

# Antidiuretics

For BSc Nursing

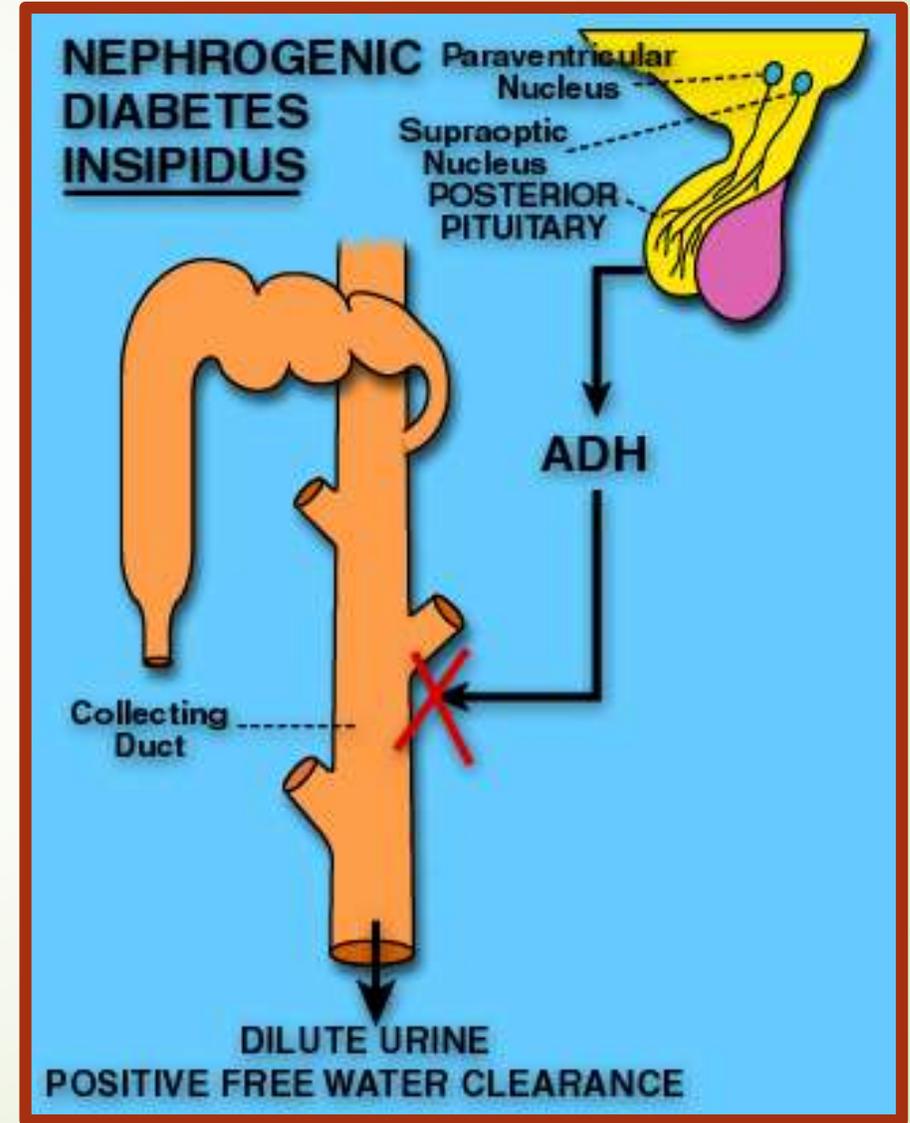
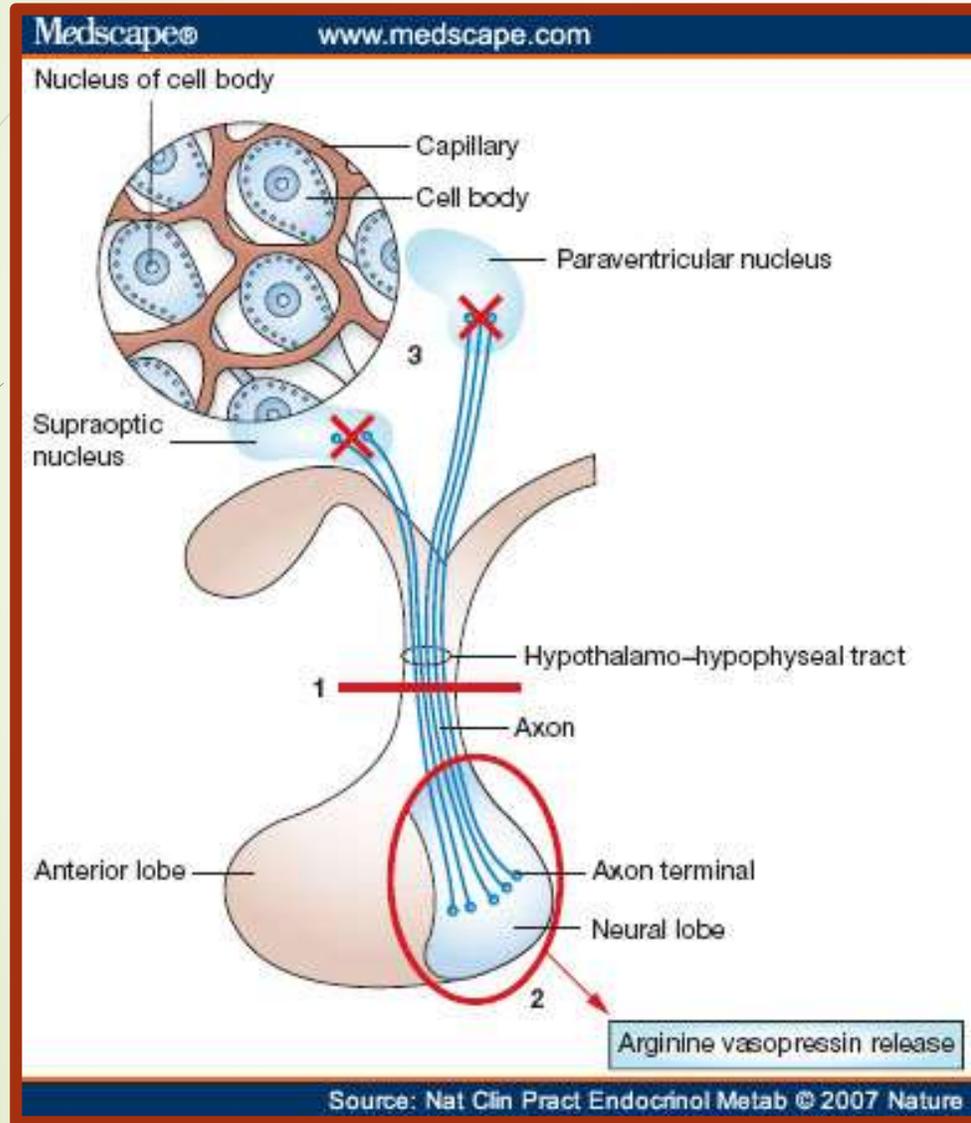
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# Diabetes Insipidus





