The neurohypophysis, or posterior pituitary gland, is formed by axons that project from large cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus to the posterior portion of the sella turcica. It produces two hormones:

1. Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), and
2. Oxytocin

AVP acts on the renal tubules to induce water retention, leading to concentration of the urine. Oxytocin stimulates postpartum milk letdown in response to suckling.

AVP deficiency causes diabetes insipidus (DI), characterized by the production of large amounts of dilute urine. Excessive or inappropriate production of AVP predisposes to hyponatremia, reflecting water retention.

There are no known clinical disorders associated with oxytocin deficiency or excess.

**DI - Etiology**

Secondary: inhibition of secretion by excessive intake of fluids → primary polydipsia - three subcategories

- Dipsogenic DI: inappropriate increase in thirst caused by a reduction in the “set” of the osmoregulatory mechanism - causes: multifocal diseases of the brain such as neurosarcoid, tuberculous meningitis, or multiple sclerosis, often idiopathic
- Psychogenic polydipsia - polydipsia is a feature of psychosis
- Iatrogenic polydipsia - recommendations of health professionals to increase fluid intake

Nephrogenic DI: primary deficiency in the antidiuretic action of AVP

- can be genetic, acquired, or caused by exposure to various drugs
Diagnosis

- Symptoms: urinary frequency, enuresis, nocturia, and/or persistent thirst
- 24-h urine output > 50 mL/kg per day (>3500 mL in a 70-kg man) is suspicious for DI
- Osmolality of the 24-h urine is >300 mosmol/kg, should be evaluated for uncontrolled diabetes mellitus or other causes of excessive solute excretion
- If the 24-h urine osmolality is <300 mosmol/kg, should be evaluated further to determine which type of DI is present.
- Differentiating between the various types of DI: history, physical examination, and routine laboratory tests may be helpful

Fluid deprivation test

- Contraindication: if the patient is clearly dehydrated
- The test should be started in the morning and water balance should be monitored closely with hourly measurements of body weight, plasma osmolality, and/or sodium concentration, and urine volume and osmolality
- In primary polydipsia and in partial defect in AVP secretion or action – urine gets concentrated
- In severe pituitary or nephrogenic DI - fluid deprivation does not result in urine concentration (osmolality>300 mosmol/kg, specific gravity>1.010) before body weight decreases by 5% or plasma osmolality/sodium exceed the upper limit of normal

Desmopressin test

- Used to distinguish between severe pituitary and nephrogenic DI
- Administer desmopressin (0.03 μg/kg sc. or iv.), then repeat the measurement of urine osmolality 1 to 2 h later
- An increase of >50% indicates severe pituitary DI
- A smaller or absent response is strongly suggestive of nephrogenic DI

MRI

- MRI of the pituitary and hypothalamus
- The posterior pituitary emits a hyperintense signal in T1 weighted mid-saggital images
- This ‘bright spot’ is absent or abnormally small in patients with pituitary DI but is present in 90 to 90% of those with primary polydipsia
- The presence of a normal bright spot virtually excludes pituitary DI, whereas its absence supports but does not prove this diagnosis
- MRI findings must be interpreted with caution and only in conjunction with other diagnostic studies

TREATMENT

- DDAVP - synthetic analogue of AVP – iv. or sc. inj., nasal inhalation or oral tablet
- Acts selectively at V2-receptors to increase urine concentration and decrease urine flow in a dose-dependent manner
- The doses required to control pituitary DI completely vary widely, depending on the patient and the route of administration – usual range is 1 to 2 μg qd or bid by injection, 10 to 20 μg bid or tid by nasal spray, and 100 to 400 μg bid or tid orally
- Onset of action is rapid (15 min for inj., 60 min for tablet)

Chlorpropamide

- Pituitary DI can also be treated with chlorpropamide
- Mechanism of its antidiuretic action is uncertain (may potentiate the effect of small amounts of AVP or direct activation of the V2 receptor)
- Dose: 125 to 500 mg once daily
- It increase urine concentration and decrease urine flow, thirst, and polydipsia in a manner similar to DDAVP
- Reduce urine output by 30 to 70%
- Its antidiuretic effect can be enhanced with a thiazide diuretic
- Side effects: hypoglycemia, exhibits a disulfiram-like reaction to ethanol
- Contraindicated in the treatment of gestational DI because its teratogenicity is unknown
Primary polydipsia cannot be treated with DDAVP – might lead to serious water intoxication. This complication can also be caused by thiazide diuretic, smoking, or other nonosmotic stimuli to endogenous AVP secretion.

