Physiology Team 439

MED439
KING SAUD UNIVERSITY

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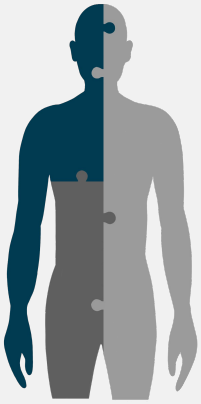


Posterior Pituitary gland

Objectives:

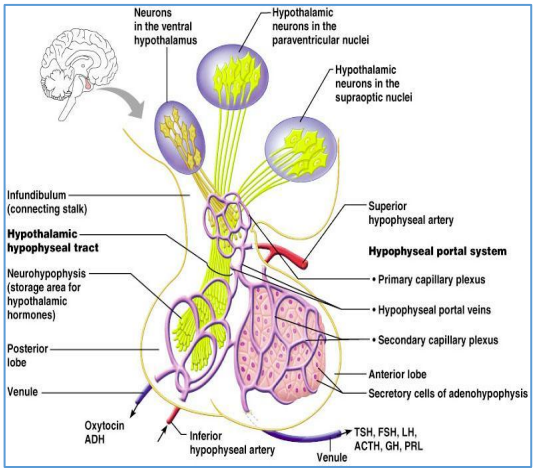
- Describe the posterior pituitary relationship with the hypothalamus
- List the target organs and functional effects of oxytocin.
- Name the stimuli for oxytocin release in relation to its reproductive and lactation functions.
- List the target cells for ADH and explain why ADH is also known as vasopressin.
- Describe the stimuli and mechanisms that control ADH erection.
- Identify disease states caused by a) over-secretion, and b) under-secretion of ADH and list the principle symptoms of each.

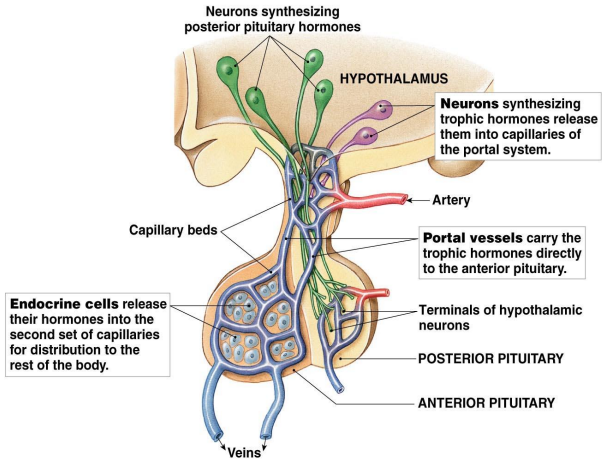
Color index:

- Important.
- Girls slide only.
- Boys slide only.
- Dr's note.
- Extra information.

Editing File

Pituitary (Hypophysis)





Pituitary is connected with hypothalamus by two ways

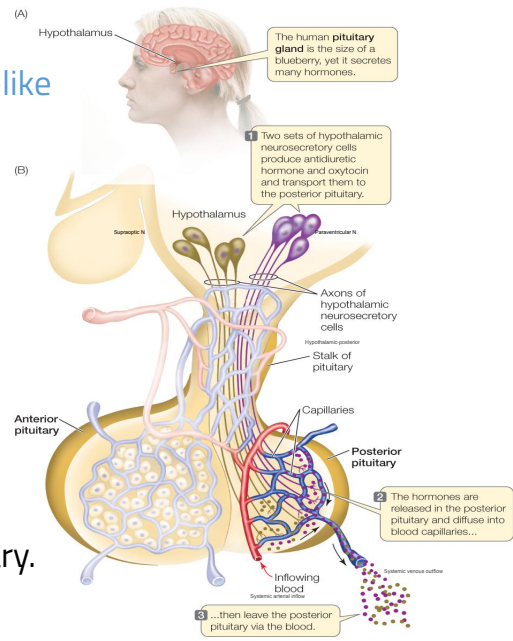
1) with adenohypophysis by hypophyseal portal system which receive inhibiting or releasing hormones from infundibulum or medial eminence to their target cells.
2) And with neurohypophysis through hypothalamic hypophyseal tract -neural connection- to store hormones. If there's cut surgically or by accident in stalk hormones will still be produced (ADH, Oxytocin).

