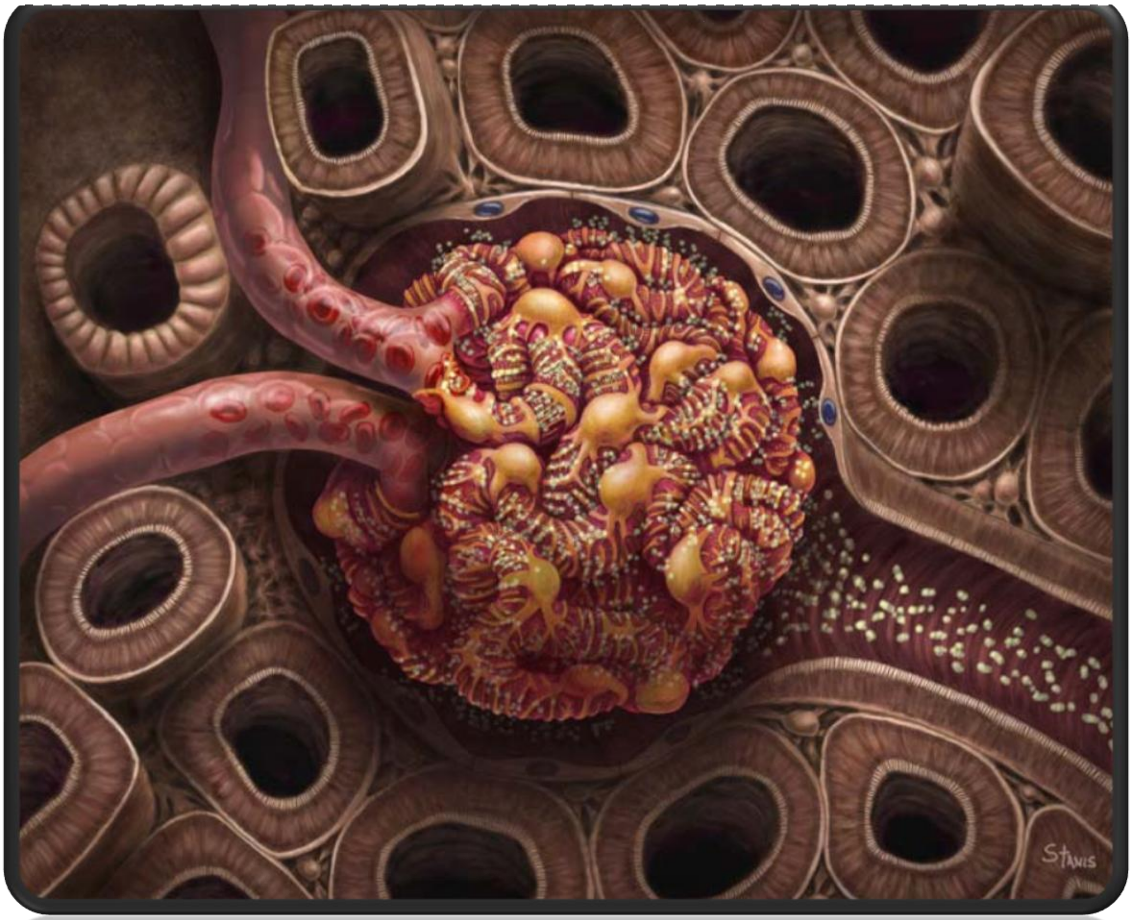
Physiology Team 431



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Regulation of Glomerular Filtration

Objectives

- Mechanisms of urine formation Composition of filtrate
- Filtration pressures
- Filtration Membrane
- Calculation of GFR, FF and Factors affecting GFR
- Autoregulation of GFR

