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Water Balance

M2 – Endocrine Sequence

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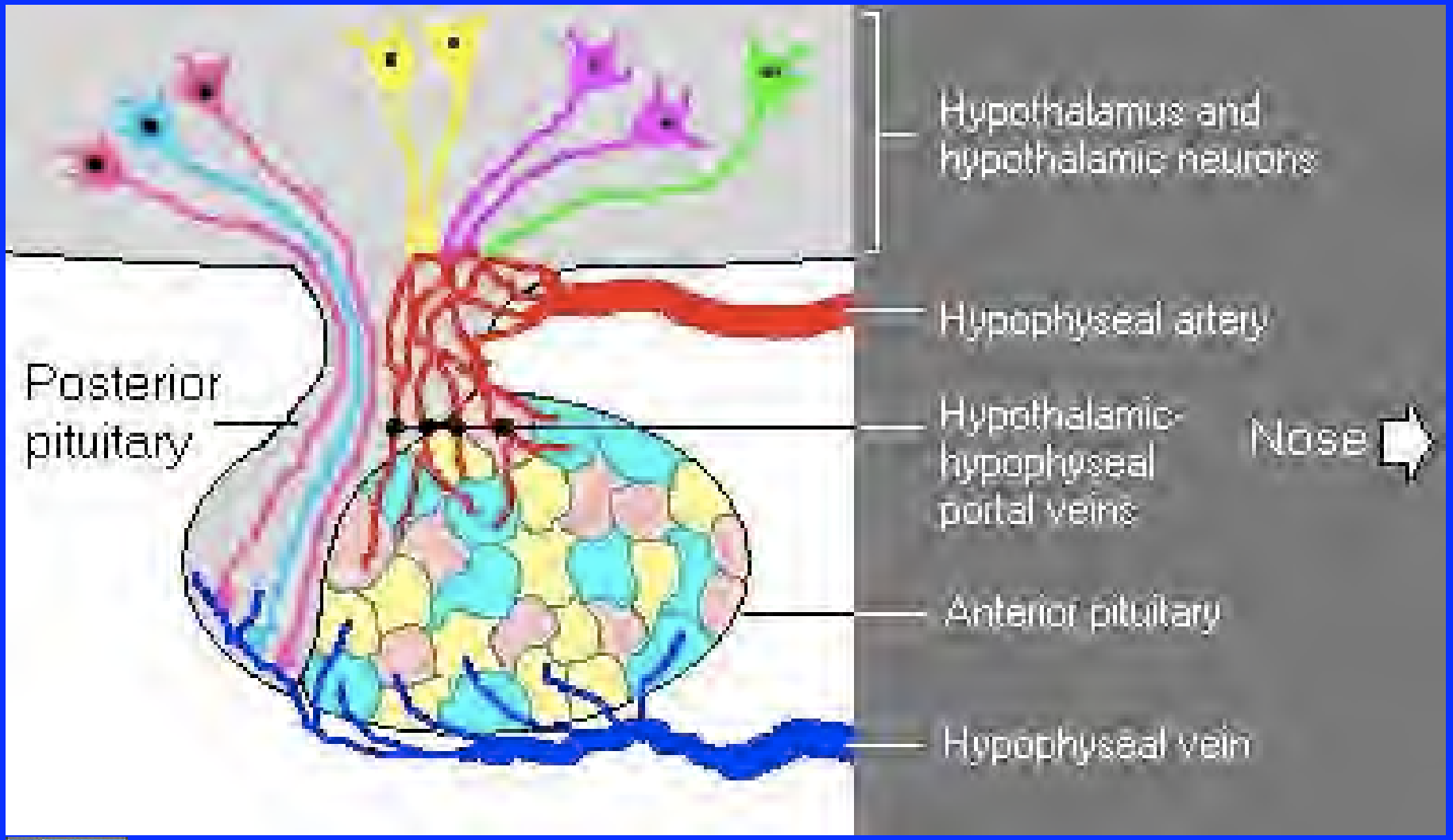
Winter 2009

University of Michigan
Medical School

POSTERIOR PITUITARY

- **Derived from neural tissue.**
- **Infundibulum and posterior pituitary are primarily nonmyelinated nerve fibers.**
- **Originate in the supraoptic and paraventricular nuclei**