The Posterior Pituitary and Hypothalamic Hormones

- The posterior lobe is a downgrowth of hypothalamic neural tissue embryologically originating from the hypothalamus
- The posterior pituitary gland is Composed mainly of glial-like cells called pituicytes. (Glial like cells are supportive cells to the neurons).

  Brain cancer **can** happen to glial cells because they divide)
- Has a neural connection with the hypothalamus (hypothalamic-hypophyseal tract)
- Nuclei of the hypothalamus synthesize oxytocin and antidiuretic hormone (ADH)
- Their axons pass through the pituitary stalk to the neurohypophysis and terminate in the posterior pituitary.

  hormones are stored there until they are released into the circulation
- Posterior pituitary does not synthesize hormones
- Consists of axon terminals of hypothalamic neurons



Oxytocin and vasopressin

ADH

1 2 3 4 5 6 7 8 9

Cys – Tyr – Phe – Gln – Asn – Cys – Pro – Arg – Gly – NH_2

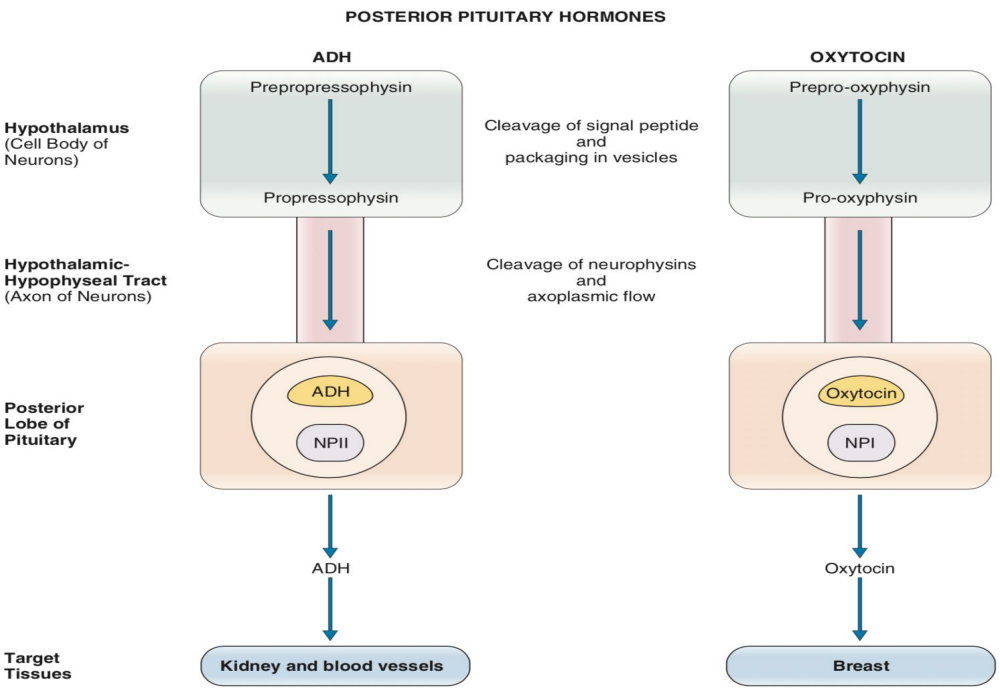
Oxytocin

1 2 3 4 5 6 7 8 9

Cys – Tyr – Ile – Gln – Asn – Cys – Pro – Leu – Gly – NH_2

They are peptides hormones
Note that these two hormones are almost identical except that in vasopressin, phenylalanine and arginine replace isoleucine and leucine of the oxytocin molecule. This similarity of the molecules explains their partial functional similarities.