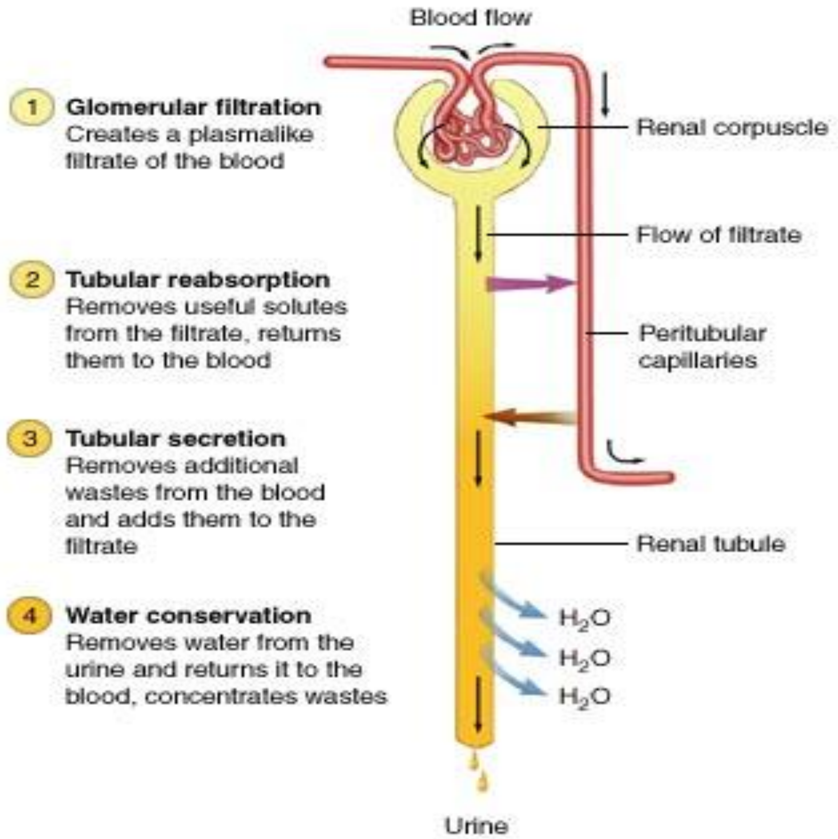
Principle of urine formation:

1. Filtration

    Glomerulus

2. Absorption & Secretion

    Tubule



Basic Mechanisms of Urine Formation:

1. Glomerular filtration
2. Reabsorption
3. Secretion
4. Urine concentration

- **Glomerular filtration:**

    Large quantity of water and solutes pass through the filtration membrane from the blood into the glomerular capsule

    - Plasma Ultrafiltration
    - Composition of filtrate (same as plasma except plasma protein)
    - Isaotonic (~300 mosmo/l) *same as the osmolality of the blood plasma*

        - Water
        - Electrolytes
        - Glucose
        - Urea
        - Creatinine

Ultrafiltration means filtration of small molecules, which are the plasma, electrolyte and the organic substances (Red blood cells, white blood cells, proteins, & platelet are **not filtered**)

Filtration membrane:

1. Capillary endothelial
    - Fenestration 70-100 nm (pores)
2. Basement layer (mesengial cell)

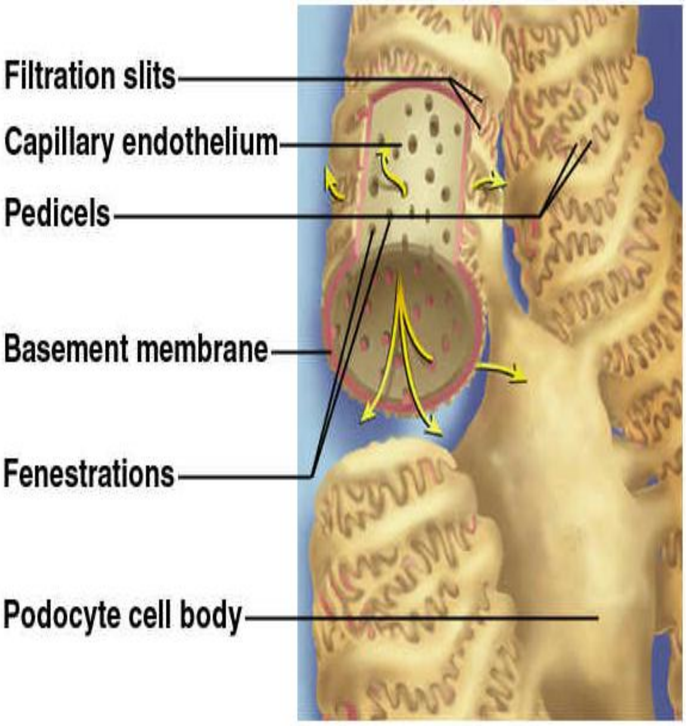
Filtration membrane are the layers that the plasma pass through to get into the Bowman's capsule

