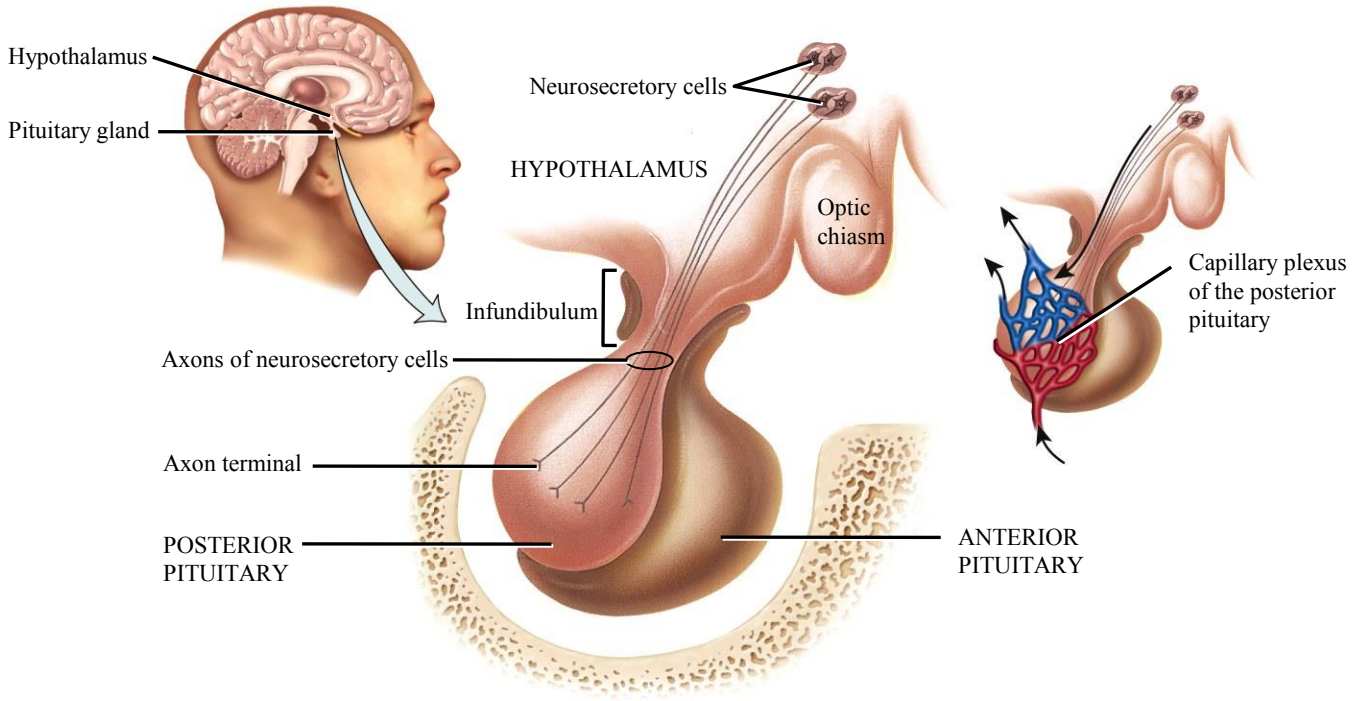
Lecture No 5
Posterior Pituitary Hormone

Zuheir A Hasan
Professor of Physiology
College of Medicine
HU

Posterior pituitary
Review of physiological Anatomy



Posterior pituitary
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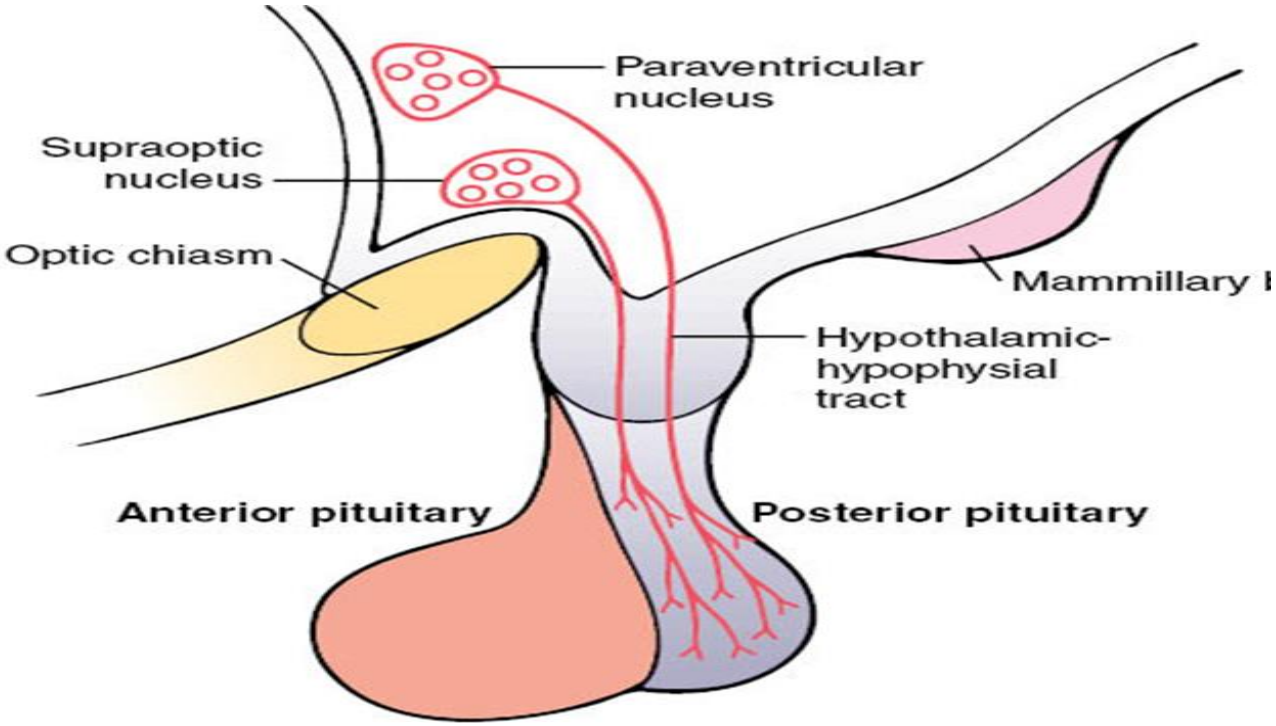
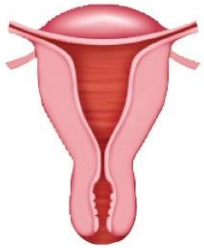
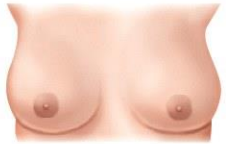


