PC
Pharmacology Concepts
By Rajesh Choudhary

Drugs Used in Kidney (Diuretics & Antidiuretics)

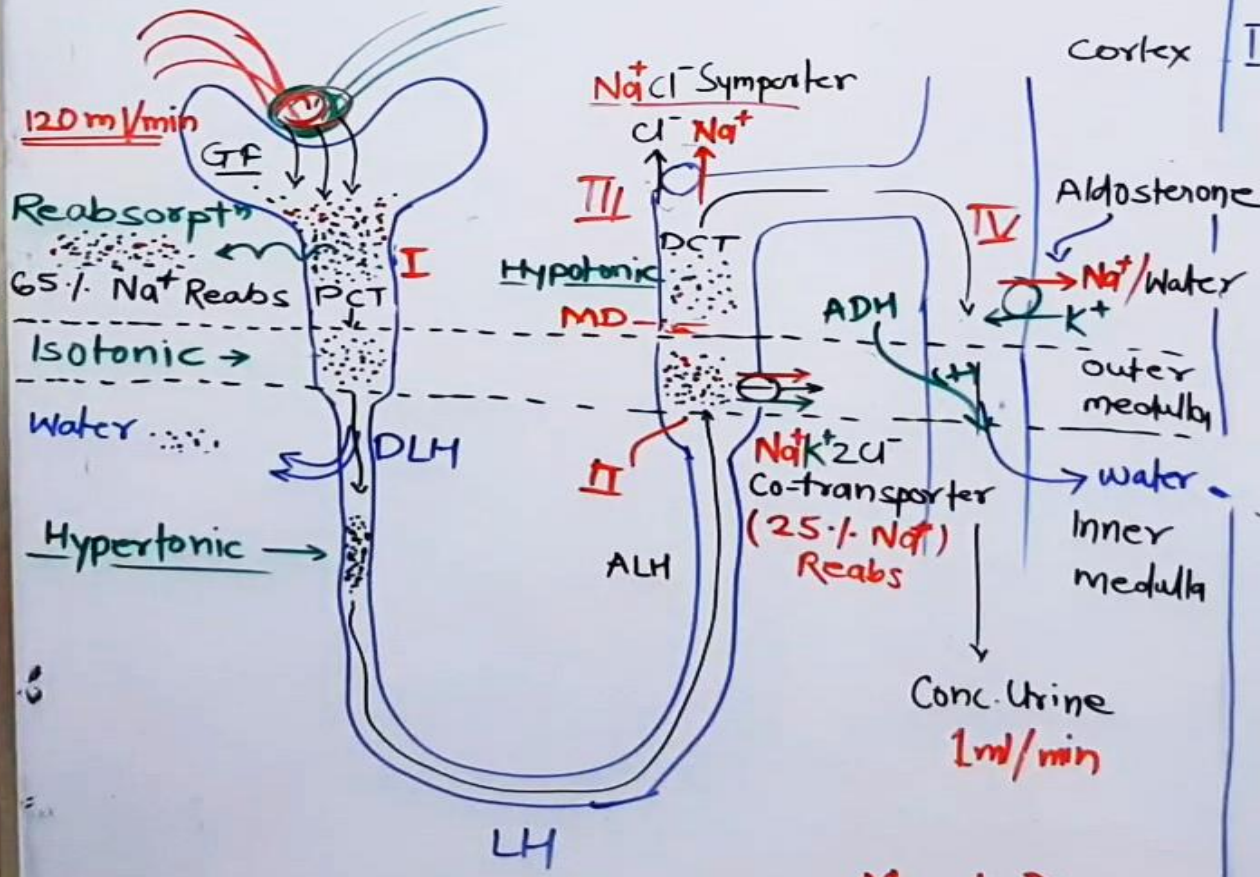
Pharmacology 2 | U2

DIURETICS

Diuretics are the drugs, which increase the Excretion of Na^+/water

↳ ↑ Urin Output
↳ mobelizing the Fluids
↳ ↓ fluid Volume / Edema
↳ ↓ Venous Return (↓ Preload)

↳↓ HTN
↳ ↑Excretion of unwated drugs/ Poison



MD = Macula Densa

I. Carbonic Anhydrase Inhibitors :-
Acetazolamide, Methazolamide, dichlorphenamide

II Loop Diuretics - Furosemide, Bumetanide, Ethacrinic acid.

