

POSTERIOR PITUITARY GLAND (neurohypophysis)

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Overview.

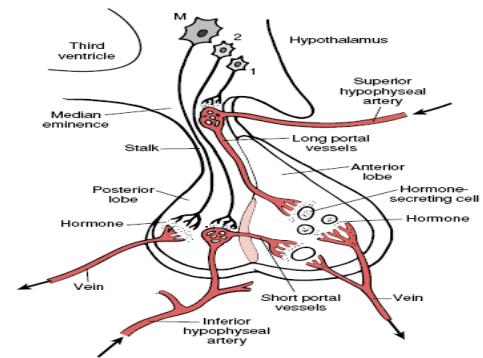
- Review (histology)
- Hormones produced by the posterior pituitary.
 - Synthesis and transport of hormones
 - Functions of hormones
 - Metabolic clearance of hormones
- Diabetes insipidus
 - Types
 - Diagnosis
 - Treatment

Review

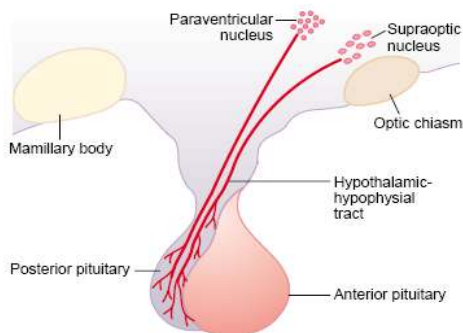
The *posterior pituitary gland*, also called the *neurohypophysis*, is composed mainly of glial-like cells called *pituitocytes*.

- The *pituitocytes do not secrete hormones*; they act simply as a supporting structure for large numbers of *terminal nerve fibers and terminal nerve endings* from nerve tracts that originate in the *supraoptic and paraventricular nuclei of the hypothalamus*.
- The nerve endings are bulbous knobs that contain many secretory granules.
- These endings lie on the surfaces of capillaries, where they secrete the posterior pituitary hormones

Vascularization



Hypothalamic-pituitary relationship



Hormones

- The posterior pituitary secretes two hormones.
 - Arginine vasopressin (in humans); lysine vasopressin (in pigs)
 - Oxytocin

Synthesis

- *Arginine vasopressin is formed **primarily** in the paired supraoptic nuclei,*
- *whereas oxytocin is formed **primarily** in the paired paraventricular nuclei.*
- *Each of these nuclei can synthesize about one sixth as much of the second hormone as of its primary hormone.*
- Synthesis is by special neurons called magnocellular neurons.

Synthesis cont..

- The gene for the vasopressin precursor, known as propressophysin or vasopressin neurophysin II encodes, respectively,
 - (a) a signal peptide, vasopressin, and the variable amino-terminal end of neurophysin;
 - (b) the highly conserved middle portion of neurophysin; and
 - (c) the variable, carboxy-terminal end of neurophysin and copeptin, a glycosylated peptide of unknown function.
- The gene for the oxytocin precursor is similar except that exon C is shorter and codes only for the variable carboxy terminus of neurophysin and a single histidine residue. The copeptin moiety is absent
- In humans and other mammals, the vasopressin and oxytocin genes are expressed in different magnocellular neurons

- Following transcription, the mRNA is translated into a preprohormone.
- the preprohormones are then translocated into the endoplasmic reticulum,
- There, the signal peptide is removed and the prohormones fold and self-associate before moving through the Golgi apparatus and on into the neurosecretory granules together with processing enzymes. (packaging)
- the granules are transported down the axons and the prohormone is cleaved into intact hormone, neurophysin, and, in the case of vasopressin, copeptin.
- Translocation through the supraopticohypophysial tract ends in the nerve ending in the posterior pituitary gland.

Secretion of hormones: vasopressin

- Basically, two stimuli trigger the secretion of vasopressin,
 - increase in Plasma osmolality } CNS stimuli
 - Decrease in circulatory volume }
- The osmostats are located in the hypothalamus and anatomically related to the thirst centre; they respond differently to different solutes, Na⁺ being the most potent
- On the other hand, pressor receptors are anatomically diffuse;
 - In the carotid sinus } High pressure receptors
 - Aortic arches }
 - Left atrium } low pressure volume receptors

Secretion of hormones cont.

