



Antidiuretics

For BSc Nursing

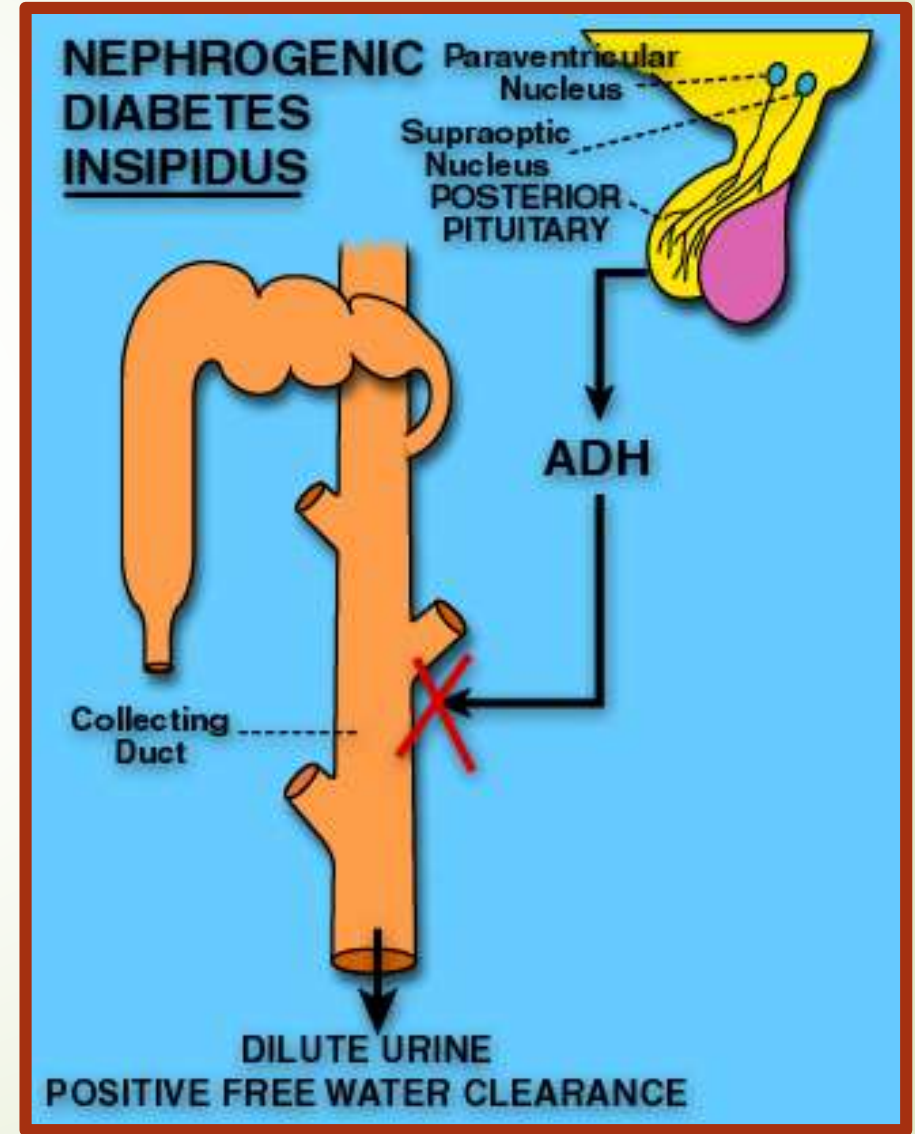
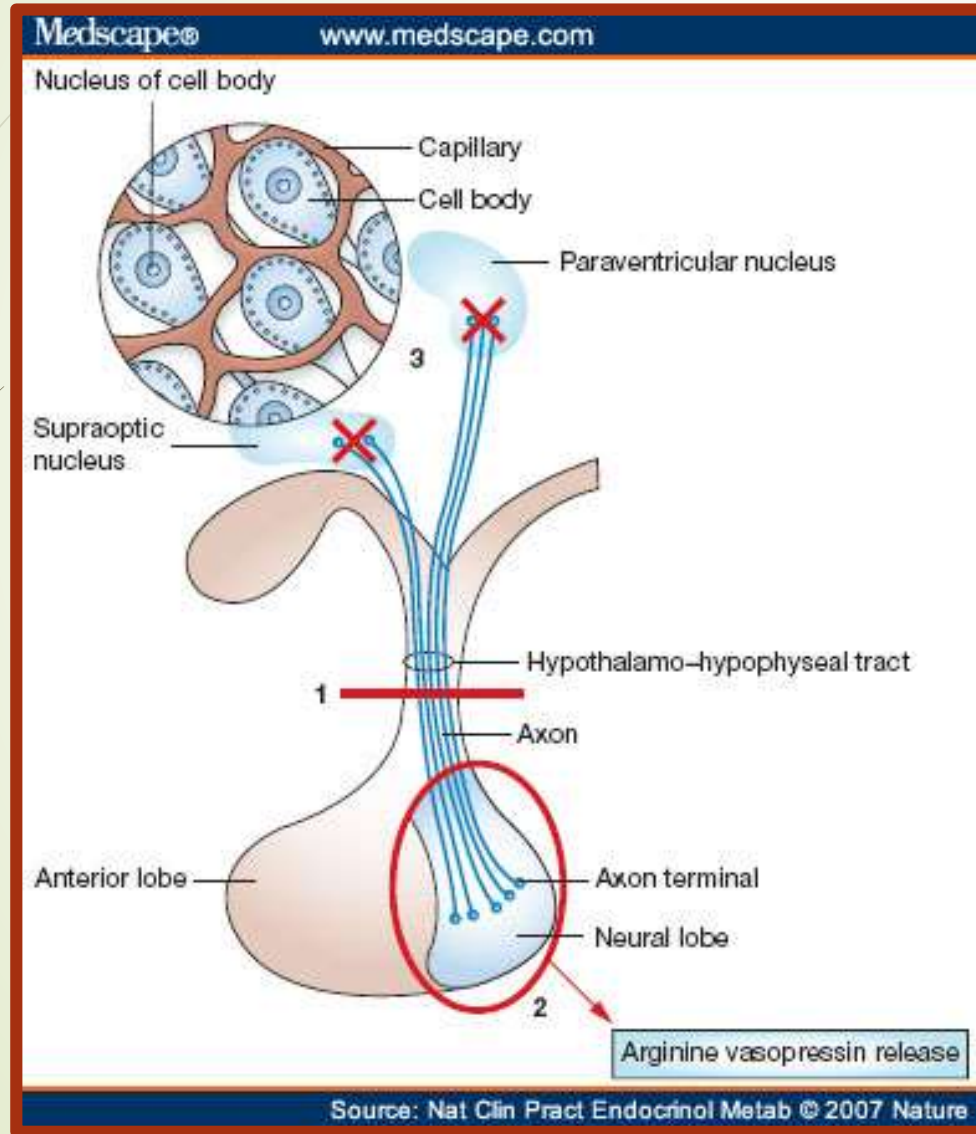
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Diabetes Insipidus





