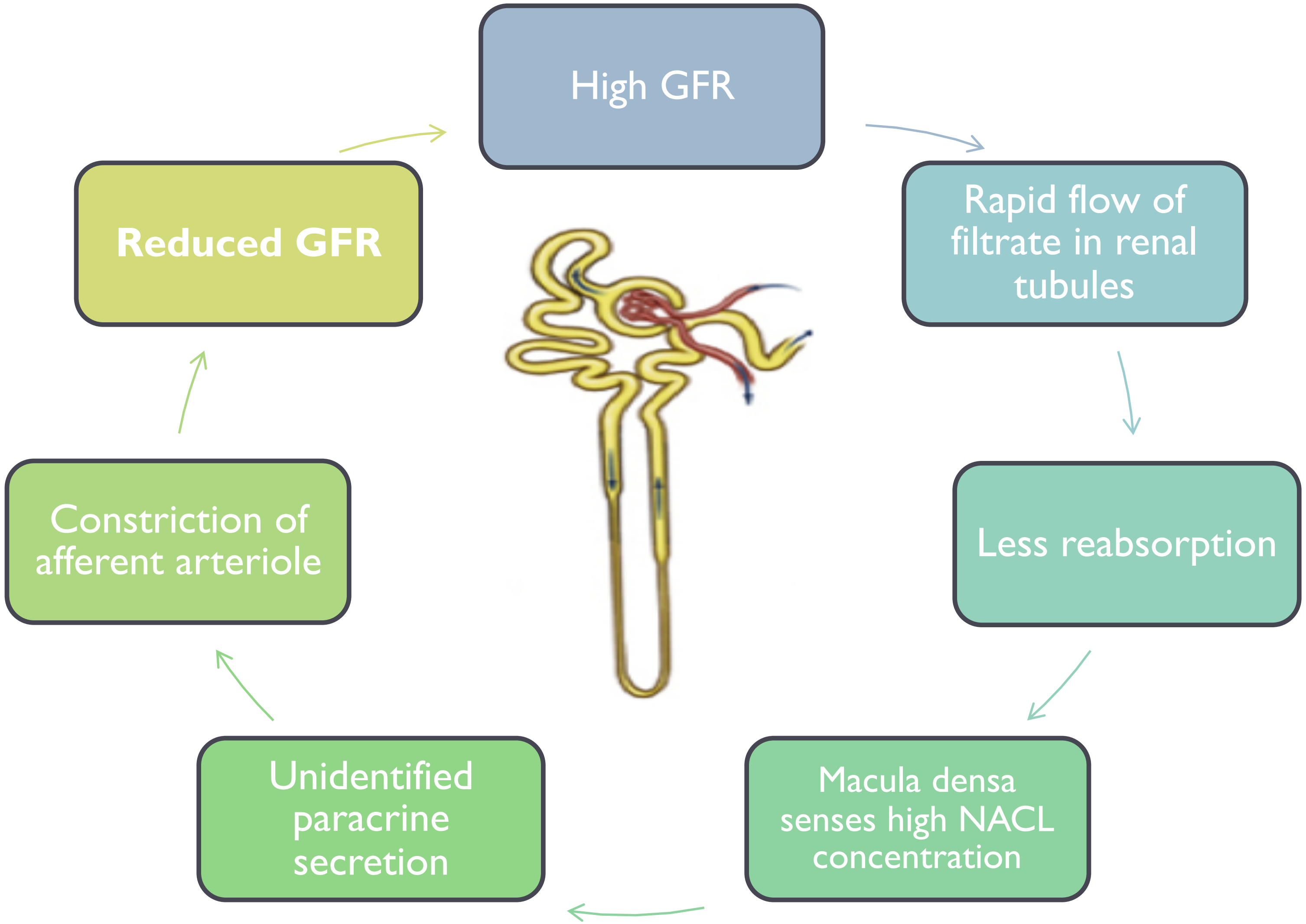
It is the intrinsic capability of blood vessels to **constrict** when blood pressure is increased

This constriction prevents excess increase in renal blood flow and GFR when blood pressure rises

