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REGULATION OF NEUROHYPOPHYSEAL FUNCTION

Roger J. Grekin, M.D.

Key words: ADH, vasopressin, osmolality, water, oxytocin

Objectives

- A. Describe the anatomy of the posterior pituitary
- B. Know the factors which regulate ADH secretion
- C. Describe the vascular and renal effects of ADH
- D. State the regulation of oxytocin secretion and describe its actions on breast and uterus

I. Anatomy of the posterior pituitary and hypothalamic tracts

- A. Posterior pituitary
 - 1. Derived from neural tissue.
 - 2. Infundibulum (stalk) and posterior pituitary are primarily composed of nonmyelinated nerve fibers.
 - 3. Fibers originate in the supraoptic and paraventricular nuclei of the hypothalamus.

II. Antidiuretic hormone (ADH, vasopressin)

- A. Structure and synthesis
 - 1. Nine amino acid peptide, sometimes termed arginine vasopressin or AVP.
 - 2. Synthesized in cell bodies of hypothalamic nuclei as large prohormone.
 - 3. After cleavage, both ADH and the remainder of the prohormone are packaged in secretory vesicles and transported to nerve terminals in the stalk and posterior pituitary.
 - 4. The large prohormone, termed neurophysin, appears to play an important role in neural transport.
- B. Regulation of ADH secretion
 - 1. Mechanism of secretion
 - a. Stimulation of hypothalamic nuclei results in axon potentials to the posterior pituitary.
 - b. Resultant calcium influx mediates exocytosis of secretory granules.
 - 2. Osmolality
 - a. Osmoreceptors in third ventricle, outside the blood brain barrier, respond to small changes in "effective" osmolality.
 - b. Osmoreceptor stimulation results in stimulation of ADH producing cells and release of ADH.
 - c. Normal individuals have an osmotic threshold between 280 and 285 mosm/L. When plasma osmolality is below this level, ADH is not secreted. Above this level, ADH secretion is proportional to the increase in osmolality.
 - d. Under most circumstances, osmolality is the only important regulator of ADH secretion.
 - 3. Blood volume and arterial pressure
 - a. Hypotension results in decreased neural traffic from high pressure (aorta and carotid) receptors which can trigger secretion of ADH.
 - b. Similarly, volume depletion results in decreased stimulation of low pressure (atria or great vessels) which also can trigger secretion of ADH.
 - b. Usually this only happens after substantial changes in pressure or volume.
 - c. When baroreceptor stimuli are present, they override the effects of osmolality.
 - 4. Other regulators of ADH secretion
 - a. Emesis
 - b. Stress
 - c. Drugs

5. Circulating hormone
 - a. Circulates in an unbound form, all circulating ADH is available for binding to receptors
 - b. Short half life (4-8 minutes)

C. Actions of ADH

1. Renal
 - a. Renders collecting duct permeable to water.
 - b. Increases sodium reabsorption in the thick ascending limb of Henle
2. Vascular
 - a. Potent vasoconstrictor
 - b. Probably vasoconstrictive effects are only important in states of severe hypovolemia or hypotension.
3. Cellular
 - a. V_1 receptors mediate vascular smooth muscle effects.
 - b. V_2 receptors are present in renal tubular cells. Their effects are mediated by cAMP.
 - c. Aquaporins are membrane proteins that act as water channels. ADH stimulates translocation of aquaporin to the luminal membrane of collecting duct cells.
 - d. Desmopressin (DDAVP), a synthetic ADH like agent, is used to treat ADH deficiency. It binds to V_2 receptors, but not to V_1 receptors.

D. Thirst

1. Thirst centers are located in the hypothalamus, near the supraoptic and paraventricular nuclei.
2. They also respond to osmoreceptors.
3. Increased osmolality is a potent thirst stimulator
4. Decreased osmolality does not suppress thirst.
5. Baroreceptor stimulation increases thirst.
6. Angiotensin II, within the brain, is a mediator of increased thirst center activity.

E. Regulation of water balance in normal individuals

1. Water follows salt.
2. During states of water depletion
 - a. Osmolality rises (less water than salt)
 - b. Thirst and ADH are stimulated
 - c. Increased water intake and decreased water excretion restore osmolality to normal.
 - d. During times of inadequate access to water, increased ADH secretion minimizes renal water losses.
3. During states of water excess
 - a. Osmolality falls
 - b. ADH secretion is suppressed (thirst is usually not suppressed)
 - c. Renal water excretion is increased

III. Oxytocin

A. Structure and synthesis

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

B. Regulation of secretion

1. Suckling
 - a. Nerve endings in the nipple relay signals to the hypothalamic nuclei
 - b. May be stimulated by external cues
2. Uterine stretch: positive feedback effects during parturition eventually result in high enough oxytocin levels to cause expulsion of the fetus

- C. Action of oxytocin
1. Milk let-down
 - a. Milk secretion requires contraction of myoepithelial cells lining alveoli
 - b. Oxytocin stimulates contraction of myoepithelial cells; without it, lactation does not occur.
 2. Parturition
 - a. At the end of pregnancy, myometrium is highly sensitive to oxytocin
 - b. As labor progresses, increasing oxytocin levels cause uterine contraction
 - c. Postpartum, oxytocin induced myometrial contraction is important in minimizing blood loss
 - d. Oxytocin is sometimes used to induce labor.

