Posterior Pituitary Hormones

Done by Aseel Abdeen

Concerned with homeostasis of water and sodium

Concerned with ejection of milk and contraction of the uterus, it is an important hormone for delivery

- **ADH (Vasopressin) & Oxytocin**

Nonapeptides (9 a.a)

Known as neurohormones Meaning that they are released from neurons

Synthesized in the hypothalamus

Stored in the posterior pituitary → release

(In vesicles)

? Role as neurotransmitters (V_1R's in CNS)

Vasopressin 1 receptor

Role of Oxytocin in man is unknown

Release is quick unlike synthesis which is slow. Therefore, drugs in synthesis usually are characterized by delayed onset of action as compared to those drugs that act immediately on the release process

Remember that small peptides are synthesized from larger precursors

Structure is not for memorization, just observe the similarity

Oxytocin

1 2 3 4 5 6 7 8 9

Cys-Tyr-**Ile**-Gln-Asn-Cys-Pro-**Leu**-Gly-NH_2

S—S

ADH (Vasopressin)

Also known as arginine vasopressin due to the presence of arginine at position 8

1 2 3 4 5 6 7 8 9

Cys-Tyr-**Phe**-Gln-Asn-Cys-Pro-**Arg**-Gly-NH_2

S—S

Due to their similarity in structure, oxytocin has some ADH-like activity and vice versa.
Knowing the structures of hormones allows us to synthesize agonists (in case of deficiency of the hormone, which is more common) and antagonists (in case of excess of the hormone).

Physiological and pharmacological actions: (For ADH)

- 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)
- ↑ ACTH release (V1b 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…

ADH agonists are used for a condition known as nocturnal enuresis, which is involuntary urination that happens at night while sleeping, after the age when a person should be able to control his or her bladder.

- **Factors/Drugs ↓ ADH release:**

- Hypervolemia

- Hypoosmlarity

- Alcohol

- Atrial natriuretic peptide

- Phenytoin

- Cortisol

- Anticholinergics, α-adrenergics, GABA...

Water intoxication or hyper hydration occurs due to an excessive intake of water which leads to inappropriate ADH secretion and hyponatremia (decreased sodium in blood)

- **Disorders affecting ADH release:**

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

Causes:

Because they are synthesized in the hypothalamus

- 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 Unlike diabetes mellitus

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)

Subcutaneous

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

So it's only given once daily

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

Selective for V2 receptors without affecting V1

- Felypressin (synthetic ADH-like drug)

Has strong vasoconstrictor activity

Usually it's combined with local anesthetic drugs, and it's less toxic than the combination of local anesthetics with epinephrine

Mainly used in dentistry to reduce bleeding

■ 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

- **Oxytocin MOA:**

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

- ↑ intracellular Ca^{++}

- ↑ prostaglandin release

For the sake of the exam:
Best drug for delivery: oxytocin
Best drug for abortion : prostaglandins

- **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

Still, prostaglandins are better since they have many routes of administration

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

I.V infusion and intramniotic

Same uses as dinoprostone

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

I.M and intramniotic

Abortifacient and postpartum hemorrhage

* Gemeprost (PGE_1)

Vaginal pessaries

Used to prime the cervix

3. Ergot alkaloids:

Ergonovine, Methylergonovine

I.M, oral

Drug of choice for post partum hemorrhage

- 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: Are the best for management of premature delivery

↑ cAMP → ↓ cytoplasmic Ca^{++}

* 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

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

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

**** Major contraindication to tocolytics: fetal distress**