THE RENAL SYSTEM

Introduction :-

- Kidneys are "regulatory organs"
  - Body fluid osmolality and volume
  - Acid Base balance → Maintain pH
  - Electrolytes

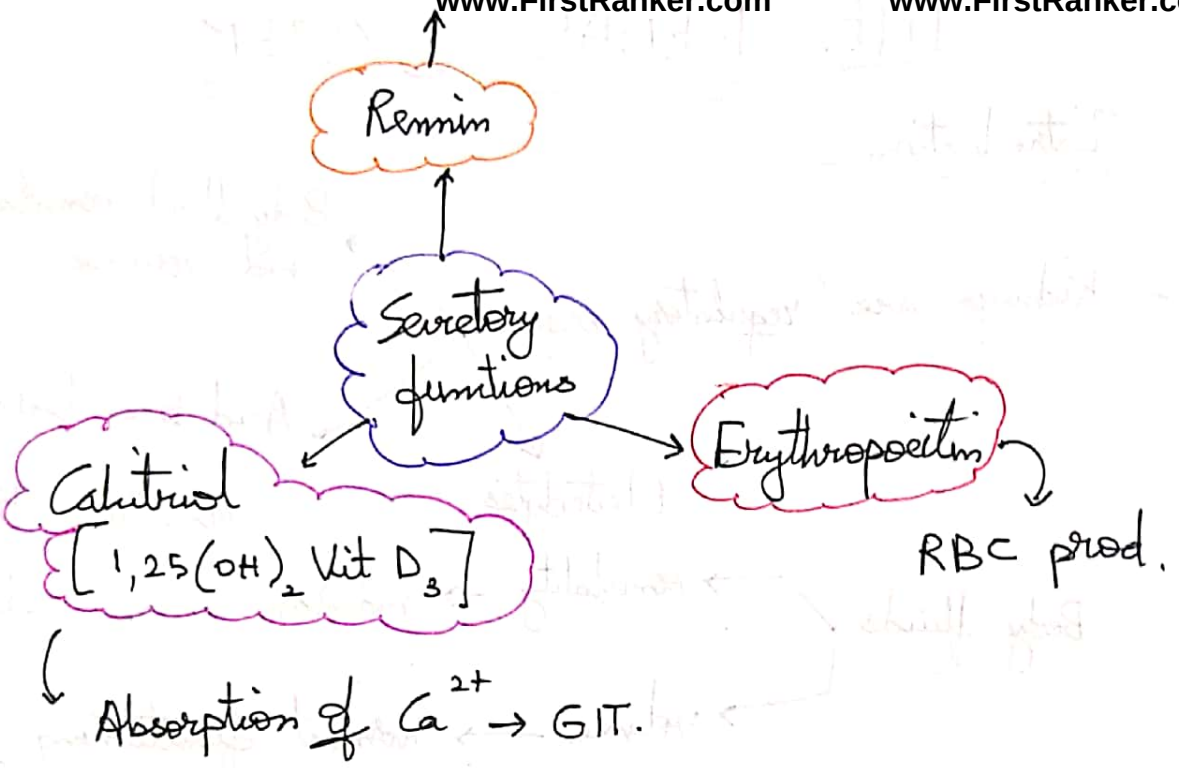
Body fluids
- → osmolality → maintain normal cell vol
- → volume → normal functioning of CVS

=> Functions of Kidneys
- Excretory
- Secretory

Maintain body fluid > osmolality > volume

- Excretory functions
  - ← Acid base balance
  - → Maintain electrolyte balance
  - → Excrete metabolic > foreign subs.
    - drugs
    - toxins
    1. Urea
    2. Uric acid
    3. Creatinine
    4. metabolites of hormones
    5. End prod of Hb metab.

RAAS mech.



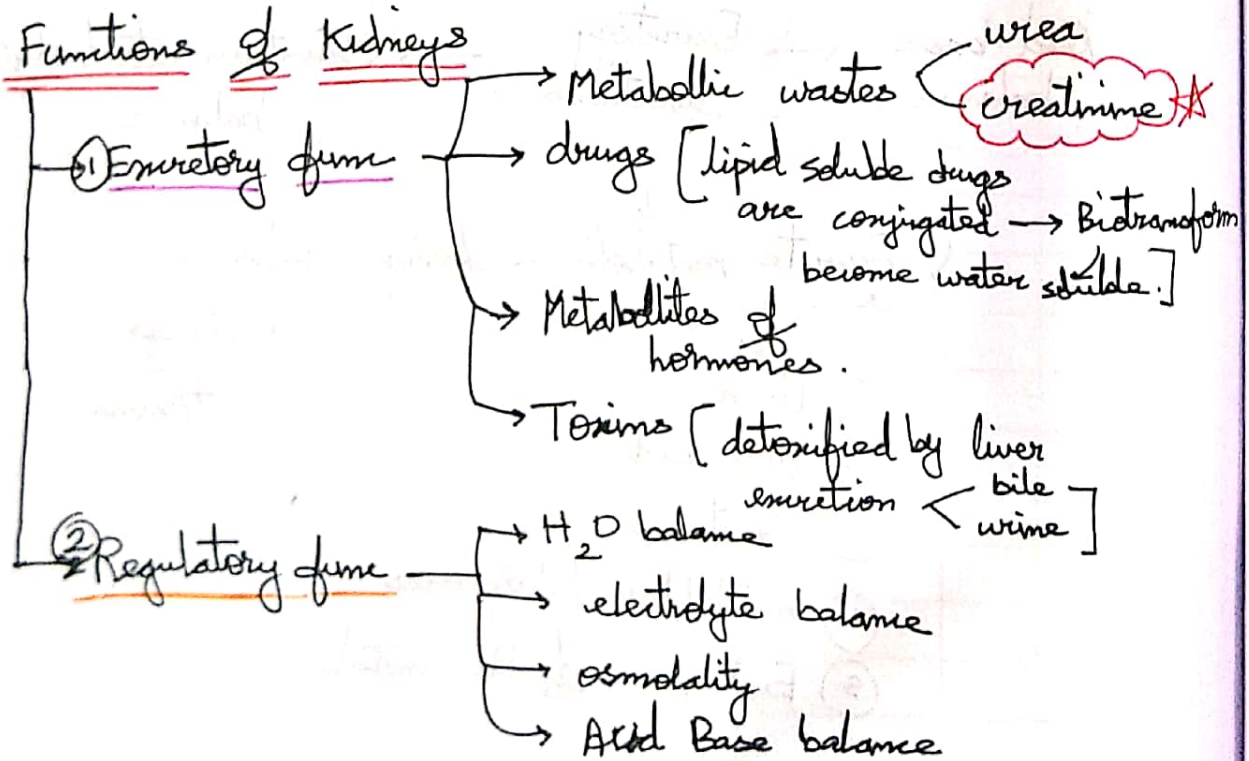
- other functions :-

① Regulation of BP

② gluconeogenesis

DR NAJEEB VID :-

=> Functions of Kidneys



Standard Renal function test → serum creatinine

Serum urea not used as it ↑ in many other conditions like dehydration, high prtn diet.

- Anything which has to go out thru the kidney must be water soluble

- Each kidney has 1.2 million nephrons

- Note :-

  Na^+ blood conc = 140 mmoles/L

  [135 - 145 mEq or m mol/L]

  ✱ K^+ = 3.5 - 5.5 mEq/L

  ↳ even lil fluctuation can kill the patient.

- K^+ controlled at distal level. → kidneys.