Target organs of ADH and oxytocin

Oxytocin (OT)

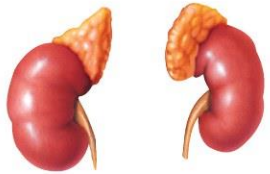


Uterus

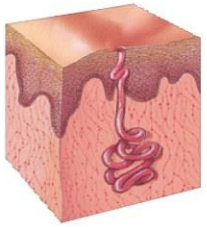


Mammary glands

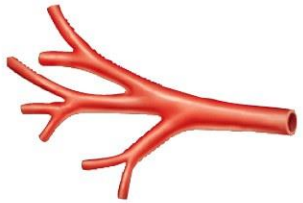
Antidiuretic hormone (ADH) or vasopressin



Kidneys



Sudoriferous (sweat) glands



Arterioles

ADH (vasopressin)

Functions and regulations of secretion

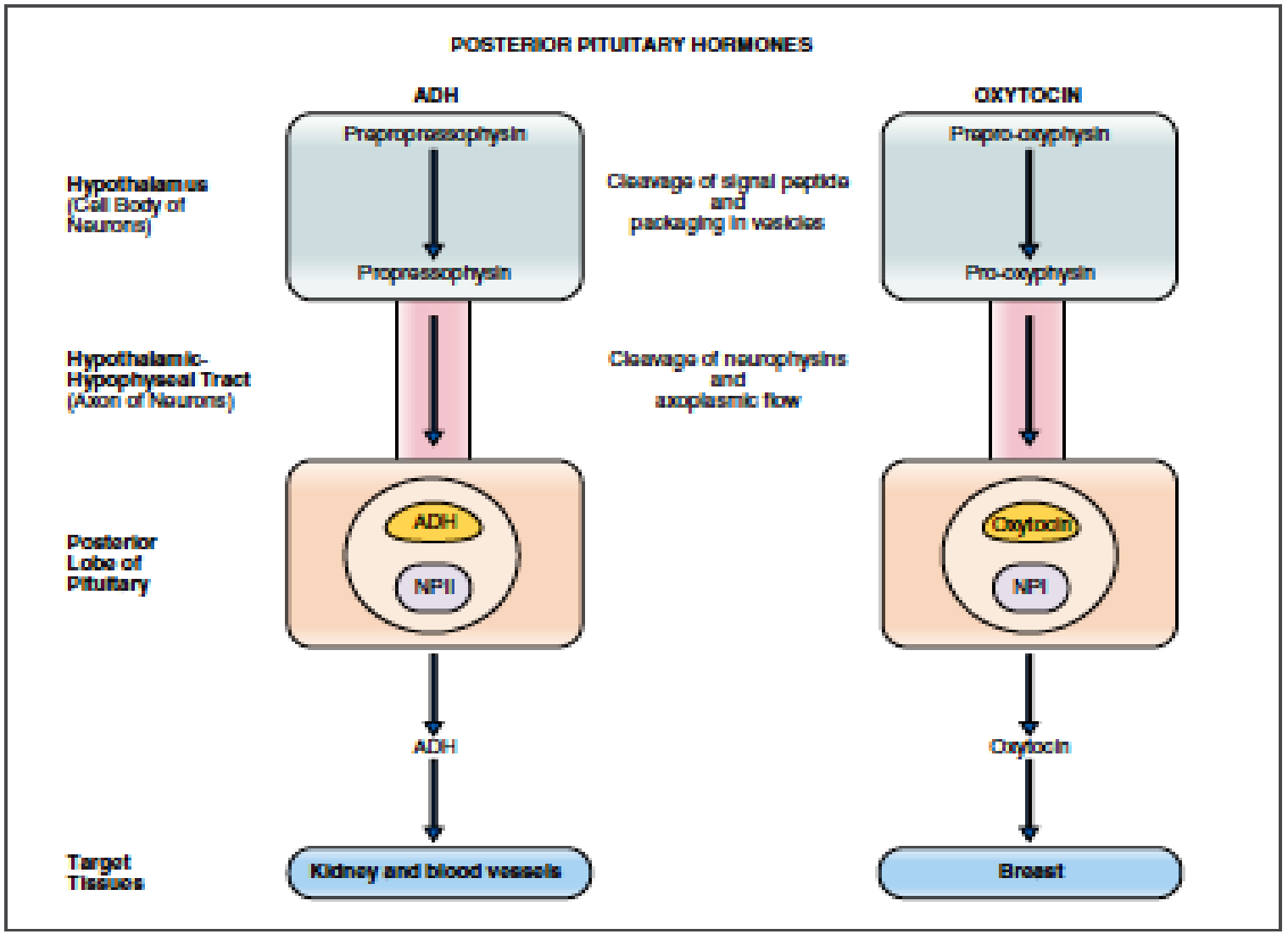
Hormones of the posterior lobe of the pituitary

