ANTIDIURETICS

→ Antidiuretic Hormone (ADH) VASOPRESSIN.

→ BENZOTHIADIAZINES ; CHLORPROPAMIDE

→ VASOPRESSIN RECEPTOR ANTAGONISTS. ?.

VASOPRESSIN :→

Arginine vasopressin → main hormone that regulates body fluid osmolality.

↓

acts at site in Nephron other than collecting duct & on tissues other than kidney.

→ Potent Vasopressor → thus the name for its Vasoconstrictor action.

→ Neurotransmitter → actions in CNS → role in secretion of ACTH ; regulation of CVS , Temp. & other Visceral secretions.

→ Promotes release of coagulation factors by Vascular endothelium & ↑ platelet aggregability.

PHYSIOLOGY :→

ADH action.

↓ CNS

↓ for syn. transport storage & release of Vasopressin.

↓ Called Hypothalamiconeurohypophyseal System

↓ Supraoptic Nucleus , Paraventricular Nucleus → terminate in neural lobe of posterior pituitary → release VP, oxytocin

↓ Renal system

↓ respond to released Vasopressin by ↑ their H_2O permeability

↓

PVN Axons → project to external zone & release directly into pituitary portal circulation

Synthesis → 168 - amino acid preprohormone

↓ in ribosomes

↓ Send in golgi apparatus

↓ processed

↓ Stored in granules

Prohormone contains 3 domains

1) Vasopressin (VP) (1-9)
2) VP- Neurophysin (13-105) } ①
3) VP-glycopeptide (107-145) } ②

① linked VP & glycine - lysine - arginine bridge

② + , " Arginine

Act upon by Endopeptidase exopeptidase, Monooxygenase & lyase sequentially to produce VP,

(NP II) → VP-NP

(Copeptin) → VP-Gly

Transport & Storage

Through axonal Transport & the peptides appear within 30 min & released by exocytosis

* Abnormal by Heart & Adrenal gland.

↓

↑ Na⁺ & Ca²⁺ → ↑ VP Syn. →

→ Contribute to impaired Ventricular relaxation & Coronary vasoconstriction.

Adrenal medulla → VP syn. → Stimulates Catecholamine secretion from Chromaffin cells.
↓
promote adrenal cortical growth & stimulate aldosterone syn.

Regulation :→

⇒ ↑ in plasma osmolality is the principal physiological stimulus of Vasopressin secretion by posterior pituitary.

⇒ Severe hypovolemia / Hypotension also is a powerful stimulus

⇒ Pain, Nausea, Hypoxia can also stimulate & modify VP release.

Hyperosmolality :→

Osmolality threshold for secretion ~ 280 mOsm/kg.

Below this threshold → VP not detectable in plasma.

Above this threshold → VP levels are steep & relatively linear of plasma levels.

A small ↑ in Plasma osmolality → ↑ 2-3 fold of VP release.

> 290 mOsm/kg → intense thirst.

The release of VP is regulated by osmoreceptive complex in CNS. (PVN, SNP neurons)
also Hepatic portal osmoreceptors

Hepatic portal osmoreceptors

↓

an oral salt load activates these receptors

↓

leading to ↑ VP release.

↳ This action is seen before ↑ in plasma osmolality.

Hypovolemia & Hypotension :→

VP secretion regulated by changes in effective blood volume / arterial B.P.

Regardless of the cause, reductions in the volume & B.P may be associated with high circulating VP conc.

20-30 % ↓ in Blood volume } → 20-30 times ↑ in VP levels.

VP → most potent vasoconstrictor & provides to serve in Hypotension to save CV collapse during Blood loss / Hypotension.

Neurons that regulate the VP release are from Baroreceptors in left Atrium, Ventricle & pulmonary veins, ↓ aorta etc.

↓

through Vagal & glossopharyngeal nerve.

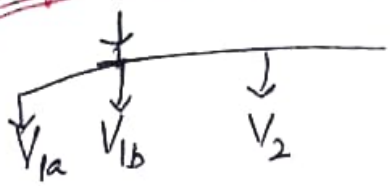
↓

Brainstem

↓

Solitary nucleus → SON, PVN → VP release.

