Urine Concentration & Dilution :-

- Normal osmolarity of blood = 290 mosm/L ★.
  For descriptive purposes → 300 mosm/L
- Major func of Kidneys → osmoregulation.

Water intake ↑↑ → Threatening to dilute body fl
↓
Kidneys pass out (↑) H_2O
↓
urine vol (↑) but wastes going out remain the same.

- Prod of Metab waste per day in a normal individual = 600 mosm

Person 1

Water intake (↑↑)
↓
Body fluids diluted [hyposmolar]
↓
Kidneys prod larger volume of urine with same metab wastes
↓
Large vol of diluted urine
↓
osmolarity is restored

Person 2

Water loss (↑↑) ← sweat, urine, faeces, Resp sys
↓
Body fluids concentrated [hyperosmolar]
↓
Kidneys prod small volume of concentrated urine
↓
osmolarity restored

- In both persons amt of metals wastes excreted is same
- whenever Bld osmolarity (↑) → urine osmolarity (↑) and vice versa.

⇒ Mechanism of Urine concentration & dilution :-

- Requirements :-

① Medullary interstitium => hyperosmolar

As we move from renal cortex to medulla [300 mOsm] there is progressive (↑) in interstitial osmolarity.

There is corticopapillary osmolarity gradient.

↳ How is this prod? How is it maintained?

↳ ① counter current multipliers [Henle's loop]
② Urea recycling in renal medulla

↳ Vasa recta as counter current exchangers

② Role of ADH

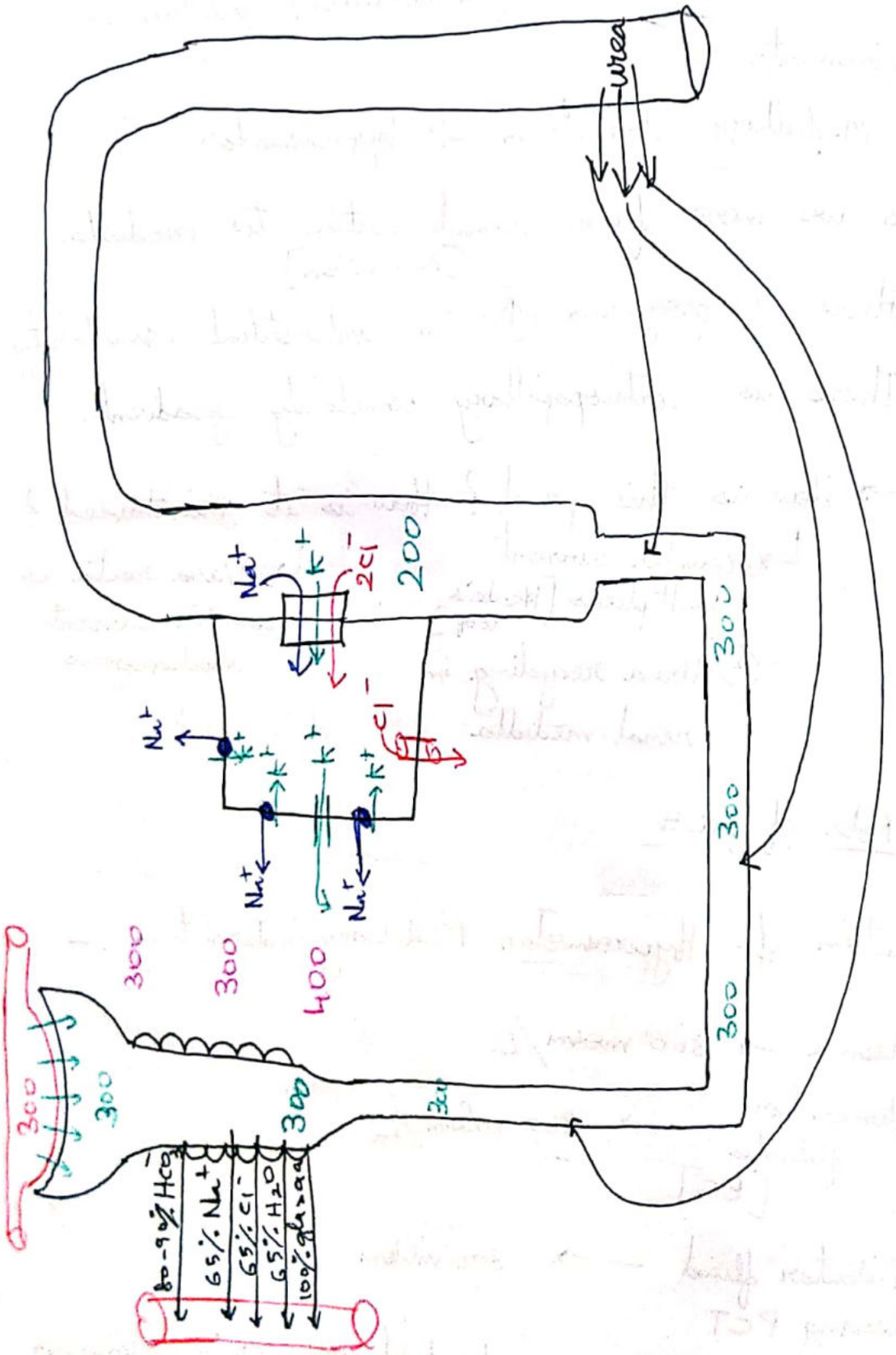
⇒ Production of Hyperosmolar Medullary interstitium :-