  Cl^- = 100 mEq/L

  HCO_3^- = 22 - 28 mEq/L

  Ca^{2+} = 2.5 m mole/L

③ Endocrine functions :-

↳ Erythropoietin → RBC prod

↳ Rennin → RAAS

↳ Calcitriol

↳ prostaglandins

Erythropoietin is prod by endothelial cells of peritubular capillaries.

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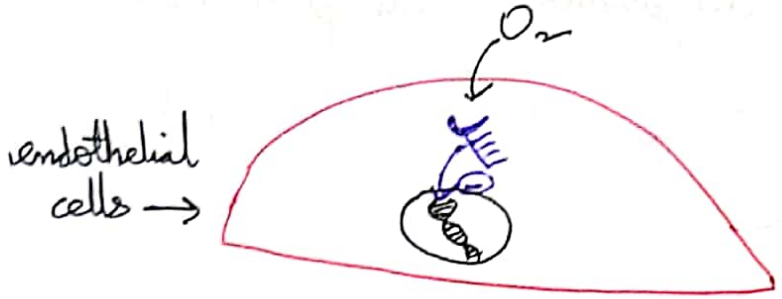
O_2 ⟶ O_2 sensing ptn ⟶ (−) transcription of gene for erythropoietin



But in Anemia ⟶ ↓ O_2 ⟶ (↓) inhibition of erythropoietin gene ⟶ (↑) prod of erythropoietin

Erythropoietin ⟶ (+) Bone marrow ⟶ RBC (↑)

— (4) Metabolic func :-

PTH (+) ⟶ α-1 hydroxylase ⟶ Activates Vit D_3 ⟶ 1, 25 $(OH)_2$ cholecalciferol

↳ done by cells of PCT as they have α1 hydroxylase enzyme.

B/W CO → RBF → RPF → GFR

Urine output ← Tubular flow

- Urine formation by kidneys is determined by very close interplay B/W renal blood flow system and renal nephron systems.

— Renal Vasculature :-

Aorta
↓
Renal artery
↓
Anterior div Posterior div
↓
Interlobar arteries
↓
Arcuate arteries
↓
Interlobular arteries
↓
Afferent arterioles
↓
glomerular capillaries [embedded in connective tissue called Mesangium]
↓
Efferent arteriole
↳ Peritubular capillaries

glomerulus → high pressure capillary system.

- peritubular capillary network
  ↳ Reabsorption & secretion.

- Types of Nephrons :-

Nephrons

Cortical / superficial nephron

- glomerulus in outer regions of cortex
- Henle's loop short
- Peritubular capillaries only
  ↳ (1) conveys O_2 & other nutrients to nephron segments in cortex
  (2) delivers substances to nephron for secretion
  Pathway for return of
  (3) reabsorbed H_2O & solut.
- 85% of total nephrons

Juxtamedullary nephron

glomerulus in cortex close to medulla

Long loop of Henle

Vasa recta.
↳ concentrating and diluting urine

Peritubular capillary network – small.

15% of Tot.

vasa little Blood flow = 0.7% of RBF

- C.O = HR × SV
= 72 × 70
= 5000 ml = **5 l/min**

- Renal Blood flow (R.B.F) = 20% of CO [20 - 25%]
= 1 litre/min [1 - 1.25 L/min]

- cells → 400 ml
- Plasma → 600 ml [R.P.F]
  - 20% of this filtered [120 ml/min is filtered]
    - 65% is reab in PCT
    - 15% in descending limb of Henle's loop (No H_2O absorb in ascending limb)
    - 15% in DCT
      - 5% Remaining absorption under control of ADH & aldosterone

< 1 ml/min urine formed

Urine is formed per min ie.
Approx 1.5 L per day of urine is formed.

- Normal urine output per day = 500 ml to 3500 ml
  - < 500 ⇒ oliguria
  - > 3500 ⇒ polyuria.

- Why a healthy person shouldn't prod > 3.5 L of urine per day and < 500 ml per day. ??

(1) If urine output > 3.5 L/day → nocturia is produced [has to wake in middle of sleep as the bladder gets filled].

(2) < 500 ml/day :-
- Normally the kidney can conc 1200 mOsm/L of metabolic wastes in 1000 ml of H_2O.
- daily prod of metabolic wastes → 600 mosm/L
  The water req to conc 600 mosm/L ⇒ 500 ml → in kidney.
  If H_2O < 500 ml metab wastes start accumulating in blood. → Bld chemistry will be altered.

Urine output ↓ → ↓ <500 ml/day of urine output

↓

Metab wastes start collecting

↓

Blood chemistry altered but there is no signs & symptoms of Renal failure

↓

Azotemia ← Azotemia + signs of Renal failure

↑

Uremia.

=> Unique features of Renal blood flow :-

① RBF = 20 - 25% of cardiac output
= 1 - 1.25 L/min

② Kidneys constitute less than 0.5% body wt still it recieves large amount of blood & O_2

O_2 supply 2 times that of the brain

blood supply 7 times that of brain.

③ O_2 consumption ↑ with ↑ in active reabsorption of Na^+

④ High RBF ⟶ high GFR

$RBF = \frac{P_A - P_V}{\text{Tot vascular resistance}}$

Major resistance vessels

Tot vascular resistance →
- Interlobular arteries
- Afferent arteriole
- Efferent arteriole

(6) Kidney Bld supply →
- Most of it → cortex
- 1-2% → Medulla.

(7) Capillaries of Kidney

Glomerular capillaries	Peritubular capillaries
High hydrostatic pressure	Low hydrostatic pressure
60 mm Hg	13 mm Hg
Filtration function	Reabsorption & secretion.

Each human kidney → 1.2 million nephrons

(8) Filtration fraction = $\frac{GFR}{RPF} = \frac{120}{600} = 0.2$

Structure of Nephron :-

Part of Nephron	Apical Membrane [urine side of cell]	Basolateral membrane [Blood side of cell]
① PCT	Brush border	Invaginated & with mitochondria
② Descending & thin ascending limbs of Henle's loop	Poorly dev.	Poorly dev & with few mito.
③ Thick ascending limb of HL and DCT	Well dev	Extensive infoldings of BLM Abundant mito.
④ Collecting duct Principle cells		Moderately invaginated few mito.
Reab of Na^+ Secretion of K^+		
Intercalated cells		Moderately invaginated Many mito.
α: Reab HCO_3^- & K^+; Secrete H^+	β: Secrete HCO_3^-; Reab $H^+ + Cl^-$	
⑤ Inner medullary collecting duct		Poorly dev with few mito.

Apical membrane of all cells except intercalated cells presents a single non motile primary cilium that protrudes into tubule

- Mechanosensor → Rate of flow
- Chemosensor → chem comp of tubular fluid.

⇒ Glomerular structure

- Each kidney → 1-1.2 million nephrons.
- Aff arteriole breaks down into capillaries called glomerulus / glomerular capillary tuft.
- glomerulus is surrounded by spl visceral epithelial cells with foot process

  Visceral epithelial cells join with parietal epithelial cells → Bowman's capsule.
- B/W the capillaries → Mesangial cells → prod connective tissue.