# 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

## ➤ **V<sub>1</sub> Receptors**

- **At all sites except for sites of V<sub>2</sub> (i.e. Collecting Duct cells)**
- **Further classified as V<sub>1a</sub> and V<sub>1b</sub>**
  - **V<sub>1a</sub>: 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<sub>1b</sub>: anterior pituitary, certain areas in brain and in pancreas**

## ➤ **V<sub>2</sub> Receptors: more sensitive**

- **Collecting Duct Principal cells in Kidney: Regulates their water permeability**
- **Also present in AscLH cells: Activates Na<sup>+</sup>K<sup>+</sup>2Cl<sup>-</sup> 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:

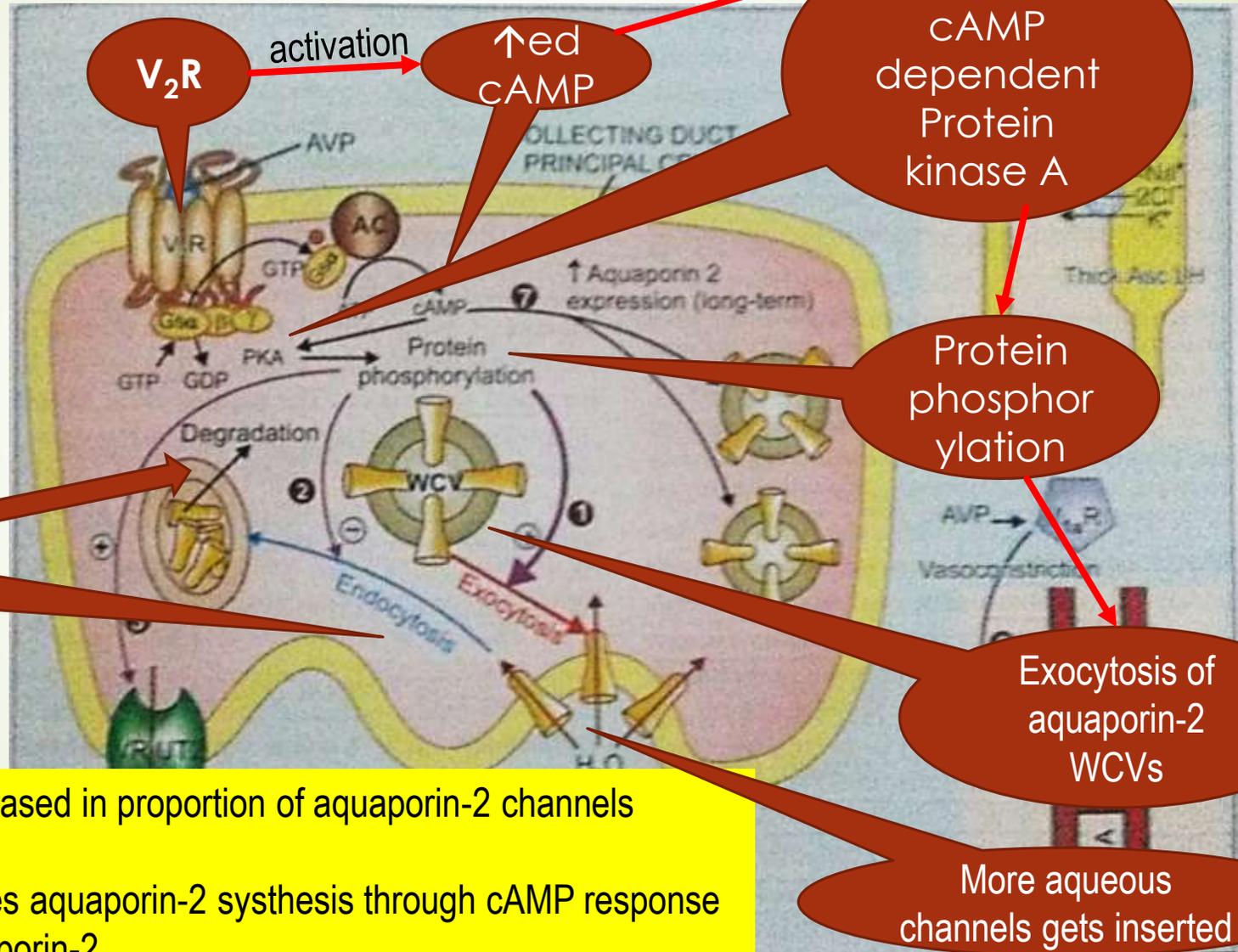
- ▶ Constricts through  $V_1$  receptors : raises blood pressure
- ▶ Dilates through  $V_2$  receptors: endothelium dependent NO production