III Thiazides :- Chlorthiazide, HCT, Benzthiazide

IV. K^+ Sparing :→ Spiranolactone, Amiloride, Triamterene

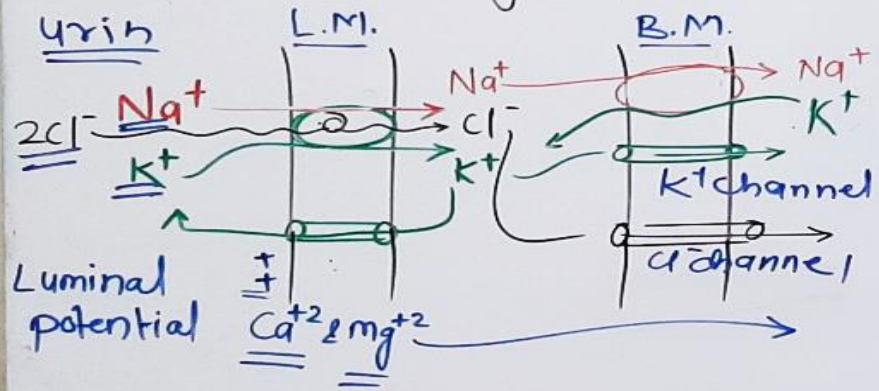
⑤ Osmotic Diuretic :- Glycerine, Mannitol, Urea

LOOP DIURETICS :- FUROSEMIDE

Old - Ethacrynic a, Organomercurials

New - "Frusemide", Bumetanide, Torasemide

MOA : ⇒ Inhibit $Na^+ K^+ 2Cl^-$ Cotransporter at thick Ascending loop of Henle (site - II)



$\frac{Na^+}{K^+} > 2$

$\frac{Na^+}{K} > 10$

PHARMACOLOGY - High Ceiling Diuretics / max. Efficacy

It has maximum "Natriuretic Effects" → Na^+ Excretn

It can produce up to 10L of urine per day

It works even in patient with Sever Renal failure

#4 It abolishes the corticomedullary Osmotic gradient and ↓ (+) & (-) Free water clearance.

It has weak CA Inhibitory action.

#4# It alters the Systemic & Renal Haemodynamic due to ↑ renal blood flow, but GFR is unchanged by compansatory mechanism. Net result ↓ in PCT Reabsorption

Main Effect →

⇒ Natriuresis - ↑ Na^+ Excretion

= Saluretic effect - K^+, Cl^-, Mg^{2+} & Ca^{+2}

⇒ Improve Venous Capicitance → ↓ LV Filling Pressure = ↓ CHF

⇒ (+) Local PGs Synthesis

→ ↑ Blood urea - Hyperuricemia

P'kinetics - Absorb orally, BA = 60% (↓ in CHF)

→ Reach to site by Org. Acid Transport System.

- Onset - N = 2-5min, IM = 10-20, Oral - 20-40min

→ Excrete the Glucoronic Conjugation & T. Secretion

ADR = Ototoxic Effect, Hypokalemia, Hypocalcemia, Carbohydrate intolerence, Interfere with lipid profile