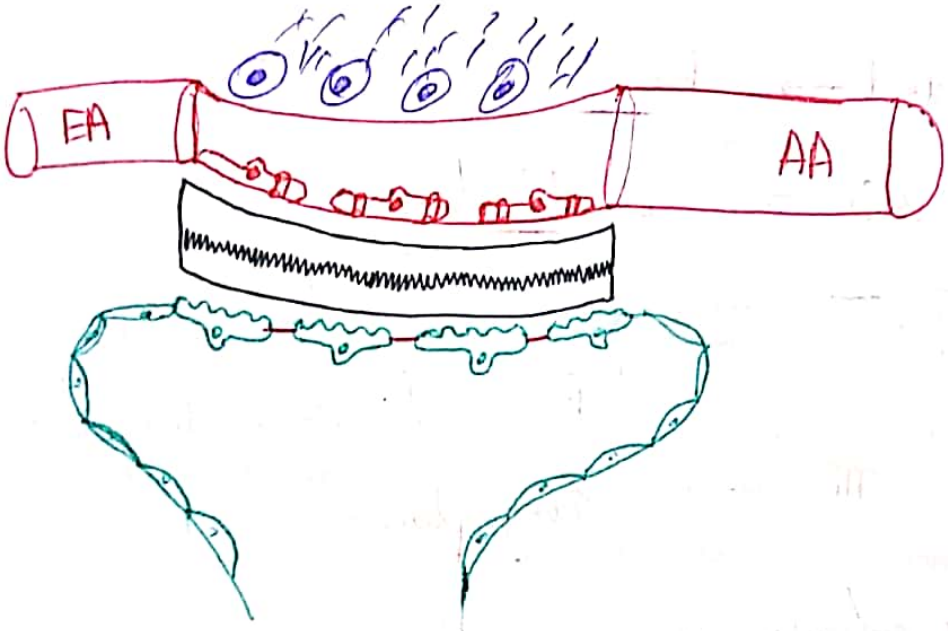
  Mesangial cells + surr. connective tissue = Mesangium.

- Glomerulus is a grp of anastomosing capillaries present within the kidney invested by double layer of epithelial cells forming Bowman's capsule and capillaries are embedded within mesangium.

3) Fenestrated endothelial cells of capillaries + podocytes there is a Basement membrane

- glomerular capill. → endothelial cells are fenestrated → fenestrated capillaries
  [each pore → 70 – 100 nm]

⇒ Glomerular capillary membrane :–



① Layer of endothelial cells :- Endothelium of capillary
- endothelial cells have many pores which facilitate filtration [pore size :- 70 – 100 nm]
- The glomerular capillaries are thus said to be fenestrated

② Basement Membrane
- Has three layers :- [under electron microscope]

I Lamina rara interna :-
Luscent [rarer] part of BM towards capillaries

II Lamina densa :- middle denser part.

III Lamina rara externa :-
Lucent [rarer] part of BM towards podocytes

- BM — made up of mainly collagen type IV.

Types of collagen

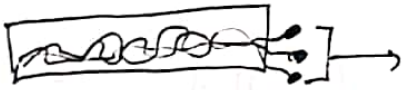
Type I → Bone

Type II → cartwolage

Type IV → four under floor
Basement is under the floor.

III → Many places.

collagen molecule :-



→ globular non collagenous domain of collagen

Auto antibodies against this → damage of GBM
[Anti GBM antibodies]

↓
Proteinuria
Hematuria
↓
Anti GBM Antibodies
Anti GBM glomerulonephritis.

Mutations → altering of collagen damaged
↓
Weak GBM
↓
Hereditary nephritis

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antibodies against GBM & alveolar BM → hematuria, hemoptysis
↳ Good's Pasteur syndrome.

(2) ~~Layer of visceral epithelial cells / Podocytes~~ :-

- There is deposition of an polyionic electro-ve proteoglycan, lemenins, fibronectin etc → Basement mem becomes highly electro-ve

- Sialoglycoproteins → pront on endothelial & epithelial cells
↳ -ve

All these make the filtration mem -vely charged.

(3) Layer of visceral epithelial cells / Podocytes :-

- epithelial cells have finger like projections thru which it is attached to BM.
- These finger like processes interdigitate leaving a narrow gap in B/w called as filtration slits. [20-30 nm] → filtration barrier
- Filtration slits are made up of a diaphragm called filtration diaphragm → made up of Nephrin → if damaged → proteinuria.
- Beoz of filtration diaphragm :-
  Large molecules cannot be filtered.

neutral → best filtered
-ve → worst filtered

- Filtration of a sub depends on → Size, charge

Hence glomerular capillaries are charge as well as size barriers.

- RBC :- 7-8 μ
  WBC :- 12-14 μ
  platelets :- 1-24 μ
  } V. large prevented by size barrier of glomerulus.

- Plasma prtns

	size
Albumin :-	small
globulin :-	large
fibrinogen :-	v. large } prevented by size barrier too large to be filtered

Albumin can easily pass thru the filtration barrier due to its size does not get filtered due to its charge

Albumin => -ve charged. → gets repelled by -ve charges of endothelium, BM, podocytes.

Minimal change glomerulopathy :-

Lot of albumin leaks into urine

some cytokines prod in body neutralize the -ve charges of glomerular capillary mem.

charge barrier to albumin is lost.

⇒ Mesangial cells :-

- contractile cells
- have receptors for Angiotensin II
- can phagocytose
- can proliferate
- can deposit mesangium (connective tissue)

BERNE AND LEVY :-

⇒ Ultrastructure of glomerulus :-

Filtration Barrier → Capillary Endothelium
→ Basement mem
→ Podocytes / visceral epithelium

① Capillary endothelium :-

- Fenestrated [700 Å holes]
- freely permeable to H_2O, Na^+, urea, glucose and most proteins
- Not permeable to Bld cells.
- Express -vely charged glycoprtns on their surface → ① filtration of Albumin.

Vasoactive substances → Vasodilator NO
→ Vasoconst. endothelin I

(2) Basement membrane :-
- Porous matrix
- collagen IV, proteoglycans, perlecan, fibronectin (-ve charge)
- Acts as charge selective filter

(3) Podocytes :-
- Finger like processes cover BM leaving slits called filtration slits.
- Slits are covered by a diaphragm having minute pores [dimension - 40 × 140 Å]
- slit diaphragm made up of prtn Nephrin [NPHS1]
- Size selective filter.
  ↳ prents filtration of large prtns & macromolecules.

⇒ Mesangium :-
Mesangial cells + mesangial matrix
Like Smooth m/s cells

Mesangial cells
- ↑ provide str. support to glomerulus
- Secrete EC matrix
- Phagocytic activity
- Secrete prostaglandins & cytokines
- Alter GFR by altering bld flow
  - due to contractile ability
  - Reduce capillary surf area.