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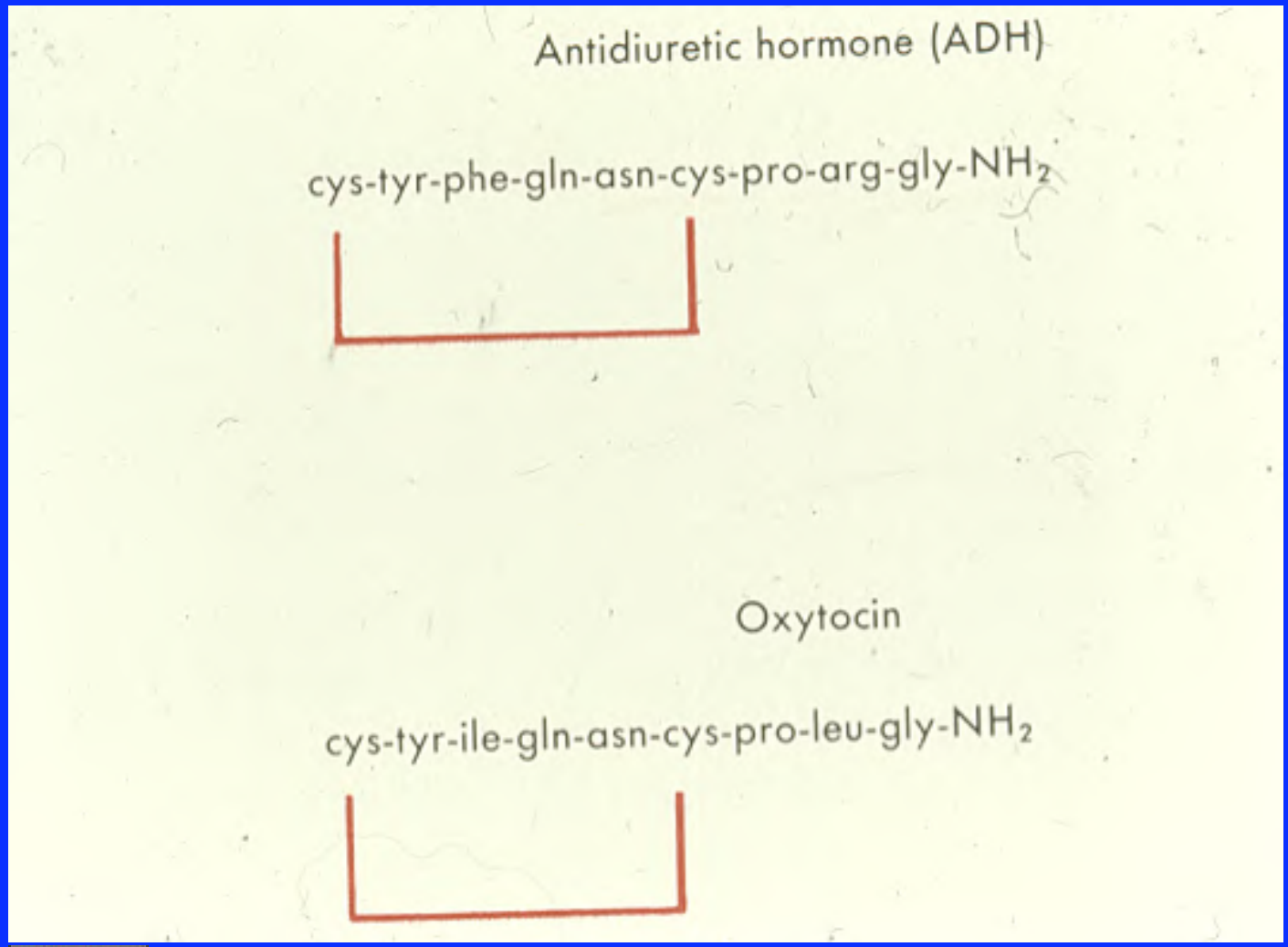
ADH STRUCTURE AND SYNTHESIS

- Nine amino acid peptide, sometimes termed arginine vasopression or AVP.
- Synthesized in cell bodies of hypothalamic nuclei as large prohormone.
- ADH and the prohormone are packaged in secretory vesicles and transported to nerve terminals in the stalk and posterior pituitary.
- The large prohormone, termed neurophysin, appears to play an important role in neural transport.