- Plasma → 300 mosm/L
- glomerular filtrate [BC] → 300 mOsm/L
- Tubular fluid leaving PCT → 300 mOsm/L

↳ even tho solutes are absorbed osmolarity remains same → Tot solute & solvent (↓) in same ratio

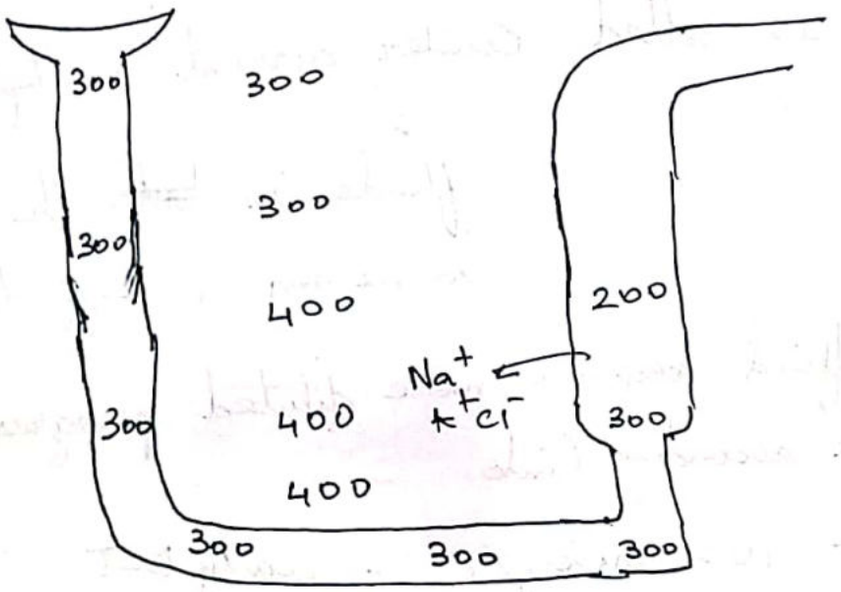
solutes and H_2O in PCT are absorbed in the same proportion as PCT is freely permeable to water → osmolarity remains 300 mOsm/L

PCT reabsorbs solute & H_2O isosmotically.