- Involves 3 steps

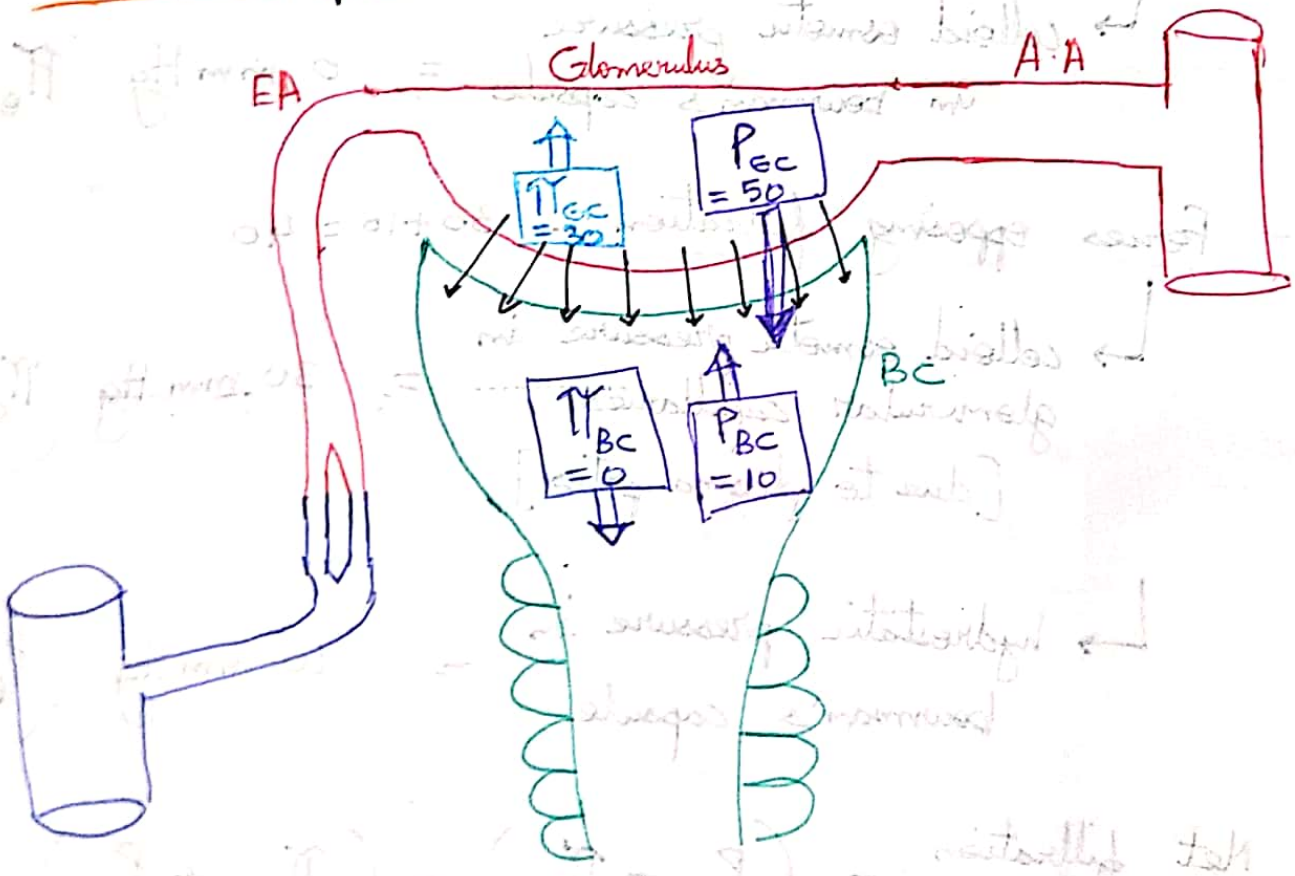
step 1:- ultrafiltration / glomerular filtration.

2:- Tubular reabsorption [glucose]

3:- Tubular secretion

- Urinary excretion = ultrafiltration − Tub. Reab. + Tubular secretion

=> Glomerular filtration :-



Glomerular filtration rate :- how much plasma is filtered per unit time

GFR depends on

① Net filtration pressure

Forces favoring filtration — Forces opposing filtration.

② Filtration coefficient (K_f)

Permeability × Surface area.

⇒ Net filtration pressure :- determined by 2 types of forces

- Forces favouring filtration :- 50
  - → Pressure in glomerular capillaries = 50 mm Hg (P_{GC})
  - → colloid osmotic pressure in bowman's capsule = 0 mm Hg (Π_{BC})
- Forces opposing filtration :- 30+10 = 40
  - → colloid osmotic pressure in glomerular capillaries [due to plasma prtns] = 30 mm Hg (Π_{GC})
  - → hydrostatic pressure in bowman's capsule = 10 mm Hg (P_{BC})

Net filtration pressure [N·F·P] $= (P_{GC} + \Pi_{BC}) - (\Pi_{GC} + P_{BC})$

$50 - (30+10)$

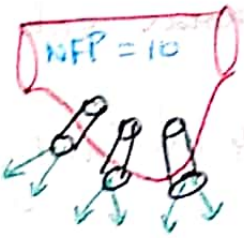
$50 - 40$

N·F·P = 10 mm Hg

Filtration coefficient (K_f)

① Permeability of filtering membrane
= hydraulic conductivity

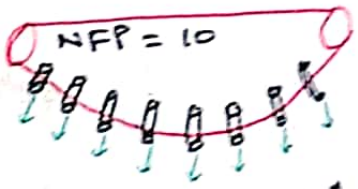
Less HC



More HC

② Total surface area of filtering membrane.

Less SA
↓ filtration



More SA
↑ filtration

even the permeability of both is same

- Product of permeability & surface area of capillaries is the Filtration coefficient (K_f).

⇒ GFR ∝ N.F.P

GFR ∝ K_f

GFR = Net filtration pressure × K_f

⇒ Factors affecting K_f :-

GFR = NFP × K_f

K_f = $\frac{GFR}{NFP}$ = $\frac{125\ ml/min}{10\ mmHg}$ = 12 ml/min/mmHg

by Tot glomeruli in Tot renal subs of both kidneys

K_f = 12 ml / mmHg / min / Tot glomeruli in Tot renal sub of both kidneys [300g]

Wt of one kidney = 150

of both = 300

K_f for 100 gm of renal sub?

$K_f = \frac{12}{3} = 4$ ml/mmHg/min/100g of renal sub

① Hydraulic conductivity :-

If membrane is thickened → ↓ HC → ↓ GFR

↑

Diabetes mellitus

Hypertension

② Tot surf area :-

glomerulus becomes fibrotic → ↓ SA → ↓ GFR

↳ chronic pyelonephritis

chronic glomerulonephritis

⇒ Factors affecting NFP :-

↳ varies more frequently

- frequent changes in GFR are due to changes in NFP

① Hydrostatic Press in capillaries =

② Colloid osmotic pressure in Bowman's capsule

③ Hydro. Press in Bowman's capsule.

Pre renal failure ⟵ ↓ Blood flow

Renal failure → Renal failure → if glomeruli fail

Post renal failure → obstruction in urine drainage system.

↓ GFR

- Hydrostatic pressure of Bowman's capsule :- P_{BC} = 10 mmHg
  - obstruction in renal tubule
    ↓
    ↑ Back pressure in nephron tubule
    ↓
    ↑s P_{BC} ⟶ filtration opposition ↑s
    ↓
    ↓ in GFR

- Colloid osm press of GC :- π_{GC} = 30 mm Hg
  - Prtn loosing enteropathy / liver cirrhosis / Prtn energy malnutrition
  - ~~of~~ prtn loosing nephropathy
    ↓
    ↓ Plasma prtns
    ↓
    π_{GC} becomes ↓d
    ↓
    ↑ GFR

Multiple myeloma → Plasma cells prod ↑d amnts of abnormal prtns

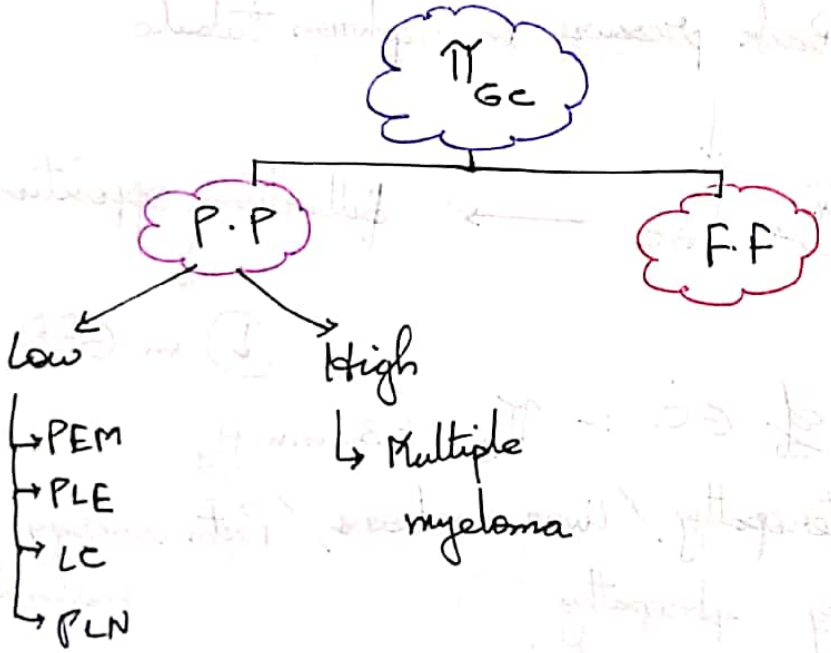
↑ plasma prtns

↓

↑ ∏ Gc

↓

↓ GFR



Note :-

As blood moves from afferent arteriole end of glomerulus to its efferent art. end :-