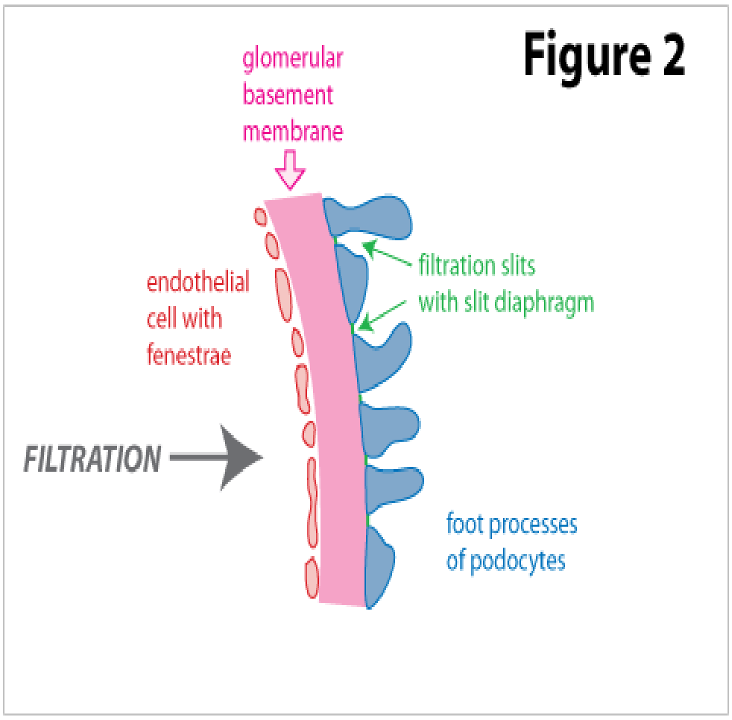
- Homogenous collagenous fibers *(not cells)* with no pores
- -vely charge (sailoprotein) *(the negative charge repel the proteins [which are negative molecules] from passing through the membrane)*
- Contractile mesengial cells *(if these cells contract they will reduce the size of the membrane [surface area] which will lead to a decrease in filtration)*

3. Capsule epithelial layer podocytes
    - Podocytes
    - Slit pores 25-60nm

Podocytes means legs

These three membranes are 100 times more permeable than any membrane in your body





Filtration of Molecules:

Molecular size and charge regulate filtration

- Molecules less than 4 nm are freely filtered
- Molecules between (4-8) nm filtration is controlled by the molecule's charge **(negatively charged molecules are poorly filtered compared to neutral and positively charged molecules)**
- Molecules more than 8 nm are not filtered

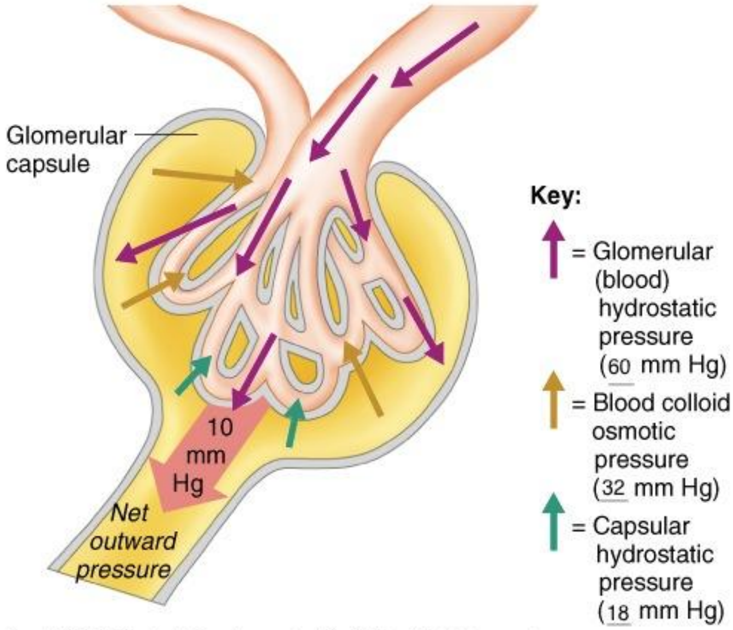
- *If there was a problem in the membrane, which caused it to loose its negative charge; protein will appear in the urine this is a disease called nephrotic syndrome occur in children*

Filtration pressure

- Pressure that moves plasma out of the glomerulus capillary into the Bowman's capsule space
- Four different pressures affect filtration
- The algebraic sum of these pressures is the driving pressure for filtration

Filtration pressure (Starling forces):

1. Glomerular hydrostatic pressure (PGC)
2. Glomerular osmotic pressure (□GC)
3. Bowman hydrostatic pressure (PBS)
4. Bowman osmotic pressure (□BS) = zero