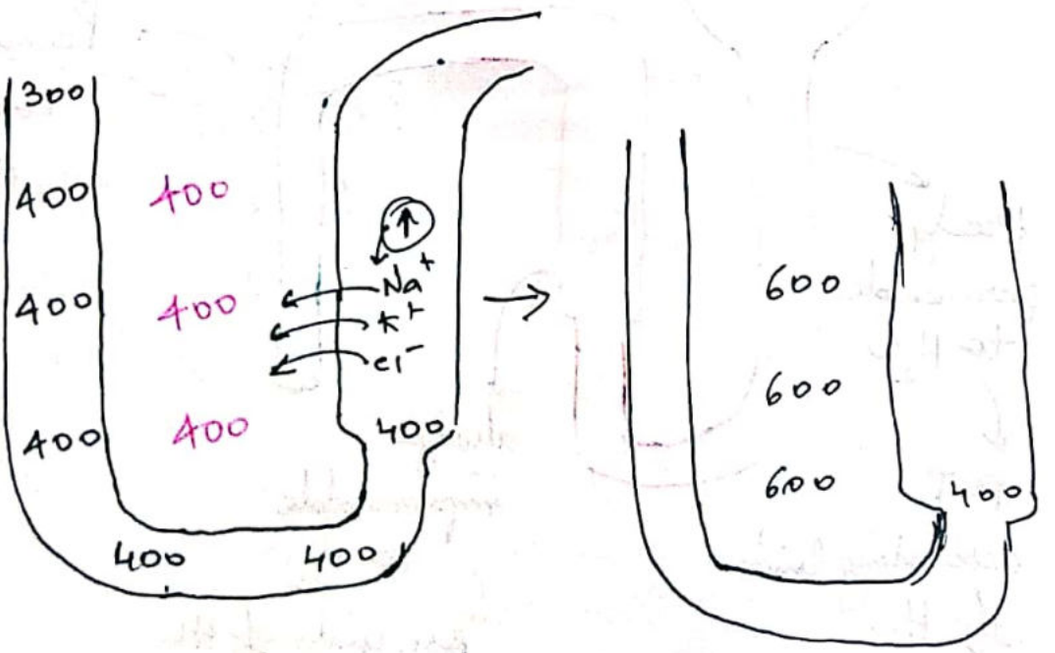
- Thick ascending limb :-
  ↳ solute permeable but completely impermeable to H_2O
  ↳ dilutes tubular fluid and conc medullary interstitium
  - cells of this segment can prod a more gradient of 200 mOsm/L B/W tubular fluid & interstitium.
    ← if the tube was straight

1st step :-



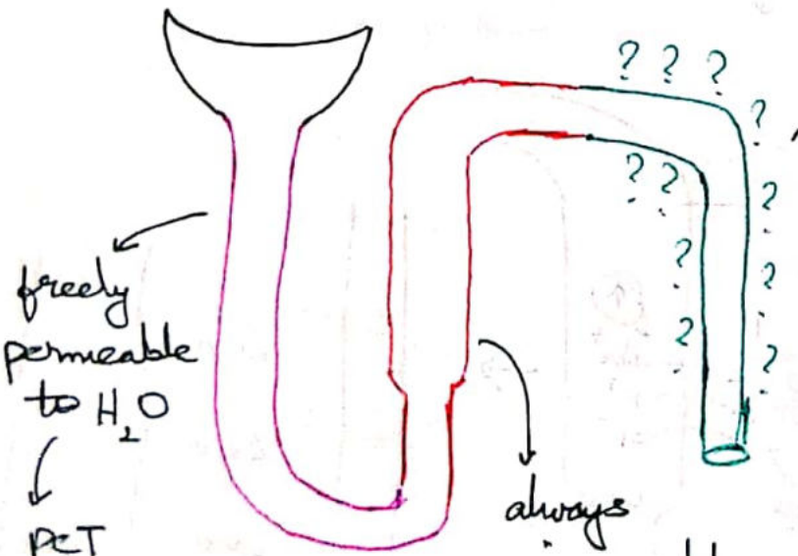
↓

2nd step :-



- This cycle continues until the interstitium becomes 1200 mOsm/L.
- Thick ascending part of Henle's loop is progressively making the interstitium more hyperosmolar & the descending part provides more hyperosmolar fluid to ascend. part by losing H_2O.
- This mech is called Counter current multiplier system.
  - fluids in the limbs is moving in opp direction
- Tubular fluid becomes more diluted progressively in Thick ascending limb

DCT — 100 mOsm/L - early DCT
Late DCT — 60 mOsm/L



- Thick asc limb → medullary diluting segment
  DCT → cortical " "

⇒ Role of urea recycling :-

- Part of nephron distal to thin asc limb of HL is urea impermeable - upto inner medullary collecting duct.
- Inner med. collecting duct cells are highly permeable to urea → urea is reab into interstitium → 30 - 40% contribution to hyperosmolarity
- This reab urea can again enter the descending thin asc limb of HL and can be recycled.