↳ filtration ↓

↳ conc of plasma prtns ↑

↳ colloid osmotic p ↑.

filtration fraction ↑ → More filtration of plasma

↓

↑ plasma prtn conc in remaining plasma → ↑ Π_{GC} → reduces further filtration ie ↓ GFR

- When FF ↓ → opp occurs. → less plasma filtered

↓

less ↑ in Π_{GC} ← less ↑ in prtn conc

Filtration is opposed less → GFR ↑.

- Hydrostatic press in glomerular capillaries (P_{GC}) :-

P_{GC} ↑ → GFR ↑

P_{GC} ↓ → GFR ↓

P_{GC}

- Systemic B.P
- Afferent arteriolar resistance
- Efferent arteriolar resistance

① Systemic B.P :-

If B.P ↑ → Blood comes to glomerulus with high pressure

↓

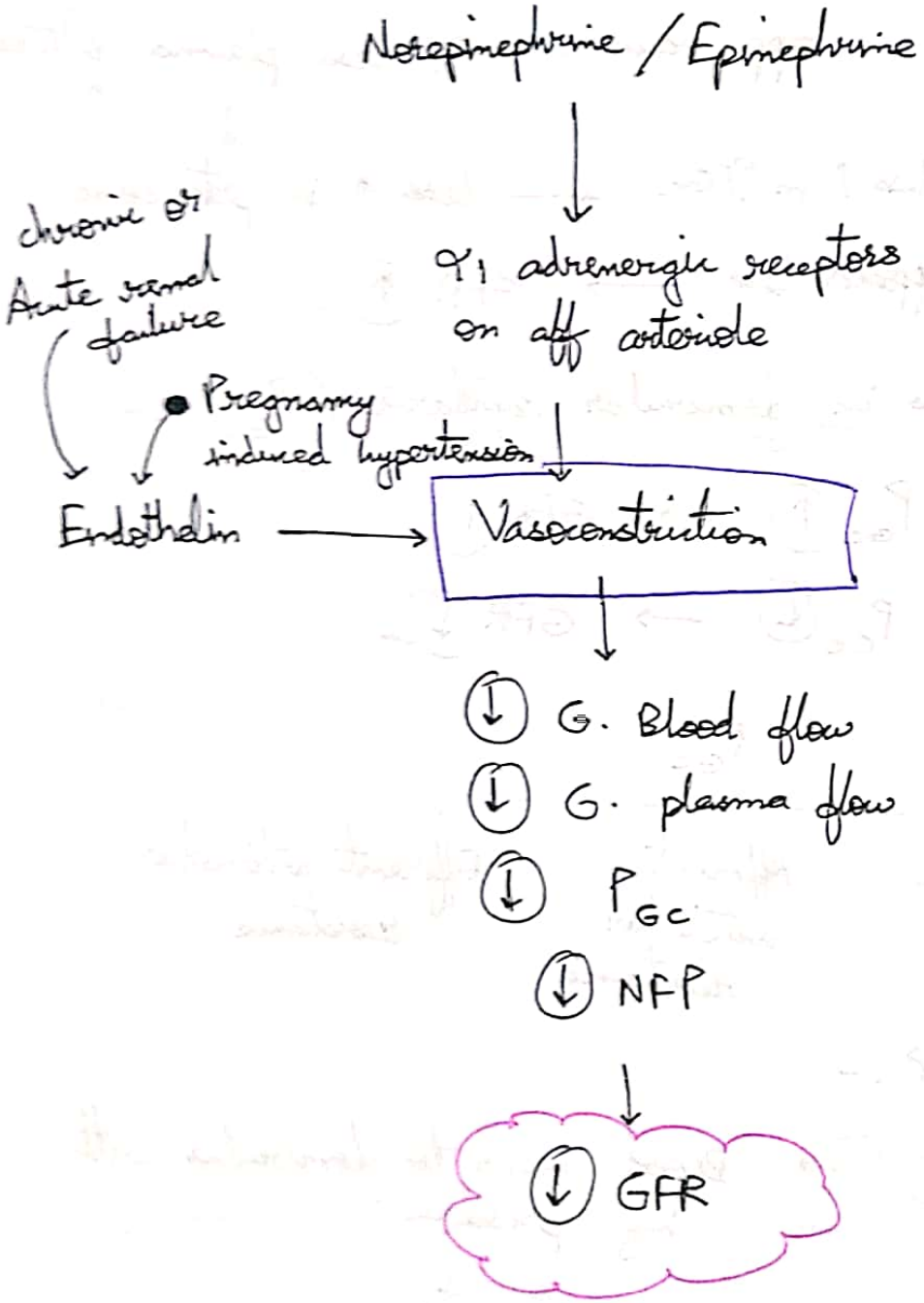
↑ P_{GC} → ↑ GFR

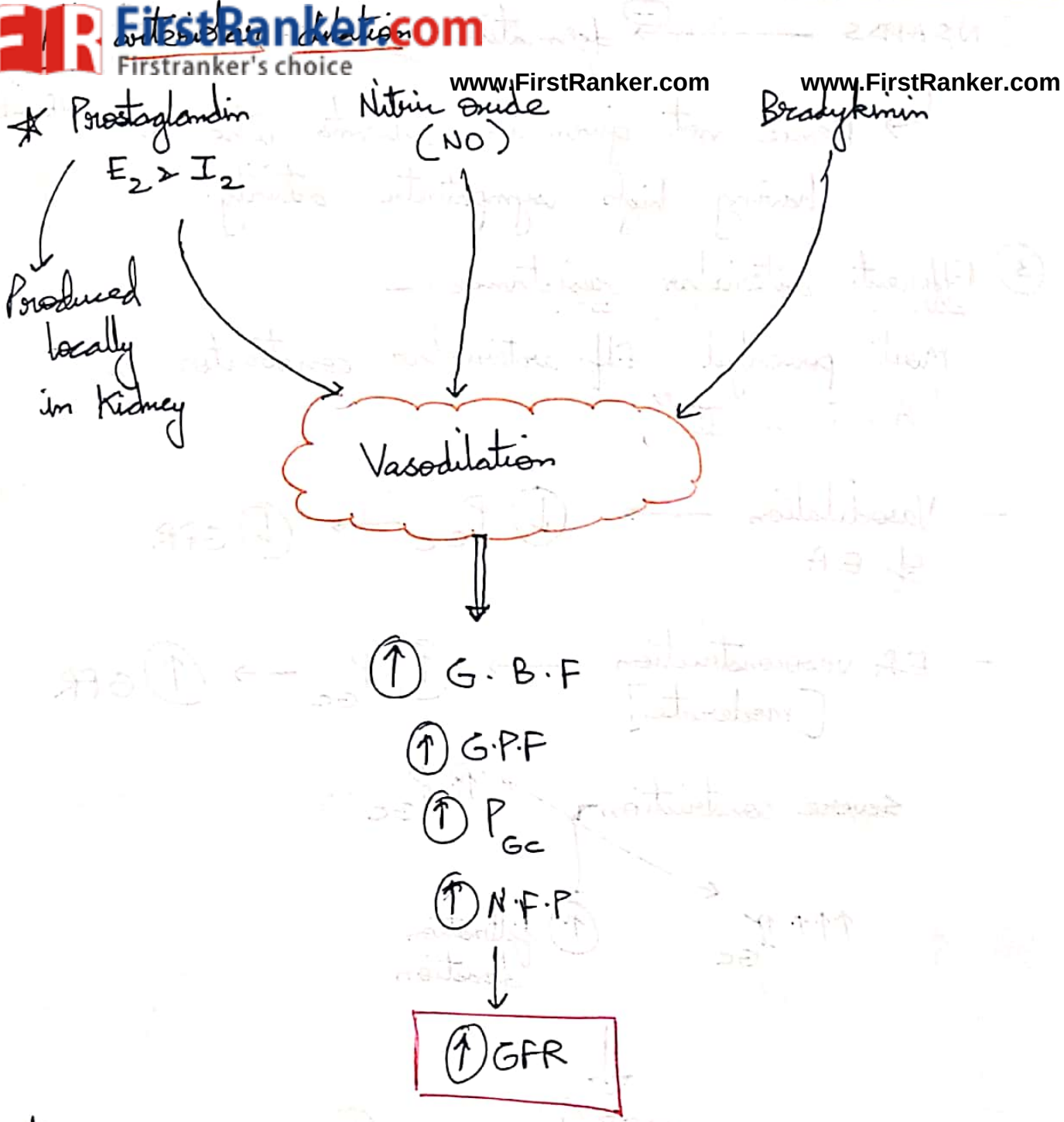
Systemic B.P ↓ → ↓ P_{GC} → ↓ GFR

Even in a healthy kidney GFR is maintained over a range of pressures due to Autoregulation.

(2) Aff arteriolar constriction :-

- Aff arteriole constriction :-





Note :-

Extreme stress/ shock/Trauma → ↑↑↑ SNS → ↑ Rb of Norepi > epi

danger of constricting the off arteriole powerfully → ↓↓ GFR