# 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

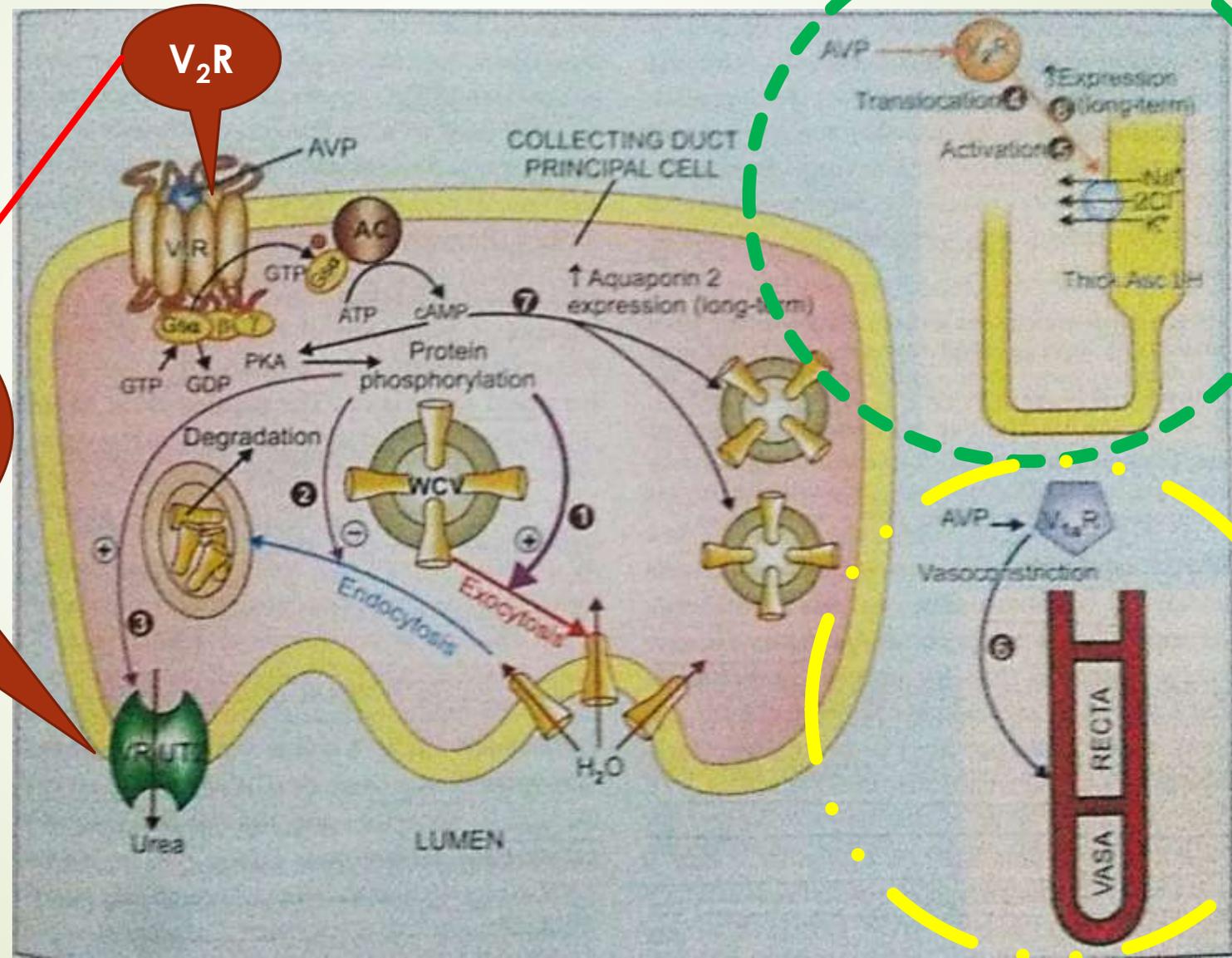
Protein phosphorylation

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 V<sub>2</sub> stimulation upregulates aquaporin-2 synthesis through cAMP response element of the gene encoding aquaporin-2