Antidiuretics or Anti- Aquarectics?

- **What are Anti-Diuretics??**

- **Hint: Remember the term diuretics??**

- **Antidiuretics essentially:**

- **Inhibit water excretion**

- **“Without” affecting salt excretion**

- **So which term would you prefer??**



Antidiuretics: Drug List

- **Antidiuretic Hormone (ADH, Vasopressin)**
 - **Desmopressin, Lypressin, Terlipressin**
- **Thiazide Diuretics:**
 - **Amiloride**
- **Miscellaneous:**
 - **Indomethacin,**
 - **Chlorpropamide,**
 - **Carbamazepine**



Antidiuretic Hormone(ADH)

- ▶ **Hormone (protein) secreted by posterior pituitary (neurohypophysis)**
 - ▶ **Where is it formed?**
 - ▶ **What are the other hormones secreted by neurohypophysis?**
- ▶ **Rate of ADH Release controlled by:**
 - ▶ **Osmoreceptors present in hypothalamus**
 - ▶ **Volume receptors present in left atrium, ventricles and pulmonary veins**
- ▶ **Physiological Stimuli for ADH release:**
 - ▶ **Rise in plasma osmolarity**
 - ▶ **Contraction of plasma extracellular fluid (e.c.f.) volume**

ADH receptors

➤ **V₁ Receptors**

- **At all sites except for sites of V₂ (i.e. Collecting Duct cells)**
- **Further classified as V_{1a} and V_{1b}**
 - **V_{1a}: vascular smooth muscles (including that of vasa recta in renal medulla), uterine, visceral smooth muscles, interstitial cells in renal medulla, cortical CD cells, adipose tissue, brain, platelets, liver, etc.**
 - **V_{1b}: anterior pituitary, certain areas in brain and in pancreas**