This is ~~prented~~ prevented by local prosta-glandins.

formation of PG's → potentiate effect of NE

↳ Hence not given in patients who are having high sympathetic activity.

(3) Efferent arteriolar resistance :-

- Most powerful Eff arteriolar constrictor is "Angiotensin II"

- Vasodilation of EA → ↓ P_{GC} → ↓ GFR

- EA vasoconstriction [moderate] → ↑ P_{GC} → ↑ GFR

Severe constriction → ↑↑ P_{GC}

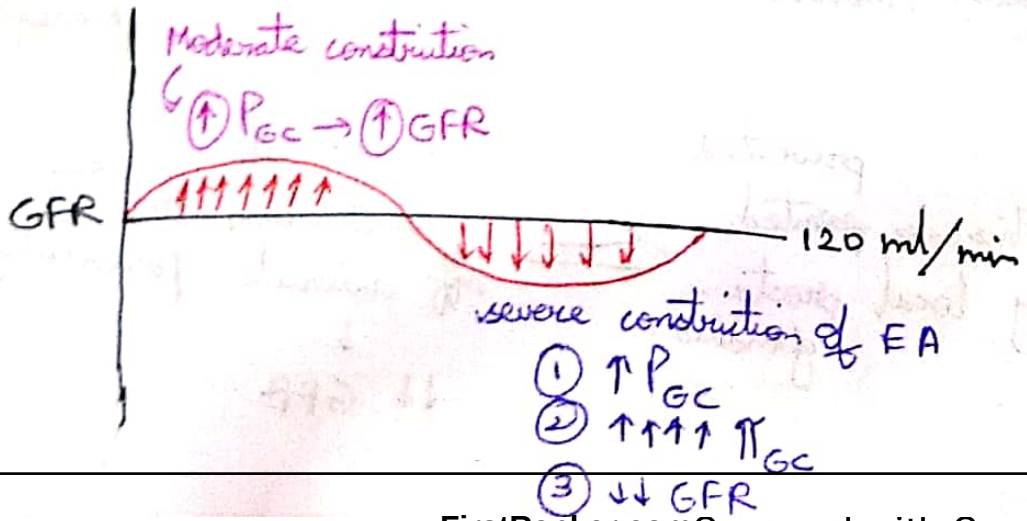
→ ↑↑↑ π_{GC}

→ ↑ filtration fraction

↓↓

NFP ↓ → ↓ GFR

Bcz ↑ π_{GC} is more



Renal Plasma flow | GFR | FF = GFR/RPF

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1. Aff arteriole constriction — ↓ — ↓ — No change
2. Aff arteriole dilation — ↑ — ↑ — No change

Note:-
1. ↑ ureteric stricture
2. ? RPF
   ? GFR
   ? FF

Answer:- ↑ RPF ↑ GFR FF → no change.

3. Eff arteriole constriction [moderate] — ↓ — ↑ — GFR ↑ / RPF ↓ — ↑

Severe constriction — ↓ — ↓↓↓ — GFR ↓↓↓ / RPF ↓ — No change or ↓

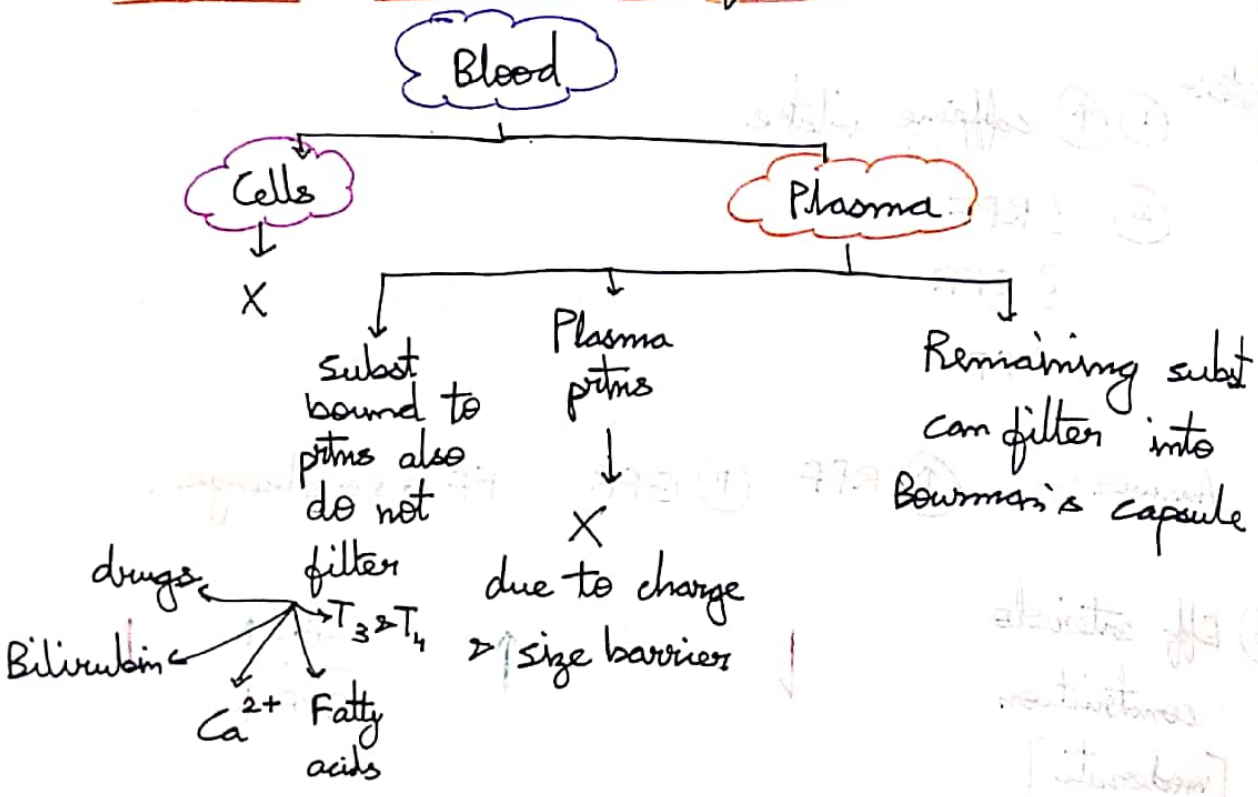
4. T. Plasma ptns ↑ Eff arteriole — No change — ↓ — GFR ↓ / RPF — ↓