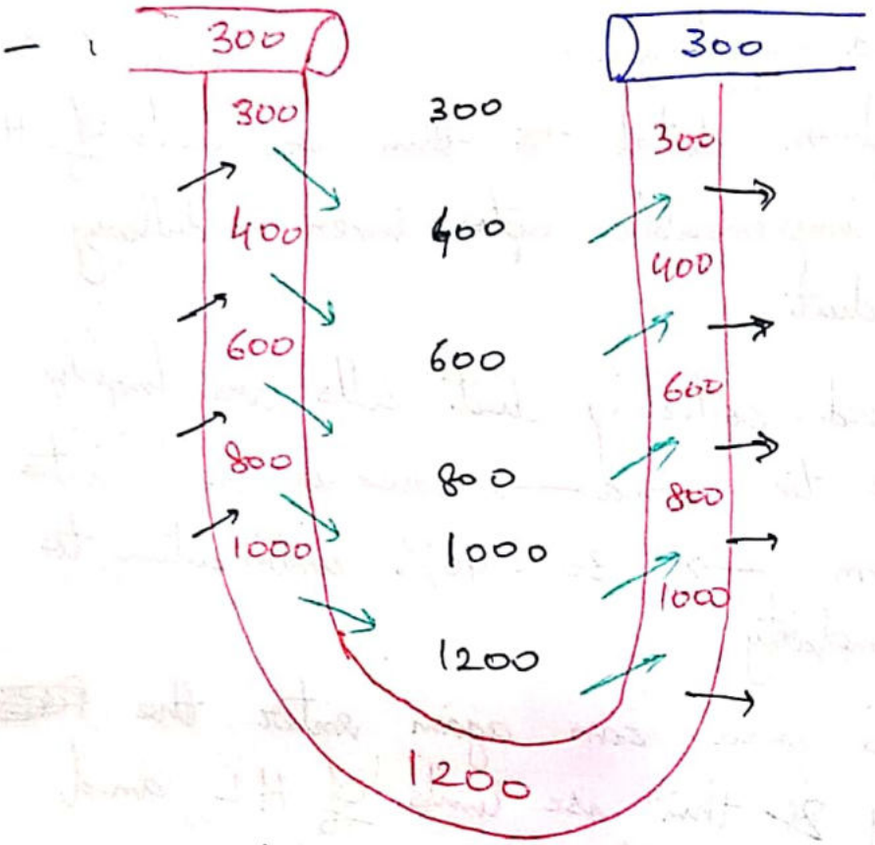
These mech are enhanced by ADH.

— Why there is a gradient in Medullary interstitium as we go deeper from 300 to 1200 mOsm/L

- There is high blood flow in cortex & less in medulla.
- ∴ As we go down from cortex into medulla the blood flow ↓s and capability to wash away the solute ↓s.

⇒ Maintenance of Hyperosmolar Medullary interstitium :-

VASA RECTA AS COUNTER CURRENT EXCHANGER



→ :- solutes → :- H_2O

- There is passive movt of solute & H_2O unlike counter current multiplier.

⇒ ADH :-

- Act on principal cells of DCT, CD.
  - sensitive to both ADH & Aldosterone
  - only reab of H_2O.
  - ↳ Reab of H_2O & Na^+ Secretion of K^+
- ADH receptor → GPCR / Serpentine receptor
  - Prsnt on basolateral mem of cell.

ADH binds to ADH receptor

↓

Gs is activated

↓ (+)

Adenylyl cyclase

↓ (+)

ATP ⟶ cAMP (↑)

↓ (+)

Protein kinase A.

Phosphorylates transport prtns

Also phosphorylate prtns associated with secretory vesicles containing aquaporins

↓

Vesicle fuses with membrane [luminal]

↓

Aquaporins transported to mem [inserted into mem]

↓

(↑) water permeability

Aquaporin 3 & 4 always present on basolateral mem.

- In a healthy kidney fluid coming to the last part of nephron is highly diluted.

↳ If ADH not prsnt → H_2O not reab from last part of nephron

↓

Large vol of dilute urine.

ADH prsnt → H_2O reab ↑↑ from principal cells

↓

Small vol of conc. urine.

