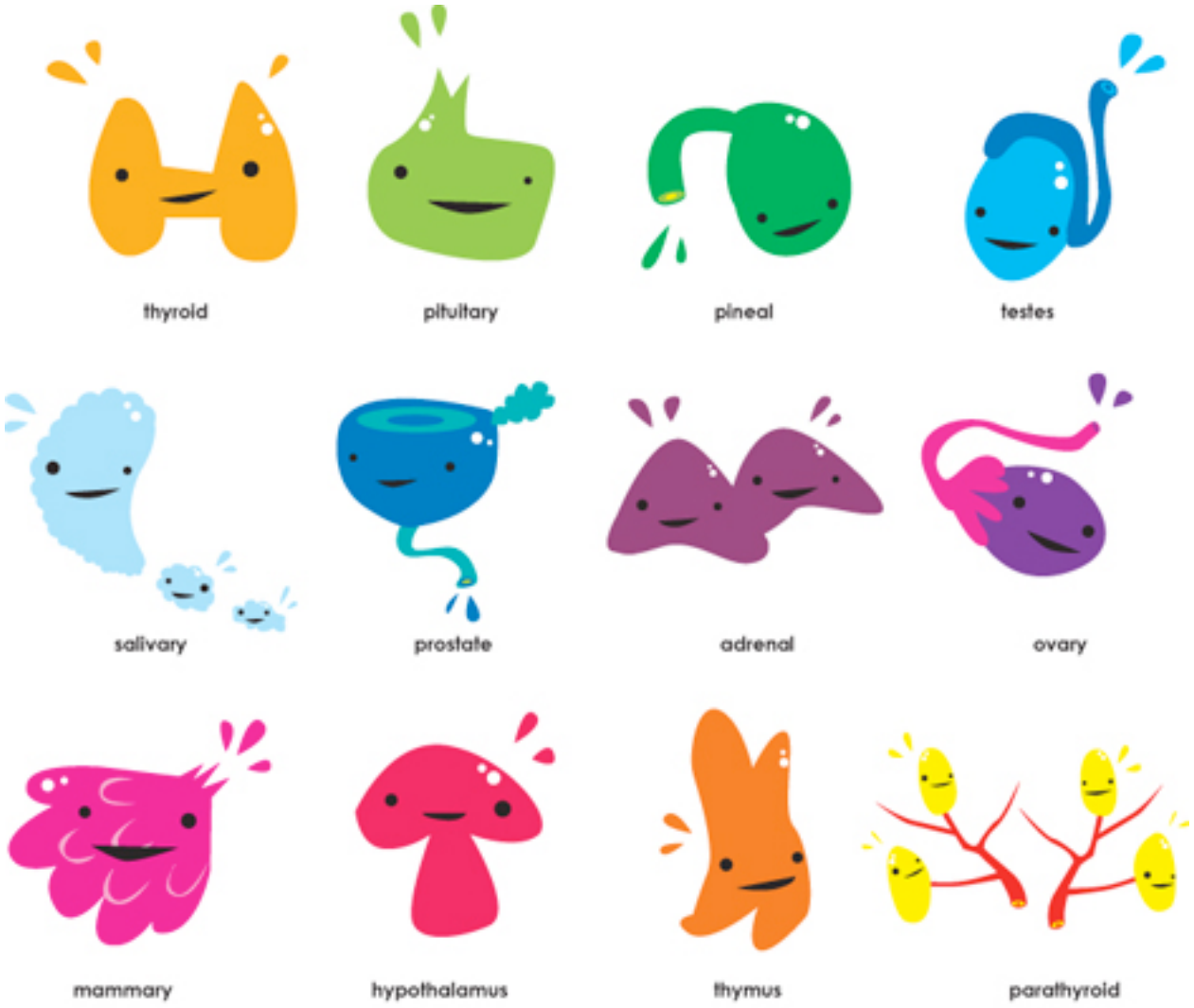
Lecture 4 & 5: Physiology of posterior Pituitary Gland & Diabetes Insipidus