There is no effective treatment for either psychogenic or dipsogenic DI. (nocturia or nocturnal enuresis can often be controlled safely by administering a single small dose of DDAVP at bedtime)

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n nephrogenic DI – no use of DDAVP or chlorpropamide, but symptoms and signs may be reduced with a thiazide diuretic and/or amiloride in conjunction with a low-sodium diet. Inhibitors of prostaglandin synthesis (e.g., indomethacin) are also effective in many patients.

EXCESS VASOPRESSIN SECRETION AND ACTION

Clinical Characteristics
- Excessive secretion or action of AVP → decreased volume of highly concentrated urine
- Water retention and a decrease in plasma osmolality/sodium
- Hyponatremia:
  - Slowly developing - may be asymptomatic
  - Acute - symptoms and signs of water intoxication: mild headache, confusion, anorexia, nausea, vomiting, coma, and convulsions
- Severe hyponatremia may be lethal.

Etiology

Primary form: SIADH (Syndrome of Inappropriate Antidiuretic Hormone) or also called as euvoletic (type III) hyponatremia

Secondary forms:
- Type I (hypervolemic) hyponatremia: sodium-retaining, edema-forming states such as congestive heart failure, cirrhosis, or nephrosis
- Type II (hypovolemic) hyponatremia: sodium-depleted states such as severe gastroenteritis, diuretic abuse, or mineralocorticoid deficiency

Causes of SIADH

- Neoplasms:
  - Ca: Lung, duodenum, pancreas, ovary, bladder, ureter
  - Others: Hematoma, mesothelioma, bronchial adenoma, carcinoid, gangliocytoma, Ewing's sarcoma
- Head trauma
- Infections: Pneumonia, abscess (lung, brain), aspergillosis, TB, meningitis, encephalitis, AIDS
- Vascular: CVA (isch., haemorrh.), cavernous sinus thrombosis
- Neurologic: Guillain-Barré syndrome, Multiple sclerosis, Demyelinating diseases, Encephalitis, Hydrocephalus, Psychosis, Peripheral neuropathy
- Pulm.: Asthma, pneumothorax, positive-pressure respiration
- Drugs: Vasopressin or desmopressin, Chlorpropamide, Oxytocin, Vincristine, Carbamazepine, Nicotine, Phenothiazines, Cyclophosphamide, Tricyclic antidepressants, Monamine oxidase inhibitors, Serotonin reuptake inhibitors

Treatment of acute SIADH

- Keystone: restrict total fluid intake to less than the sum of insensible losses and urinary output
- Total intake at least 500 mL/day less than urinary output. This deficit usually reduces body water and increases serum sodium by about 1 to 2% per day
- If more rapid correction of the hyponatremia is desired – iv infusion of hypertonic (3%) saline → corrects hyponatremia and also helps to produce diuresis to remove excess water
- If hyponatremia lasts for more than 24 to 48 h and is corrected too rapidly, the same infusion also has the potential to produce central pontine myelinolysis, an acute, potentially fatal neurologic syndrome characterized by quadriparesis, anoxia, and abnormal extracellular movements

How to prevent central pontine myelinolysis

- Increase in serum sodium conc. should be max. 8 mmol/L in 24 hours
- The 3% saline should be infused at a rate of 0.05 mL/kg body weight per minute
- The effect should be monitored continuously by STAT measurements of serum sodium at least once every hour
- Urinary output should also be monitored continuously since spontaneous remission of the SIADH can result in an acute water diuresis that greatly accelerates the rate of rise in serum sodium
Treatment of chronic SIADH

demeclocycline, 150 to 300 mg orally 3 or 4 times a day, or
• effect manifests in 7 to 14 days and is due to production of a reversible form of nephrogenic DI
• side effects: phototoxicity and azotemia
fludrocortisone, 0.05 to 0.2 mg orally twice a day
• effect manifests in 1 to 2 weeks and is partly due to increased retention of sodium and possibly inhibition of thirst
• increases urinary potassium excretion, which may require replacement through dietary adjustments or supplements
• may induce hypertension, occasionally necessitating discontinuation of the treatment