Brisk Diuresis induced in cirrhotic may cause mental Disturbance & Hepatic Coma

Use - Edema → Peripheral, Pulmonary & Cerebral Edema

↳ ✓ CHF → LV failure

↳ ✓ HTN

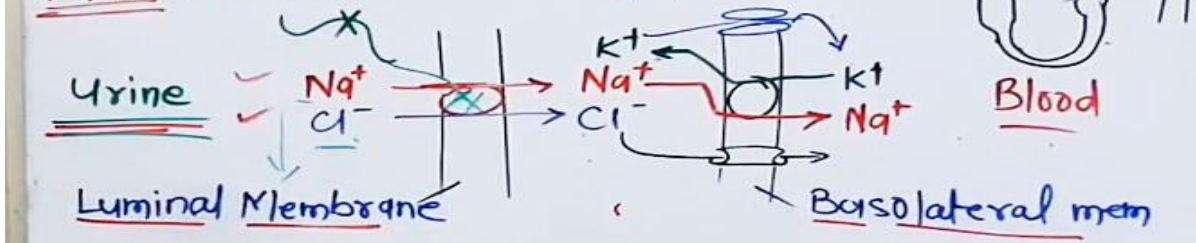
↳ ✓ Poisoning - Forced Diuresis

THIAZIDE DIURETICS

Benzothiadiazine (Thiazides)
- Hydrochlorthiazide, Benzthiazide, Clopamide.
- Hydroflumethazide

Thiazide like (Related) Diuretics -
- Chlorthalidone, Indapamide, Xipamide

MOA = Inhibit Na^+Cl^- Symport-pump



Pharmacology:- Medium Efficacy Diuretics

Site:- Cortical Diluting Segments or Early DCT (III)

↳ Not act on corticomedullary region

↳ ↓ Positive Free water Clearance (Very dilute urine can not be passed in the absence of ADH)

↳ Not affect (-) Free water Clearance (In presence of ADH)

* Free Water Clearance - Volume of blood plasma that is Cleared Solute-Free Water per unit time

+FWC = diluted urine

-FWC = Conc. urine

\# Additionaly They have CA inhibitory action at PCT

\# Main Action → ↑Exc. of → Na^+, Cl^-, K^+, mg^{+2}

→ ↓Exc. of Ca^{+2}

→ ↓ Plasma Volume, ECF, CO (* CHF)

→ ↓TPR → ↓HTN

→ ↓Insulin release due to hypokalemia ⇒ ↑ Sugar

* No effective in low GFR (<30 ml/min) Patients

PKinetics - Reach to the site by Org. Acid Secretory Pathway. Only Oral route is used. Onset - 1h durat^n 8-48h depends upon lipid Solubility

USE - Edema, HTN, Diabetes Insipidus (to reduce urine Volume). Hypocalciuria

ADR - Hypokalemia
- Dehydration
- Hearing loss/impairement
- Allergy
- Hyperurecemia
- Hyperglycemia & hyperlipidemia

Interactn: - T+ Digitalis → ↑ Hypokalemia toxicity
T+ Aminoglycoside - ↑ ototoxic & Nephrotoxic effect
T + Cotrimoxazole - Thrombocytopenia

K^+ Sparing Diuretics – Week Diuretic

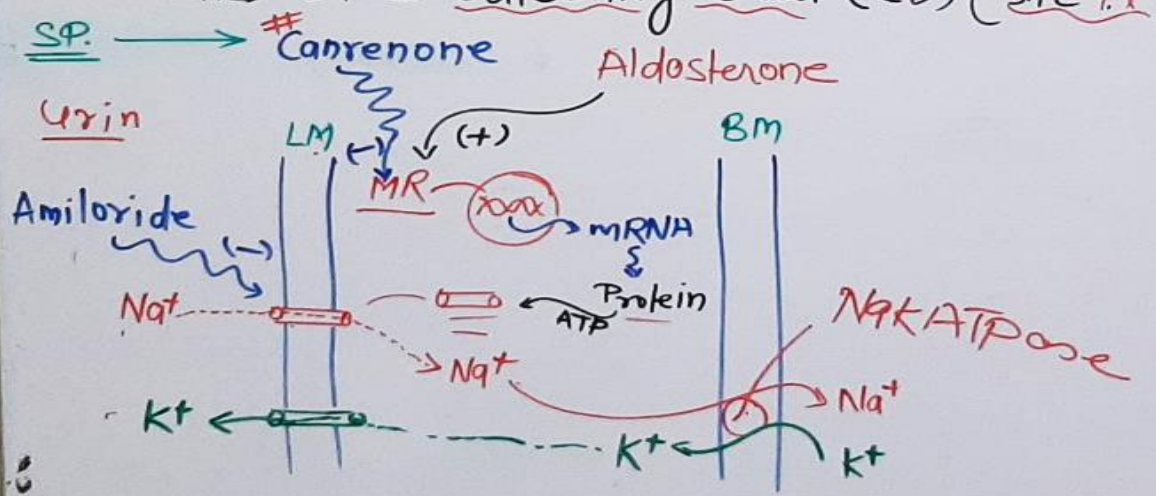
Aldosterone Antagonist → Spironolactone, Eplerenone