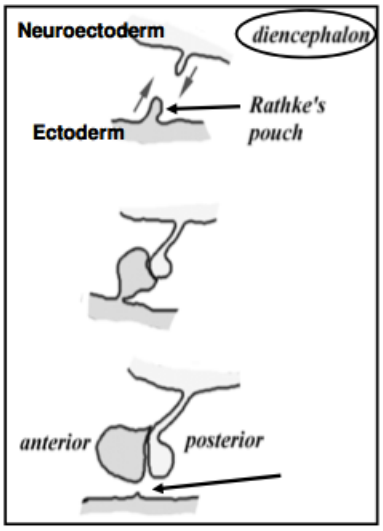
Note: 1) This is a rearrangement of the slides + Few notes

2) Focus on every figure and graph. Do not ignore them!

notes are in purple

IBRAHIM ALSHIDDI . ISMAIL RASLAN . TAMARA ALHOBAYB

Posterior pituitary(neurohypophysis):



– Formed by downgrowth of the brain [diencephalon] during fetal development.

- Embryologically it's originated from neuroectoderm while the anterior pituitary is a growth of ectoderm called Rathke's pouch.

– Is in contact with the infundibulum.
• Nerve fibers extend through the infundibulum.

Relationship to the Hypothalamus:

The connections between the hypothalamus & the posterior lobe of the pituitary are neural.

the posterior pituitary is a collection of nerve axons whose cell bodies are located in the hypothalamus.

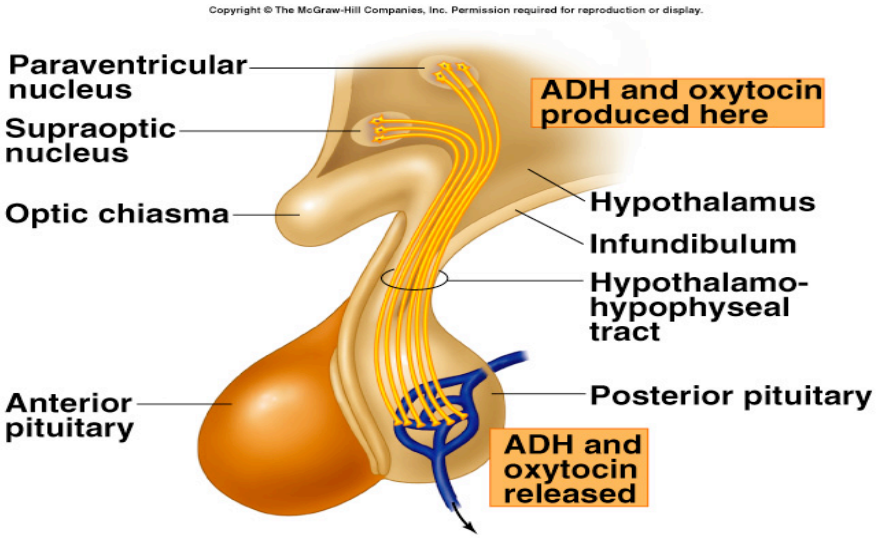
Secretions of the posterior pituitary are controlled by ***Nervous*** signals from hypothalamus

The posterior pituitary does not produce any hormones, it simply stores & secretes hormones produced by the hypothalamus

