Diseases of the posterior pituitary

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Figure 11-3: Autonomic control centers in the brain
POSTERIOR PITUITARY GLAND

Paraventricular nucleus

Supraoptic nucleus

Hering bodies

Optic chiasm

Posterior pituitary
Pituitary - Embryology and Anatomy

- posterior pituitary - neurohypophysis
  - outpouching floor 3rd ventricle
  - nervous connection to hypothalamus
  - octapeptides - oxytocin, vasopressin (ADH)
POSTERIOR PITUITARY

Comprised of the endings of axons from cell bodies in the hypothalamus (supraoptic and paraventricular)

Axons pass from the hypothalamus to the posterior pituitary via the hypothalamohypophysial tract

Posterior pituitary hormones are synthesized in the cell bodies of neurons in the supraoptic and paraventricular nuclei
Figure 7-12: Synthesis, storage, and release of posterior pituitary hormones

Hormone is made and packaged in the cell body of a neuron.

Vesicles are transported down the cell.

Vesicles containing hormone are stored in the posterior pituitary.

Hormones are released into the blood.
POSTERIOR PITUITARY

Hormones synthesized in the hypothalamus are transported down the axons to the endings in the posterior pituitary.

Hormones are stored in vesicles in the posterior pituitary until release into the circulation.

Principal Hormones: Vasopressin & Oxytocin
vasopressin

Phe  Tyr  Cys

Glu  Asn

Cys  Pro  Arg  Gly  (NH₂)

oxytocin

Ile  Tyr  Cys

Glu  Asn

Cys  Pro  Leu  Gly  (NH₂)
POSTERIOR PITUITARY HORMONES

• ANTI DIURETIC HORMONE (ADH):
  – Also called Vasopressin
  – Produced predominantly by the Supra Optic Nucleus (SON) of the Hypothalamus.

• OXYTOCIN:
  – Produced predominantly by the ParaVentricular Nucleus (PVN) of the Hypothalamus.
  (Note: Both hormones are produced by both the nuclei.)
ANTIDIURETIC HORMONE (ADH)

– ALSO CALLED **VASOPRESSIN**
– AN OCTAPEPTIDE SECRETED MAINLY FROM THE SUPRA-OPTIC NUCLEUS.
NET WATER LOSS FROM BODY (water loss exceeds electrolyte loss)

ECF Osm

SENSOR

INCREASED OSMOLALITY IS SENSED IN HYPOTHALAMUS

EFFECTOR

THIRST CENTER TRIGGERED

WATER INTAKE

WATER ADDED TO THE BODY

BODY FLUID OSMOLALITY NORMALIZED

EFFECTOR

ADH RELEASED INTO BLOOD

ADH STIMULATES KIDNEY TO RETAIN FREE WATER

Université d'Ottawa
University of Ottawa
ADH receptors

Four subtypes of receptors identified
All G protein-coupled
V1 – smooth muscle in vascular tissue
  - V1a – liver
  - V1b (V3) – anterior pituitary
V2
  - renal collecting ducts, mediates the principal physiological action of vasopressin
V2 on collecting ducts epithelium → cAMP → PKA → CREBP (cAMP regulatory element-binding protein) → ↑ aquaporin (water channel) formation

V2 → cAMP → PKA → phosphorylation of aquaporin → ↑ insertion of aquaporin in the process of exocytosis

Leads to increased H2O reabsorption by kidney
• ADH acts on the Aquaporin 2 channels
  - formation
  - opening
10 different Aquaporin channel is known, the A2 channel expression is ADH mediated
A2 is responsible for the water transport on the luminal side of the CT from the nephron to the collecting tubule
AQP3 and AQP4

These are constitutively expressed

AQP2 is in the apical membrane only when ADH activates its’ V2 receptor

CCD – Collecting Duct
IMCD - Inner Medullary Collecting Duct

http://www2.kumc.edu/ki/physiology/course/six/6_1.htm
Dr. Bolliger Kansas University Medical Center 1999
- ADH also decreases the medullar blood flow, and enhances the urea transport in the DT and the sodium transport towards the interstitium.
- Result is ADH dependent water resorption due to hypertonic interstitium.
ADH: FUNCTIONS

• Increased Re-absorption of water from the DT/CT of the renal nephrons.
  – Mode of Action: Aquaporins

• Increases the permeability of nephrons for Urea.