- H_2O reab from last part of nephron is facilitated by hyperosmolar med. interstitium.

H_2O moves from hyposmolar tubular fluid → hyperosmolar medullary interstitum

- High ADH ⊕→ $Na^+/K^+/2Cl^-$ symporter

⊕→ urea recycling

↓

↑ Medullary interstitum hyperosmolarity.

- Anterior part of hypothalamus → Osmoreceptors
Supra optic nucleus synthesise ADH

↑↑↑ water loss

↓

↑ blood osmolarity

↓ ⊕

osmoreceptors

↓ ⊕

Supraoptic nucleus neurons

↓

AP initiated → reach nerve endings

↓

ADH rlyd from nerve endings in posterior pituitary.

↓

ADH acts on principle cells

↓

Aquaporins incorporated into cell mem [luminal side]

↓

↑ H_2O permeability → ↑ H_2O reabsorption.

↓

Small vol of highly conc urine.

↑ osmolarity of Med. inters.

↑ urea reab

↑ solute reab from Asc limb

- Absence of ADH → last part of nephron becomes a diluting segment.

$\Rightarrow \frac{TF_{osm}}{P_{osm}}$ ratio

- PCT = $\frac{TF_{osm}}{P_{osm}} \approx \frac{300}{300} = 1$ => isosmotic tubular fluid

- Bowman's capsule - $\frac{TF}{P} = \frac{300}{300} = 1$

- descending limb of HL = $\frac{TF\uparrow}{P} = \frac{TF(\uparrow)}{300} > 1$ => hyperosmolar

- Ascending limb [uppermost end] = $\frac{TF(\downarrow)}{300} < 1$ => hyposmolar.

Renin Angiotensin Aldosterone System (RAAS) :-

- Involves CNS, Kidney, Liver, pulmonary circulation and Adrenal cortex.

- Bleeding ⟶ BP (↓) ⟶ Renal perfusion (↓)
  ↓
  Renin rels from kidney.

- Modified afferent arteriole smooth m/s ⟶ Renin [granular cells]
  ↳ Baroreceptors ⟶ (↓) BP ⟶ (↑) rels of renin from them

→ Macula densa of DCT → Na^+ sensing system. [chemoreceptors]

Granular cells → Renin [Mod. Smith m/c of AA] rely renin

↳ pressure sensing system – Baroreceptors

JGA → Macula densa → chemoreceptors [Na^+ sensors].

(stimulated by ↓ Na^+ → activate pathway.

↓

↑ rely of renin.

– Blood P ↓ → (+) carotid sinus [Baroreceptors] → (+) CNS [Medulla]

↓ (+)

Sympathetic outflow. → Norepinephrine → (+) β, adrenergic receptors

↳ ↑ Renin rely.

– Renin is an enzyme.

– Hepatocytes → prod Angiotensinogen

↓ Renin

Angiotensin I [10 a.a]

↓ ACE [present on surface of endothelial cells of pulmonary capillaries

Angiotensin II [8 a.a] → powerful vasoconstrictor

Bradykinin broken down by ACE
[vasodilator]

AT-II → (1) → Vasoconstriction [Blood return to Hrt ↑]
↓
↑ cardiac filling → ↑ EDV
↓
↑ EDP
↓
Preload more ← SV ↑ ← CO ↑ ← sys. BP ↑

(2) Arteriolconstriction → Pressure ↑ in arterial tree
↓
↑ diastolic BP.

(3) AT-II → (+) Zona glomerulosa → ↑ Aldosterone

↓
Principle cells of DCT
↓
Binds to its receptor in cell
↓ (+)
Transcription & Translation
↓
↑ New prtns
↑ K^+ channels.
↑ no. of Na/K^+ ATPases in basolateral membrane
↑ no of Na^+ channels in apical mem.
↑ Na^+ reab.
Water follows Na^+ → ↑ H_2O reab.

↑ Na^+ & H_2O reab → ↑ Blood volume

↓ venous return ↑

↓ cardiac filling ↑ → Sys B.P ↑

④ AT-II → (+) Hypothalamus [Supraoptic nucleus] → ADH → Last part of nephron ↑ H_2O permeable

↑ H_2O reab.