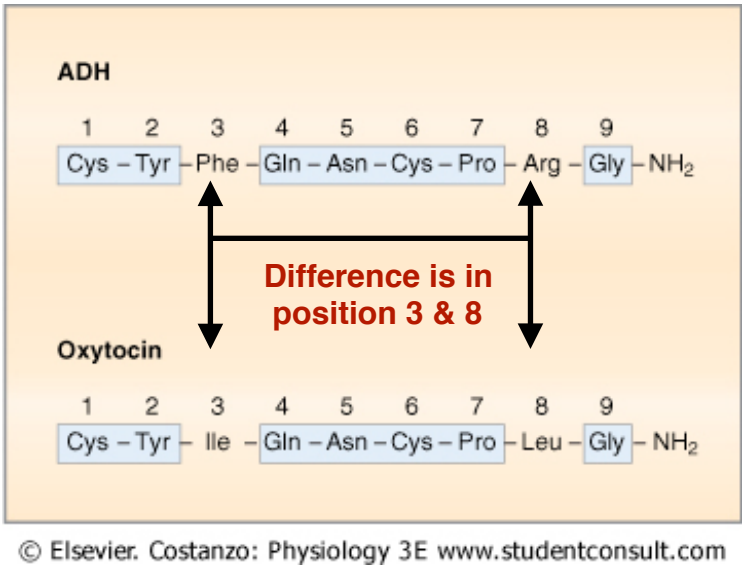
Once synthesized in the cell bodies, the hormones (neuropeptides) are transported down the axons in neurosecretory vesicles and stored in bulbous nerve terminals in the posterior pituitary.

When the cell body is stimulated, the neurosecretory vesicles are released from the nerve terminals by exocytosis, and the secreted hormone enters the nearby capillaries.

Venous blood from the posterior pituitary enters the systemic circulation, which delivers the hormones to their target tissues.



Posterior pituitary hormones:



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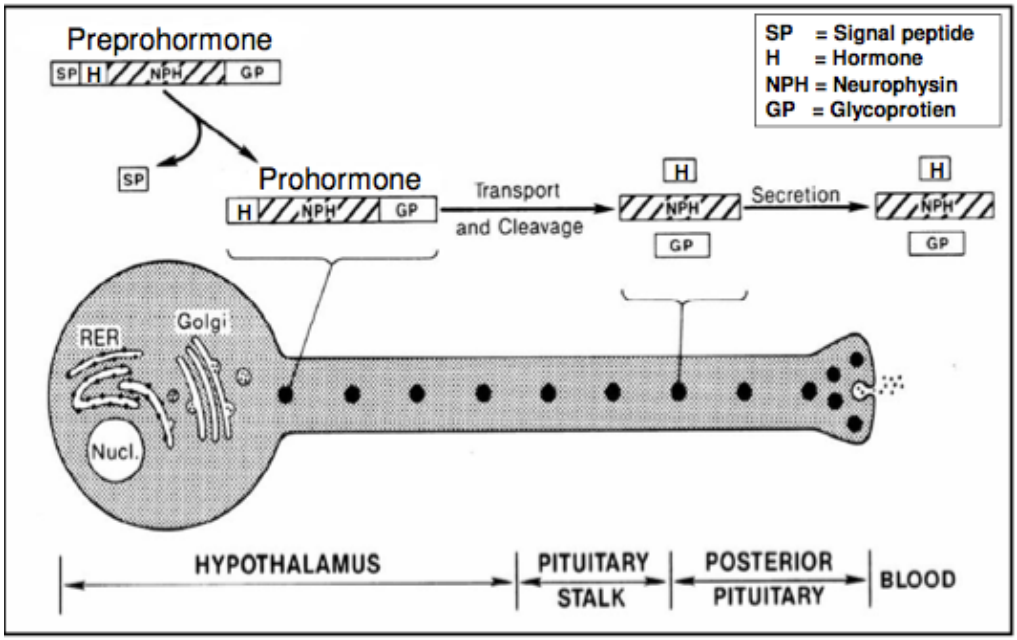
- As you see, they are structurally similar. Therefore, at high doses, one of them may produce the other's effect as a side effect.

- High doses are usually pharmacological not physiological

Synthesis and secretion:



Note:

The peptide precursor for **ADH** is **prepropressophysin,**

which consists of:
a signal peptide,
ADH,
neurophysin **II**,
a glycoprotein.

The precursor for **oxytocin** is **prepro-oxyphysin**,

which comprises
a signal peptide,
oxytocin,
neurophysin **I**.