• Vasoconstriction: Only in extremely high, pharmacological dosages.
ADH as a neurotransmitter in the brain

Antipyresis
Memory consolidation and learning
Analgesia
Increases paternal behavior, territorial aggression and partner preference
“Perfect husband hormone”
Necessary and sufficient for partner preference (monogamy)
V1 antagonist blocked partner preference
Diabetes insipidus
Diabetes Insipidus

- partial or complete absence of vasopressin
- tumor, inflammation, granuloma, trauma, vascular

TABLE 22
Etiology of Central Diabetes Insipidus

<table>
<thead>
<tr>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Pituitary surgery</td>
</tr>
<tr>
<td>Suprasellar tumor</td>
</tr>
<tr>
<td>Graniopharyngioma</td>
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<tr>
<td>Meningioma</td>
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<tr>
<td>Dysgerminoma</td>
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<tr>
<td>Hamartoma</td>
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<tr>
<td>Metastatic malignancy</td>
</tr>
<tr>
<td>Breast</td>
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<tr>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Sarcoidosis</td>
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<tr>
<td>Hand–Schuller–Christian disease (histiocytosis X)</td>
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<tr>
<td>Vascular</td>
</tr>
<tr>
<td>Sheehan’s apoplexy</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Encephalitis</td>
</tr>
<tr>
<td>Rarely, basal meningitis</td>
</tr>
<tr>
<td>Traumatic</td>
</tr>
<tr>
<td>Basal skull fracture</td>
</tr>
</tbody>
</table>
• Central DI
  – occurs suddenly
    • after intracranial surgery
    • Usually has triphasic pattern
      – acute phase - abrupt onset of polyuria
      – Interphase - urine volume apparently normalizes
      – third phase - central DI is permanent-the third phase is usually apparent within 10-14 days postoperatively

• Neurogenic DI
  – occurs from head trauma and is usually self-limiting
  – may improve with treatment of the underlying problem
  – If oral fluid cannot keep up with urinary losses, severe fluid volume deficit occurs
Clinical manifestations

- Characterized by
  - increased thirst (polydipsia)
  - Increased urination (polyuria)
• Primary characteristic of DI is
  – the excretion of large quantities of urine (5-20 liters/day)
  – urine has low specific gravity (less than 1.003)
  – urine osmolality of less than 100 mOsm/kg
  – Serum osmolality is greater than 295 mOsm/kg
  – in the milder form urine output may be only 2-4 liters/day
  – the client compensates by drinking large amounts of water so that serum osmolality is normal or only moderately elevated
Diabetes Insipidus

- clinical features
  - associated features: visual field loss, optic atrophy, papilledema, other pituitary hormone abnormalities
- Severe fluid volume deficit results in
  - hypovolemia
  - poor tissue turgor
  - hypotension
  - tachycardia
  - constipation
  - signs of shock, CNS manifestations
  - irritability
  - mental dullness
  - coma

- These symptoms are a result of rising serum osmolality and hypernatremia

- Because of the polyuria, severe dehydration and hypovolemic shock may occur
• Must identify the cause
  – Pituitary (central or neurogenic)
  – Renal (Nephrogenic)
  – Psychologic (psychogenic)
• Rule out psychogenic DI related to emotional disturbances—occurs with overhydration and hypervolema rather than dehydration and hypovolemia seen in other forms of DI
• Therapeutic goal-
  – maintenance of adequate fluid and electrolyte balance
  – May be accomplished by IV administration of fluid (saline and glucose)
  – Hormone replacement with ADH(vasopressin)-IV, SC or IM
  – In acute DI fluids should be administered at a rate that decreases the serum sodium by about 1 mEq/l every two hours
- Atromid, tegretol and thiazide diuretics may also be prescribed for symptomatic DI
- Long term therapy may be controlled with desmopressin acetate (DDAVP)-an analog of ADH that is administered nasally.
- It does not have the vasoconstrictive effect of vasopressin
Long-term care