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MECHANISM OF ADH SECRETION

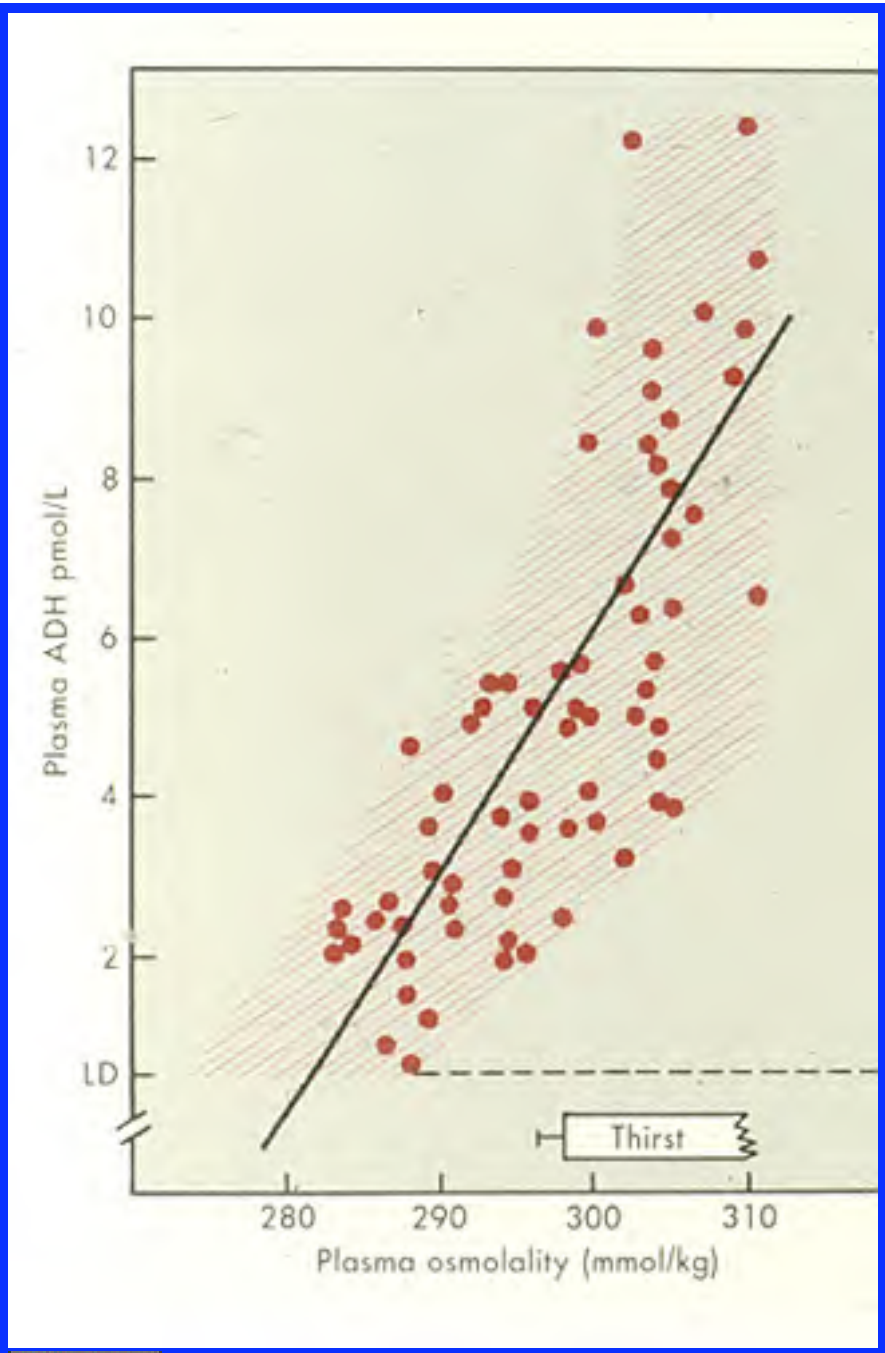
- **Stimulation of hypothalamic nuclei results in axon potentials to the posterior pituitary.**
- **Resultant calcium influx mediates exocytosis of secretory granules.**

OSMOLALITY

- Osmoreceptors in third ventricle, outside the blood brain barrier, respond to small change in "effective" osmolality.
- Osmoreceptor stimulation results in stimulation of ADH producing cells and release of ADH.

OSMOLALITY

- Normal individuals have an osmotic threshold between 280 and 285 mosm/L.
- When plasma osmolality is below threshold, ADH is not secreted.
- Above threshold, ADH secretion is proportional to the increase in osmolality.
- Under most circumstances, osmolality is the only important regulator of ADH secretion.



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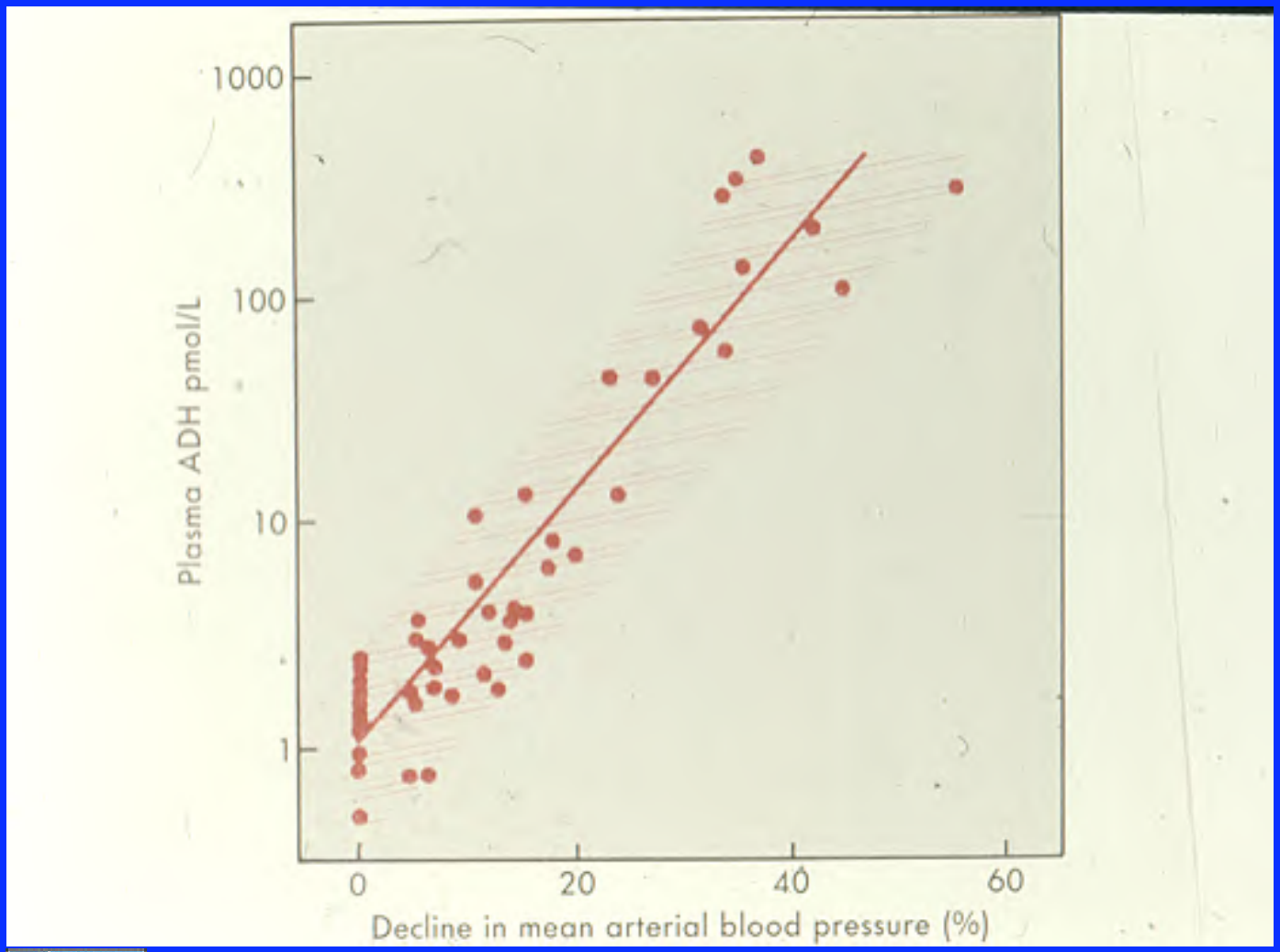
BLOOD VOLUME AND ARTERIAL PRESSURE