✦ **In the Golgi apparatus:**
the signal peptides are removed from the ***preprohormones*** to form ***prohormones*** [**propressophysin** and **pro-oxyphysin**],
and the prohormones are packaged in secretory vesicles.

✦ The secretory vesicles, containing the ***prohormones***, then travel down the axon of the neuron, through the hypothalamic-hypophysial tract, to the posterior pituitary.

✦ In route to the posterior pituitary, the neurophysins are cleaved from their respective prohormones within the secretory vesicles.

OXYTOCIN

- **Source Hypothalamus (Primarily Paraventricular Nucleus)**
- **Released from Posterior Pituitary (**also little amounts from **Gonads, Adrenal Cortex, Thymus)**
- **Chemistry Peptide 9 aa**
- **Half Life 6-20 min [**short**]**
- **Daily Output**
- **Basal Levels 1-10 pg/ml**
- **Pattern of Secretion Synchronous high frequency discharge.**

Synchronous = only when needed [e.g. labor]
High frequency = multiple times

• Actions:

- **Breast-feeding**
  - contracts the myoepithelial cells of the alveoli
    - (classic neuroendocrine reflex)
- **Childbirth** (parturition)
  - in late pregnancy, uterine smooth muscle (myometrium) becomes sensitive to oxytocin
  - (positive feedback)
- **Establishment of maternal behavior .**
- **Facilitate Sperm transport in Female Genital Tract**
- **Increased Contraction of Vas Deferens (Ejaculation)**

This action of oxytocin is the basis for its use in: - Inducing labor
-Reducing postpartum bleeding

• Mechanism of Actions: **Phospholipase C mechanism** through Ca\IP3 to cause Ca influx and releasing Ca from endoplasmic reticulum leading to contraction.

• Regulation of Secretion:

Table 9-7. Factors Affecting Oxytocin Secretion

Stimulatory Factors	Inhibitory Factors
Suckling	Opioids (endorphins)
Sight, sound, or smell of the infant	
Dilation of the cervix	Alcohol
Orgasm	

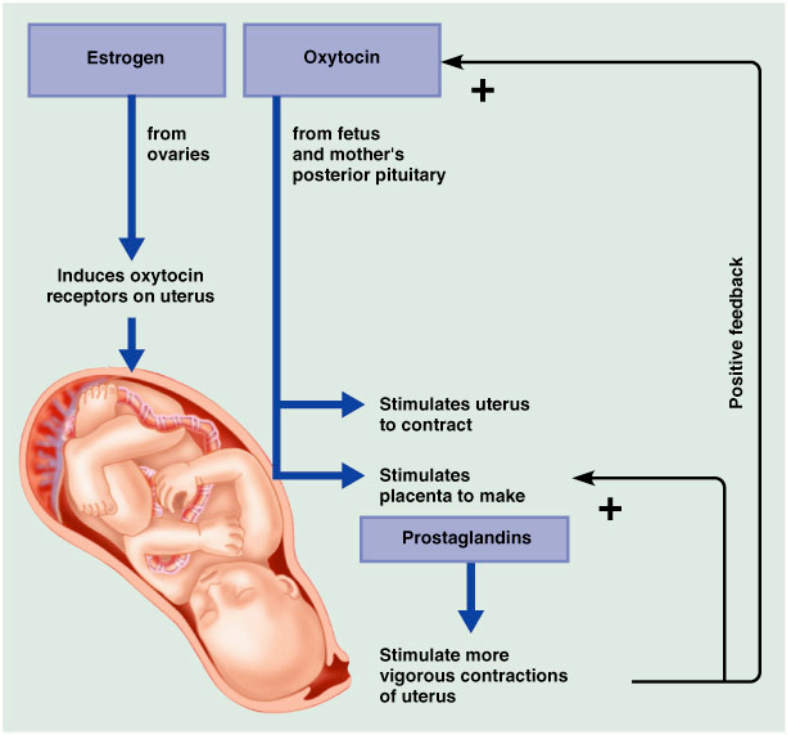
➡ ***Positive feedback mechanism during labor:***