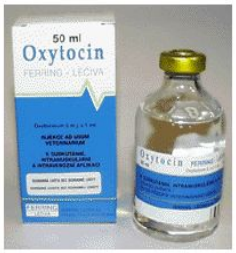
Extra:



Secretion is initiated when an action potential is transmitted from the cell body in the hypothalamus, down the axon to the nerve terminal in the posterior pituitary. When the nerve terminal is depolarized by the action potential, Ca_{2+} enters the terminal, causing exocytosis of the secretory granules containing ADH or oxytocin and their neurophysins. The secreted hormones enter nearby fenestrated capillaries and are carried to the systemic circulation, which delivers the hormones to their target tissues.

Oxytocin

Synthesis of oxytocin

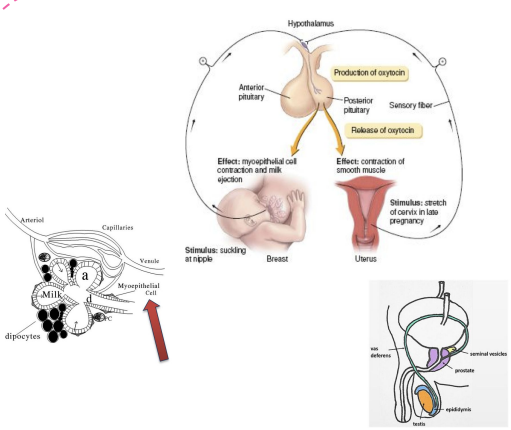


- Oxytocin is synthesized in the cell bodies of hypothalamic neurons (paraventricular nucleus) and some are synthesized from the Supraoptic nucleus.
- Oxytocin is stored in the posterior pituitary, in the distal nerve terminal (Herring bodies)

Function of oxytocin

- Oxytocin is a strong stimulant of uterine contraction
- Regulated by a positive feedback mechanism (more opening of cervix->more release of oxytocin)
- This leads to increased intensity of uterine contractions, ending in birth
- Oxytocin triggers milk ejection (**not production**) the milk is already synthesized by prolactin ("letdown" reflex) Contracts the myoepithelial cells of the alveoli in mammary glands
- Increases contraction of smooth muscle of the vas deferens, helping in the ejaculation process.(increase during sexual arousal)
- So, Myometrial and Myoepithelial cells both contract in response to Oxytocin.

(The **myometrium** is the middle layer of the uterine wall)



-Oxytocin is synthesized in the hypothalamus and stored in the posterior pituitary gland
-Release of oxytocin will cause :
1-uterine muscle contraction until childbirth occurs (positive feedback).
2- contraction of myoepithelial cells, which are located around the mammary glands and that will cause milk release (letdown reflex).
3- contraction of vas deferens which helps in ejaculation

Antidiuretic Hormone (ADH) (vasopressin)

Synthesis of ADH

It is synthesized as pre-prohormone same as insulin and processed into a nonapeptide (9 amino acids)

- ADH synthesized in the cell bodies of hypothalamic neurons(supraoptic nucleus) and some are synthesized from the paraventricular nucleus.
- ADH is stored in the posterior pituitary

Receptors of ADH (vasopressin)

There are 2 types of receptors for ADH: (G protein coupled receptors)

- V1 (found in blood vessels) , there are Two types: V1a (vasoconstriction) V1b (corticotrophs) , so both CRH and ADH both induce ACTH release ,but of course CRH is far more imp.
- V2 (found in principle cells in kidneys)