- Decreased activity of low pressure or high pressure receptors can trigger secretion of ADH.
- Usually this only happens after substantial changes in blood pressure or volume.
- When baroreceptor stimuli are present, they override the effects of osmolality.



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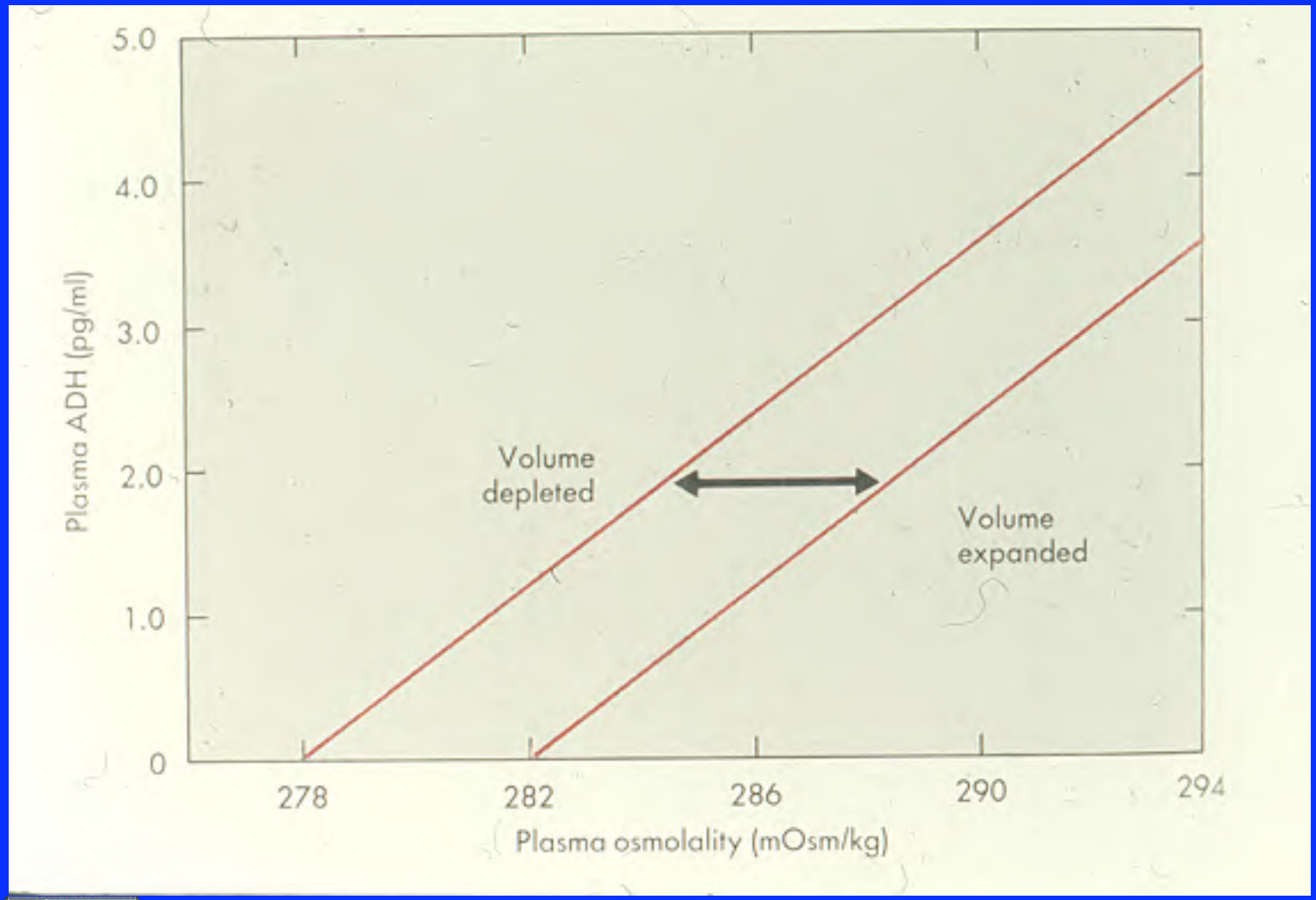