Vasopressin Receptors & Pharmacological actions

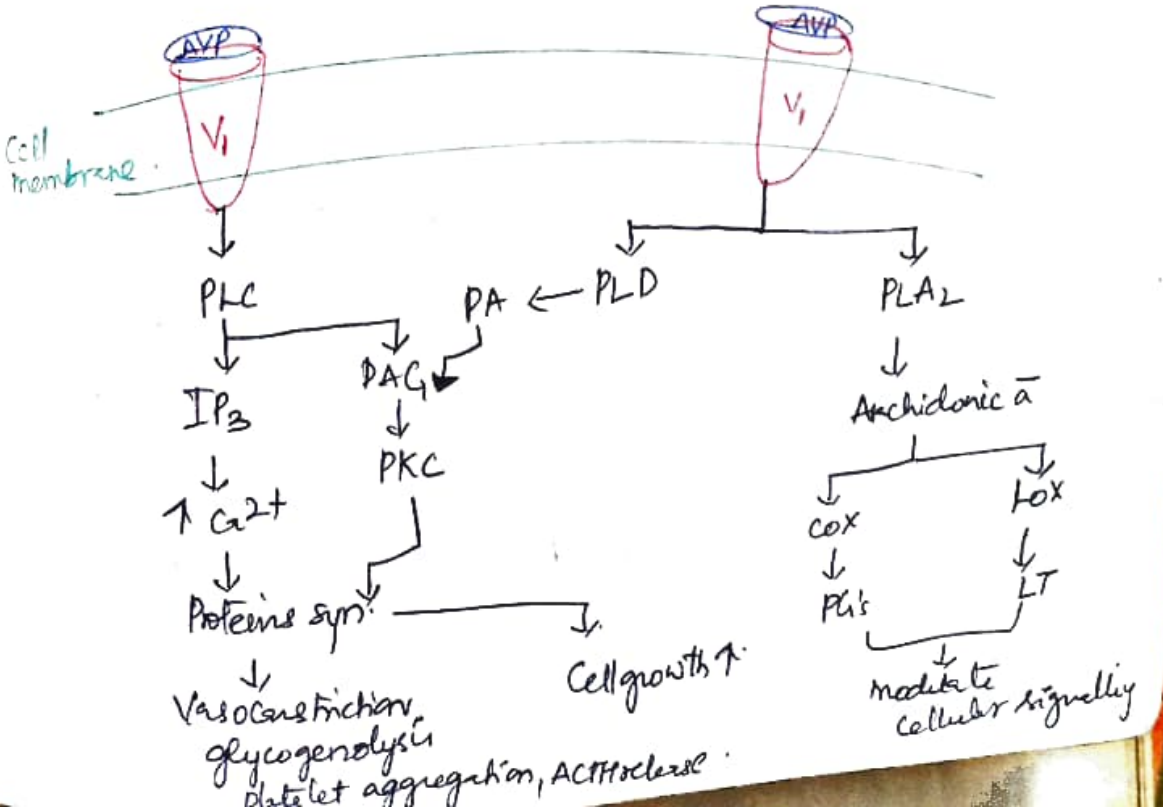


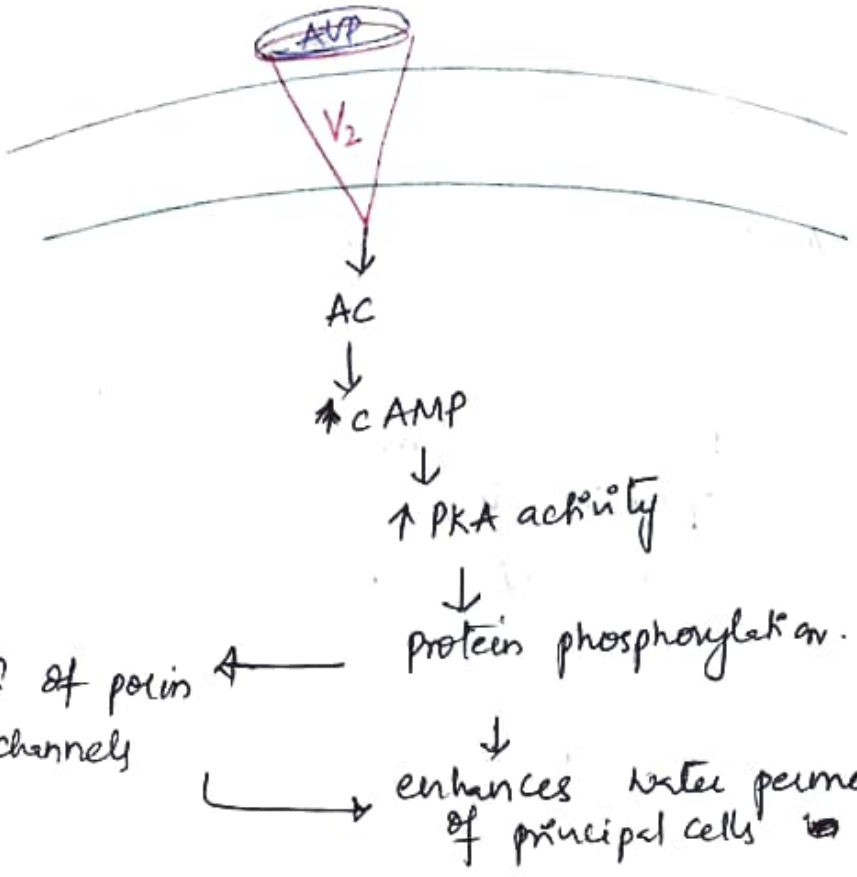
V_{1a} → most wide spread subtype found in Vascular smooth muscle, Adrenal gland, Myometrium, bladder, Adipocytes, Hepatocytes, platelets, renal medullary interstitial cells, epithelial cells in renal-Cortical collecting duct, Spleen, Testis & many CNS structures.

V_{1b} → limited distribution found in Anterior pituitary, Several brain regions, Pancreas, & adrenal medulla.

V_2 → located predominantly in principal cells of renal collecting-duct system, thick ascending limb & Vascular endothelial cells.

GPCR's





Non-renal actions of vasopressin :→

CVS : V_1 receptor mediated actions - Vasoconstriction
Helps to maintain arterial B.P during severe Hypotension / Hypovolemia