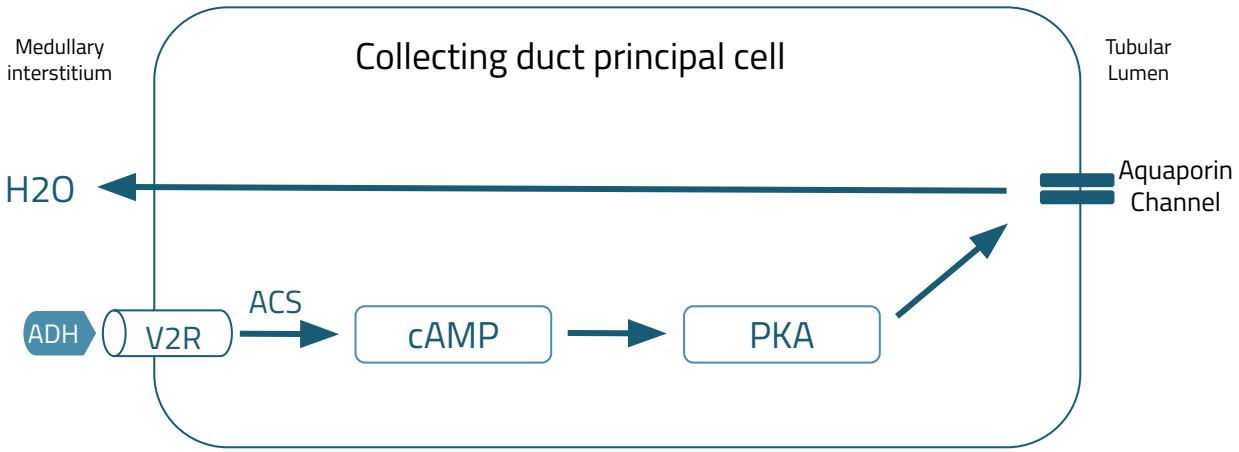
V1 receptors mediate vasoconstriction
V2 receptors are located in the principle cells in distal convoluted tubule and collecting ducts in the kidneys. We have 2 kidneys (V2)

**In the absence of ADH

- The collecting tubules and ducts become almost impermeable to water Which allows extreme loss of water into the urine
- When ADH binds to its receptor, it activates the translocation of vesicles containing aquaporins to the apical cell membranes

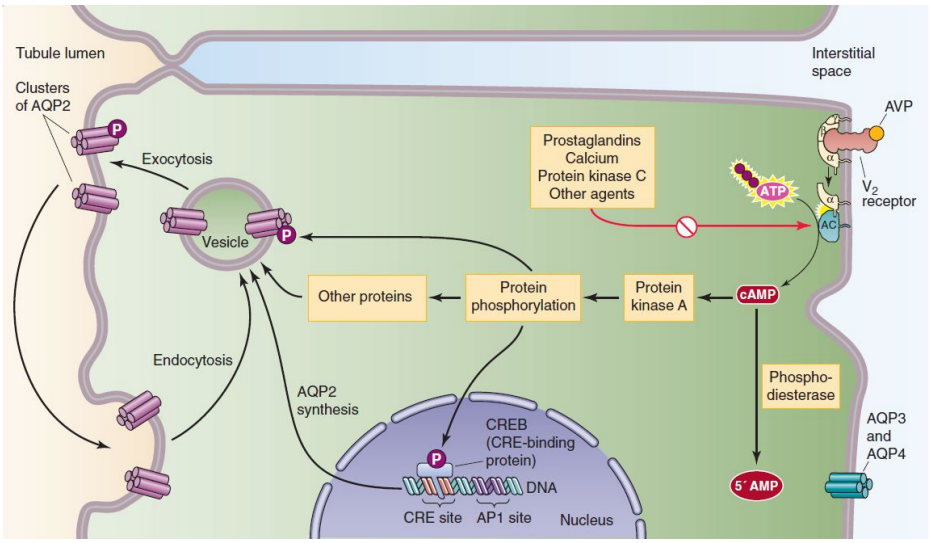
Antidiuretic Hormone (ADH) (vasopressin)

Mechanism of Actions of ADH



ADH is a peptide hormone its receptor (V2R) is present on the cell membrane. Through a second messenger it stimulates the aquaporin channel for water uptake to increase blood volume and arterial blood pressure

Mechanism of Actions of ADH



Binding of AVP (ADH) to V2 will activate adenylyl cyclase (AC) which makes cAMP that'll activate Protein kinase A, this'll lead to phosphorylation and the insertion or exocytosis of AQP2 and water from the luminal side will enter through it and then throw AQP3 &4 wich are located at the basolateral side.
So, ADH leads to both transcription of AQP2 and exocytosis of already made AQP2.