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STIMULATORS OF ADH SECRETION

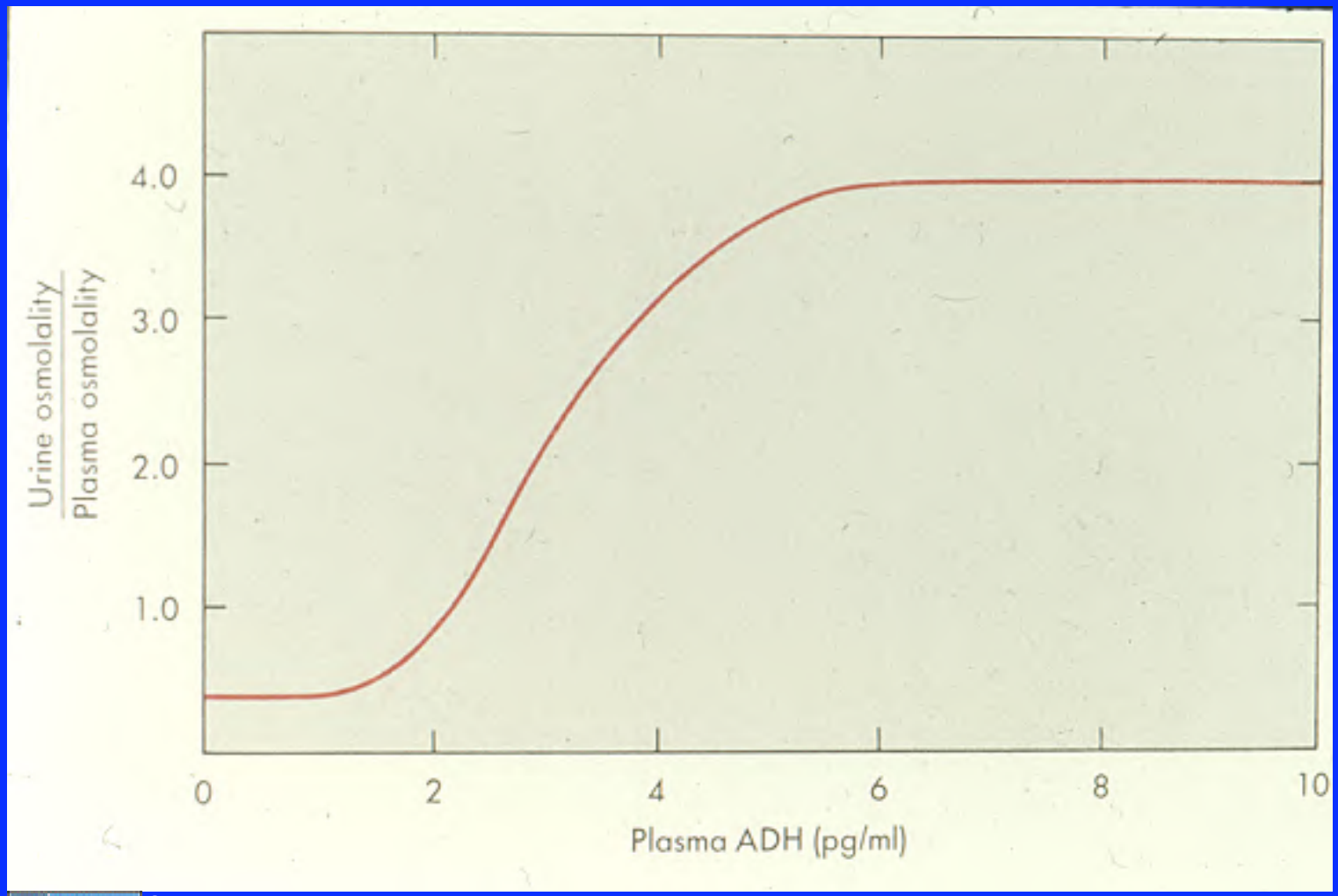
- **Emesis**
- **Stress**
- **Drugs**

ADH IN CIRCULATION

- **Circulates in an unbound form**
- **Short half life (4-8 minutes)**

RENAL ACTIONS OF ADH

- **Renders collecting duct permeable to water**
- **Increases sodium reabsorption in the thick ascending limb of Henle**