• Long-term ADH replacement needs instruction in self-management
  – DDAVP- is usually taken intranasally twice daily
  – side effects include
    • nasal irritation
    • headache
    • nausea
  – These can indicate overdosage.
  – Adequate client teaching of the outcomes expected of the medication is necessary to insure adequate treatment
Diabetes Insipidus

- treatment
  - acute- liberal fluid replacement, short-acting aqueous vasopressin
  - chronic- dDAVP intranasally BID
Nephrogenic DI (NDI)

- Rare disease
  - inherited
  - genetical variant
- X-chromosome associated recessive NDI: (Xq28) – ADH receptor 2 genetic mutation
- Autosomal recessive NDI: Aquaporin 2 channel defect
Nephrogenic DI

**Primary NDI**

- A congenital defect in which the kidneys are unable to respond to AVP (due to ADH receptor defect)
SIADH

Syndrome of inappropriate ADH
• Etiology and pathophysiology
  – occurs when ADH is released in amounts far in excess of those indicated by plasma osmotic pressure
  – this syndrome is associated with disease that affect osmoreceptors in the hypothalamus
  – is more common in the elderly
• SIADH is characterized by
  – fluid retention
  – serum hypoosmolality
  – dilutional hyponatremia
  – hypchloremia
  – concentrated urine in the presence of normal or increased intravascular volume
  – normal renal function
Clinical Manifestations

- Excess ADH increases renal tubular permeability and reabsorption of water into the circulation
- ECF volume expands, plasma osmolality declines and GFR increases
- Sodium levels decline (dilutional hyponatremia)
- This hyponatremia causes muscle cramps, weakness etc
- The client with SIADH experiences
  - low Urine output
  - increased body weight without edema
SIADH has various causes

- pulmonary conditions-pneumonia, TB, lung abscesses, Positive pressure ventilation
- Trauma (most frequently head related)
- meningitis, subarachnoid hemorrhage
- AIDS, Addison’s disease
- peripheral neuropathy, psychoses
- vomiting, stress and many medications
- symptoms may also be caused by ADH secreting tumors
Drugs associated with SIADH

- Drugs that stimulate AVP release:
  - Acetylcholine
  - Antineoplastic agents - Adenine arabinoside, cyclophosphamide, ifosfamide, vincristine, vinblastine
  - Barbiturates, Bromocriptine, Carbachol, Chlorpropamide,
  - Dibenzazepines (eg, carbamazepine Tegretol®, oxcarbazepine)
  - Halothane, Haloperidol, Histamine, Isoproterenol, Lorcanide
  - Opiates e.g. Morphine, Nicotine (inhaled tobacco)
  - Monoamine oxidase inhibitors (eg, tranylcypromine)
  - Tricyclic antidepressants (eg, amitriptyline, desipramine)
Drugs associated with SIADH

- Drugs that potentiate the effects of AVP action (primarily facilitates peripheral action of ADH):
  - Griseofulvin
  - Hypoglycemic agents – Metformin, phenformin, tolbutamide
  - Oxytocin (large doses)
  - Prostaglandin synthetase inhibitors (inhibit renal PGE\textsubscript{2} synthesis) – Indomethacin, aspirin, nonsteroidal anti-inflammatory drugs
  - Theophylline
  - Triiodothyronine
  - Vasopressin analogs (eg, AVP, DDAVP)
Drugs associated with SIADH

• Drugs with an uncertain mechanism:
  • Antineoplastic agents – Cisplatin, melphalan, methotrexate, imatinib
  • Ciprofloxacin
  • Clomipramine
  • Ecstasy (MDMA) 3,4-Methylenedioxymethamphetamine
  • Phenoxybenzamine
  • Na⁺ valproate
  • SSRIs (eg, sertraline, fluoxetine, paroxetine)
• As serum sodium levels continue to decline
  – cerebral edema occurs
  – lethargy
  – anorexia
  – confusion
  – headache, seizures, coma and possibly death if untreated
### TABLE 1  Drugs that may cause SIADH