⑤ AT-II → (+)(+) Sympathetic N.S

↓ Norepinephrine rly ↑

↑ no of adrenergic receptors

⑥ AT-II → (+) central thirst system

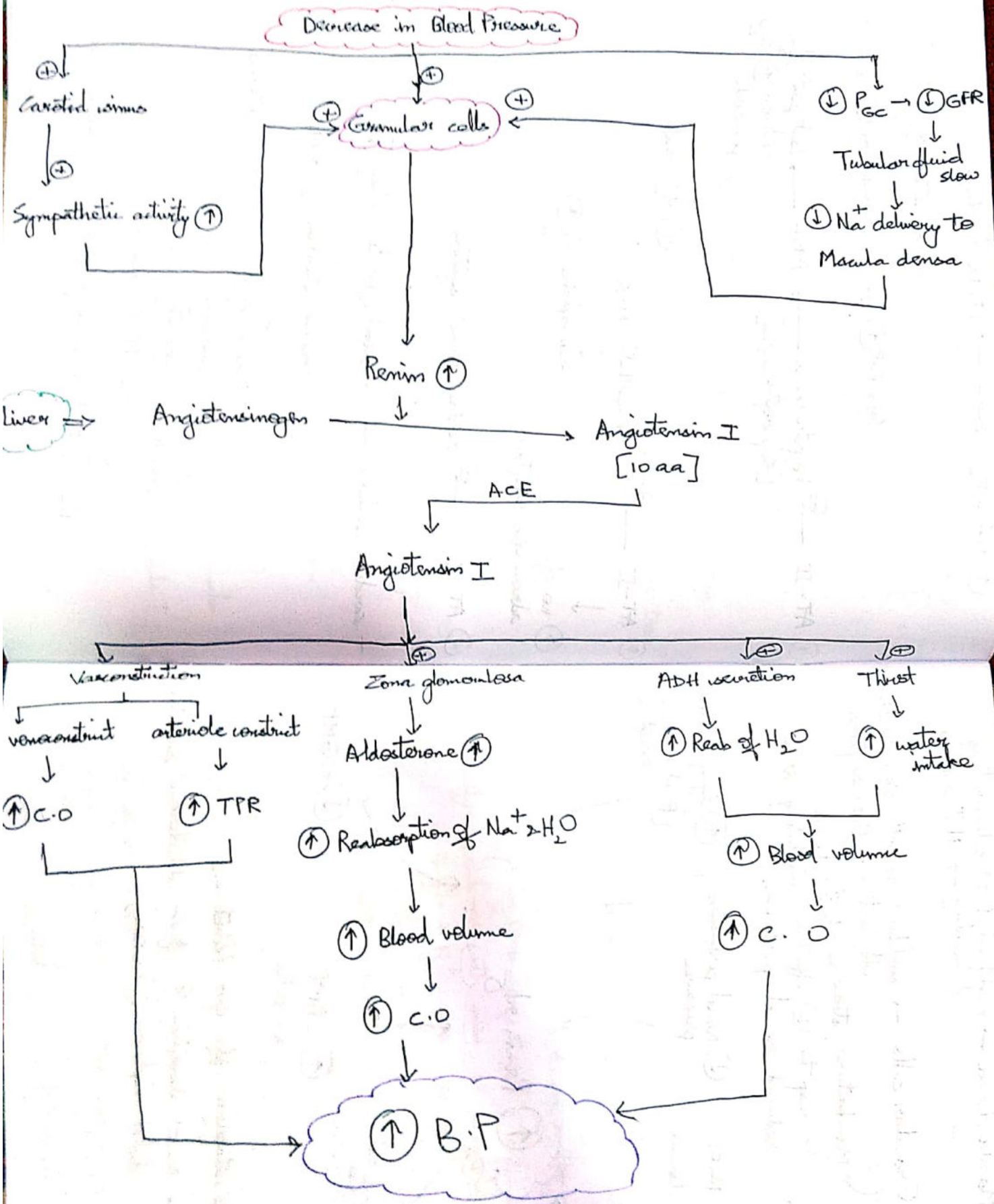
– cardiac failure → Blood flow to kidneys ↓