- The posterior pituitary gland store and release antidiuretic hormone (ADH) and oxytocin.
- **These hormones are synthesized in hypothalamic nuclei**
- Both hormones are packaged in secretory granules with their respective **neurophysins.**
- Both hormones are homologous nonapeptides.
- ADH and oxytocin are synthesized by neurosecretory neurons in the supraoptic (SO) and PVN of the hypothalamus
- Hormones travel down the nerve axons for storage and secretion by the posterior pituitary.
- ADH is the primary hormone secreted by SO nucleus
- Oxytocin is the primary hormone secreted by PVN nucleus

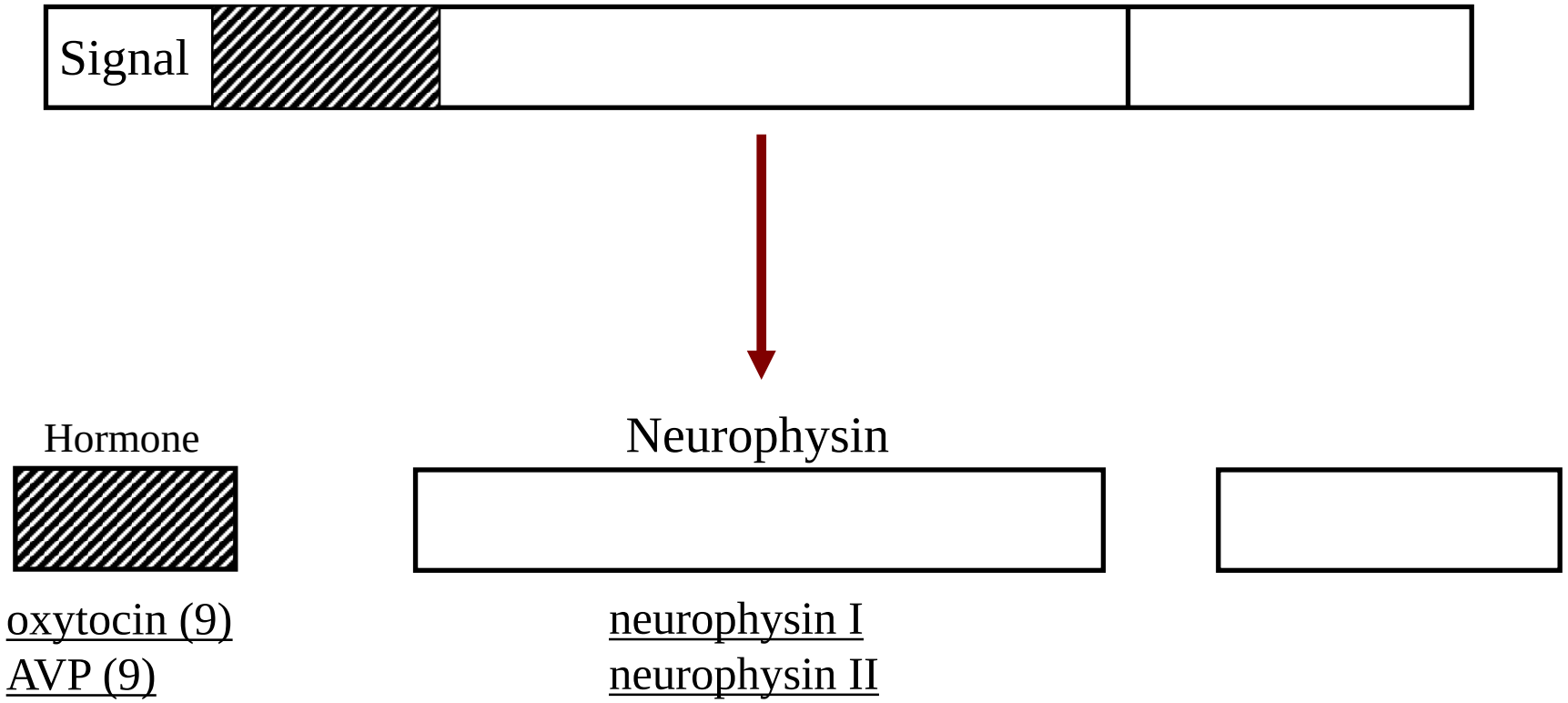
Synthesis, processing, and secretion of antidiuretic hormone (ADH) and oxytocin.

NPI, Neurophysin I;
NPII, neurophysin II.

Prepro-oxyphysin &
Prepropressophysin



Processing of Prepro-oxyphysin & Prepropressophysin



Structure-Activity Relationships for Neurohypophyseal Hormones

Peptide	Oxytocic (O)	Milk Ejection (ME)	Vasopessor (P)	Antidiuretic (A)
Oxytocin	520	475	4	4
Arginine Vasopressin (AVP)	14	70	370	320
Desmopressin (dDAVP)			0.5	955

Oxytocin

1 2 3 4 5 6 7 8 9
Cy-Tyr-Ile-Gln-Asn-Cy-Pro-Leu-Gly-NH_2
S ——————— S

AVP

1 2 3 4 5 6 7 8 9
Cy-Tyr-Phe-Gln-Asn-Cy-Pro-L-Arg-Gly-NH_2
S ——————— S

dDAVP

1 2 3 4 5 6 7 8 9
$(CH_2)_2$-CO-Tyr-Phe-Gln-Asn-Cy-Pro-D-Arg-Gly-NH_2
S ——————— S