➤ **V₂ Receptors: more sensitive**

- **Collecting Duct Principal cells in Kidney: Regulates their water permeability**
- **Also present in AscLH cells: Activates Na⁺K⁺2Cl⁻ cotransporter**
- **Endothelium: vasodilator**



ADH: Action on Various Organs

- ▶ Kidneys:

- ▶ Acts on CD principal cells → renders them water permeable → water absorbed → concentrated urine (equilibrating with hyperosmolar medulla) passed

- ▶ Blood Vessels:

- ▶ Constricts through V_1 receptors : raises blood pressure

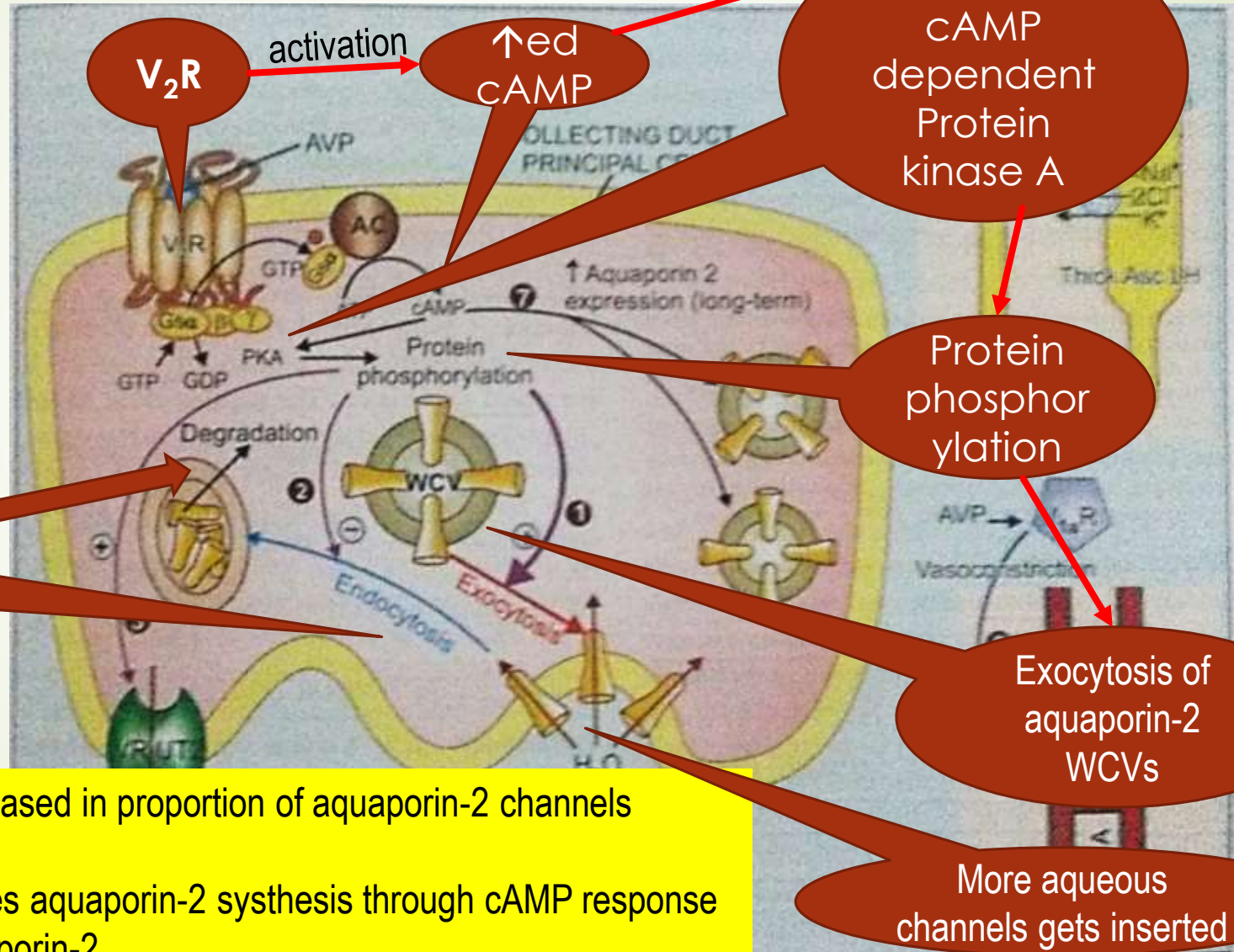
- ▶ Dilates through V_2 receptors: endothelium dependent NO production