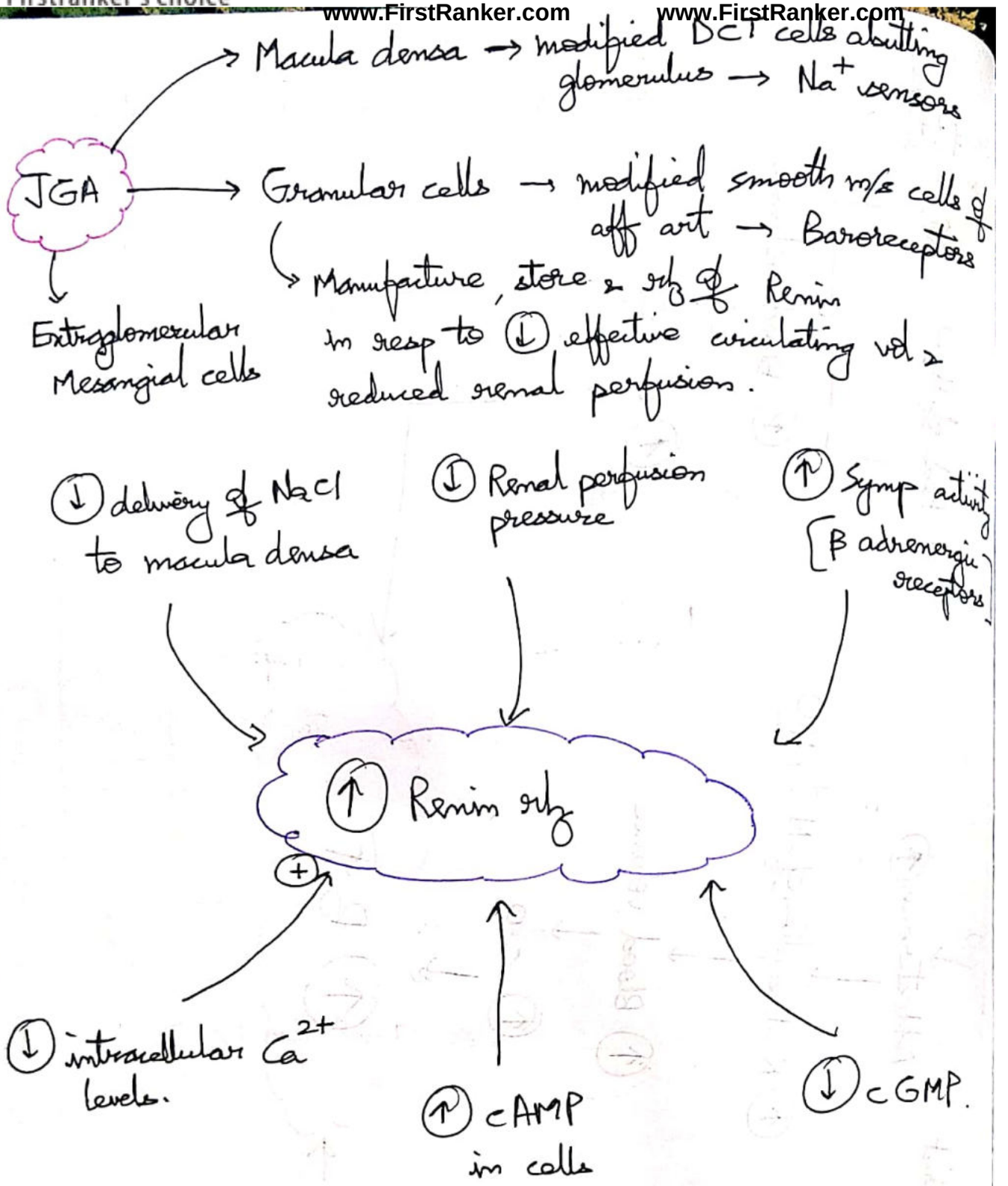
↓ chronic activation of RAAS.

↓ Cardiac remodelling.

- Morphology of myocardium altered
- undergoes hypertrophy.
- geometry altered.
- ↑↑ EC matrix

⇓ Poor contraction → progressive cardiac failure.





AT-II impt secretagogue for Aldosterone.

Aldosterone → NaCl absorption ↑ from aldosterone sensitive distal nephron (ASDN).