Renal Ep. Na^+ channel Inhibitor – Amiloride, Triamterene

"They Conserve K^+ ion with having mild Natriuretic / saluretic effects

"Spironolactone Pharmacology"

MOA = Antagonise the Ald. Receptor that may lead to inhibition of Na^+ channel expression at late DT & Collecting Duct (CD) (Site I.V)



* Spironolactone – Steroidal Mineralocorticoid
  - Aldosterone Derivative.
  - Canrenone (–) MR → Ald-Induced Proteins → Na^+ Reabsorption

Main Effects –
- Mild Saluretic effects
- ↓ K^+ loss → K Sparing Effect
- ↑ Ca^{+2} Excretion

Pkinetics – 75% BA of microfine powder.
- Metabolised in liver – Canrenone (1/2 - 2/3 action)
- $t_{1/2}$ ⇒ Sp. → 1-2 h & Can. – 18 h

USE – Edema, CHF, HTN, Hypokalemia

ADR – Gynaecomastia (Anti-Androgenic effect)
- Hirsutism, Impotence, Menstrual irregular
- Hyperkalemia
- Drowsiness, Atexia, Mental Confusion

Contraindicatn: – Renal insufficiency
- Acidosis may produce in cirrhotic Patients
- Peptic Ulcer

Eplerenone – Newer Ald. Antagonist having lower Hormonal disturbance Side effects

Amiloride: – Inhibits Na^+ channel, used in Edema, CHF and HTN, Symptomatic improvement in Cystic Fibrosis

DRUG INTERACTION = Sp + ACEIs → Hyperkalemia
- Aspirin inhibit Sp. action by ↓ Tᵤ Secretion
- Sp. increase Digoxin plasma conc. by ↓ T.S.

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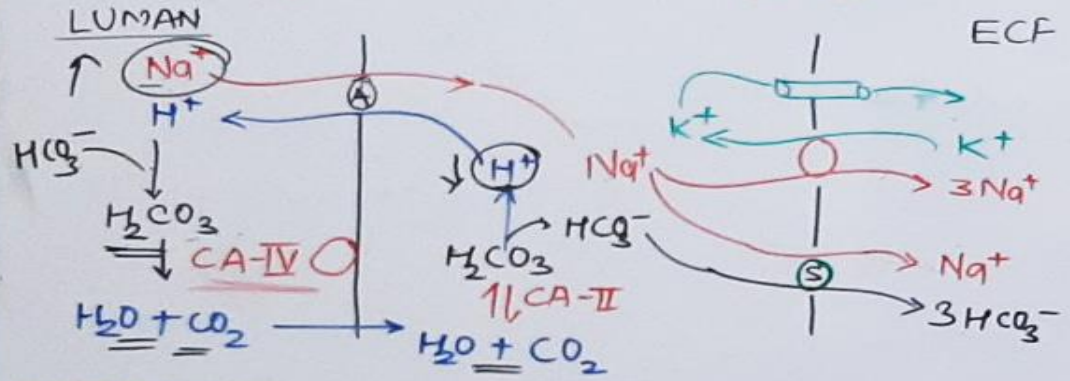
Carbonic Anhydrase Inhibitors

"Acetazolamide", Methazolamide, Dichlorphenamide

CAs - 1. $H_2O + CO_2 \rightleftharpoons H_2CO_3$ Carbonic acid
2. $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$



In PCT (LM & BM) - Zn-Metallo Enz-CA-IV
Cytoplasm - CA-II

CAs found in Renal (PT), GI mucosa, Ciliary body (eye), RBC, Brain

99% inhibition of CAs is required to produce an effect.