ADH: Action on Various Organs

- ▶ GIT:
 - ▶ Increased peristalsis: evacuation and expulsion of gases
- ▶ Uterus:
 - ▶ Contracted by acting on oxytocin receptors
- ▶ Central Nervous System
 - ▶ Endogenous AVP may be involved in regulation of temperature, systemic circulation, ACTH release, learning of tasks
- ▶ Others:
 - ▶ Induces platelet aggregation, hepatic glycogenolysis
 - ▶ Release of factor VIII and von Willebrand's factor from vascular endothelium : V_2 mediated

ADH: Mechanism of Action



Rate of endocytosis and concurrent degradation reduced

Activation of cAMP dependent Protein kinase A

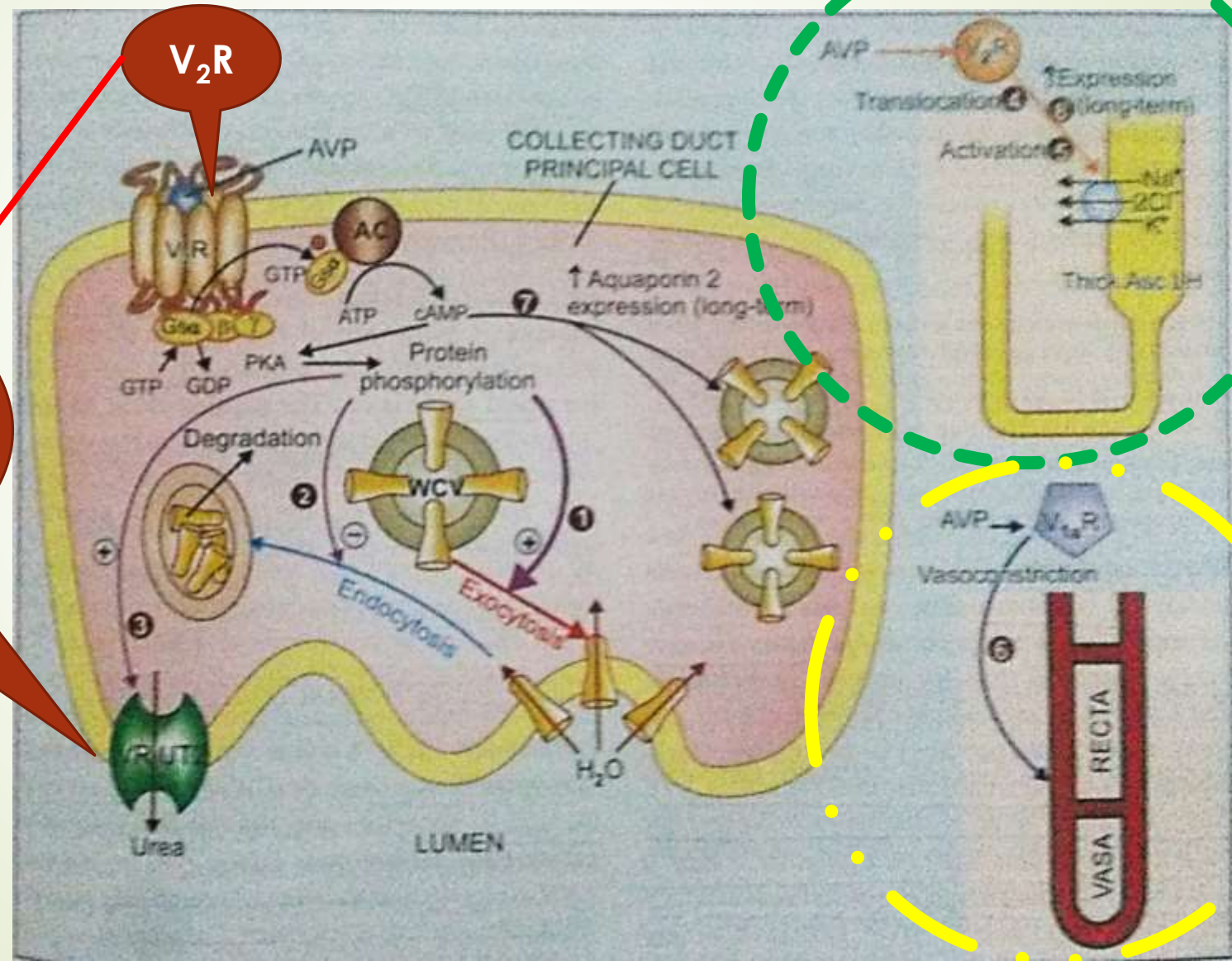
Protein phosphorylation

Exocytosis of aquaporin-2 WCVs

More aqueous channels gets inserted

- ✓ Water permeability of CD cells increased in proportion of aquaporin-2 channels inserted in the apical membrane
- ✓ Continued V₂ stimulation upregulates aquaporin-2 synthesis through cAMP response element of the gene encoding aquaporin-2

Achieving Maximum Concentration Urine



V₂R

Increases urea permeability in terminal CD in inner medulla by stimulating vasopressin regulated urea transporter

Medullary hypertonicity augmented

ADH: Mechanism of Action

▶ V_2R :

- ▶ Principal cells of Collecting Duct: increased aquaporins expression leading to increased water absorption → decreased urine formed.
 - ▶ Augmented by concurrent decrease in endocytosis and degradation of aquaporins
 - ▶ Continued stimulation leads to increased production of aquaporins
- ▶ Increased Vasopressin regulated urea transporter expression in terminal CD cells → increased medullary hypertonicity → increased water absorption → decreased urine formed
- ▶ Increased translocation and synthesis of $Na^+K^+2Cl^-$ channels in ascending limb of loop of Henle → increased medullary hypertonicity → concentrated urine formed

▶ V_1R

- ▶ Constricts vasa recta: diminished blood flow to inner medulla: reduces washing off effect and helps in maintaining high osmolarity; contributing to antidiuresis




AVP Interactions

- ▶ Lithium, demeclocycline: partially antagonise AVP action (limiting cAMP formation)
 - ▶ Used in patients with inappropriate ADH secretion