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VASCULAR ACTIONS OF ADH

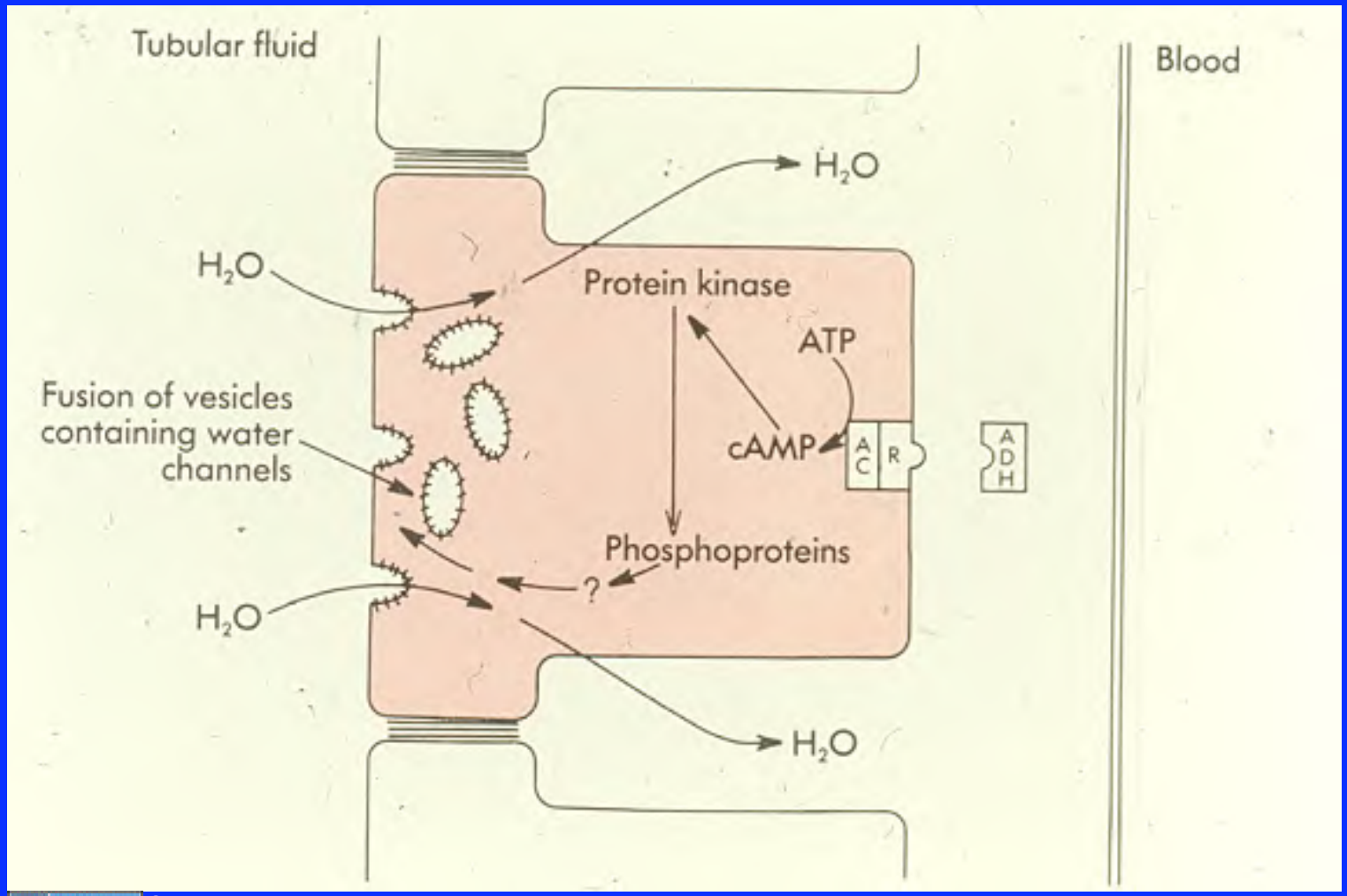
- **Potent vasoconstrictor**
- **Vasoconstrictive effects are probably only important in states of severe hypovolemia or hypotension.**

CELLULAR ACTIONS OF ADH

- **V_1 receptors mediate vascular smooth muscle effects**
- **V_2 receptors are present in renal tubular cells. Their effects are mediated by cAMP**

CELLULAR ACTIONS OF ADH

- **Aquaporins are membrane proteins that act as water channels.**
- **ADH stimulates translocation of aquaporin to the membrane of collecting duct cells.**



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dDAVP

- **Synthetic ADH like agent used to treat patients with ADH deficiency.**
- **Binds to V_2 receptors, but not to V_1 receptors.**

THIRST

- Thirst centers are located in the hypothalamus, near the supraoptic and paraventricular nuclei
- Respond to stimulation of osmoreceptors
- Increased osmolality is a potent thirst stimulator

THIRST

- Decreased osmolality does not appear to suppress thirst
- Decreased baroreceptor stimulation increases thirst
- Angiotensin II, within the brain, is a mediator of increased thirst center activity