- Chemical mediators of vasopressin release includes, catecholamines, angiotensin, atrial natriuretic peptide.
- Release of the hormones and their associated neurophysins occurs via a calcium-dependent exocytotic process.
- An electrical impulse propagated along the neuron depolarizes the cell membrane,
- this causes an influx of calcium, fusion of secretory granules with the outer cell membranes, and extrusion of their content

Secretion of hormone: Oxytocin

- Stimuli that cause oxytocin release include:
 - Sucking of the nipple of a lactating mother.
 - Stretching of the vaginal wall during delivery.
- These stimuli are mediated through the CNS.

Functions

- Vasopressin.
 - Depending on which receptor is stimulated, vasopressin can function as an anti diuretic or vasoconstricting hormones.
 - stimulation of the V2 receptors in the renal collecting tubule increases its permeability to water by inserting water channels called Aquaporin-2 in the apical surface of the tubular cells. Water is reabsorbed.
 - Stimulation of V1 receptors in the vascular smooth muscle, leads to vasoconstriction – increase in blood pressure.

- Oxytocin
 - Stimulation of the nipple of lactating mothers during sucking causes the release of oxytocin to induce myocontraction of the ductile smooth muscles in the breast to eject milk.
 - At parturition, the uterus becomes increasingly sensitive to oxytocin and pulses of oxytocin enhances uterine tone at term and delivery.
 - In enhancing uterine contraction, it inhibits blood loss after delivery.

Mechanism of action

- Action of vasopressin is mediated by two receptors;
 - V1 receptors found in the vascular smooth muscles
 - V2 receptors found in the collecting duct of the renal tubules
- Stimulation of the V2 receptors leads to the activation of the G-protein, then the activation of adenylate cyclase which produces the 2nd messenger cAMP. The latter mediates synthesis and/or insertion of aquaporin-2 at the apical surface of the collecting duct cells.
- for V1 receptor (stimulated at high vasopressin conc.), effect is mediated by increase in intracellular Ca⁺⁺ conc. Increase in intracellular Ca⁺⁺ increases contraction of the smooth muscles hence vasoconstriction.
- Osmostats are more sensitive than the baroreceptors; they respond to as small as 1% change in plasma osmolality.

Mechanism cont.

- Oxytocin
 - Like the receptors of vasopressin which mediate its different effect, that of oxytocin is similar.
 - Activation of these receptors ends up in an increase in intracellular Ca⁺⁺.
 - Ca⁺⁺ promotes smooth muscle contraction hence release of milk, contraction of uterus.

DIABETES INSIPIDUS

Diabetes insipidus refers to the passage of large volume (>4L/day) of hypotonic insipid urine, usually accompanied by polyuria and polydipsia.

- Three pathophysiologic conditions result in diabetes insipidus
 - An absolute or partial deficiency of vasopressin secretion from the neurohypophysis in response to normal osmotic stimulation is termed **hypothalamic diabetes insipidus**
 - decreased renal sensitivity to the antidiuretic effect of vasopressin circulating in normal or high concentrations is usually called **nephrogenic diabetes insipidus**
 - ingestion of excessive volumes of fluid, which results in suppression of vasopressin release and consequent polyuria. This condition is referred to as dipsogenic diabetes insipidus, sometimes termed primary polydipsia.
- All three conditions are characterised by polyuria, polydipsia, and normal Na⁺ concentration.

Clinical features/Etiology

1. Hypothalamic diabetes insipidus (HDI)
 - Following cranial surgery or trauma to the head
 - Characterised by sudden appearance of hypotonic polyuria,
 - Thirst
 - Hypernatraemia in situation where patient can't respond to thirst.
 - Most patients do not complain of polyuria until urine volume exceeds 4L/day and this only occurs in the absence of vasopressin.