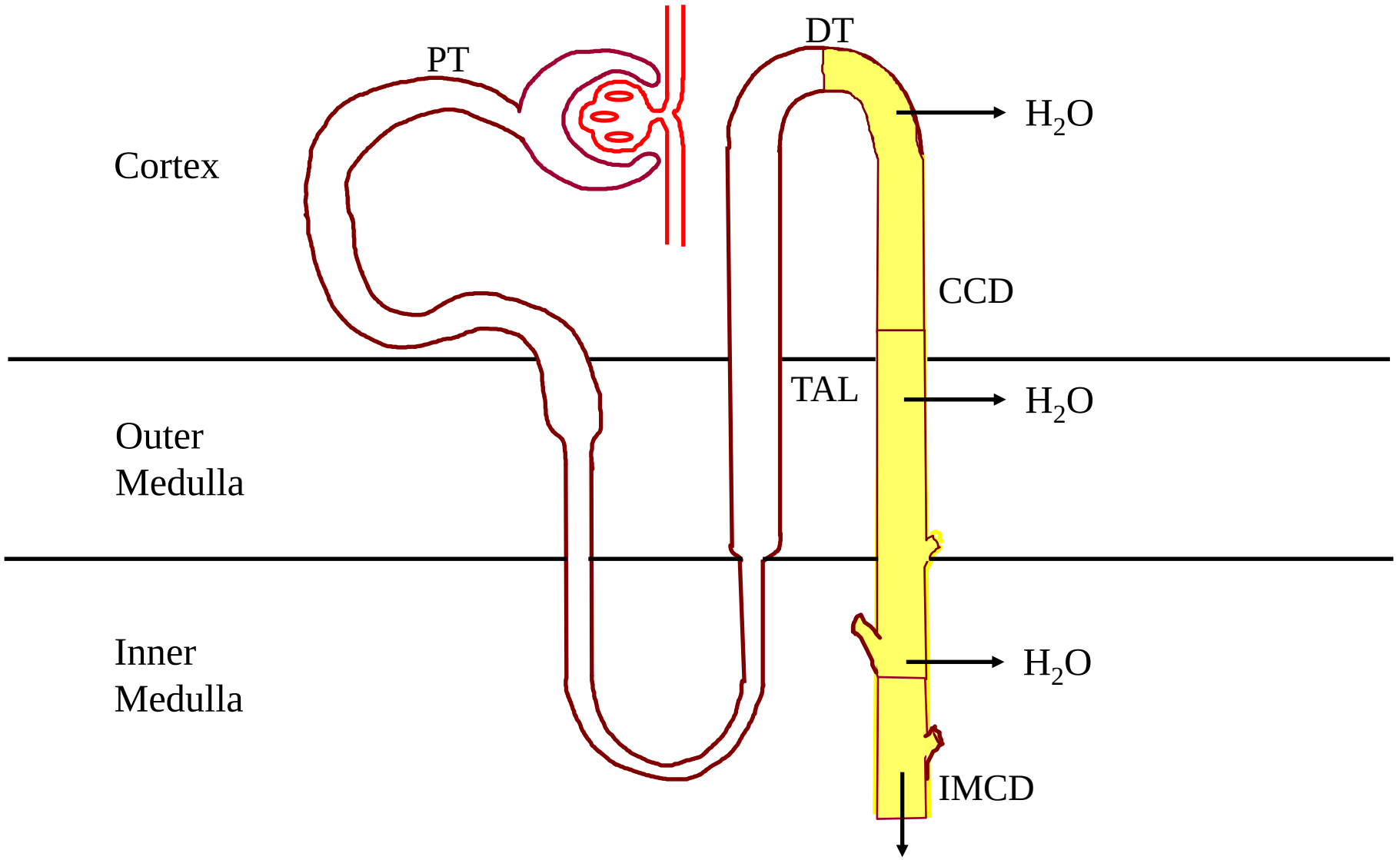
Actions of ADH

Regulates serum osmolarity by increasing the H2O permeability of the late distal tubules and collecting ducts