When the fetus head reaches the cervix it stretches it causing activation of mechanoreceptors which send signals to hypothalamus >> secretion of oxytocin >>

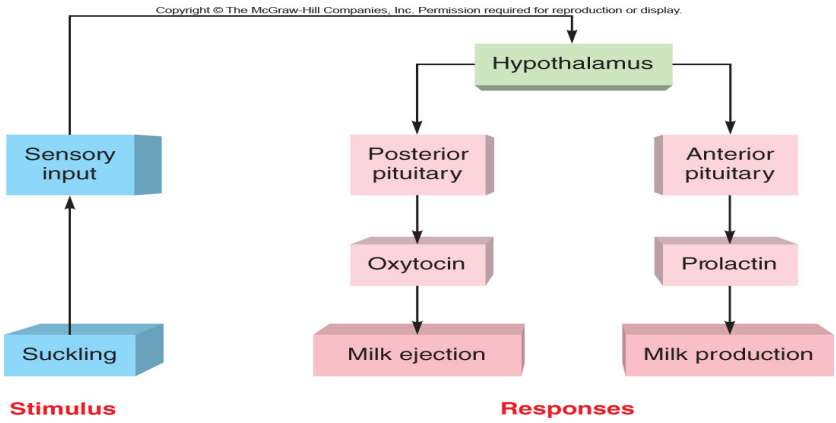
More oxytocin << Further activation of mechanoreceptors <<

① synthesis of prostaglandins

② increase rhythm and strength of contractions



➡ ***Suckling reflex:***



Antidiuretic hormone [ADH]

- **Also called Vasopressin**
- **Source Hypothalamus Posterior Pituitary (Primarily SupraOptic Nucleus)**
- **Released from Posterior Pituitary (**also little amounts from **Gonads, Adrenal Cortex)**
- **Chemistry Peptide 9 aa**
- **Half Life 2-3 minutes [short]**
- **Basal Levels 1pg/ml**
- **Transport Neurophysins**
- **Pattern of Secretion Initial steady increase in discharge**
- **Prolonged Phasic Bursting**

	Water retention [Antidiuretic effect]	Vasoconstriction
Site of Action	The **principal cells** of late **distal tubule and collecting duct.**	vascular smooth muscle
Receptor	**V2 receptors** which is coupled to adenyl cyclase via a Gs protein.	**V1A receptor** which is coupled to phospholipase C via a Gq protein.
Mechanism of Action	The second messenger: **cAMP**, which, via phosphorylation steps, directs the insertion of water channels, **aquaporin 2 (AQP2)**, in the luminal membranes.	The second messenger: **IP3/Ca2+**, which produces contraction of vascular smooth muscle, constriction of arterioles, and increased total peripheral resistance.

Vasoconstriction is achieved at higher levels [doses]

- **Actions:**

- Other actions:

-Glycogenolysis in Liver (V1A receptors)
-Neurotransmitter in brain & spinal cord
-Lowers body temperature
-Facilitate memory Consolidation & Retrieval
-V1B receptors are unique to anterior pituitary and mediate increased ACTH secretion

MECHANISM OF ACTION OF ADH: ANTIDIURESIS

ADH binds to V2 receptors on the peritubular(serosal) surface of cells (principle cells) of the distal convoluted tubules and medullary collecting ducts.

Via adenylate cyclase/cAMP induces production and insertion of aquaporin2 into the luminal membrane and enhances permeability of cell to water.

Increased membrane permeability to water permits back diffusion of solute-free water, resulting in increased urine osmolality (concentrates urine).

• **Regulation of Secretion:**

Osmotic stimuli

↑ **plasma osmolarity** is sensed by osmorecptors in hypothalamus

↑ ADH secretion

↓ urine output

restore plasma osmolarity

✳ ADH secretion is very sensitive to changes in osmolality.