# Achieving Maximum Concentration Urine



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 <sub>2</sub> agonist
V <sub>1</sub> and V <sub>2</sub> 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 <sub>1</sub> actions		Longer duration of action 8-12 hrs
		Preparation of choice for all V <sub>2</sub> 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

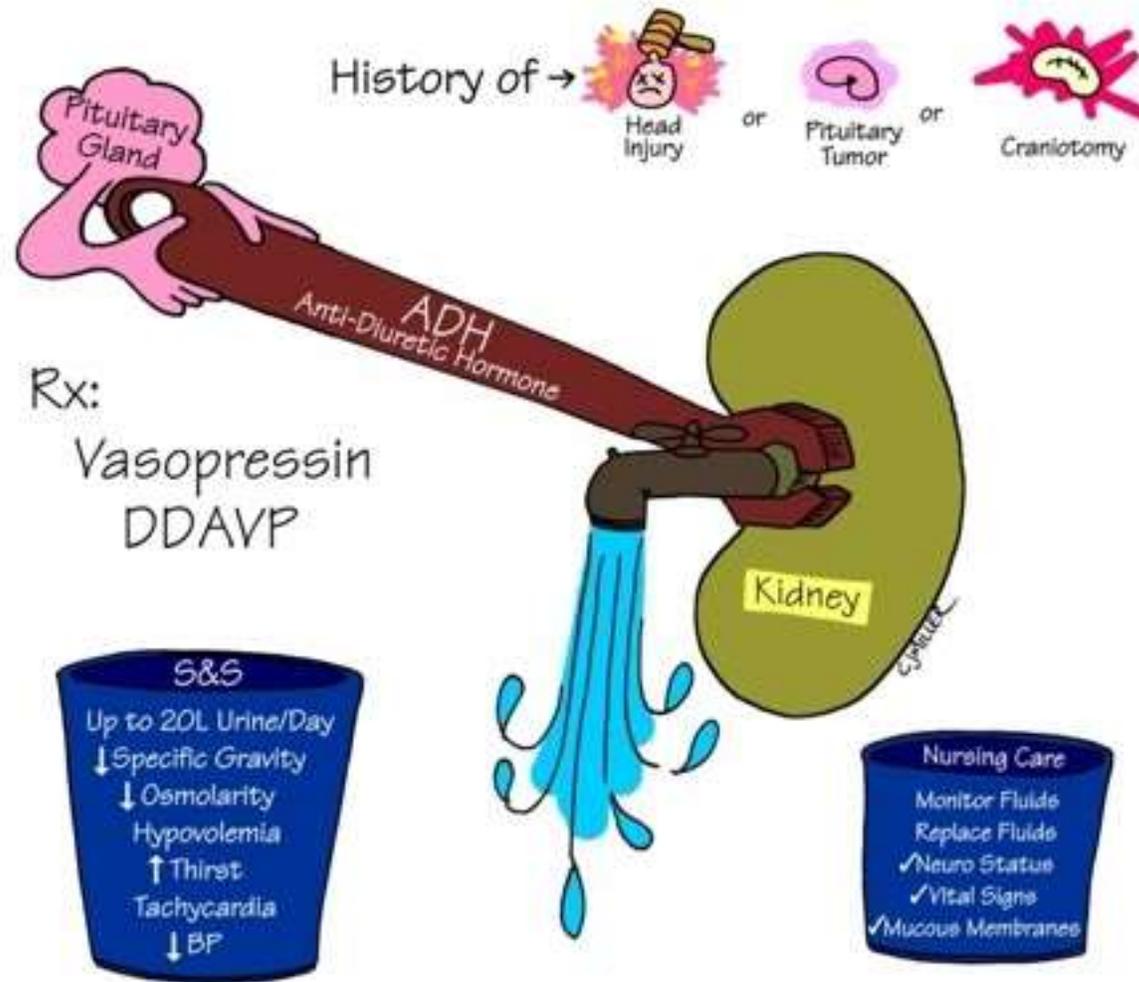
## ➤ Chlorpropamide

- 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.