CAs play imp role in $NaHCO_3$ reabsorption and aid Secretion.

MOA: → CAs Inhibitors inhibit the formation of H^+ and ↓ exchange of H^+ with Na^+ → ↑ Na^+ Excretion

↳# They work at PCT (Site I) as 1° site and CD (Site IV) as 2° site

→ ↑ Excretn of HCO_3^-, Na^+,
→ ↓ Secretion of Tetratable acid & NH_4^+ in C.D. results in ↑ in urin pH & produce metabolic Acidosis

Haemodynamic effect → By ↓ CAs at PCT, ↑ Solute delivery at Mecula densa that triggers TGF, which ↑ afferent arteriole resistance & ↓ Renal blood flow & GFR

Other effects - ① ↓ Aqeous formatn (eye) - ↓ IOP
② CNS - Anticonvulsant, direct & indirect (M. acidosis)
③ ↑ CO_2 level in Peripheral Tissue
④ ↓ Acid Secretion at large dose
⑤ Vasodilatn by opening Ca^{+2} dependent K^+ channels

PKinetics: - BA: 100%, $t_{1/2}$ = 6-9 h, Renal Excretn

USES: - ① Open Angle Glaucoma ② As Diuretics

ADR ⇒ ①# Bone Marrow Supression
② Allergy, Skin Reactn
#(3) Hepatic Encephelopathy
(4) Renal calculi due to metabolic Acidosis
#(5) Paresthesis - "Pin & Needle" pain percept^n

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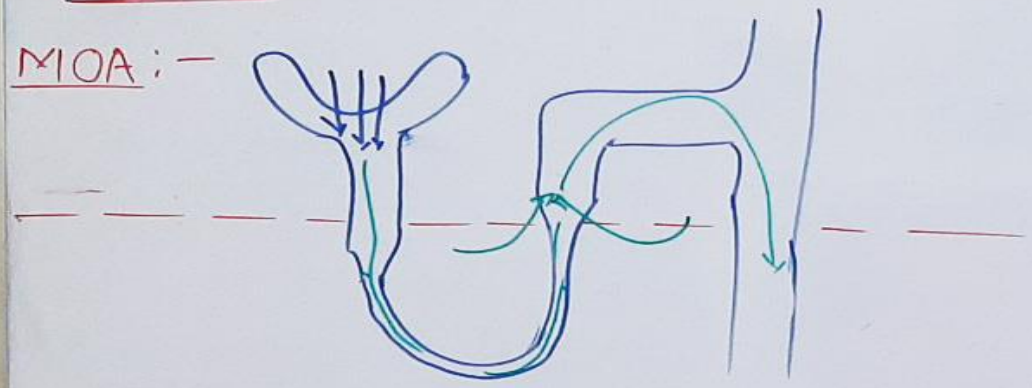
Osmotic Diuretics

↳ Mannitol, Glycerine, Urea

MOA :-



↳ Osmotic Diuretics easly filter by G.F. but limited to Tubular Reabsorption.

↳ They Increase the Osmotic pressure and extract water from Intracellular Compartment-

↳ They also decrease the blood Viscosity and inhibit Renin Release

↳ These effects increase the renal blood Flow that may lead to removal of Nacl and Urea from the renal medulla, Thus reducing medullary Tonicity

Diuretic Action :-

↑ Excretion of all electrolyte - Na^+, K^+, Cl^-, Ca^{2+}, Mg^{+2}, HCO_3^-

Admistration :- 10-20% iv., Excreted $t_{1/2}$ = 0.5-1.5 h

USES :→ Glaucoma (↓IOP)

↳ ↓ Intracerebral Pressure

↳ Oliguric State

↳ Acute Renal Failure

↳ Post operative eye/brain Surgery

↳ Poisoning, alongwith Salin=

ADR- Hyponatramia, Hypovolemia

CI :- CHF, Acute Tubular Necrosis, Pulmonary Edema, Cerebral Haemorrhage

Mannito never use in Chronic Edema or as a Natriuretic effect-

ANTI DIURETICS OR ANTI AQUARETICS

The drugs, which inhibit the WATER excretion without affecting the excretion of SALTS