✳ Increased plasma osmolarity is the most important stimulant

Non-Osmotic stimuli

Hypovolemia and hypotension is sensed by "baroreceptors" --

carotid and aortic baroreceptors, and stretch receptors in left atrium and pulmonary veins.

↑ ADH secretion

↓ urine output

restore plasma volume and blood pressure

✳ Normally, pressure receptors tonically inhibit ADH release.

✳ Sensitivity to baroreceptors is less than osmoreceptors– senses 5 to 10% change in volume

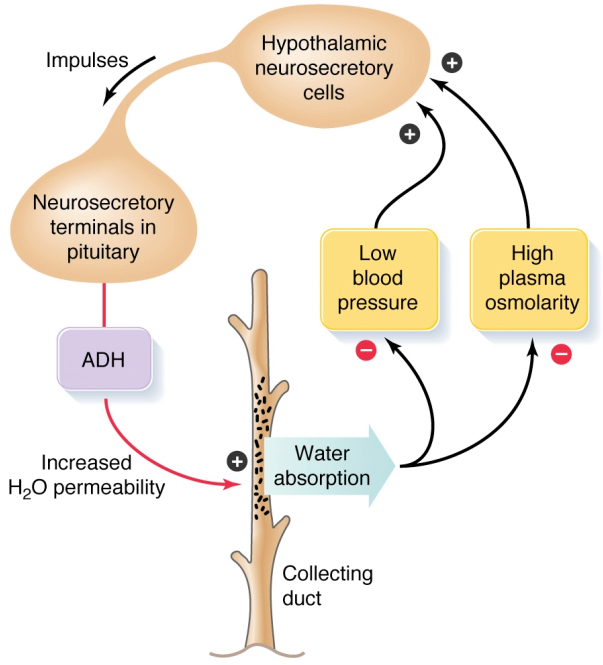


Table 28–2

Regulation of ADH Secretion

Increase ADH	Decrease ADH
↑ Plasma osmolarity ↓ Blood volume ↓ Blood pressure	↓ Plasma osmolarity ↑ Blood volume ↑ Blood pressure
Nausea Hypoxia	
Drugs: Morphine Nicotine Cyclophosphamide	Drugs: Alcohol Clonidine (antihypertensive drug) Haloperidol (dopamine blocker)

Alcohol inhibit ADH that why they cause diuresis [frequent urination]

Receptors	Osmoreceptors	Baroreceptors
Location	Anterolateral hypothalamus	Carotid sinus & aortic arch
Value Measured	Plasma osmolality	Circulating volume
ADH Release Stimulated By	Activation of receptor	Suppression of receptor
Change Required for Action	1% above 280 mosm/kg	10-15% decrease
Resulting Amount of ADH	Small	Large (vasoconstriction)
Override Other?	no	yes

DISORDERS OF URINARY CONCENTRATING ABILITY

①Diabetes insipidus ② SIADH

DIABETES INSIPIDUS (DI):

- DI is a disorder resulting from deficiency of anti-diuretic hormone (ADH) or its action and is characterized by the passage of copious amounts of dilute urine.
- It must be differentiated from other polyuric states such as primary polydipsia & osmotic duiresis.
- Types of DI:

- **Central DI is due to failure of the pituitary gland to secrete adequate ADH**
  - **Defect in hypothalamus**
  - **Defect in pituitary stalk**
  - **Defect in posterior pituitary**

- **Nephrogenic DI results when the renal tubules of the kidneys fail to respond to circulating ADH.**

In this condition, renal tubules are resistant to normal or high levels of plasma vasopressin
Cause: abnormality in the vasopressin-2 receptor, or as an autosomal post-receptor defect in an ADH-sensitive water channel, aquaporin-2

- Causes of DI:

-Tumors

  - Lung cancer, leukemia, lymphoma most common

-Head trauma

-Post-neurosurgery

-Idiopathic – 30-50%

  - Pituitary atrophy, possible autoimmune

-Congenital

  - Mutations of ADH gene, usually autosomal dominant

-Infiltrative diseases, such as Histiocytosis X or sarcoidosis

-

-Acquired

-Drugs: lithium, amphotericin, gentamicin, loop diuretics

-Electrolyte disorders: hypercalcemia, hypokalemia

-Renal disease: obstructive uropathy, chronic renal failear , polysystic kidney, post-transplant, pyelonephritis

-Systemic processes: sarcoid, amyloid, multiple myeloma, sickle cell disease, pregnancy

-Congenital – rare

-Present in 1st week of life

-V2 ADH receptor defect – X-linked recessive

-AQP2 water channel defect – not respond to ADH

- Symptoms and signs of DI:

1. **Polyuria** > 3 liters in 24 hrs
2. Sudden onset more typical of central DI
3. Nocturia
4. Polydipsia
5. **Dilute urine**, urine osm < 200
6. Anorexia, constipation
7. Serum **Na** > 150 **[high]**, rare if patient drink enough water
8. **Dehydration** when patient doesn't drink enough water
9. Hyperthermia & lack of sweating
10. Rapid heart rate
11. Weight loss

Complications of DI:

1.Diabetes insipidus can cause dehydration which can cause:

a)Dry mouth
b)Muscle weakness
c)Hypotension (low blood pressure)
d)Sunken appearance of the eyes

2.Diabetes insipidus can also cause an electrolyte imbalance:

a)Hypernatremia
b)Hyperchloremia

3.Electrolyte imbalance can cause

a)Headache
b)Fatigue
c)Irritability and muscle pains

4.Seizure secondary to Hypernatremia can happen

Diagnosis of DI:

- **High or high-normal plasma osmolality**
- **low urine osmolality**
- **High 24-h urine volumes**
- **Water-deprivation test: patient is deprived of water and serum osmolality is measured:**

Normally:

- Serum osmolality remains within normal range (275–295 mOsm/kg).

- Urine osmolality rises to > 600 mOsm/kg.

in DI:

- Serum osmolality rises above normal

- Urine osmolality is low.

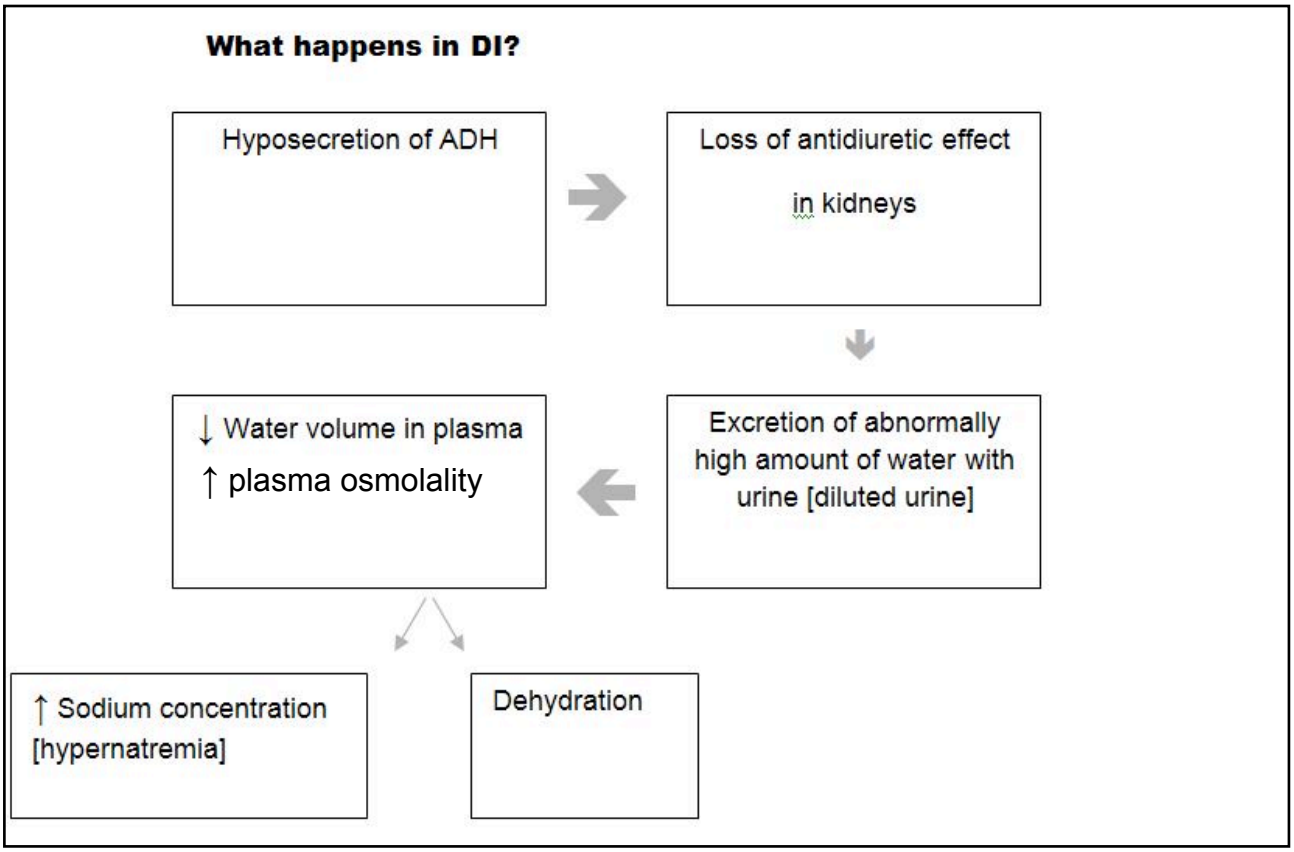
• To defferentiate between central and nephrogenic, use desmopressin therapy;
*** if no response nephrogenic,**
*** if there's response central.**