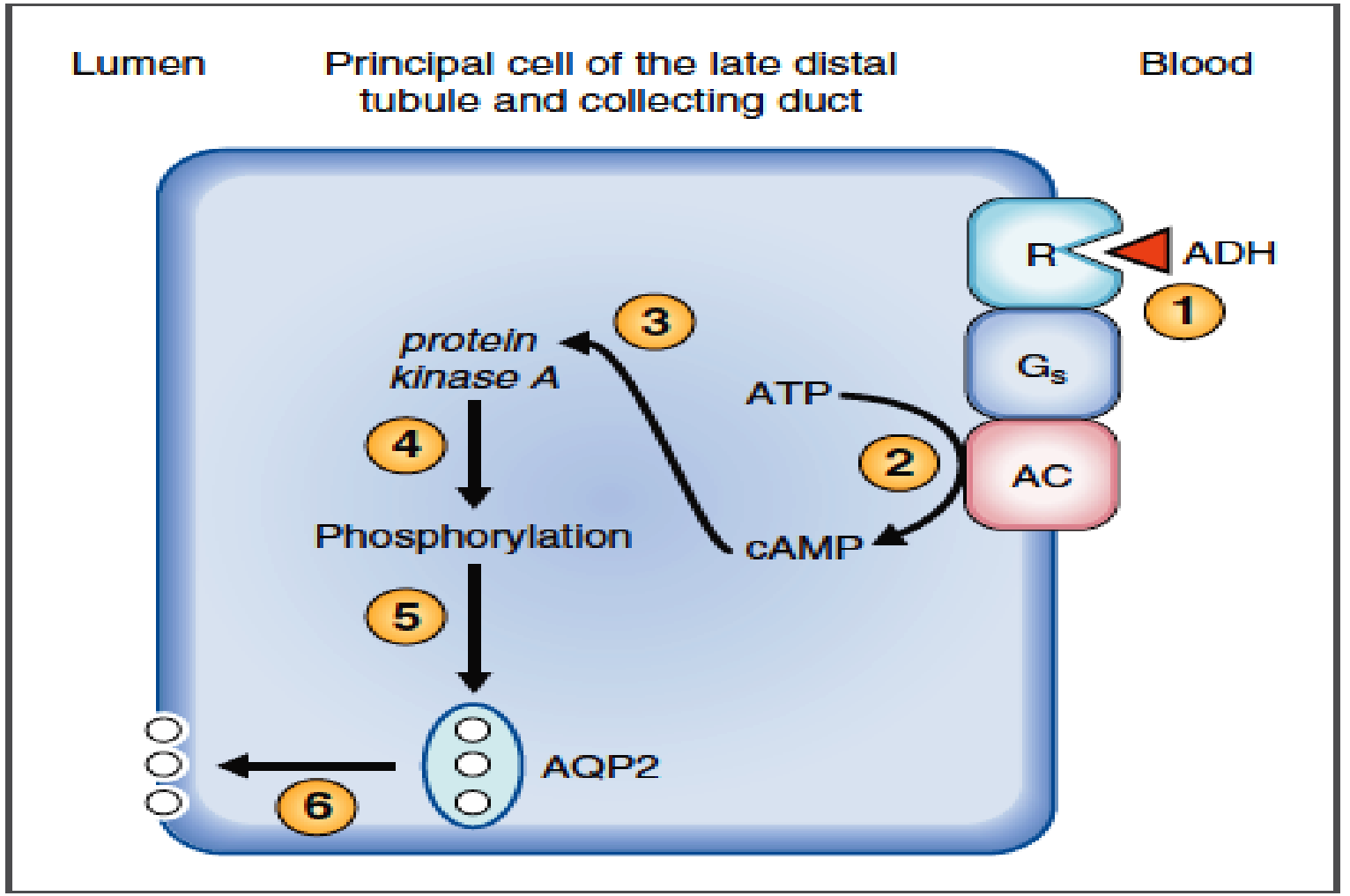
It increases H2O permeability via a V2 receptor and an adenylate cyclase–cAMP mechanism) which increase synthesis of water channels (aquaporin 2, AQP2) of the principal cells of the late distal tubule and collecting duct

Constriction of vascular smooth muscle (via a V1 receptor and an IP3/Ca2+ mechanism). This action increases the TPR