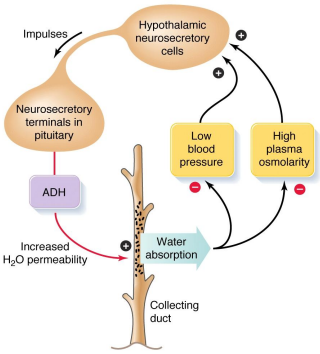
Antidiuretic Hormone (ADH) (vasopressin)

Control of ADH release

Osmotic pressure:

Increased Extracellular Fluid Osmolarity Stimulates ADH Secretion:

- Osmoreceptors in or near the hypothalamus:
- Concentrated solution ↑osmotic pressure →↑ADH secretion
- Dilute solution ↓ osmotic pressure →↓ ADH secretion



Blood volume:

Low Blood Volume and Low Blood Pressure Stimulate ADH Secretion—Vasoconstrictor Effects of ADH:

- Baroreceptor in carotid artery and aortic arch, and left atrium:
- ↑ blood pressure →↓ ADH secretion
- ↓blood pressure → ↑ ADH secretion

Physiological stress: pain, fear, trauma, and stress stimulate ADH release.

The ADH level will rise to prevent diuresis and decrease the number of times going to the bathroom

Regulation of ADH

Hypothalamus receives feedback from:

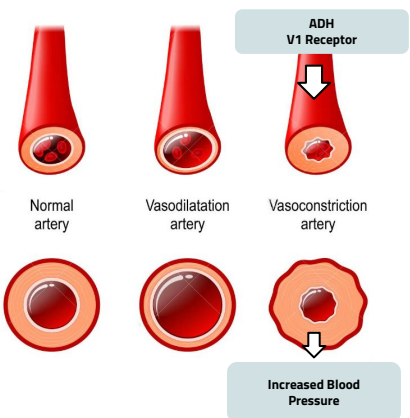
- Osmoreceptors

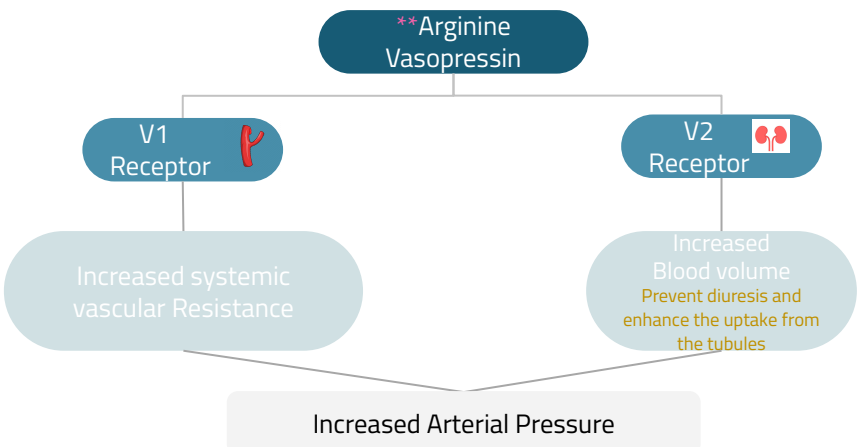
When the extracellular fluid becomes too concentrated, fluid is pulled by osmosis out of the osmoreceptor cell, decreasing its size and initiating appropriate nerve signals in the hypothalamus to cause additional ADH secretion

- Aortic arch baroreceptors
- Carotid baroreceptors
- Atrial stretch receptors

Any increase in osmolality or decrease in blood volume will stimulate ADH secretion from posterior pituitary.This occurs strongly when the blood volume decreases 15 to 25 percent or more

Effect on Blood vessels





Antidiuretic Hormone (ADH) Disorders

1

Diabetes Insipidus:

Is a disorder resulting from deficiency of antidiuretic hormone (ADH) or its action and is characterized by the passage of copious amounts of dilute urine with no glucose, this is known as Polyuria.
It must be differentiated from other polyuric states such as primary polydipsia, which is a psychiatric disorders where some people drink and excessive amount of water & osmotic diuresis.