WATER FOLLOWS SALT

RESPONSE TO WATER DEPLETION

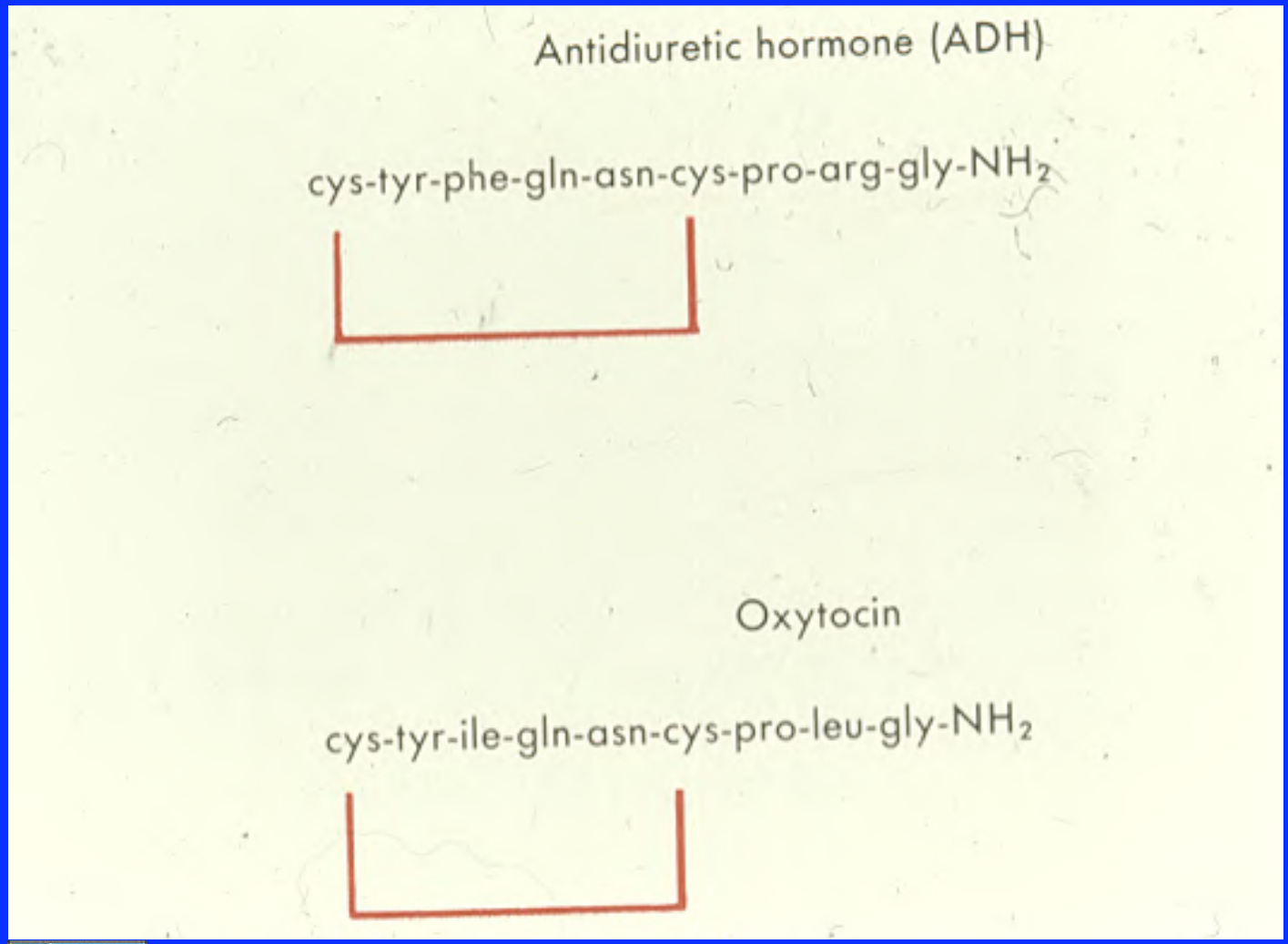
- Osmolality rises (less water than salt)
- Thirst and ADH are stimulated
- Increased water intake and decreased water excretion restore osmolality to normal

RESPONSE TO WATER EXCESS

- **Osmolality falls**
- **ADH secretion is suppressed (thirst is usually not suppressed)**
- **Renal water excretion is increased**

OXYTOCIN: SYNTHESIS AND SECRETION

- Nine amino acid peptide, all but two amino acids are the same as ADH.
- Synthesis and storage are identical to ADH
- Oxytocin has a different neurophysin than ADH.



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SECRETION OF OXYTOCIN

- **Suckling**
- **Uterine stretch**

MILK LET DOWN

- **Milk secretion requires contraction of myoepithelial cells lining alveoli**
- **Oxytocin simulates contraction of myoepithelial cells, without it, lactation does not occur**

PARTURITION

- At the end of pregnancy, myometrium is highly sensitive to oxytocin
- As labor progresses, increasing oxytocin levels cause uterine contraction
- Postpartum, oxytocin induced myometrial contraction is important in minimizing blood loss
- Oxytocin is sometimes used to induce labor

A 25 year old man had the sudden onset of marked polyuria and polydipsia. He never slept for more than 2-3 hours at a time, spending much of the night in the bathroom. Except for some fatigue, he felt well, with no other symptoms.

Routine labs revealed:
Na = 142 mEq/l (137-144)
K = 3.8 mEq/l (3.6-5.0)
Cl = 100 mEq/l (95-102)
HCO3 = 29 mEq/l (25-31)
BUN = 18 mg/dl (0-20)
Creat = 1.2 mg./dl (0-1.4)
Plasma osmolality = 286 mosm/l(278-288)
Urine osmolality = 68 mosm/l
24 hour Urine volume = 9540 ml

	Plasma Osm	Urine Osm
Basal	285	64
1 hr		59
2 hr		67
3 hr		82
4 hr	294	74
5 hr	301	77
DdAVP administered		
6 hr		352
7 hr		504

He was treated with desmopressin (DdAVP), 0.1 mg twice daily. Thirst and frequency of urination returned to normal.