Tubular Effects of AVP



ADH mechanism of action



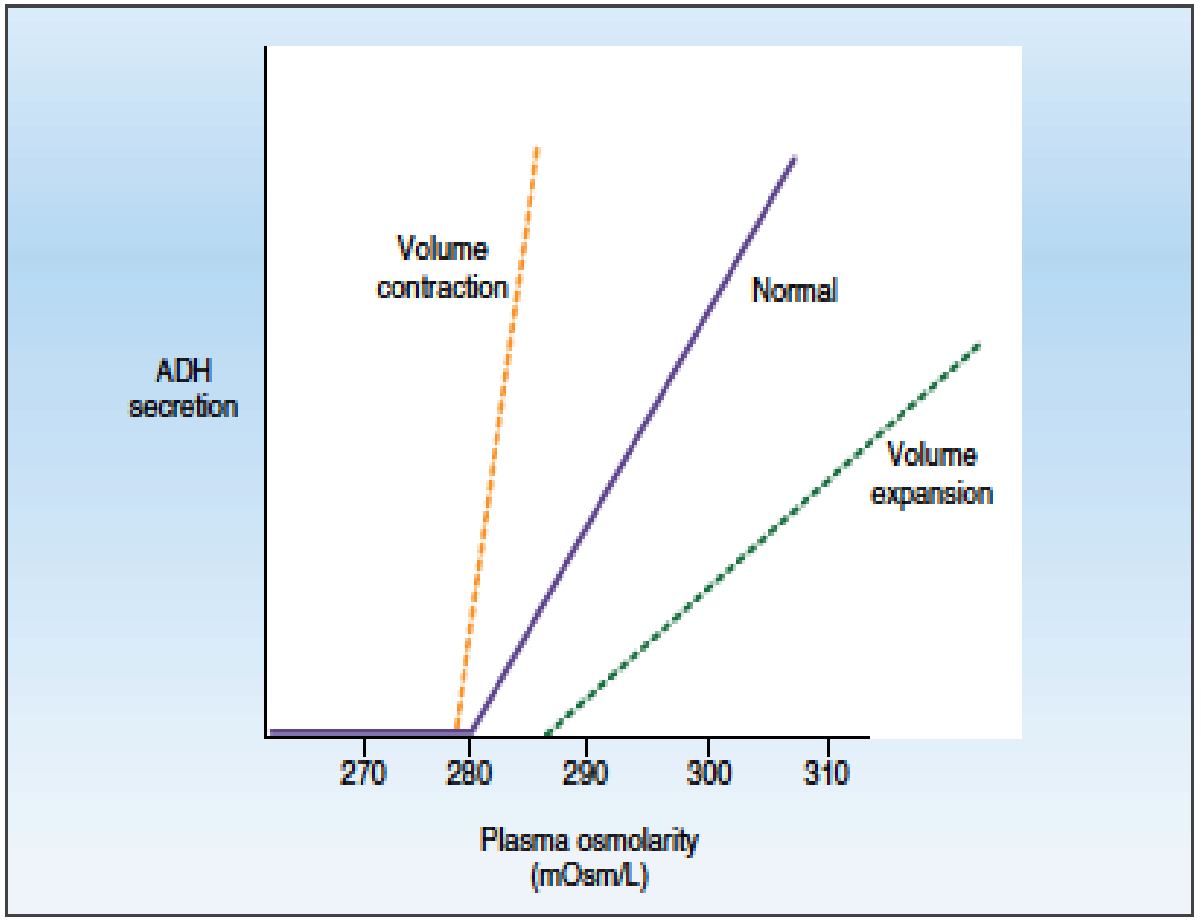
Regulation of ADH secretion

- **Osmoregulation**
- An increase of only 1% in the osmolality of the ECF bathing the hypothalamic osmoreceptors evokes an increased in ADH secretion.
- A similarly sized decrease in osmolality decreases ADH secretion.
- In this manner, ECF osmolality is kept very close to 285 mOsm/Kg.
- Osmoreceptor cells are located in hypothalamus, primarly *in organum vasculosum in the third ventricle*)
- Osmoreceptors are neurons that respond to increased plasma osmolarity, (principally plasma sodium concentration).
- They synapse with neurons of the SO and PVN and stimulates the release of ADH from neurosecretory cells and posterior pituitary
- Osmoreceptors also stimulate thirst hypothalamic centers that regulate water intake.

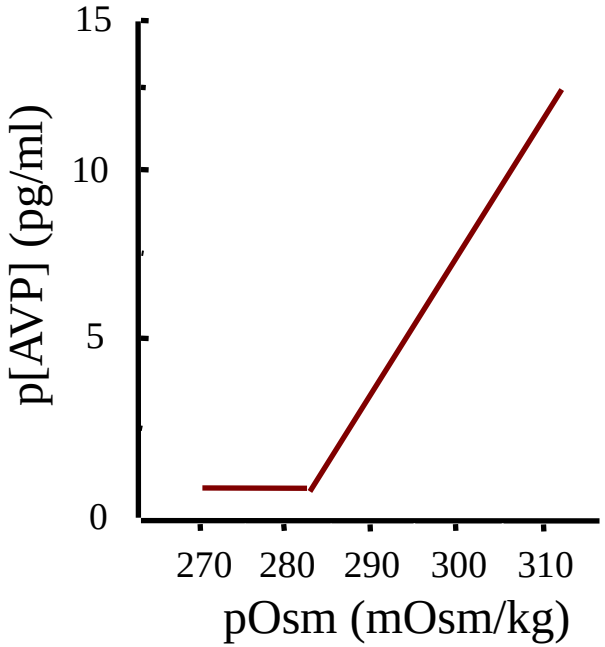
Regulation of ADH secretion

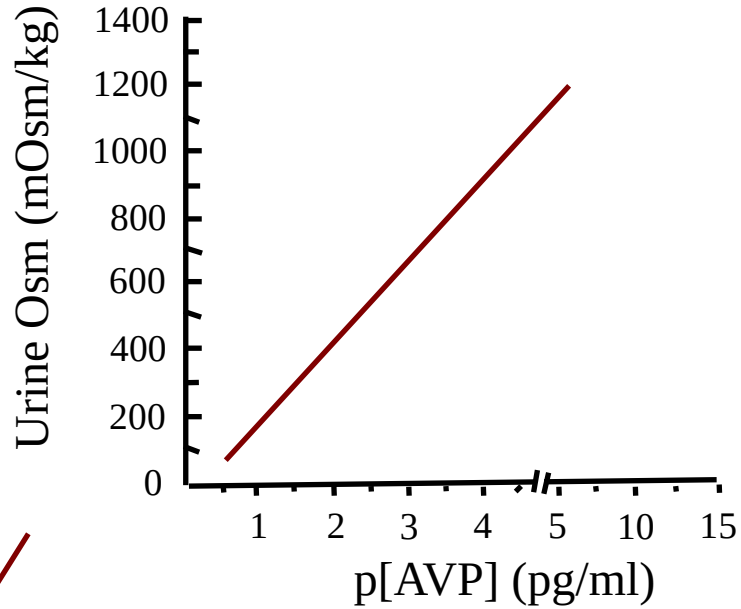
- **Volume Regulation**
- 15-25% blood volume reduction will severely stimulate ADH secretion.
- Decline in blood volume cause a drop in blood pressure
- Amount of blood volume is detected by atrial stretch receptors, and the drop in blood pressure is detected by baroreceptors of carotid, aortic receptors
- A signal transmitted via the baroreceptor afferents to the hypothalamus and increase ADH secretion
- This mechanism is especially important for restoring ECF volume following a hemorrhage.