Types	Neurogenic (central)	Nephrogenic
Definition	Failure of hypothalamus or neurohypophysis to synthesize or secrete (Producing) adequate ADH. (it's due to block production of ADH in cells resulting from mutation, infection, trauma)	Results when the renal tubules of of the kidneys fail to respond appropriately to circulating ADH . The resulting renal concentration defect leads to the loss of large volumes of dilute urine. This causes cellular and extracellular dehydration and hypernatremia. (ADH is normally secreted, but there is either a mutation of V2 receptor or the kidney is diseased)
ADH levels	Low	Normal or high
Treatment	Desmopressin (DDAVP) is a synthetic analog that is superior to native Arginine vasopressin (AVP). (taken as a nasal spray or I.V.) BECAUSE: ▪ It has longer duration of action(8-10 h vs 2-3 h) ▪ More potent, its Antidiuretic activity is 3000 times greater than Its pressor activity	▪ Correction of underlying cause ▪ Provision of adequate fluids & calorie ▪ Low sodium diet, to dcrease diuresis ▪ Diuretics (Thiazide) ▪ High dose of DDAVP

2

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

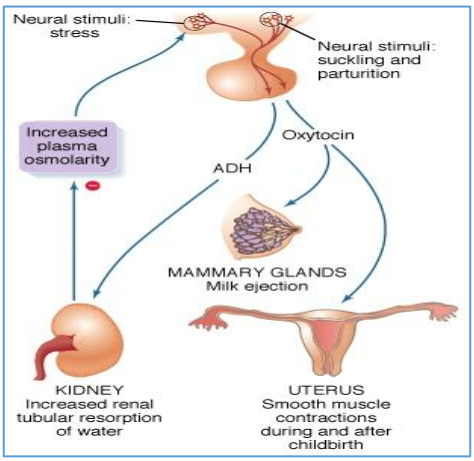
Girls Dr : for your own interest (just read it)

- ↑ ADH levels → water retention → ECF is hypo-osmotic and urine is hyperosmotic.
- Urine volume is low, while its concentration is high.
- It causes Hyponatremia, because water levels are high which leads to Hypo-osmolarity

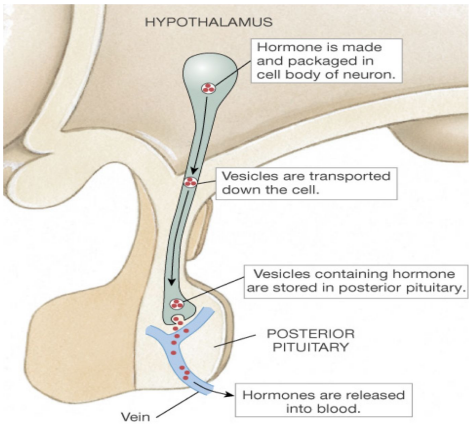
Females slides*	Diabetes Insipidus (DI)	SIADH
ADH	Low	High
Water	Low	Water intoxication → Weight gain
Urine Output	High, polyuria	Low , Oliguria
Sodium	High	Low
serum osmolality	High and high H&H (Hemoglobin and Hematocrit) from dehydration	Low
Risk	Hypovolemic shock	seizures
Treatment	DDAVP (ADH)	Hypertonic saline