DIABETES INSIPIDUS

The clinical manifestation of ADH deficiency

ETIOLOGY OF DIABETES INSIPIDUS

- **Trauma**
- **Neoplasm**
- **Idiopathic**
- **Familial**
- **Other pituitary and hypothalamic lesions**

PATHOPHYSIOLOGY OF DIABETES INSIPIDUS

- In the absence of ADH, patients are unable to concentrate urine, even when there is water deprivation and hyperosmolality
- As water deprivation occurs, it constitutes a potent stimulus for thrist
- Otherwise healthy patients are able to maintain normal osmolality by drinking large amounts

SYMPTOMS OF DIABETES INSIPIDUS

- **Marked polyuria and polydipsia**
- **Usually not dehydrated as long as they are conscious and thirst center is intact**
- **If access to water is limited, hypernatremia rapidly occurs**

WATER DEPRIVATION TEST

- **Normals will increase urine osmolality to 800 mOsm/L**
- **After urine osmolality has plateaued, inject dDAVP if levels are less than 800 mOsm/L**
- **In borderline cases, measurement of ADH after water deprivation is helpful.**

WATER DEPRIVATION TEST

- **Pituitary DI: unable to concentrate urine despite hyperosmolar serum. After dDAVP injection, Uosm increases.**
- **Nephrogenic DI: unable to increase urine osmolality after water deprivation and after dDAVP.**
- **Primary polydipsia: should concentrate urine normally following water deprivation**

NEPHROGENIC DIABETES INSIPIDUS

- Familial
- Renal disease
- Hypercalcemia
- Hypokalemia
- Lithium therapy

A 61 year old man was admitted to the VA Hospital for evaluation of convulsions. He had been well until 3 months before admission when he developed anorexia and nausea. He lost 14 lbs in the 3 months before admission. Two weeks before admission he became confused, and his wife noted he was unable to dress himself. The confusion improved, but he then had two generalized convulsions in the three days before admission.

Physical examination revealed a cachectic appearing man. Weight 137; height 5'11". Blood pressure 115/75, pulse 92 and regular. He was oriented to person and place but not to time. He could not name the president nor subtract 7 from 100. Proverb interpretation was concrete. The rest of the neurologic exam was normal.

Na = 109 mEq/l (137-144)
K = 3.7 mEq/l (3.6-5.0)
Cl = 84 mEq/l (95-102)
HCO3 = 20 mEq/l (24-31)
BUN = 4 mg/dl (6-20)
Creat = 0.8 mg/dl (0-1.4)

Plasma osmolality = 232 mosm/l (278-288)
Urine osmolality = 552 mosm/l

Chest film: 3 cm right hilar mass

He was treated with a 500 ml per day water restriction, with a rise in serum Na to 129 and marked improvement in mental status.

CT scan demonstrated mediastinal metastases. He was treated with chemotherapy, but attempts to liberalize his fluid intake consistently resulted in recurrent hyponatremia. Demeclocycline was added to his regimen, and serum sodium ranged from 124 to 135 mEq/l without water restriction.

SYNDROME OF INAPPROPRIATE ADH (SIADH)

Secretion of ADH despite water retention and plasma hypotonicity

ETIOLOGY OF SIADH

- **CNS disorders**
- **Malignant tumors secreting ADH**
- **Pulmonary disease**
- **Drugs**

PATHOPHYSIOLOGY OF SIADH

- **Drinking continues despite inability to dilute urine and excrete excess water**
- **Volume expansion and hypotonicity ensue**
- **New steady state is attained, but only after significant water retention has occurred**

SYMPTOMS OF SIADH

- Na>120, patients are usually asymptomatic
- Na between 110 and 120, confusion and lethargy may occur
- Na<110, convulsions, coma, and death may result
- Rate of fall of Na is more important than the absolute level

DIAGNOSIS OF SIADH (PART 1)

- Hypotonic, hyponatremic plasma, with inappropriately hypertonic urine.
- Usually urine osmolality is greater than serum osmolality.
- Exclude other causes of hyponatremia
  - Hyperglycemia
  - Hyperlipidemia

DIAGNOSIS OF SIADH (PART 2)

- **Evaluate for conditions known to stimulate ADH secretion.**
  - **Volume depletion**
  - **Heart failure**
  - **Cirrhosis**
  - **Nephrotic syndrome**
  - **Hypothyroidism**
  - **Cortisol deficiency**

TREATMENT OF SIADH

- **Acutely ill patients should receive hypertonic saline. Furosemide may be added to promote water excretion**
- **Conivaptan, an intravenous ADH V2 receptor antagonist, promotes water excretion and increases osmolality**
- **Excessively rapid correction of hyponatremia can cause brain stem damage and should be avoided**

CHRONIC TREATMENT OF SIADH

- **Treat underlying disorder**
- **Water restriction**
- **Drugs which cause nephrogenic diabetes insipidus:**
  Demeclocycline
- **Oral ADH antagonists are under development**

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