<table>
<thead>
<tr>
<th>ADH analogues</th>
<th>Antineoplasticss</th>
<th>Cardiovascular agents</th>
<th>Psychotropics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmopressin (DDAVP)</td>
<td>Alemuzumab</td>
<td>Amiodarone</td>
<td>Antipsychotics</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Aminogluthethimide</td>
<td>Cilazapril</td>
<td>– amisulpride</td>
<td>nortriptyline</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Chlorambucil</td>
<td>Clofibrate</td>
<td>– aripiprazole</td>
<td>MDMA (ecstasy)</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>Clonidine</td>
<td>– chlorpromazine</td>
<td>Nicotine</td>
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<tr>
<td></td>
<td>Cisplatin</td>
<td>Enalapril</td>
<td>– clozapine</td>
<td>Omeprazole</td>
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<tr>
<td>Analgesics</td>
<td>Cyclophosphamide</td>
<td>Hydrochlorothiazide</td>
<td>– fluphenazine</td>
<td>Tacrolimus</td>
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<tr>
<td>Diclofenac</td>
<td>Docetaxel</td>
<td>(and other thiazide</td>
<td>– haloperidol</td>
<td>Theophylline</td>
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<tr>
<td>Fentanyl</td>
<td>Etoposide</td>
<td>diuretics)</td>
<td>– pimozide</td>
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<tr>
<td>Ibuprofen</td>
<td>Ifosfamide</td>
<td>Lisinopril</td>
<td>– risperidone</td>
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<td></td>
<td>Levamisole</td>
<td>Lorcanide</td>
<td>– thioridazine</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine</td>
<td>Meplhalan</td>
<td>– trifluoperazine</td>
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<tr>
<td>Levetiracetam</td>
<td>Rituximab</td>
<td>Methyldopa</td>
<td>– thiothixene</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Thiopeta</td>
<td>Phenoxybenzamine</td>
<td>Bupropion</td>
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<tr>
<td>Valproic acid</td>
<td>Vinblastine</td>
<td>Propafenone</td>
<td>Reboxetine</td>
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<tr>
<td></td>
<td>Vincristine</td>
<td>Ramipril</td>
<td>Duloxetine</td>
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</tr>
<tr>
<td>Anti-infectives</td>
<td>Vino relbine</td>
<td>Hypoglycemic agents</td>
<td>Lorazepam</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Amphotericin</td>
<td>Chlorpropamide</td>
<td>Mirazapine</td>
<td></td>
</tr>
<tr>
<td>Dalrafpristin/quinupristin</td>
<td>Levodopa</td>
<td>Glimepiride</td>
<td>Phenelzine</td>
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</tr>
<tr>
<td>Lopinavir</td>
<td>Pramipexole</td>
<td>Tolbutamide</td>
<td>SSRIs</td>
<td></td>
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<tr>
<td>Miconazole</td>
<td>Trihexyphenidyl</td>
<td></td>
<td>– citalopram</td>
<td>– escitalopram</td>
</tr>
<tr>
<td>Rifabutin</td>
<td></td>
<td></td>
<td>– fluoxetine</td>
<td>– fluvoxamine</td>
</tr>
</tbody>
</table>
Diagnosis

• Diagnosis of SIADH is made by simultaneous measurement of urine and serum osmolality
  – A serum osmolality lower than the urine osmolality indicates the inappropriate excretion of concentrated urine in the presence of very dilute serum
  – Dilutional hyponatremia is indicated by serum sodium less than 134 mEq/l, serum osmolality less than 280 mOsm/kg, and specific gravity greater than 1.005
• Associated clinical manifestations correlate with serum sodium levels
  – initially
    • thirst, dyspnea on exertion, fatigue and dulled sensorium
  – as serum sodium falls below 120mEq/l
    • symptoms are more severe with
      • vomiting
      • abdominal cramps, muscle twitching
      • seizures
  – other Labs include decreased BUN, creatinine clearance
Treatment Goal

- restore normal fluid volume and osmolality
  - If symptoms are mild and serum sodium is greater than 125 mEq/l
    - the only treatment may be fluid restriction of 800-1000ml/day
    - This restriction should result in a gradual daily reduction in weight, a progressive rise in serum sodium concentration and osmolality, and symptomatic improvement
• If fluid restriction alone does not improve the symptoms
  – 3-5% saline solution (hypertonic) is administered IV
  – Diuretic therapy may be indicated to promote diuresis
  – Lasix (furosemide) is usually used - it does not spare potassium and replacement may be necessary
Chronic SIADH