- ▶ NSAIDs (Indomethacin): augments AVP (increased renal PG synthesis)
- ▶ Carbamazepine, chlorpropamide: potentiates AVP action on kidney

VASOPRESSIN ANALOUGES

Lypressin	Terlipressin	Desmopressin (dDAVP)
8-lysine vasopressin	Synthetic prodrug of vasopressin	Synthetic peptide
Less potent than AVP	Bleeding esophageal varices	Selective V ₂ agonist
V ₁ and V ₂ activity	Less severe adverse effects than lypressin	12 times more potent than AVP
Longer duration of action 4-6 hrs		Negligible vasoconstrictor activity
Substitute for AVP for V ₁ actions		Longer duration of action 8-12 hrs
		Preparation of choice for all V ₂ mediated actions
		Intranasal route preferred (bioavailability 10-20%) oral (1-2%; avoids nasal side effects)



AVP: USES

➤ Based on V_2 Actions:

- Diabetes Insipidus (Neurogenic)
- Bedwetting in children and nocturia in adults
- Renal Concentration Test
- Hemophilia, von Willebrand's Disease

➤ Based on V_1 Actions:

- Bleeding Esophageal Varices
- Before abdominal radiography

Vasopressin: Adverse Effects

- Selective drugs produce lesser side effects
- Transient headache and flushing: frequent
- Local Application: Nasal irritation, congestion, rhinitis, ulceration, epistaxis
- Systemic Side effects: belching, nausea, vomiting, abdominal cramps, pallor, urge to defecate, backache in females (uterine contraction)
- Fluid retention, hyponatremia
- AVP:
 - Bradycardia, increased cardiac afterload, precipitate angina

Contraindicated in patients with Ischaemic heart disease, hypertension, chronic nephritis, psychogenic polydipsia

Thiazide: Hydrochlorothiazide

- Paradoxical Effect
- Furosemide: effective but less desirable: short and brisk action
- Effective in both neurogenic as well as nephrogenic DI
- Mechanism of Action:
 1. similar to salt restriction
 - State of sustained electrolyte depletion
 - Glomerular filtrate completely reabsorbed iso-osmotically in PT
 - Urine passing has low solutes → presented to cortical DT → salt reabsorption decreases → less dilute urine presented to CD → same is passed out
 2. Reduces glomerular filtration rate → reduced fluid load on tubules
- Amiloride: Lithium induced nephrogenic DI