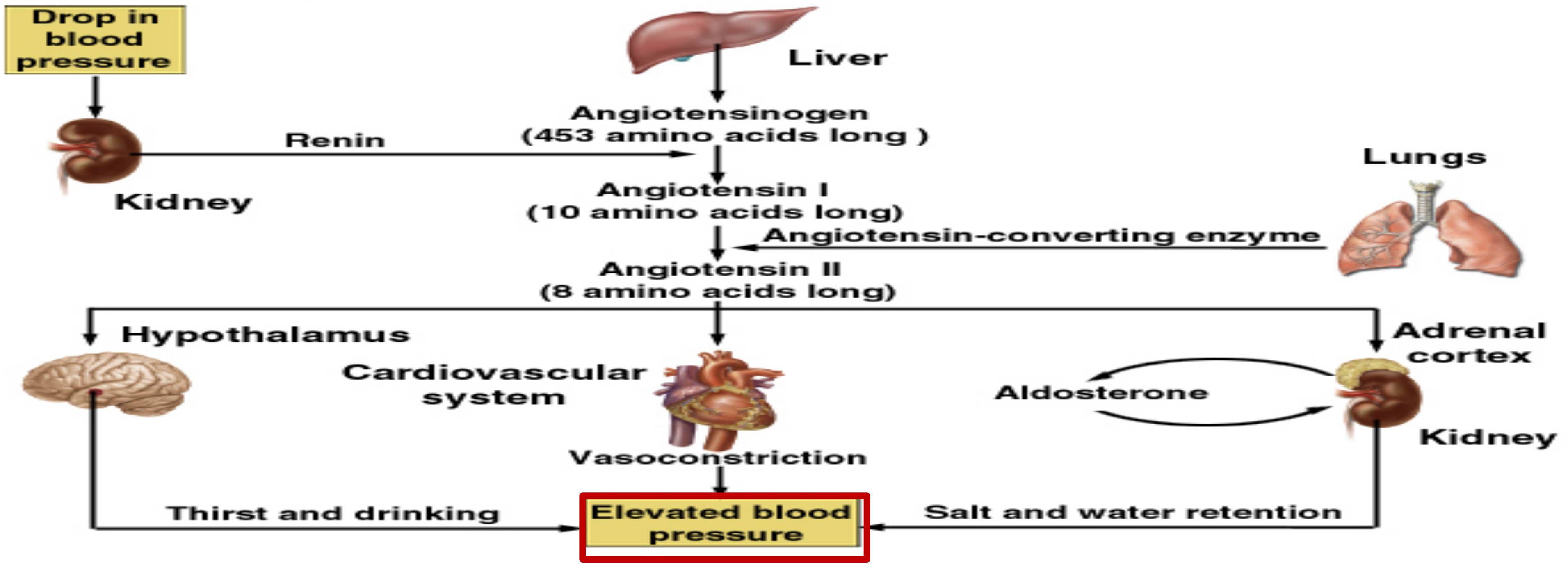
When blood pressure decreases , the myogenic mechanism reduces vascular resistance and the vessel **dilates**

Increase in blood pressure → Stretch of the vessel's well (Arterioles) → activation of stretch receptor → stretch-induced vascular depolarization → open the calcium channel → rapidly increases calcium ion entry → Vasoconstriction → decease the blood flow → decrease GFR

Example of autoregulation



2-(Extrinsic): Hormonal Control of GFR



Hormonal control through Ang II – low BP → stimulate renin release will result in production of Ang II .
Ang II release result in vasoconstriction of E.A → increase GFR, and also it will affect hypothalamus to stimulate thirst and drinking → increase fluid → normal GFR , also Ang II stimulate the suprarenal gland to release aldosterone → salt and water retention. All these mechanisms work together to maintain the GFR constant .

