Posterior Pituitary Hormones

- **ADH (Vasopressin) & Oxytocin**

Nonapeptides (9 a.a)

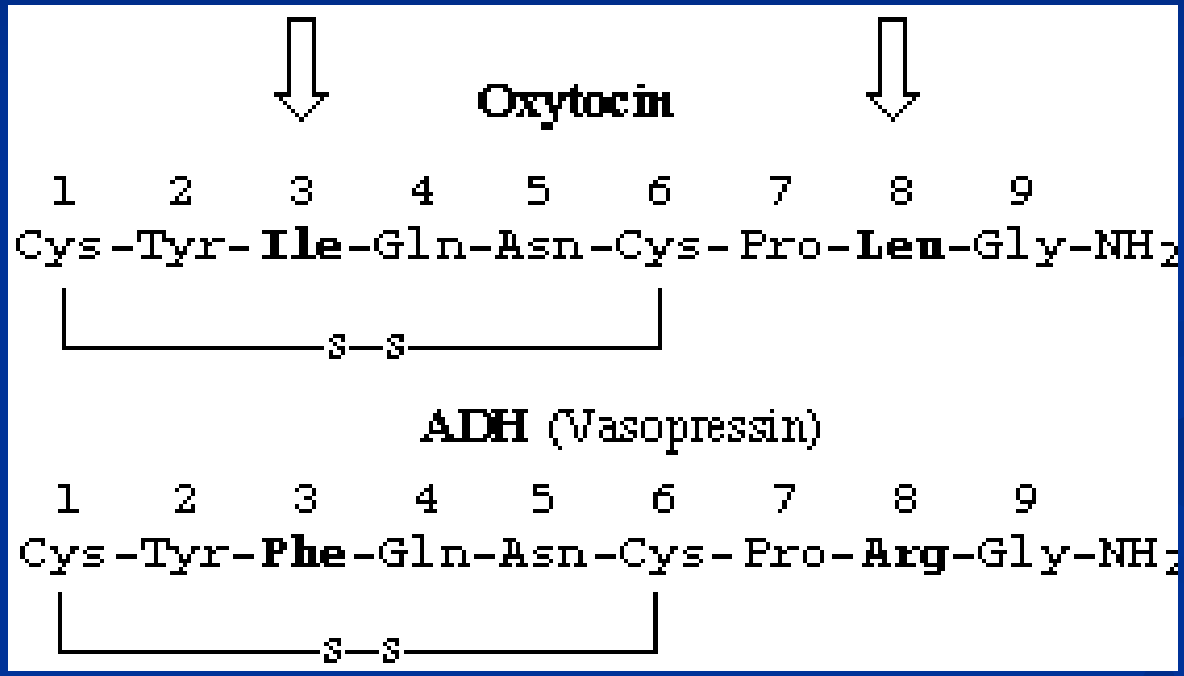
Known as neurohormones

Synthesized in the hypothalamus

Stored in the posterior pituitary → release

? Role as neurotransmitters (V_1R's in CNS)

Role of Oxytocin in man is unknown


Oxytocin
1 2 3 4 5 6 7 8 9
Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH2
S—S
ADH (Vasopressin)
1 2 3 4 5 6 7 8 9
Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH2
S—S

- **ADH (Vasopressin) (arginine vasopressin; argipressin)**

Physiological and pharmacological actions:

- Vasoconstriction & ↑ platelet aggregation (V_1a receptors)
- ↑ reabsorption of H_2O from collecting ducts (V_2 receptors)
- ↑ synthesis of certain clotting factors (VIII, Von Willebrand) (V_2 receptors)
- ↑ ACTH release (V_1b receptors)
- Oxytocin-like activity

- **Factors/Drugs ↑ ADH release:**

- Hypovolemia, hyperosmolarity, pain, stress, nausea, fever, hypoxia
- Angiotensin II
- Certain prostaglandins
- Nicotine, cholinergic agonists, β-adrenergics
- Tricyclic antidepressants
- Insulin, morphine, vincristine…

- **Factors/Drugs ↓ ADH release:**

- Hypervolemia
- Hypoosmlarity
- Alcohol
- Atrial natriuretic peptide
- Phenytoin
- Cortisol
- Anticholinergics, α-adrenergics, GABA...