Treatment:

Desmopressin
Desamino-desarginino-vasopressin(DDAVP)
V2-selective analogue
Little V1 (vasoconstrictor) activity
Drug of choice in Diabetes insipidus [only in central DI]

Administration:

Oral, sub-cut, nasal spray



SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)

- The syndrome of inappropriate secretion of ADH (SIADH) is characterized by
  - Non-physiologic release of ADH [high levels of ADH]
  - Impaired water excretion with normal sodium excretion
- SIADH is associated with disease that affect osmoreceptor in the hypothalamus

- Causes of SIADH:
  - Cancer - Many tumors.
  - **Most common is small cell cancer of the lung [ADH-secreting tumors]**
  - Brain –
    - Meningitis
    - Cerebral abscess
    - Head injury
    - Tumors
  - Lung
    - pneumonia
    - Tuberculosis, lung abscess
  - Metabolic
  - Drugs

Manifestations :

SIADH is characterized by:

- **Fluid retention**
- **Serum hypo-osmolarity**
- **Dilutional hyponatremia**
- Hypochloremia
- **Concentrated urine** in the presence of normal or increased intravascular volume
- Normal renal function
- Hyponatremia and hypo-osmolarity lead to **acute edema of the brain cells**
- An increase in brain water content of more than 5-10% is incompatible with life

Body loses sodium and keeps water in large amounts >> sodium get diluted in water.

Symptoms and signs of SIADH:

Symptoms are

- Headache
- Nausea & Vomiting
- Impaired consciousness
- Neurological signs **(due to severe hyponatremia)**
  - Drowsiness
  - Disorientation
  - Delirium
  - **Seizures**
- Coma & death (severe cases)

Recall that cells in hypotonic solution swell and burst.

Comparison between the two conditions:

	Diabetes Insipidus	**SIADH**
ADH	Low ADH	High ADH
Urine	High amount of hypoosmolar [diluted] urine	Low amount of hyperosmolar [cosentreated] urine
Plasma	↑ plasma osmolality	↓ plasma osmolality
Complications	Dehydration & Hypernatremia	Edema & Hyponatremia