They ↓ urine vol. in Diabetes insipidus

DRUGS –

A. Natriuretics – Thiazides, Amiloride

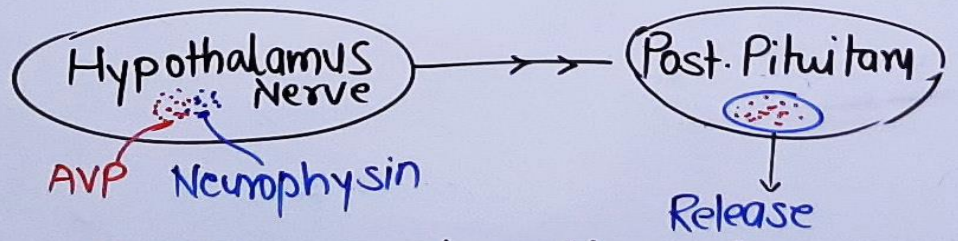
B. Hormone → Vasopressin (ADH), Lypressin
Desmopressin, Terlipressin

C. Others – Carbamazepine, chlorpropamide, Indomethacin

"ANTI DIURETIC HARMONE" (Arg. Vasopressin)

↳ Human ADH – 8-arginine Vasopressin (AVP)

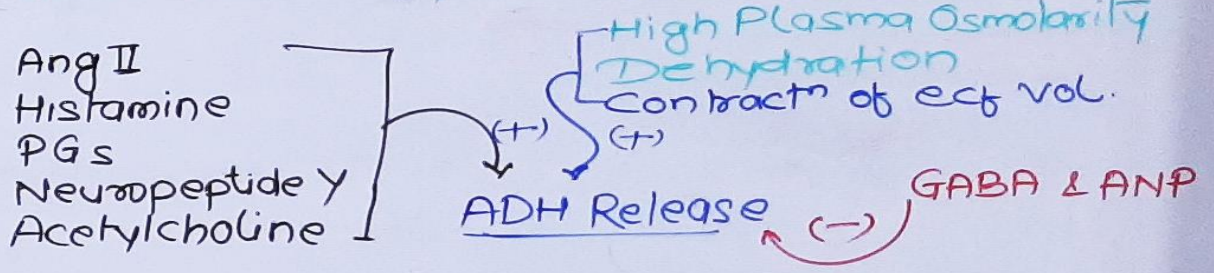
↳ It is a nanopeptide hormone, secreted by posterior pituitary gland.



Regulator ① Osmoreceptor – Hypothalamus,
② Volume Receptors → Heart (LA & LV) & Pulmonary veins

Body Hydration state → (+)/(−)

High salt intake → OsmoR (Hepatic Portal System)
↓ Plasma Osmolarity ← (+) ADH Release



ADH RECEPTORS

Ⓐ V_1R = GqPCR (IP_3/DAG Signalling Pathway)

$V_{1a}R$ = Blood Vessels, Vasa recta in R. medulla, uterine & interstitial cells in R. medulla

$V_{1b}R$ = ant. pituitary, Brain, & pencreas

Function – Smooth mus. contraction, Vasoconstriction, Glycogenolysis & ACTH release, PGs Synthesis (PLA_2) platelets aggregation.