5. Tot Plasma ptns ↓ — No change — ↑ — GFR ↑↑ / RPF — ↑

Ureteric constriction (P_{BC} ↑) — RPF: No change — GFR: ↓ — FF: ↓

⇒ Substances filtered :-

① Substances which are not filtered :-



② Subst which can be filtered

- H_2O – freely filtered
- ~~free~~ major electrolytes
  - Cations
    - Na^+
    - K^+
    - ionized Ca^{2+}
  - Anions
    - Cl^-
    - HCO_3^-
- Metabolic wastes → urea, creatinine
- Metabolites → glucose, amino acids, Ketone bodies (organic acids)

① Insulin → captured back by PCT thru pinocytosis

↓

In cells of PCT insulin is catabolised / broken down to give amino acids

↓

Amino acids converted to glucose

② Hemoglobin dimers :- if present in free form in blood.

↓

freely filtered into BC

↓

Taken up by PCT cells

↓

Become toxic → iron is rlzd which damages PCT cells ← Hb catabolism

↓

Acute tubular necrosis

Non compatible blood transfusion

↳ donor's RBC's are destroyed in recipient's blood

↓

free Hb in blood

↓

Hb filtered → taken up by PCT cells

↓

Hb catabolised → Fe rlzd damages cells

↓

Acute tubular necrosis ← Hemoglobinuria, Flank pains, oliguria or complete renal shutdown

Non natural sugar → Inulin, Paraamino hippuric acid
used to measure GFR
marker of R.P.F.

⇒ Measurement of GFR :- Inulin is used

Inulin :-

- Non toxic
- does not bind with plasma prtn
- Not charged
- small molecule. → can freely filter.
- Not reabsorbed by renal tubule.
- Cannot be secreted by cells of Renal tubule from blood.
- Can only be filtered.
- Hence called inert molecule.

Filtered load of inulin = urinary load of inulin

$[P]_{inulin} \times GFR = [U]_{inulin} \times V$ $\quad V = \frac{vol}{min}$

$$GFR = \frac{[U]_{inulin} \times V}{[P]_{inulin}}$$

Suppose $[U]_{inulin} = 120\ mg/ml$

$[P]_{inulin} = 1\ mg/ml$

$V = 1\ ml/min$

GFR = $\frac{120 \times 1}{}$

= 120 ml/min

Case 2 :-

[P] = 2 mg/ml

[U] = 120 mg/ml

V = 1 ml/min

GFR = $\frac{120 \times 1}{2}$ = 60 ml/min

Case 3 :-

[P] = 10 mg/ml

[U] = 600 mg/ml

V = 1 ml/min

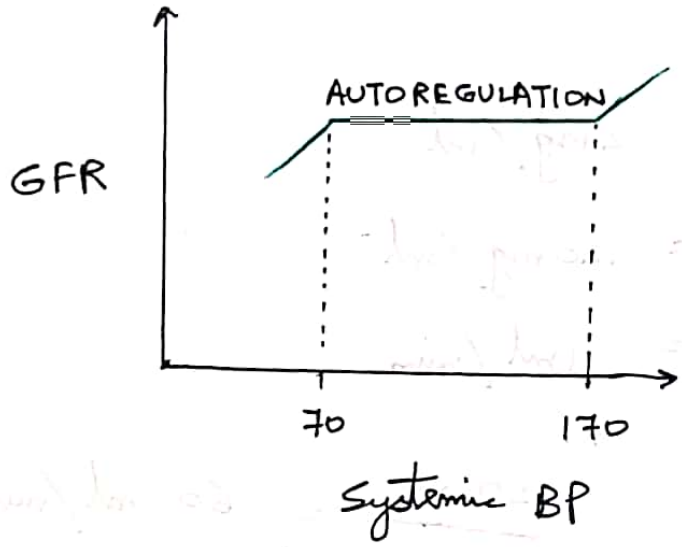
GFR = $\frac{600 \times 1}{10}$ = 60 ml/min

=> Measurement of GFR by creatinine :-

- creatinine is also freely filtered into renal tubule but there is also slight secretion of creatinine → slight overestimation of GFR
- Advantages → it is endogenous unlike inulin.

Autoregulation of GFR & RBF :-

- Inspite of major fluctuations in B.P, kidneys can maintain their GFR almost constant.



Mechanism

GFR stable B/W 70 to 170 mm of Hg BP.

(1) ↑↑↑ B.P → (↑) Renal arteries → (↑) P_{GC}

↓

(↑) GFR for a short time → filtrate formed is more → (↑) Tubular flow

↓

Tubular cells cannot efficiently reabsorb NaCl > H_2O as they are given less time to work → Tot NaCl load reaching the beginning of DCT is more

↓

(↑) NaCl is sensed by the specialized sensitive Macula densa cells of DCT

↓

Rly of vasoactive subs from macula densa cells ← Reduce prod of renin

↓

Aff arteriolo constriction → (↓) Glomerular BF → (↓) GFR to normal.

(↓) Angiotensin II

↑ NaCl load to Macula densa

↓ Rly of vasoactive sub → Afferent arteriole construction

↓ prod of renin → ↓ Angiotensin II → Efferent art. dilation.

↓ P_{GC} → ↓ GFR

Mechanism II :- Myogenic mech :- present in almost all arterioles of body.