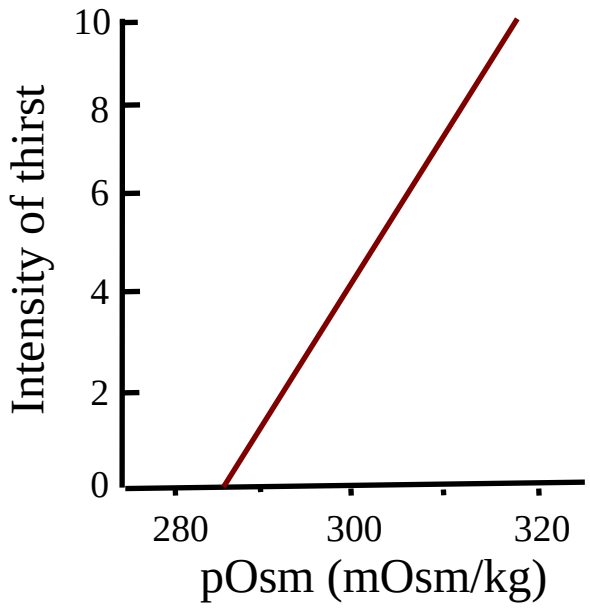
Control of antidiuretic hormone (ADH) secretion by osmolarity and extracellular fluid volume



AVP Responses to Changes in Plasma Osmolality







Factors Affecting AVP Secretion

Stimulation	Inhibition
Increase extracellular fluid osmolality	Decrease extracellular fluid osmolality
Increased serum osmolarity	Increase ECF Volume
Decrease blood volume	Decreased serum osmolarity
Decreased ECF volume	Ethanol
Pressure BP decrease	Atrial natriuretic peptide(ANP)
Pain	
Nausea and vomiting	
Stress	
Drugs	
Nicotine	
Morphine (Opiates)	
Barbituates	
Angotensin II	

Pathophysiology of ADH

- Diabetes insipidus
  - Central DI
  - Nephrogenic DI

- SIADH
- Gestational diabetes insipidus. Is rare. It occurs only during pregnancy when an enzyme made by the placenta destroys ADH in the mother.

Pathophysiology of ADH dh secretion

Diabetes Insipidus

Central diabetes insipidus (CDI)

Causes

- Deficiency of Plasma ADH synthesis or section
- Hypothalamic destruction by stroke, hypoxia, head trauma, infection,
- Tumors (craniopharyngioma)

Signs and symptoms

- Increased serum osmolarity
- Dehydration
- Polyuria
- polydepsia
- Colourless urine instead of pale yellow.
- Dry skin.
- Constipation.
- Weak muscles.
- Bedwetting.
-

Nephrogenic diabetes insipidus

- **T**he posterior pituitary and hypothalamic secretory neurons are normal
- Principal cells of the collecting duct are unresponsive to ADH due to a defect in the V2 receptor, Gs protein, or adenylyl cyclase.
- Genetics Autosomal recessive aquaporin-2 channel gene alterations
  X-linked recessive V-2 receptor gene alteration
- ADH levels are elevated in nephrogenic diabetes
- Other Causes:
  - Hypokalemia Hypercalcemia
  - Lithium, low potassium, and high calcium all diminish ADH's effectiveness on principal cells. The precise mechanism is still unclear, but it may involve disruption in the ability to traffic aquaporins to the luminal membrane of principal cells of the kidney
  - Chronic kidney disease or renal infarction

  Management : Thiazide diuretic

Differential Diagnosis Following Water Deprivation

	Plasma Osm	Urine Osm	Plasma ADH	Urine Osm Post Desmopressin
Normal	297	814	↑	815
Central DI*	342	102	↓	622
Nephrogenic	327	106	↑	118

*Patients with partial central DI will concentrate their urine somewhat but will achieve an additional boost following desmopressin.

Syndrome of Inappropriate ADH Secretion (SIADH)

- Excessive secretion of ADH causes an inappropriate increased reabsorption of water in the renal collecting duct.
  - **hypoosmotic volume expansion.**
  - *The osmolarity of ECF decreases* because excess water is retained.
  - *ECF and ICF volumes increases* because of the water retention **volume increases.**
  - *Plasma protein concentration decreases* because of the increase in ECF volume
  - Increased water retention leads hyponatremia, normal sodium stores)
  - Inappropriate concentration of urine, often greater than plasma osmolarity
- *Causes*
- Ectopic production of ADH by tumors (for example small cell lung)
- Drug induced: carbamazepine

Management

- Syndrome of Inappropriate ADH Secretion (SIADH)
- Fluid restriction but not salt restriction
- Only mild hyponatremia from SIADH can be managed with fluid restriction.
- Severe disease needs 3% hypertonic saline or V2 receptor antagonists.
- Nonpeptide V2 vasopressin antagonists (Conivaptan and tolvaptan)
- Demeclocycline it acts on collecting tubule cells to diminish their responsiveness to **ADH**
- Central diabetes insipidus

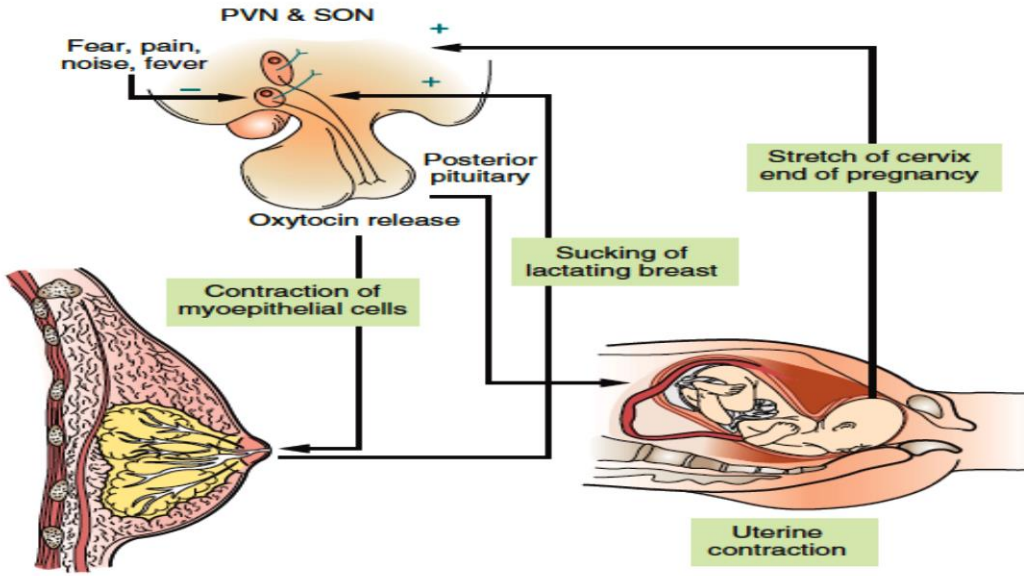
  DDAVP
- Nephrogenic diabetes insipidus
  - Thiazide diuretics

