The Posterior Pituitary Gland and Related Issues
(Vasopressin and Oxytocin)
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OBJECTIVES:

At the end of this lecture, the student should be able to:

1. Construct the relationships between the hypothalamus and anterior and posterior lobes of the pituitary gland and explain how neurosecretion participates in these relationships.
2. Characterize the chemical nature of the 2 hormones of the posterior pituitary, vasopressin and oxytocin, as well as their relationship with their precursor molecules.
3. Describe the physiological function of vasopressin, as well as its actions at the cellular and subcellular levels.
4. Describe how vasopressin secretion is regulated by plasma volume and osmolarity.
5. Explain the etiologies of diabetes insipidus and SIADH.


I. THE CONCEPT OF NEUROSECRETION

A. Neurosecretion is the capacity of a nerve cell to secrete a hormone (a substance that produces an effect at a remote site).

B. A neurosecretory cell possesses all of the features of the nerve cell (cell body, axon, Nissl substance, conveys electrical impulses, etc.) but has the capacity to secrete hormones.

II. ELEMENTS OF THE HYPOTHALAMO-NEUROHYPOPHYSEAL SYSTEM
Figure 1. Hypothalamus - Pituitary Relationships

A. Hypothalamic nuclei

1. Also referred to as magnocellular nuclei, hypothalamic nuclei are comprised of cell bodies of neurosecretory cells.
2. They are sites of hormone precursor transcription, translation and vesicle formation, processes that involve cell nuclei, ribosomes, and Golgi apparatus.
3. Two nuclei of the hypothalamus regulate the hypothalamo-neurohypophyseal system:
   a. Supraoptic nucleus, located above optic chiasm;
   b. Paraventricular nucleus, located on either side of third ventricle.

B. Hypothalamo-neurohypophyseal tract (pituitary stalk)

1. Is comprised of axons of neurosecretory cells.
2. Is the site of transport of the prohormone by axoplasmic flow, and post ribosomal processing (proteolytic cleavage) to actual hormone and its associated products.
3. Hypothalamo-neurohypophyseal tract contains glycoprotein enriched material that is transported by axoplasmic flow. This material is also termed “neurosecretory material” (NSM) and “neurophysins.”

C. Posterior pituitary gland (also referred to as pars nervosa or infundibular process)

1. This structure is comprised of terminals of the neurosecretory cell and is the site of storage and release of hormones and associated products.
2. Posterior pituitary gland also contains pituicytes (sustentacular cells).

III. ELEMENTS OF HYPOTHALAMO-ADENOHYPOPSEAL SYSTEM (Fig. 1)

A. This system controls anterior and intermediate lobe function (also referred to as adenohypophysis because of its glandular nature).

B. The hypothalamus is connected to the adenohypophysis by a neurovascular link, the hypothalamo-hypophyseal portal system.

1. A portal system is a system of veins that starts as capillaries and ends as capillaries.

C. Neurosecretory neurons in the hypothalamus make releasing and inhibiting hormones that are secreted into the median eminence in the base of hypothalamus and transported to the adenohypophysis by the portal system.

1. The median eminence, a midline protuberance in the base of the brain, is the origin of the a portal venous system.

IV. HORMONES OF THE POSTERIOR PITUITARY

A. Vasopressin (antidiuretic hormone, ADH) and oxytocin.

B. Chemistry of posterior pituitary hormones (Fig. 2)

1. Both are nonapeptides containing a 6 amino acid ring (S-S bond between cysteine residues 1 and 6) and 3 amino acid side chain.
2. Vasopressin (ADH) and oxytocin differ in 2 amino acid residues (3, 8).
3. Both hormones weigh about 1100 dalton.
V. SYNTHESIS, PROCESSING, AXOPLASMIC FLOW, AND RELEASE OF VASOPRESSIN AND OXYTOCIN (Fig. 3)

A. Synthesis of vasopressin and oxytocin occur in hypothalamic nuclei first as pre-prohormones.

1. In humans both hormones are made in both the supraoptic and paraventricular nuclei.

   a. The content of both hormones in supraoptic nucleus exceeds that of paraventricular nucleus.
   b. Synthesis of pre-prohormones involve transcription and translation.
   c. Pre-propressophysin, the precursor for vasopressin, is comprised of a signal peptide (19 amino acids), vasopressin (9 amino acids), neurophysin II (95 amino acids), and glycoprotein (39 amino acids).
   d. Pre-prooxyphysin, the precursor for oxytocin is comprised of a signal peptide (19 amino acids), oxytocin (9 amino acids), and neurophysin I (93 amino acids).
   e. Initial processing of pre-prohormones occurs by removal of signal peptide from N-terminal ends of both precursor molecules producing a prohormone (propressophysin and prooxyphysin).