2-(Extrinsic): Hormonal Control of GFR

Hormonal factors

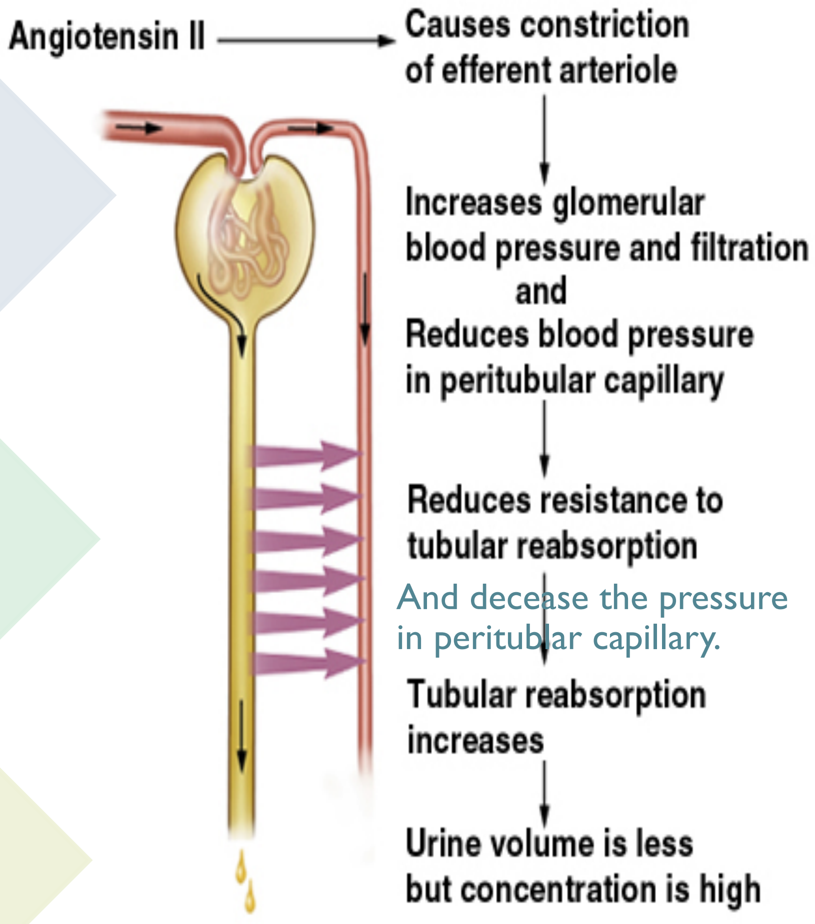
- Epinephrine, Nor-Epinephrine, Angiotensin II, Prostaglandin (F) and Thromboxane cause renal vasoconstriction and results in decrease in RBF and GFR.
- Acetylcholine, Bradykinin, Prostaglandin (D, E, and I), and bacterial pyogens cause renal vasodilation and results in increase in RBF and GFR.

Physiological factors

- Cold, deep anesthesia, fright, sever exercise, hypoxia and ischemia stimulate sympathetic nerve fibers leading to renal vasoconstriction and decrease in RBF.

Posture

- RBF increase in supine than sitting than standing. Changing the posture from lying to standing leads to a decrease of about 15% in RBF due to the stimulation of sympathetic NF.



And the blood return back to the body.

RBF = Renal Blood Flow

3- Sympathetic Control of GFR.

Under stress

- **Norepinephrine** is released by the sympathetic nervous system.
- **Epinephrine** is released by the adrenal medulla
- Afferent arteriole constrict and filtration is **inhibited**
- stimulation of renin angiotensin mechanism → This induces vasoconstriction of efferent arteriole

At rest

- Renal blood vessels are maximally dilated
- Autoregulation mechanisms prevail

- Note: during fight or flight blood is shunted away from kidneys

Such as in the shock we may have renal failure due to this effect, which direct the blood away from the kidney to brain and heart. It does not a daily mechanism

Factors Affecting Renal Blood Flow and GFR

Factors that decrease GFR + RBF

- Aging
- Sympathetic Stimulation of Renal Arterioles
- Norepinephrine

Factors that increase GFR+RBF

- High Protein Diet
- Hyperglycemia
  Same (glucose is reabsorbed with Na+)
- Fever

Factors that decrease RBF

- Angiotensin II (Constricts efferent arteriole more than afferent)

Why ? A high-protein meal ↑ release of amino acids into the blood, which are reabsorbed in the proximal tubule. Because amino acids and sodium are reabsorbed together by the proximal tubules, ↑ amino acid reabsorption → stimulates sodium reabsorption in the proximal tubules. This decreases sodium delivery to the macula densa which elicits a tubuloglomerular feedback–mediated ↓ in resistance of the afferent arterioles,→ ↓ afferent arteriolar resistance then ↑ renal blood flow and GFR. This ↑ GFR allows sodium excretion to be maintained at a nearly normal level while ↑ excretion of the waste products of protein metabolism, such as urea.

Thank you!

اعمل لترسم بسمة، اعمل لتمسح دمعة، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

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Link to Editing File

Special thanks to Team435!

References:

- Girls' and boys' slides.
- 435 Team.
- Guyton and Hall Textbook of Medical Physiology (13th Edition).
- Linda (5th Edition).