Oxytocin

Functions and regulation of secretion

Primary functions of oxytocin
Milk Let down and labor

Milk let down reflex Afferent fibers carry impulses from the nipple to the spinal cord. Relays in the hypothalamus trigger the release of oxytocin from the posterior pituitary



Effects of Oxytocin

- The Milk Ejection through the milk neuroendocrine reflex Reflex
- Oxytocin causes contraction of the myoepithelial cells that line the ducts of the breast.
- This squeezes the milk out of the alveoli of the lactating breast into the large ducts (sinuses) and thence out of the nipple (milk ejection)
- Can also be released before suckling (anticipatory) causing spontaneous milk ejection.
- The sight or sound of the infant may stimulate the hypothalamic neurons to secrete oxytocin, even in the absence of suckling.
- in males, circulating oxytocin increases at the time of ejaculation, and it is possible that this causes increased contraction of the smooth muscle of the vas deferens, propelling sperm toward the urethra.

Oxytocin functions

- Oxytocin causes contraction of the smooth muscle of the uterus and involved in labor and parturition.
- The sensitivity of the uterine musculature to oxytocin is enhanced by estrogen and inhibited by progesterone.
- In late pregnancy, the uterus becomes very sensitive to oxytocin coincident with a marked increase in the number of oxytocin receptors
- Oxytocin secretion is then increased during labor likely due to d*ilation of the cervix*
- Oxytocin can be used to induce labor and **reduce postpartum bleeding.**
- Oxytocin may also act on the nonpregnant uterus to facilitate sperm transport. The passage of sperm up the female genital tract to the uterine tube

Other functions of oxytocin

- in males, circulating oxytocin increases at the time of ejaculation, and it is possible that this causes increased contraction of the smooth muscle of the vas deferens, propelling sperm toward the urethra
- the secretion of oxytocin is believed to increase during *orgasm*
- The secretion of oxytocin is also increased by stressful stimuli and, like that of vasopressin, is inhibited by alcohol
- stimulates various types of positive social interaction

CLINICAL CASE AND CLINICAL CORRELATION

- A head trauma patient on his third day in the surgical intensive care unit is reported to have an excessive urine output of 20 L in the past 24 hours.
- Laboratory findings show ***hypernatremia*** (high serum Na) and hypotonic urine. Withholding drinking water did not decrease urine output or increase urine osmolarity. Urine osmolarity increased in response to exogenous antidiuretic hormone (vasopressin) administration. He is diagnosed as having ***posttraumatic diabetes insipidus***.
- Neurogenic diabetes insipidus is the result of decreased release of ADH characterized by ***polyuria*** (increased urine output) and hypernatremia.
- This can be the result of destruction of neurons that produce and release ADH resulting from inflammation, neoplasia, vascular abnormalities, or traumatic injury. Patients are treated with ***desmopressin***, a synthetic analog of ADH, which binds to V2 receptors, increasing water reabsorption in the kidney, decreasing urine output, and restoring serum osmolarity.

Clinical case

- A 45-year-old woman is admitted to the hospital following a head injury. She has severe polyuria (producing 1 L of urine every 2 hours) and polydipsia (drinking 3 to 4 glasses of water every hour). During a 24-hour period in the hospital, the woman produces 10 L of urine, containing no glucose. She is placed on overnight water restriction for further evaluation. The following morning, she is weak and confused. Her serum osmolarity is 330 mOsm/L,her serum [Na+] is 164 mEq/L, and her urine osmolarity is 70 mOsm/L. She is treated with dDAVP by nasal spray. Within 24 hours of initiating the treatment, her serum osmolarity is 295 mOsm/L and her urine osmolarity is 620 mOsm/L.

- **EXPLANATION OF CASE.** Following overnight water restriction, the striking observation is that the woman is still producing dilute (hyposmotic) urine despite a severely elevated serum osmolarity. Diabetes mellitus is ruled out as a cause of her polyuria because no glucose is found in her urine. The diagnosis is that the woman has central diabetes insipidus secondary to a head injury. The woman's posterior pituitary gland does not secrete ADH, even with a strong osmotic stimulus such as a serum osmolarity of 330 mOsm/L. This absence of ADH results in a profound disturbance of water reabsorption, and she is unable to produce concentrated urine. Her distal tubule and collecting ducts are impermeable to water in the absence of ADH, no water can be reabsorbed by these segments, and her urine is hyposmotic (70 mOsm/L). Because she is excreting excessive amounts of free water, serum osmolarity and serum [Na+] increase. The high serum osmolarity is an intense stimulus for thirst, causing the woman to drink water almost continuously.
- **TREATMENT.** The woman is treated with dDAVP, an ADH analogue that activates V2 receptors on the principal cells. When ADH binds to the V2 receptors, adenylyl cyclase is activated, cAMP is generated, and water channels are inserted in the luminal membrane, which restores water permeability of the principal cells. After initiating dDAVP therapy, the woman produces hyperosmotic urine, restoring her serum osmolarity to normal.