- Absence of osmostat with intact volume receptors.
 - Characterized by increase in Na⁺, absence of thirst
 - Following dehydration, volume depletion lead to secretion of vasopressin ;
 - But if sufficient fluid replacement is given to return blood volume to normal, the patient become unable to regulate vasopressin secretion by osmolality, giving rise to characteristic HDI

- Hereditary HDI
 - It is mainly due to a single nucleotide substitution or deletion on the vasopressin gene.
 - rarely caused by autosomal dominant pattern of inherited disease.
 - In animal models DI is reported only in autosomal recessive conditions ie, expressed only in homozygote rats; 50% expression can prevent the disease.
 - In the human disorder, DI is not present at birth but only develop in childhood or early adult, speculated to be as a result of the vasopressin translation product from the mutated gene destroying the vasopressinergic neurones.

- Gestational DI
 - this is due to rapid catabolism of vasopressin by the placental enzyme vasopressinase and oxytocinase; a cystine aminopeptidase
 - This leads to an increase in the metabolic clearance.
 - Polyuria become manifested only in patient who have a limited vasopressin reserve due to
 - Decrease ability to secrete vasopressin as in partial HDI
 - Inability to respond to vasopressin as in compensated nephrogenic DI
 - In some patients, HDI of any cause become symptomatic during pregnancy and there after follow the normal course of the disease.

2. Nephrogenic DI(NDI)

- This is diabetes caused by failure to respond to vasopressin. Respond failure could be due to
 - Mutation in the V2 receptor gene
 - Mutation in the Aquaporin-2 gene.
- The V2 receptor gene has been located on the Xq28 region of the X-chromosome and the disease caused is a rare, recessive X-linked, and found in males.
- Aquaporin-2 NDI is also rare but is an autosomal recessive condition.
- NDI could be acquired as a result of drugs. Eg in the treatment of SIADH release, NDI may result.

3. Dipsogenic diabetes insipidus.

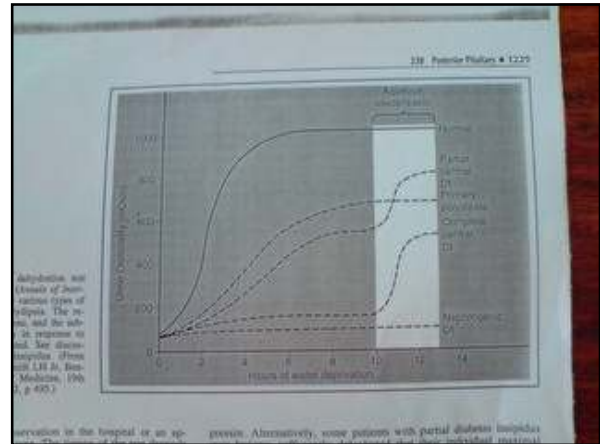
- In some patient ,primary polydipsia follow acute trauma to the hypothalamus and is severe and unremitting .
- The etiologies of hypothalamic DI can cause primary stimulation of thirst.
- Patient may drink even greater amount of fluid (>20L/day) than patient with HDI
- Some patients have psychiatric disorders that contribute to polydipsia.

diagnosis

1. Physiologic

- Polyuria resulting from renal injury , intravenous contrast agent, is differentiated from DI by isotonic urine osmolality, medical history, and routine clinical lab tests.
- Low or absent in plasma vasopressin level, inappropriately low urine osmolality in the presence of elevated serum osmolality due to Na⁺ confirms DI

- Stimulation test for differential diagnosis.
 - Dehydration plus vasopressin agonist
 - Performed in patients with normal Na⁺, polydipsia, polyuria.
 - Confirms DI if after administration urine osmolality increase and urine volume decrease.
 - <5% increase in urine osmolality --- normal
 - No urine concentration—nephrogenic DI
 - Urine concentration in response to dehydration—partial HDI or Dipsogenic DI



- Etiologic diagnosis
 - Technique used in the identification of the cause of a lack or diminished secretion or production of vasopressin. Nuclear magnetic resonance NMR of the brain is done to locate tumors interfering with normal nerve tract.

Treatment

- Since water diuresis is the primary manifestation of DI, water replacement in adequate quantity avoids metabolic complication.
- Therapy reduces polyuria, polydipsia to a tolerable level
- Over treatment can cause hyponatraemia
- Best therapeutic agent is desmopressin; it acts only on V2 receptors with minimal action on V1

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