2. Prohormones are housed as membrane encapsulated granules.

   a. Packaging of these granules involves the Golgi apparatus.
B. **Postribosomal proteolytic processing and axoplasmic flow** of vasopressin and oxytocin occur in the hypothalamo-neurohypophyseal tract.

   1. Propressophysin is proteolytically processed to vasopressin (1100 mw), neurophysin II (about 10,000 mw) and glycoproteins.
   2. Prooxyphysin is proteolytically processed to oxytocin (1100 mw) and neurophysin I (about 10,000 mw).

C. **Storage and release** of hormones and associated products occur in the pars nervosa.

   1. Release involves a process called "*excitation-secretion coupling*" which is analogous to excitation-contraction coupling.
      
      a. This process involves membrane depolarization, calcium influx and exocytosis performed by actin-myosin like proteins which translocate secretory granules.
      
      b. Hormones and by products are released from the pars nervosa, but only the hormones are associated with physiologic functions (to the best of our knowledge).
VI. TRANSPORT AND CLEARANCE OF VASOPRESSIN AND OXYTOCIN

A. Hormones circulate unbound (as do most protein/peptide hormones) and are cleared by liver and kidney (half-life estimates range from about 2-3 to 18 min).

VII. PHYSIOLOGIC ACTIONS OF VASOPRESSIN

A. Vasopressor action - generally considered a pharmacologic effect (requires high concentrations), may have some physiologic relevance since high levels of vasopressin are released in response to a 10% decrease in blood volume.
1. This action involves V1 receptor (serpentine, G-protein coupled) and a Ca\(^{++}\) dependent form of signal transduction.

   a. V1 receptor mediated signaling involves phospholipase C activation and generation of IP3 and diacylglycerol.

   ![Image of ADH action in kidney](image)

   **Figure 4. Action of ADH in Kidney**
   
   *Adapted from Rhoads and Pflanzer, 3rd Edition*

B. *Antidiuretic* action - reabsorption of water in distal convoluted tubule and collecting ducts is the major physiological action of this hormone (Fig. 4).

1. This leads to increased water permeability - water will move in response to osmotic gradient thus concentrating urine.
2. Antidiuretic action of vasopressin is adenylate cyclase mediated and involves V2 receptors which are distinct from V1 receptors.

   a. V2 receptors are found on blood (serosal) surface of nephron target cells and generate cyclic AMP (a G-protein mediated effect).
   b. Signal transduction leads to increased protein phosphorylation and water permeability at the luminal (mucosal) surface of target cell.
   c. Permeability change is due to altered activity and/or number of water channels (*aquaporin 2*).
VIII. REGULATION OF VASOPRESSIN SECRETION AND ITS ROLE IN FLUID BALANCE - OVERALL ROLE CONSERVATION OF FLUID

A. Signals that regulate vasopressin release are inversely related to extracellular fluid (ECF) volume and directly related to ECF osmolarity.

1. Hypovolemia
   a. The more potent, but less sensitive stimulus for vasopressin secretion than hyperosmolarity.
      i. Threshold for ADH release requires about a 10-20% decline in fluid volume.
      ii. Response (release of ADH) is very robust.
   b. Hypovolemic response is mediated by left atrial stretch receptors.
   c. Stretch receptors lead to increased firing of vagal inhibitory neurons leading to decreased vasopressin release.
   d. Decrease of stretch (e.g., loss of volume) would have the reverse effect (disinhibition) - increased vasopressin release.

2. Hyperosmolarity
   a. The more sensitive stimulus for vasopressin secretion than hypovolemia.
      i. occurring in response to changes in plasma osmolarity of 1-2%.
   b. This response is mediated by hypothalamic osmoreceptors (These receptors exist near, but are distinct from, magnocellular nuclei).
   c. Osmoreceptors regulating vasopressin release are related to drinking centers in the hypothalamus (where osmolarity has been shown to influence drinking behavior).

3. Interaction can occur between osmotic and volume controls of vasopressin secretion.
   a. Angiotensin II can sensitize the osmotic receptors indicating that volume depletion can enhance sensitivity of the osmotic stimuli.