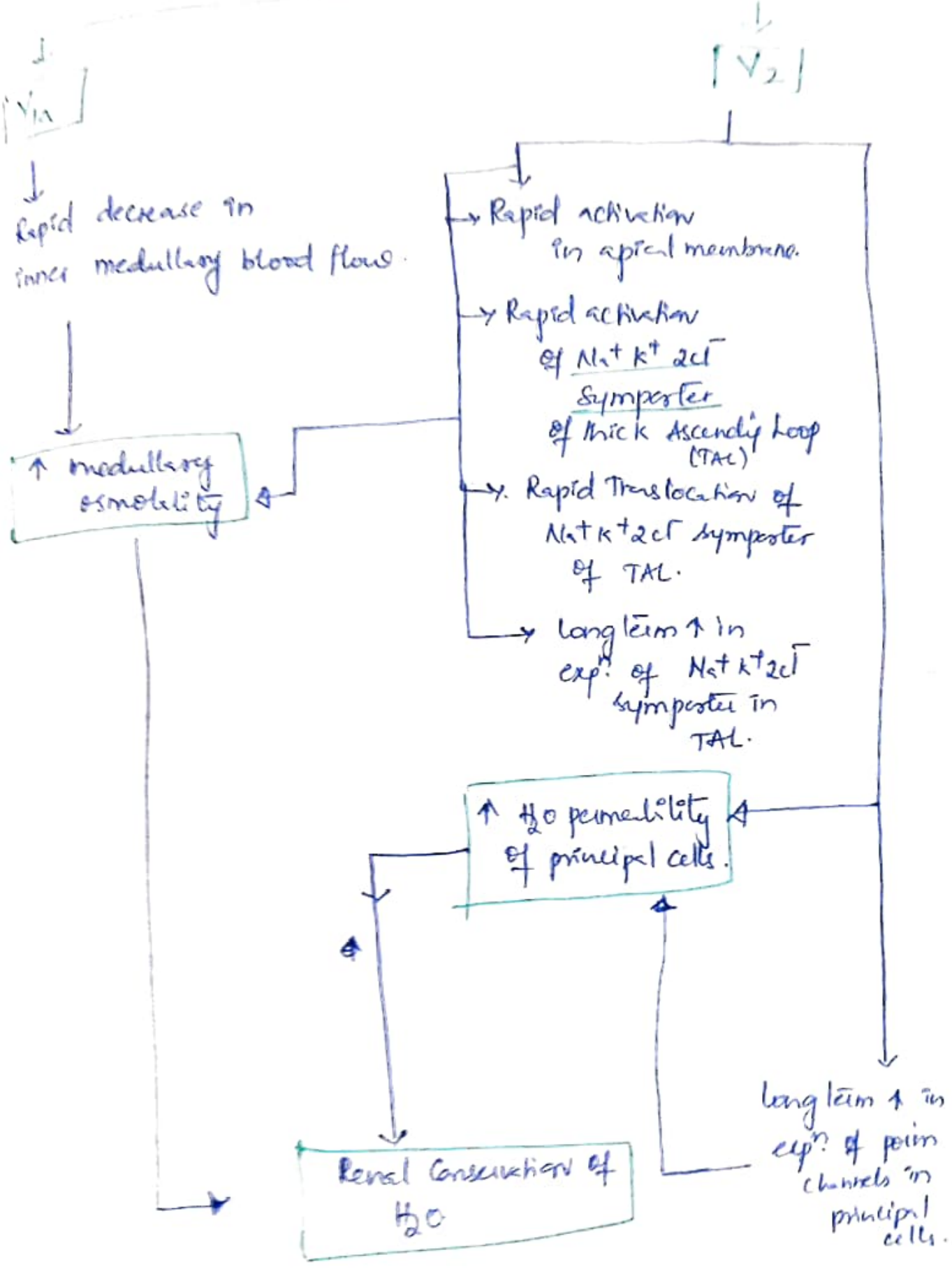
CNS (V_1) : role as neurotransmitter / modulator
helps in acquisition of certain learned behaviours in social process.
pathogenesis of specific psychiatric disease like depression.

Blood coagulation : via V_2 receptors
↑ factor VIII from storage sites of V. endothelium

Liver : ↑ glycogenolysis

Uterus : Stimulates smooth muscle contraction

VASOPRESSIN — Renal action



ADME :→

A → given either as SC & IM

↓

drug remains in body for a few hours

IV → rapidly metabolised

VP tannate in oil → SC/IM → produces an effect lasting for 24 to 48 hrs.

M → rapidly metabolised in liver & kidney

$t^{1/2}$ → 20 minutes or less.

Adverse effects :→

→ N, Biliary colic, ~~acts~~ abdominal cramps

↓

↑ peristaltic activity

→ Severe → Hypotension & shock.

Preparations

→ VP injection

→ VP tannate injection in oil

→ Synthetic VP analogue

DDAVP (1-deamino -8- D-Arginine_VP)

→ Lysine - 8 - VP

T.uses :→

- Post operative ileus & abdominal dixtension } V_1 receptor action
- Acute Haemorrhagic gastritis
- Asystolic cardiac arrest
- Diabetes insipidus } V_2 receptor actions
- Nocturnal enuresis
- Bleeding disorders.

Benzothia dizgines :→

↓
effective in Controlling central as well as Nephrogenic diabetes insipidus.

MoA is not known. but probably by causing a -ve Na^+ balance & ↓ GFR.

↓
↓ volume → ↑ in Conc^n of urine.

Hypokalemia is associated with this therapy
∴ K^+ sparing diuretic may be used as addon.

Chlorpropamide :→ effective in both types of diabetes. probably acts by ↑ the sensitivity of renal tubules to low & otherwise ineffective Conc^n of VP.

Carbamazepine :→ effective in patients with partial diabetes insipidus.
Acts probably by stimulating VP from neurohypophysis

* Actions of chlorpropamide & CBZ is overcome by Ethanol which ⊗ release of ADH.