Other Antidiuretics

➤ Indomethacin

- Reduces renal PG synthesis → reduced polyuria in nephrogenic DI.
- Combined with thiazide +/- amiloride
- Other NSAIDs less active

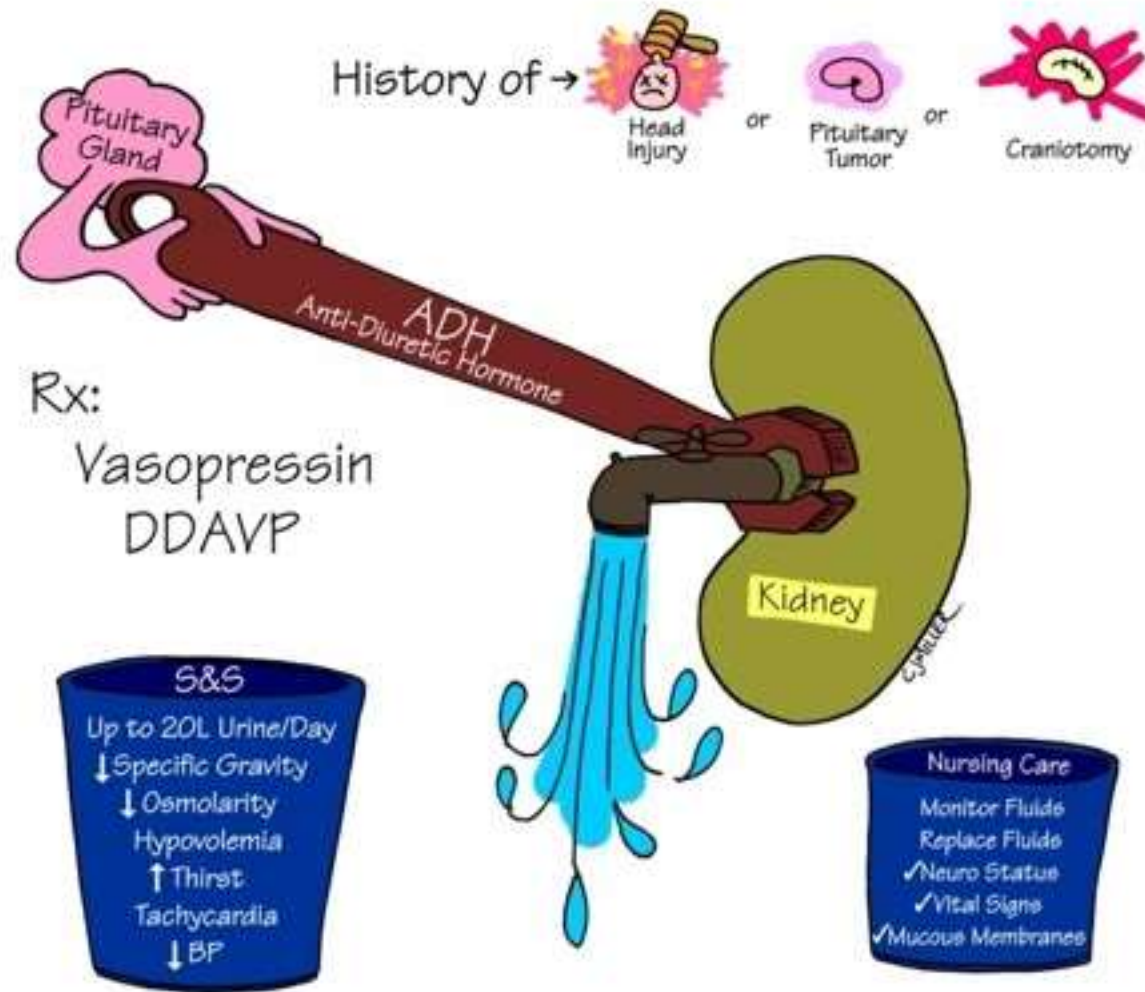
➤ Chlorpropamide

- Long acting sulfonylurea oral hypoglycaemics
- Effective in neurogenic DI: sensitizes kidney to ADH

➤ Carbamazepine

- Antiepileptic
- Effective in neurogenic DI (? M/A)
- Higher Doses needed: marked adverse effects

DIABETES INSIPIDUS



Thank you

Lets have a 10 minutes break.