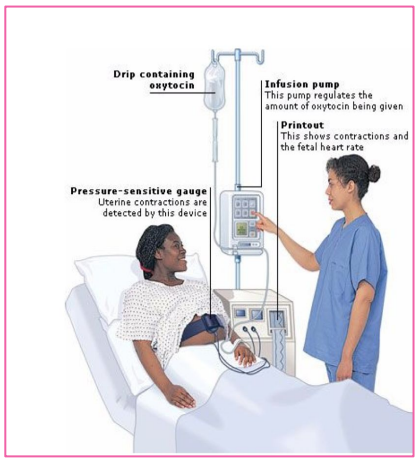
From the slides

Summary of posterior pituitary hormones actions



Secretion pituitary hormones





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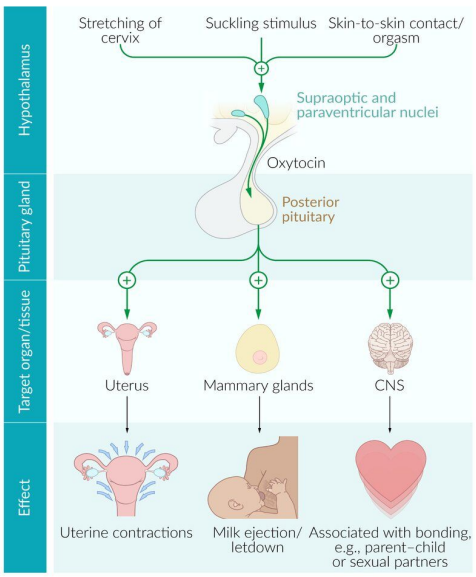

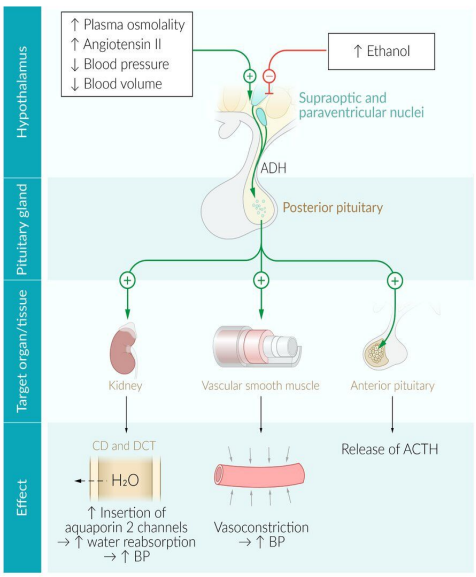

Guyton

BOX 9.1 Clinical Physiology: Syndrome of Inappropriate ADH

DESCRIPTION OF CASE. A 56-year-old man with oat cell carcinoma of the lung is admitted to the hospital after having a grand mal seizure. Laboratory studies yield the following information:

Serum	Urine
$[Na^+]$, 110 mEq/L	Osmolarity, 650 mOsm/L
Osmolarity, 225 mOsm/L	

The man's lung tumor is diagnosed as inoperable. He is treated with an intravenous infusion of hypertonic NaCl and is stabilized and discharged. He is given demeclocycline, an ADH antagonist, and is ordered to severely limit his water intake.

EXPLANATION OF CASE. Upon his admission to the hospital, the man's serum $[Na^+]$ and serum osmolarity are severely depressed (normal serum $[Na^+]$, 140 mEq/L; normal serum osmolarity, 290 mOsm/L). Simultaneously, his urine is hyperosmotic, with a measured osmolarity of 650 mOsm/L. In other words, his urine is *inappropriately* concentrated, given his very dilute serum osmolarity.

Independent of the posterior pituitary, the oat cell carcinoma synthesized and secreted ADH and caused the abnormal urine and serum values. Normally, ADH is secreted by the posterior lobe of the pituitary, which is under negative-feedback regulation by serum osmolarity. When the serum osmolarity decreases below normal, ADH secretion by the posterior pituitary is inhibited. However, ADH secretion by the tumor is not under such negative feedback regulation, and ADH secretion continues unabated (no matter how low the serum osmolarity) and causes SIADH.

The man's serum and urine values are explained as follows: The tumor is secreting large amounts of ADH (inappropriately). This ADH circulates to the kidney and acts on the principal cells of the late distal tubule and collecting duct to increase water reabsorption. The reabsorbed water is added to the total body water, diluting the solutes. Thus serum $[Na^+]$ and serum osmolarity are diluted by the excess water reabsorbed by the kidney. Although this dilution of serum osmolarity turns off ADH secretion by the posterior pituitary, it does not turn off ADH secretion by the tumor cells.