ABNORMALITIES OF WATER BALANCE

Roger J. Grekin, M.D.

Key words: ADH, diabetes insipidus, polyuria, polydipsia, SIADH, hyponatremia

- I. Objectives
- A. Describe the pathophysiology of diabetes insipidus
 - B. Understand the interpretation of the water deprivation test
 - C. List the differential diagnosis of polydipsia
 - D. Describe the pathophysiology of SIADH
 - E. List the differential diagnosis of hyponatremia
 - F. Describe the treatment of SIADH

II. Diabetes Insipidus

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

Water deprivation test was performed:

	<u>Plasma Osm</u>	<u>Urine Osm</u>
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.

- A. The clinical manifestation of ADH deficiency
- B. Etiology
 1. Trauma
 2. Neoplasm
 3. Idiopathic
 4. Familial
 5. Other pituitary and hypothalamic lesions

C. Pathophysiology

1. In the absence of ADH, patients are unable to concentrate urine, even when there is water deprivation and hyperosmolality.
2. Water deprivation results in hyperosmolality, which constitutes a potent stimulus for thirst.
3. As long as patients are conscious, have access to water, and have an intact thirst mechanism, they are able to replace the lost water by drinking, thereby maintaining plasma osmolality at or near normal.

D. Symptoms

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

E. Diagnosis

1. Low urine osmolality in the face of high serum osmolality.
2. Water deprivation test
 - a. Normals will increase urine osmolality to 800 mOsm/l
 - b. After urine osmolality has plateaued, inject desmopressin.
3. In borderline cases, measurement of ADH after water deprivation is helpful.
4. Interpretation
 - a. Patients with pituitary DI are unable to concentrate urine despite hyperosmolar serum. After desmopressin injection, urine osmolality increases.
 - b. Patients with nephrogenic DI are unable to increase urine osmolality after water deprivation and after desmopressin.
 - c. Patients with primary polydipsia should concentrate normally following water deprivation

F. Differential diagnosis

1. Compulsive water drinking
2. Thirst center lesions
3. Nephrogenic diabetes insipidus: renal disease leading to the inability of the kidney to respond to ADH.
 - a. Familial
 - b. Renal disease
 - c. Hypercalcemia
 - d. Hypokalemia
 - e. Lithium therapy

G. Treatment of pituitary DI: desmopressin

III. Syndrome of Inappropriate ADH

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.

Laboratory values: 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.

- A. Definition: secretion of ADH despite water retention and plasma hypotonicity
- B. Etiology
 - 1. CNS disorders
 - 2. Malignant tumors secreting ADH
 - 3. Pulmonary disease
 - 4. Drugs
- C. Pathophysiology
 - 1. Drinking continues despite inability to dilute urine and excrete excess water.
 - 2. Water retention and hypotonicity ensue
 - 3. New steady state is attained, but only after significant water retention has occurred.
- D. Symptoms
 - 1. If Na>120, patients are usually asymptomatic
 - 2. If Na between 110 and 120, confusion and lethargy may occur
 - 3. If Na<110, convulsions, coma, and death may result.
 - 4. Rapid change in serum Na is often more important than the absolute level.
- E. Diagnosis
 - 1. Hypotonic, hyponatremic plasma, with inappropriately hypertonic urine. Usually urine osmolality is greater than serum osmolality.
 - 2. Exclude other causes of hyponatremia
 - a. Hyperglycemia
 - b. Hyperlipidemia
 - 3. Evaluate for conditions known to stimulate ADH secretion.
 - a. Volume depletion
 - b. Heart failure
 - c. Cirrhosis
 - d. Nephrotic syndrome
 - e. Hypothyroidism
 - f. Cortisol deficiency
- F. Treatment:
 - 1. Acutely ill patients.
 - a. Intravenous hypertonic saline will rapidly reverse hyponatremia. Addition of furosemide will hasten correction
 - b. Tolvaptan, an ADH V₂ receptor antagonist, is effective in promoting water loss and raising osmolality
 - b. Rapid correction of hyponatremia may cause brain stem damage.
 - 2. Chronic hyponatremia
 - a. Treat underlying disorder
 - b. Water restriction
 - c. Drugs which cause nephrogenic diabetes insipidus: Demeclocycline
- G. Role of water restriction in treatment of edematous states.