↑↑ Sys. B.P

↓

Blood flowing thru Aff art with high Press

↓

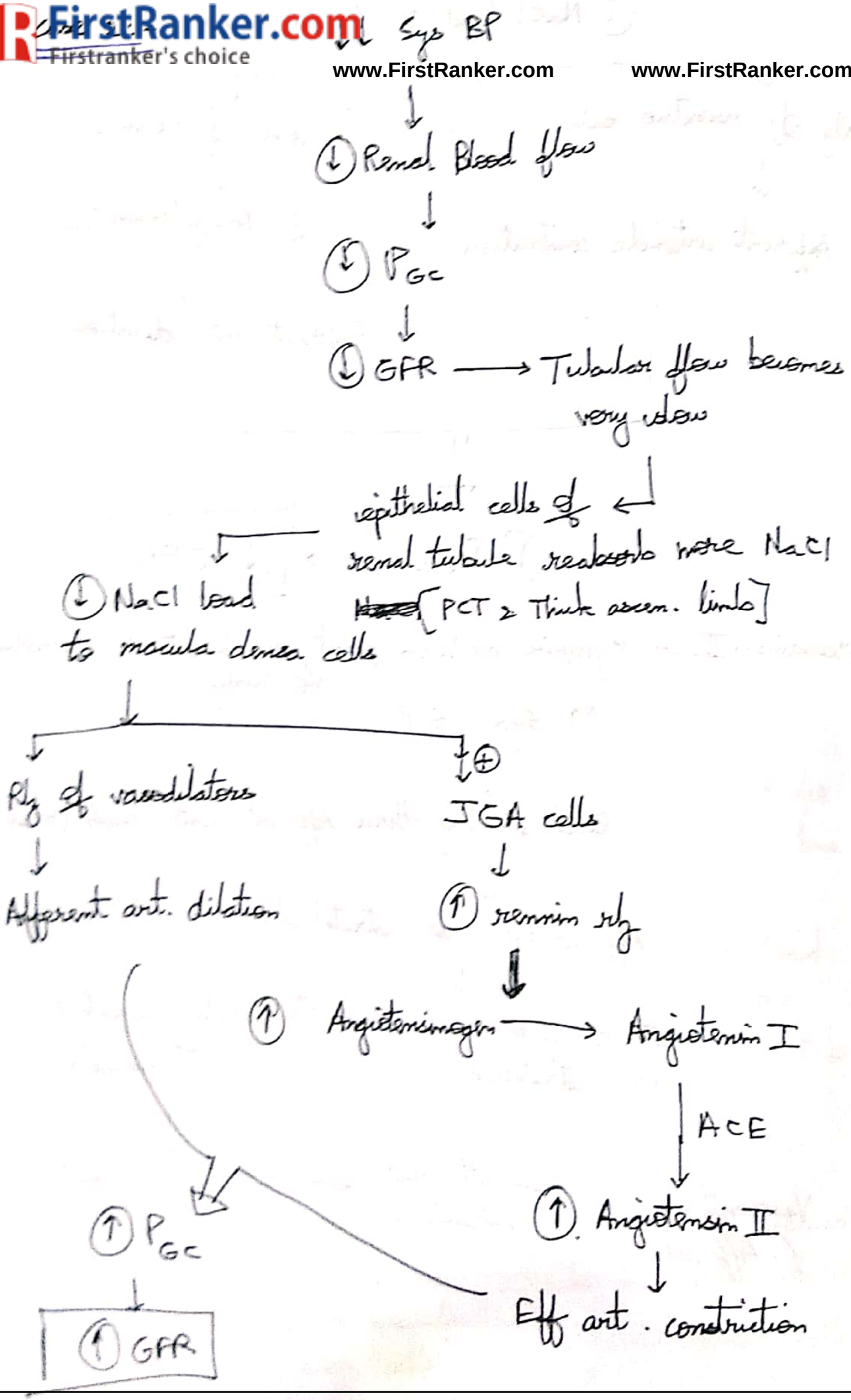
Aff arteriole is stretched

↓

Smooth m/s fibres of AA are stretched → (+) stretch sensitive Ca^{2+} channels

↓

Ca^{2+} influx → Smooth m/s contraction → Vasoconstriction of Aff art.



macula densa cells of initial DCT can stabilise GFR by adjusting the resistance of Aff & Eff arterioles.

This is called TUBULO GLOMERULAR BALANCE.

case 3 :-

When meat intake is more

↓

Amino acids in blood (↑)

↓

(↑) filtration of a.a

↓

(↑) Reab of a.a along with Na+ ci by PCT
[cotransport]

↓

(↓) NaCl load to macula densa

↓

Macula densa cells assume GFR is (↓)d

↓

Rly of vasodilators & Aff art. dilate

↓

(↑) GFR

↓

Helps to (↑) excretion of
metabolic prod of prtns like urea.

of arteriole is more sensitive than afferent arteriole to angiotensin II

- Low conc → Eff art constricts → ↑ GFR, ↓ RPF
- High conc → Both eff & aff art. constricts → ↓ GFR, ↓ RPF

⇒ Renal clearance :-

- It is based on Fick's Principle [Mass balance or conservation of mass]
- For any sub that is neither synthesised nor metabolised in kidneys the amnt that enters the kidneys is eq to the amnt that leaves the kidneys in urine plus the amnt that leaves in renal venous blood.
- For eg :- for a subst. X

$$\text{Input} = \text{Output}$$

$$P_x^a \times RPF^a = (P_x^v \times RPF_x^v) + (U_x \times V)$$

P_x^a ⇒ conc of X in R Artery

P_x^v ⇒ " " " " R Vein

U_x => conc of X in urine

RPF^a => RPF of renal artery

RPF^v => " " " vein

V => urine flow rate.

- Renal clearance of a subs. is the volume of plasma that is completely cleared of the sub by the kidneys per unit time

- The principle of Renal clearance considers only the rate at which a sub is excreted into urine & not its rate of return to renal vein.

Therefore :-

Urinary excretion rate $\propto P_x^a$

$$P_x^a \propto (U_x \times V)$$

$$C_x \times P_x^a = U_x \times V$$

$$C_x = \frac{U_x \times V}{P_x^a}$$

$$\boxed{C_x = \frac{U_x \times V}{P_x}}$$

$P_x^a \simeq P_x$ & conc in any bld vessel

Clearance units = volume / time.

- Clearance refers to the vol of plasma that wnd be necessary to supply the amt of subs excreted in urine per unit time.

- Uses :-
  To calculate GFR & RPF. Determine Tubs. Reabs & secretion.

- Measurement of GFR :-
  - Sub selected shud be freely filtered, neither reabs nor secreted

① Inulin :- polysaccharide MW = 5200

For a sub freely filtered, neither reab nor secreted urinary excretion rate = filtration rate

$$U_{inulin} \times V = GFR \times P_{inulin}$$

$$GFR = \frac{U \times V}{P} = C_{inulin}$$

$$\therefore C_{inulin} = GFR$$

But it is not naturally prod in body → has to be given intravenously.

② Creatinine :-
- Prod of m/s metab → cleared almost entirely by glomerular filtration.
- More widely used than inulin as it is endogenous

$$GFR \approx C_{Cr} = \frac{U_{Cr} \times V}{P_{Cr}}$$

$$GFR \approx C_{Creatinine} \propto \frac{1}{P_{Creatinine}}$$

- **Disadvantages :-**

  Some Cr is secreted into renal tubule leading to overestimation of GFR.

- **Measurement of RPF**
  - Sub used shud be completely cleared from the plasma only then its clearance rate will be eq to RPF.

$$RPF = \frac{U_x \times V}{P_x} = C_x$$

  - There is no such sub completely cleared.
  - However Paraaminohippuric acid (PAH) is 90% cleared and hence its clearance is used as an approx of RPF.

$$RPF \approx C_{PAH} = \frac{U_{PAH} \times V}{P_{PAH}}$$

To be more accurate :-

$$RPF = \frac{C_{PAH}}{\text{Extraction ratio}}$$

where; Extraction ratio is the % of PAH removed from blood

$$\text{Extraction ratio} = \frac{P^a_{PAH} - P^V_{PAH}}{P^a_{PAH}} = 0.9 \text{ or } 90\%$$

RBF can also be calculated

$$RBF = \frac{RPF}{1 - \text{Hematocrit}}$$

- Impt generalisations :-

If $C_x = C_{inulin}$ => sub only filtered freely

$C_x < C_{inulin}$ => sub filtered & reabsorbed

$C_x > C_{inulin}$ => subst. filtered + secreted

$$\text{Clearance ratio} = \frac{C_x}{C_{inulin}}$$