- Glomerular hydrostatic pressure (P_{GC}):
  - Favors filtration □ (main positive pressure for filtration)
  - **60 mmHg** (in the arteriole of the kidney)
  - Remain constant along the entire glomerular capillary
  - This pressure comes from the pumping of the heart

> Usually the pressure in the capillaries is 4 mmHg except in the kidneys it's 60 mmHg because the renal artery is short and close to the abdominal aorta ***(why do we need such high pressure in the kidney?*** *for filtration)*

- Hydrostatic pressure in Bowman space (P_{BS})
  - Opposes filtration (negative pressure)
  - **18 mmHg**
  - Due to filtered fluid in the capsule

- Colloid osmotic pressure in glomerular capillaries (π_{GC})
  - Opposes filtration □ (negative pressure)
  - **32 mmHg**
  - Caused by plasma protein
  - **Is not constant** *(because the fluid is filtered without the protein → protein concentration will increase → protein pressure will increase)*
- Colloid osmotic pressure in Bowman capsule (π_{BC})
  - Zero *why?* (No plasma protein)

Calculation of Net Filtration Pressure:

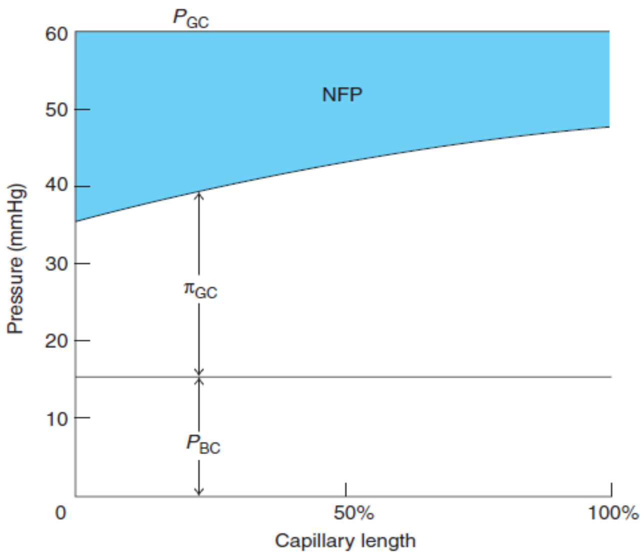
- Net filtration pressure

- = 60-18-32= 10 mmHg
- =Kf (P_{GC}-P_{BS})-(π_{GC} -π_{BS})

- Kf : Filtration coefficient depend on Filtration membrane
    - Permeability *(diseases that effect it are nephrotic syndrome ↑and diabetes ↓)*
    - Surface area
- Glomerular permeability > 100 x skeletal capillaries permeability

Net Filtration Pressure:

- Net filtration pressure decreases as passing along the glomerular capillary
- Only plasma is filtrated → ↑ plasma protein conc. → ↑ oncotic pressure → ↓ net filtration pressure



Glomerular Filtration Rate (GFR):

- Amount of plasma filtered by all nephrons in both kidneys/unit time
- 125 ml/min
- Kidney function test
- Variation in GFR between different species depend on numbers of nephrons

Measurement of GFR:

- **Characteristic of substance used (INULIN):**
    - Freely filtered (not reabsorbed or secreted)
    - Not metabolized by the kidney
    - Not toxic and stable
    - Not bound to plasma protein
    - Does not change renal plasma flow
- **Test procedure:**
    - Intravenous loading dose of inulin followed by intravenous infusion of inulin to maintain plasma level constant.
    - Urine is collected for 15 or 20 min, to measure inulin concentration in urine and urine volume.
    - Blood sample is taken half way of urine collection to measure inulin concentration.

The Dr said that you could read the test procedure on your own

Calculation of GFR:

- The amount of inulin excreted = U_{in} x U_v

- The amount of inulin filtered = P_{in} x GFR
- As inulin is not reabsorbed or secreted both quantity are equal
- P_{in} x GFR $=U_{in}$ x U_v
- $GFR = \frac{U_{in} \times U_v}{P_{in}} = ml\backslash min$

Where,
U_{in}: is the conc. Of inulin in the urine
U_v: is urine flow rate (volume/min)
P_{in}: is the conc. Of inulin in the plasma

- GFR= K_f x Net Filtration Pressure
- GFR=12.5x10=125ml/min
- $K_f \propto$ GFR ($\downarrow K_f$ in diabetes - $\downarrow$GFR)

$NFP= K_f (P_{GC}-P_{BS})-(\pi_{GC} -\pi_{BS})$

(NFP's K_f is different than the GFR K_f)

Filtration fraction:

