Posterior Pituitary Hormones

Posterior pituitary hormones: ADH (AVP) and Oxytocin

- Both are synthesized in the cell bodies of hypothalamic neurons
- ADH: supraoptic nucleus
- Oxytocin: paraventricular nucleus
- Both are synthesized as preprohormones and processed into nonapeptides (nine amino acids**).**
- They are released from the termini in response to an action potential which travels from the axon body in the hypothalamus

ADH: conserve body water and regulate tonicity of body fluids

- Also known as vasopressin
- Regulated by osmotic and volume stimuli
- Water deprivation increases osmolality of plasma which activates hypothalmic osmoreceptors to stimulate ADH release

ADH work by

- Vasoconstriction & ↑ platelet aggregation (V1a receptors)
- ↑ reabsorption of H_2O from collecting ducts (V_2 receptors)
- ↑ synthesis of certain clotting factors (VIII, Von Willebrand) (V_2 receptors)

- **Factors/Drugs ↑ ADH release:**

- Hypovolemia : decrease in blood volume
- 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 : increase in blood volume
- Hypoosmlarity
- Alcohol
- - 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
- Loop diuretics (Furosemide)
- ? ADH antagonists

Dilutional hyponatremia, also known as water intoxication, occurs when a person consumes too much water without an adequate intake of electrolytes

- **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

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

Associated with:

- 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 I.M, S.C, has short half-life (15 min)

- Lypressin (synthetic, porcine source)

Given intranasally, I.V, I.M, has short DOA (4hrs)

- Desmopressin (synthetic ADH-like drug=analogue)

Given intranasally, S.C

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

- **Side effects to ADH preparations:**

- Allergy
- Headache, nausea, abdominal pain in ♀'s (oxytocin-like activity)
- Anginal pain (coronary artery vasospasm)
- H_2O intoxication (massive doses)

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

- **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, I.V 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), 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 ($PGF_{2\alpha}$)

I.V infusion

Same uses as dinoprostone

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

I.M

Abortifacient and postpartum hemorrhage

* Gemeprost (PGE_1)

Vaginal pessaries

Used to prime the cervix

3. Ergot alkaloids:

Ergonovine, Methylergonovine

I.M, 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:

* Ritodrine

I.V infusion

Most widely used; highly effective

* Terbutaline, Oral, S.C, I.V

- Side Effects to β-adrenergics:

Sweating, tachycardia, chest pain…

2. Magnesium sulfate

I.V infusion

Uses: premature delivery and convulsions of pre- eclampsia

3. Progesterone

Oral, I.M

Dydrogesterone

4. Oxytocin competitive antagonists

Atosiban

5. Prostaglandin synthesis inhibitors

Indomethacin, Meloxicam

6. Nifedipine