Posterior Pituitary Hormones

- **ADH (Vasopressin) & Oxytocin**

Nonapeptides (9 a.a)

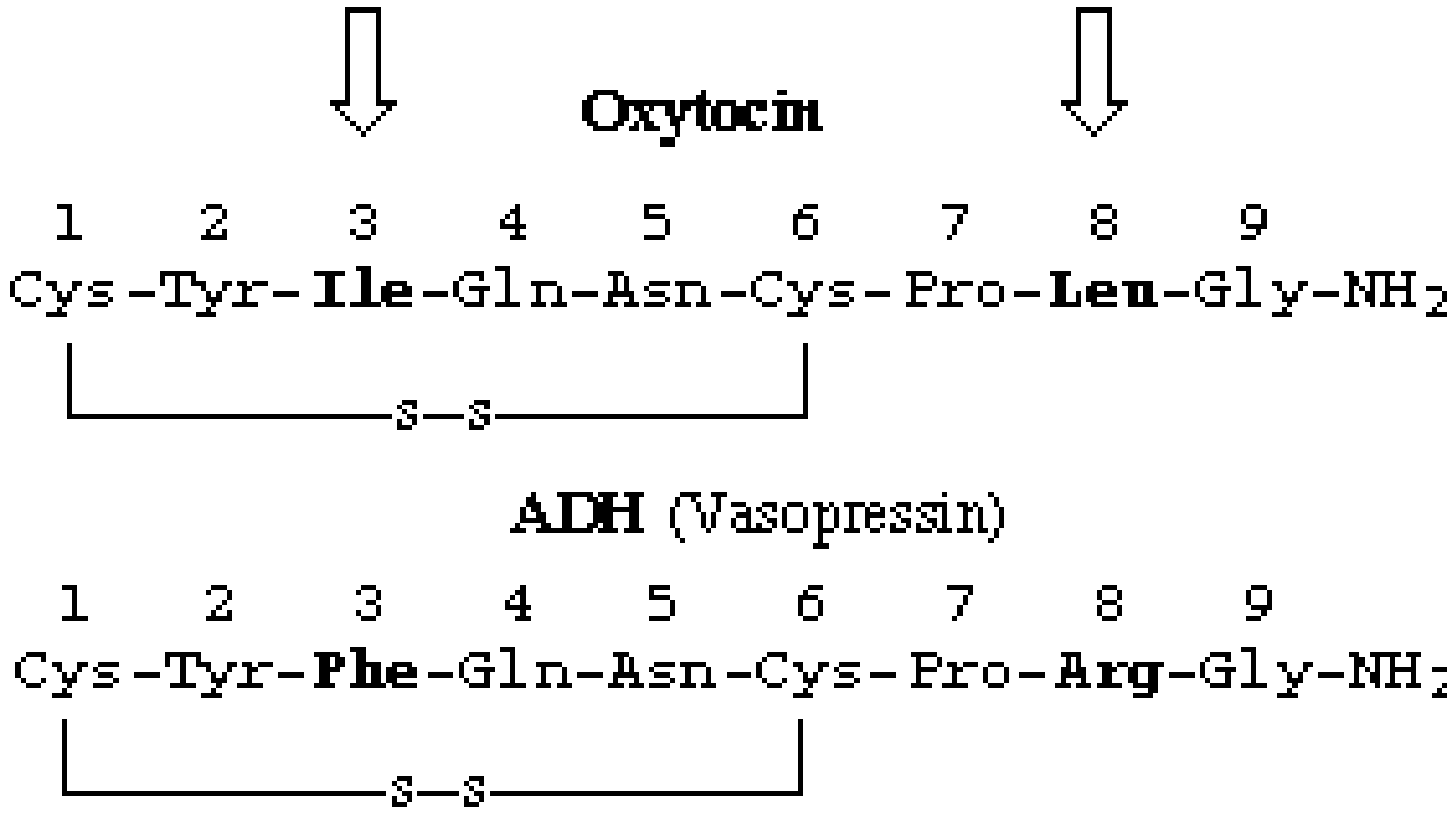
Known as neurohormones

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**