The man's grand mal seizure was caused by swelling of brain cells. The excess water reabsorbed by the kidney was distributed throughout the total body water including intracellular fluid (ICF). As water flowed into the cells, their volume increased. For brain cells, this swelling was catastrophic because the brain is encased in a fixed cavity, the skull.

TREATMENT. The man is treated promptly with an infusion of hypertonic NaCl to raise the osmolarity of his ECF. As extracellular osmolarity becomes higher than intracellular osmolarity, water flows out of the cells, driven by the osmotic gradient, and decreases ICF volume. For brain cells, the reduction in cell volume decreases the probability of another seizure.

The man's lung tumor is inoperable and will continue to secrete large quantities of ADH. His treatment includes water restriction and administration of demeclocycline, an ADH antagonist that blocks the effect of ADH on water reabsorption in the principal cells.

MCQ & SAQ:

Q1: The hormone involved in the ejection Of milk :

A. GH
B.Prolactin
C. Oxytocin
D. FSH

Q2: Which of the following is true about ADH?

A. It's synthesized in the posterior Pituitary gland
B. It's secreted from the anterior pituitary gland
C. It's mainly synthesized from the supraoptic nuclei
D. It's mainly synthesized from the Paraventricular nuclei

Q3: SIADH characterized by ?

A.Hypernatremia
B. Hypo-osmolarity of ECF
C. Hypotension
D. Hyperchloremia

Q4: Which of the following is false about Oxytocin?

A. Milk formation
B.Milk ejection
C. Uterus contraction
D. Ejaculation

Q5: Which of the following suppresses ADH secretion :

A. Acute hemorrhage
B. Decrease plasma volume
C. Decrease blood pressure
D.Decrease osmotic pressure

Q6: Failure of the kidney to respond appropriately to ADH, represent:

A. Neurogenic DI.
B. Nephrogenic DI.
C. SIADH.
D. Diabetes Mellitus.

answer key:
1: C
2: C
3: B
4: A
5: D
6: B

A 76–year-old man with lung cancer is lethargic and excreting large volumes of urine. He is thirsty and drinks water almost constantly. Laboratory values reveal an elevated serum Ca2+ concentration of 18 mg/dL, elevated serum osmolarity of 310 mOsm/L, and urine osmolarity of 90 mOsm/L. Administration of an ADH analogue does not change his serum or urine osmolarity.

1- The man's serum ADH level is ?

2- what is the cause of the patient's excess urine volume (diagnosis)?

A1: increased because the elevated serum osmolarity has stimulated ADH secretion

The man is excreting large volumes of dilute urine, which has raised his serum osmolarity and made him very thirsty. The increase in serum osmolarity would then cause an increase in serum ADH levels. The fact that exogenous ADH administration did not change his serum or urine osmolarity suggests that the collecting duct of the nephron is unresponsive to ADH. Thirst does not directly increase ADH secretion.

A2: nephrogenic diabetes insipidus

The man's urine osmolarity is very dilute, while his serum osmolarity is increased. In the face of increased serum osmolarity, there should be increased ADH secretion, which should then act on the collecting duct principal cells to increase water reabsorption and concentrate the urine. The fact that the urine is dilute, not concentrated, suggests that ADH either is absent (central diabetes insipidus) or is ineffective (nephrogenic diabetes insipidus). Administration of an exogenous ADH analogue separates these two possibilities—it was ineffective in changing serum or urine osmolarity; thus, it can be concluded that ADH unable to act on the collecting ducts, that is, nephrogenic diabetes insipidus One cause of nephrogenic diabetes insipidus is hypercalcemia, which is present in this patent secondary to his lung cancer; he likely has humoral hypercalcemia of malignancy, due to secretion of PTH-rp by the tumor. Dehydration would cause increased ADH secretion and increased urine osmolarity. Syndrome of inappropriate ADH would cause increased urine osmolarity and subsequently decreased serum osmolarity, due to excess water reabsorption.

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