- The fraction of Renal Plasma Flow (RPF) that is filtered = GFR/RPF
- 125/ 625= .2= 20% *(this is the normal FF)*

Factors affecting GFR:

1. Changes in P_{GC}:
   - $P_{GC} \propto$ GFR
   - Systemic blood pressure
   - Afferent vasoconstriction $\downarrow P_{GC}$ - $\downarrow$ GFR
   - Efferent vasoconstriction $\uparrow P_{GC}$ - $\uparrow$ GFR
2. Changes in π_{GC}:
   - π_{GC} $1/\propto$ GFR
   - $\uparrow \pi_{GC}$ - $\downarrow$GFR
   - hemo concentration (dehydration) - $\uparrow$ plasma protein concentration $\uparrow \pi_{GC}$
   - $\uparrow$ filtration fraction- $\uparrow \pi_{GC}$

The glomerular capillary colloid osmotic pressure is affected by:
1. Arterial plasma colloid osmotic pressure *(pressure caused by plasma protein)*
2. Filtration fraction: the fraction of plasma filtered by the glomerular capillaries *[↑plasma filtration (↓fluid) →↑glomerular capillary colloid osmotic pressure]*

3. Changes in P_{BS}:

  - P_{BC} 1/∝ GFR
  - ↑ P_{BC} due to obstruction to outflow - ↓ GFR
    - Urethral obstruction
    - Kidney edema

4. Changes of filtration coefficient:

  - Glomerular capillary permeability
  - Changes in surface area

If both or one is reduced they will reduce GFR

5. Changes in renal blood flow *(if renal blood flow drops GFR will decrease e.g. accidents)*

AUTOREGULATIONOF GFR

GFR remains constant over a large range of values 75-160 (some bock 50 -200)

Intrinsic

MYOGENIC:

Intrinsic property of mesangial (smooth muscle) cells and in afferent arteriolar Reflex contraction induced by increased blood pressure reduces filtration

Explanation
When there is increase in BP, The smooth muscle constrict after stretch, so the filtration will reduce

When there is decrease in blood pressure, the smooth muscle dilate, so the filtration will increase

TUBULOGLOMERULAR FEEDBACK:

Flow rate sensed by macula densa (part of juxtaglomerluar apparatus), sends chemical signal to alter afferent arteriole resistance

Explanation
macula densa is very sensitive to Nacl

1- **when BP increase , tubule can not Reabsorb Nacl so macula densa produce contraction of afferent (due to sense from Nacl)**
2- **when BP decrease , tubule can reabsorb Nacl so macula densa produce dilation of afferent (due to remove Nacl)**

Extrinsic

SYMPATHETIC INNERVATION

Sympathetic stimulation/ epinephrine released from adrenal medulla cause arteriole vasoconstriction and reduced GFR

ANGIOTENSIN II

Produced as a result of renin release from kidney
Constricts efferent arteriole; prevent decrease in GFR

NITRIC OXIDE (NO)

Causes arteriolar vasodilation
Elevated NO may result in hyperfiltration of early Diabetes Mellitus
Reduced NO after salt intake may lead to hypertension

Summary

1- Mechanisms of Urine Formation: Glomerular filtration, Reabsorption, Secretion, Urine concentration

2- Filtration pressure: Glomerular hydrostatic pressure, Glomerular osmotic pressure. Bowman hydrostatic pressure. Bowman osmotic pressure

3- GFR depend to: NFP, Kf

4- NFP depend to, P_{BC}, π_{GC} , P_{GC}

5- Kf depend on Glomerular capillary permeability and Changes in surface area

6- GFR remains constant over a large range of values 75-160 by two mechanisms: myogenic and Tubuloglomerular feedback

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

Some animations help you to understand:-

http://www.dnatube.com/video/2106/Medical-Animation-Kidney-Function-in-Filtering-Contrast

Questions:

1) Albumin (or Fibrinogens or globulins) size is 7 nm is not filtered through the membrane:

a) Because of it's big size
b) Because of it's negative charge
c) It is filtered through the membrane

2) Dehydration will cause:

a) Decrease filtration
b) Increase filtration
c) Doesn’t affect the filtration

3) If U_{in} is 850, U_v 1 and P_{in} 7 calculate the GFR:

a) 121 ml/min
b) 5950 ml/min
c) 1 ml/min

4) In normal person have blood pressure increase at 190, the GFR:

a) Increase at certain level
b) 125 ml/min
c) Small change
d) Decrease at certain level

Answers:
B – A – A -B