- **Disorders affecting ADH release:**

A. Excess production (inappropriate ADH secretion) → Dilutional hyponatremia

Causes:

- Head trauma, encephalitis
- Meningitis, oat cell carcinoma…

R_x:

- Water restriction (R_x of choice)
- Hypertonic saline solution
- Fludrocortisone → ↑ Na^+ blood level
- Loop diuretics (Furosemide)
- ? ADH antagonists

- **ADH antagonists**

- **Conivaptan**, a non-peptide V_1 & V_2 R antagonist given IV

- **Tolvaptan**; Lixivaptan & Satavaptan, a non-peptide orally effective selective V_2R antagonists

Clinical uses:

- Inappropriate ADH secretion

- CHF; liver cirrhosis…

B. Deficiency of ADH → Diabetes insipidus (DI)→ polyuria

Causes:

- Idiopathic DI
- Congenital, Familial DI
- Hypothalamic surgery, head trauma, malignancies
- Gestational DI, overproduction or decreased clearance of vasopressinase

R_x:

ADH preparations (HRT)

- **ADH preparations:**

- Natural human ADH (Pitressin)

Given IM, SC, has short half-life (15 min)

- Lypressin (synthetic, porcine source)

Given intranasally, IV, IM, has short DOA (4hrs)

- Desmopressin (synthetic ADH-like drug=analogue)

Given orally, intranasally, SC, IM

Most widely used preparation, has long DOA (12 hrs)

- Felypressin (synthetic ADH-like drug)

Has strong vasoconstrictor activity

Mainly used in dentistry

- **Clinical uses to ADH:**

- DI
- Nocturnal enuresis
- Hemophilia
- Bleeding esophageal varices

- **Side effects to ADH preparations:**

- Allergy
- Pallor
- Headache, nausea, abdominal pain in ♀'s (oxytocin-like activity)
- Anginal pain (coronary artery vasospasm)
- H_2O intoxication (massive doses)
- Gangrene (rare particularly with desmopressin= has great affinity to V_2 receptors)

Drugs acting on the uterus

I. Uterine stimulants

1. Oxytocin: (nonapeptide=9 a.a peptide)

- Contracts the myoepithelial cells of the breast → milk letdown; milk ejection

Major stimuli, baby cry and suckling

- Contracts the uterus → delivery

The uterus is insensitive to oxytocin in early pregnancy but its sensitivity increases with advanced pregnancy reaching maximum at time of delivery

- Has slight ADH-like activity
- Role in man ???

- **Oxytocin MOA:**

- Surface receptors → stimulation of voltage-sensitive Ca^{++} channels → depolarization of uterine muscles → contractions

- ↑ intracellular Ca^{++}

- ↑ prostaglandin release

- **Clinical uses to oxytocin:**

- Induction of labor

Drug of choice given in units in an I.V infusion

- Postpartum hemorrhage, I.M. Ergot alkaloids are better (ergonovine, methylergonovine, syntometrine= oxytocin+ergometrine)

- Breast engorgement, intranasally

- Abortifacient, IV infusion. ≥ 20 weeks of gestation, ineffective in early pregnancy

- **Side effects to oxytocin:**

- Rupture of the uterus

Major and most serious side effect

- H_2O intoxication and hypertension

Due to its ADH-like activity

- **Specific oxytocin antagonist**

Atosiban (inhibitor to uterine contraction=tocolytic), effective in the management of premature delivery, given IV. Has little vasopressin antagonistic effect

2. Prostaglandins:

* Dinoprostone (PGE_2)

Vaginal pessaries, inserts and gel, tab

Abortifacient, induction of labor

* Dinoprost ($PGF_{2\alpha}$)

IV infusion and intramniotic

Same uses as dinoprostone

* Carboprost ($PGF_{2\alpha}$)

IM and intramniotic

Abortifacient and postpartum hemorrhage

* Gemeprost (PGE_1)

Vaginal pessaries

Used to prime the cervix and helps to induce uterine contractions

3. Ergot alkaloids:

Ergonovine, Methylergonovine

IM, oral

Ergot alkaloids remain the drugs of choice to manage postpartum hemorrhage

As compared to oxytocin, ergot alkaloids are more potent, they produce more prolonged and sustained contractions of the uterus and they are less toxic

Ergot alkaloids are contraindicated to be used as inducers to delivery (associated with high incidence of fetal distress and mortality)

II. Uterine relaxants (Tocolytics)

Major clinical use: premature delivery (weeks 20-36)
→ improve the survival of the newborn

1. β-adrenergic agonists:

↑ cAMP → ↓ cytoplasmic Ca^{++}

* Ritodrine

IV infusion

Most widely used; highly effective

* Terbutaline, Oral, SC, IV

- Side Effects to β-adrenergics:

Sweating, tachycardia, chest pain…

2. Magnesium sulfate

IV infusion

Activates adenylate cyclase and stimulates Ca^{++} dependent ATPase

Uses: premature delivery and convulsions of pre-eclampsia

3. Progesterone

Oral, IM

Dydrogesterone

4. Oxytocin competitive antagonists

Atosiban

5. Prostaglandin synthesis inhibitors

Indomethacin, Meloxicam

6. Nifedipine

** Major contraindication to tocolytics: fetal distress