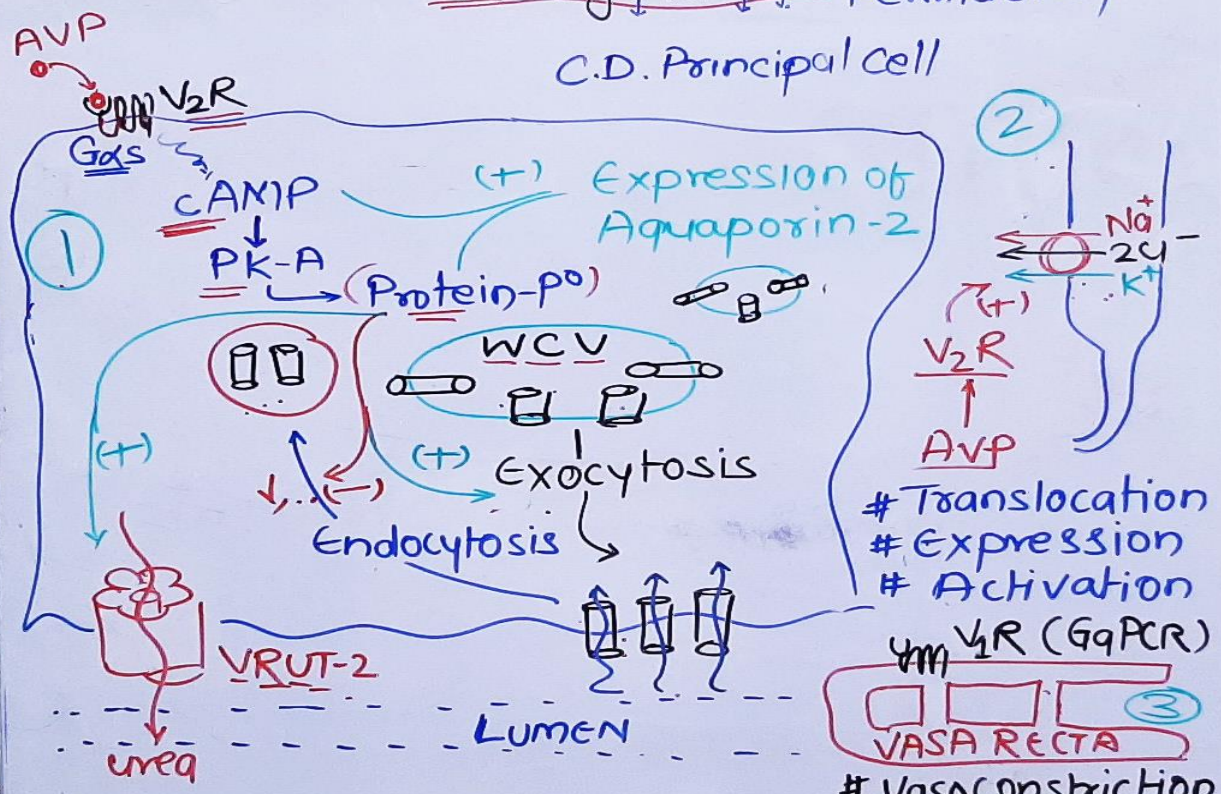
Ⓑ V_2R = GsPCR (cAMP Signalling Pathway)
= Renal Collecting Ducts, Thick ALH
= Vascular endothelial cell

Functn = ↑ water permicability, (+) $Na^+ K^+ 2Cl^-$ transporter
Vasodialation (Desmopressin)

ANTI DIURETICS OR ANTI AQUARETICS

1. Kidney = RT Collecting duct → ↑ urine → ↑ water Permiability

C.D. Principal cell



Li & Demeclocyclin partially antagonise the action of AVP by limiting cAMP Formation & reduce urine conc. ability of kidney, & produce polyurea & polydipsia

2. Blood Vessels – V_1R – ↑TPR – ↑BP (High dose)
3. Uterus → Contracting by acting on OxytocinR
3. CNS – ACTH Release, Regulation of Body temp, Learing of task
4. Others – PGs Syn., Platelet aggregation & Glycogenolysis

P'kinetic Parenterally adm., Orally inactivate by trypsin, $t_{1/2} \sim 25$ min.

Uses – ① Based on V_2R (Desmopressin)
D. Insipidus # Nocturia in adult # Bed wetting
Renal conc. test # Von Willebrand's disease

② Based on V_1R
Bleeding Esophageal varices (AVP, Terlipressin)
Before Abdominal Radiography

ADR – locally – Nasal irritation, congestion, rhinitis
Systemic – Nausea, Abdominal cramps, Backach in Female, Fluid Retention

Contraindicated – Ischemic Heart disease
Hypertension
Chronic Nephritis