• Water restriction of 800-1000ml/day is recommended
• If this is not tolerated two medications may be used
  – Stadol - which inhibits ADH secretion and is useful in central nervous system causes of SIADH
  – Declomycin (a tetracycline) - causes nephrogenic diabetes insipidus and blocks the action of ADH at the level of the distal and collecting tubules regardless of ADH source
Pituitary - SIADH

- **Clinical features**
  - fatigue, muscle weakness, dizziness, behavioral changes, drowsiness, Na < 120
  - stupor, convulsions, coma
  - urine osmolality not maximally dilute despite hypotonicity

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**TABLE 24**

<table>
<thead>
<tr>
<th>Response to Hypotonic Plasma in the Normal State and SIADH</th>
<th>Normal</th>
<th>SIADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotonic plasma</td>
<td>Hyponatremia/hypotonic plasma</td>
<td></td>
</tr>
<tr>
<td>Prompt suppression of vasopressin (ADH)</td>
<td>Failure of vasopression suppression (or increased vasopression levels)</td>
<td></td>
</tr>
<tr>
<td>Prompt suppression of water reabsorption in distal and collecting tubule</td>
<td>Continuous water reabsorption at the distal and collecting tubule</td>
<td></td>
</tr>
<tr>
<td>Dilution of urine due to increased water excretion</td>
<td>Urine relatively concentrated</td>
<td></td>
</tr>
<tr>
<td>Conservation of solute</td>
<td>Continuous natriuresis</td>
<td></td>
</tr>
<tr>
<td>Excretion of dilute urine</td>
<td>Excretion of less than maximally dilute urine</td>
<td></td>
</tr>
<tr>
<td>Restoration of plasma osmolality to normal</td>
<td>Persistence of low plasma osmolality</td>
<td></td>
</tr>
</tbody>
</table>
Pituitary - SIADH

• diagnostic criteria
  – hypotonicity of plasma
  – hyponatremia
  – less than max dilute urine
  – natriuresis
  – exclusion of other causes

• treatment
  – water restriction 600-800 ml/day
  – Demeclocycline (Declomycin) 900-1200 mg/day- blocks vasopressin at DCT
  – hypertonic saline if sodium < 115 mEq/L
OXYTOCIN : FUNCTIONS

• ON THE BREAST:
  - Causes Milk ejection and secretion through a Neuro-endocrine reflex.
• On the **NON PREGNANT uterus:**
  – Movement of the Female Genital Tract
  – Transport of the Sperm
  – Fertilization
• On the **PREGNANT** uterus:
  • Initiates Parturition or Labour.
  • Enhances Uterine contractions during labor.
  • Stretches the birth canal by a Positive feedback mechanism
  • Causes involution of the Uterus after delivery.
MILK EJECTION REFLEX

SUCKLING

↑ MILK LET DOWN

↑ MILK PRODUCTION

GENERAL SOMATIC AFFERENCE THROUGH SPINOPTHALAMIC TRACTS

PVN/ HYPOTHALAMUS

RELEASE OF OXYTOCIN

PRODUCTION OF PROLACTIN
• There are two distinctive features of this reflex.

  – It is a **NEURO-ENDOCRINE** Reflex:
    • Neural Afference
    • Hormonal Efference.

  – It is a **POSITIVE FEEDBACK** MECHANISM.
    • Can be also called as a vicious circle.
    • Is terminated only by stopping of suckling.
• Oxytocin (along with estrogen) induces maternal behavior in virgin female rats.
Oxytocin is present in high quantities in breast milk. It is also produced in detectable amounts in the brains of newly born mammals.
• Oxytocin is likely responsible for the reciprocal bonding of the offspring to their mother.
• Oxytocin is released at climax of human sexual response (both sexes)
  Females: contractions of the non-pregnant uterus
  Males: contractions of the vas deferens – ↑ sperm transport
• Increases partner preference (pair bonding) in females but not males
• No known pathologies, although deficiency of oxytocin secretion results in difficulty in nursing due inadequate milk ejection