4. Other stimulators of vasopressin release
a. Stress, anxiety, pain, nausea, nicotine, opiates, barbiturates, β-adrenergic agonists, estrogens, increased pCO$_2$, decreased pO$_2$.

5. Inhibitors of vaspressin release

a. Volume expansion, hypoosmotic stimuli, alcohol, glucocorticoids, and α-adrenergic agonists.

IX. CLINICAL DISORDERS OF VASOPRESSIN SECRETION

A. *Diabetes insipidus* (diabetes = "pass through" [Gr.]; insipidus - "tasteless" [L.]) - deficiency in vasopressin secretion.

1. Symptoms

   a. Polyuria - up to 10-fold increase in daily water excretion (15 L).
   b. Polydipsia - excess drinking secondary to polyuria.
   c. Symptoms only manifest when anterior pituitary hormones are present (related to maintenance of GFR).
   d. In normal individuals, water deprivation would concentrate urine, with diabetes insipidus this would not occur.

2. Etiologies

   a. *Neurogenic* (also referred to as central diabetes insipidus)- absence of vasopressin.

      i. Usually associated with a lesion in the tract or magnocellular nuclei rather than loss of posterior lobe.
      ii. An hereditary strain of a rat (Brattleboro strain) exists that cannot synthesize vasopressin.
      iii. A neurogenic form of diabetes insipidus requires about an 80% deficiency in vasopressin.

   b. *Nephrogenic* - vasopressin is unresponsiveness in target cells of nephron, due to the following mechanisms:

      i. receptor dysfunction - an X chromosome linked V2 receptor defect;
      ii. defect in gene that expresses water channel;
      iii. enhanced vasopressin metabolism and its clearance from the body (during pregnancy).
B. Excess vasopressin - Syndrome of inappropriate ADH secretion (SIADH)

1. Symptoms
   a. ECF expansion;
   b. Serum hypotonicity and hyponatremia.

2. Etiology - caused by enhanced sensitivity of osmoreceptors thus secreting ADH release too readily.

X. OXYTOCIN

A. Functions in the female - involve contraction of myoepithelial cells

   1. Parturition (Ferguson reflex) - to be discussed in a later lecture (Pregnancy and lactation)
   2. Milk ejection from lactating breast - to be discussed in a later lecture (Pregnancy and lactation)
   3. Sperm transport (possibly)
      a. Oxytocin release occurs during orgasm (in nonpregnant as well as pregnant individual).

B. Function in male - oxytocin release occurs during ejaculation.

   1. Sperm transport may occur as a result of vas deferens smooth muscle contraction.

XI. STUDY QUESTIONS - All Type A

1. The generation of vasopressin from its precursor molecule:

   A. occurs in the cell bodies of the paraventricular and supraoptic nucleus
   B. involves cleavage of pre-propressophysin
   C. occurs in the hypothalamo-neurohypophyseal tract
   D. involves removal of the signal peptide off the C-terminal end of the propressophysin molecule
   E. occurs in the pars nervosa

2. Which structure is differentiated to produce pre-prooxyphysin?
   . supraoptic nucleus
   A. hypothalamo-neurohypophyseal tract
   B. hypothalamo-hypophysela portal system
   C. pars nervosa
D. pars intermedia

3. V2 receptors for ADH (i.e., those mediating the principal action of the hormone)
   . are found in vascular smooth muscle
     A. are located on the luminal surface of collecting duct epithelial cells
     B. are associated with a G-protein adenylate cyclase signaling system
     C. are associated with a G-protein phospholipase C signaling system
     D. mediate sodium transport in the kidney

4. Which of the following substances contains a glycoprotein at its C-terminus?
   . oxytocin
     A. neurophysin I
     B. vasotocin
     C. prepropressophysin
     D. vasopressin

5. Which of the following structures is associated with "excitation-secretion coupling"?
   . supraventricular nucleus
     A. paraventricular nucleus
     B. hypothalamo-neurohypophyseal tract
     C. hypothalamo-hypophyseal portal system
     D. pars nervosa

6. The conversion of pre-prooxyphysin to prooxyphysin:
   . occurs in the cell bodies of the paraventricular and supraventricular nuclei
     A. involves cleavage between oxytocin and neurophysin I
     B. occurs in the hypothalamo-neurohypophyseal tract
     C. involves removal of the signal peptide off the C-terminal end of the pre-prooxyphysin molecule
     D. occurs in the pars nervosa.