Posterior pituitary hormones

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ADH (AVP) and Oxytocin

Synthesized in the cell bodies of hypothalamic neurons (ADH: supraoptic nucleus, Oxytocin: paraventricular nucleus) as preprohormones and processed into nonapeptides (nine amino acids).

ADH (vasopressin):

Function	Mechanism of action	Factors/Drugs ↑ ADH release	Factors/Drugs ↓ ADH release:
conserves body water and regulates tonicity of body fluids. Regulated by osmotic and volume stimuli: water deprivation increases osmolality of plasma which activates hypothalamic osmoreceptors to stimulate ADH release.	- Vasoconstriction & ↑ platelet aggregation (V_1a receptors) - ↑ reabsorption of H2O from collecting ducts (V_2 receptors) - ↑ synthesis of certain clotting factors (VIII, Von Willebrand) (V_2 receptors)	- Hypovolemia, Hyperosmolarity, pain, stress, nausea, fever, hypoxia. - Angiotensin II - Certain prostaglandins - Nicotine, cholinergic agonists, β-adrenergics - Tricyclic antidepressants - Insulin, morphine, vincristine…	- Hypervolemia - Hypoosmlarity - Alcohol - Phenytoin - Cortisol - Anticholinergics, α-adrenergics, GABA...

Disorders affecting ADH release.	Excess production (inappropriate ADH secretion) → Dilutional hyponatremia	Deficiency of ADH → Diabetes insipidus (DI)→ polyuria
Definition	Dilutional hyponatremia (water intoxication) occurs when consuming too much water without an adequate intake of electrolytes.	
Causes:	- Head trauma, encephalitis - Meningitis, oat cell carcinoma…	- Idiopathic DI - Congenital, Familial DI - Hypothalamic surgery, head trauma, malignancies - Gestational DI, overproduction or decreased clearance of vasopressinase.
Rx:	- Water restriction (Rx of choice) - Hypertonic saline solution - Loop diuretics (Furosemide) - ? 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.	- ADH preparations (HRT): **Natural human ADH** (Pitressin): Given I.M, S.C, has short half-life (15 min). **Lypressin** (synthetic, porcine source): intranasally, I.V, I.M, has short DOA (4hrs). **Desmopressin** (synthetic analogue): intranasally, S.C. Most widely used preparation, has long DOA (12 hrs). **Side effects to ADH preparations:** - Allergy - Headache, nausea, abdominal pain in females (oxytocin-like activity). - Anginal pain (coronary artery vasospasm). - H2O intoxication (massive doses).

Drugs acting on the uterus:

1. **Uterine stimulants**
   a. **Oxytocin:**

function (Major stimuli: baby cry and suckling)	- Contracts the myoepithelial cells of the breast → milk let-down - Contracts the uterus during 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.
MOA	- Binds to surface receptors stimulating voltage-sensitive Ca++ channels → depolarization of uterine muscles → contractions. - ↑ intracellular Ca++ - ↑ prostaglandin release
Clinical uses	- Induction of labor (Drug of choice given IV). - Postpartum hemorrhage, although intramuscular Ergot alkaloids are better (syntometrine= oxytocin+ ergometrine) - Breast engorgement, intranasally - Abortifacient, I.V infusion. ≥ 20 weeks of gestation, ineffective in early pregnancy
Side effects	- Rupture of the uterus, major and most serious side effect. - H2O intoxication and hypertension due to its ADH-like activity
Specific antagonist	Atosiban (inhibitor to uterine contraction), effective in the management of premature delivery, given IV. Has little ADH antagonistic effect.

b. Prostaglandins:

	Administration	Uses
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 before delivery

c. Ergot alkaloids: (Ergonovine, Methylergonovine):

Given I.M and 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 of delivery (associated with high incidence of fetal distress and mortality).

2.Uterine relaxants (Tocolytics) Major clinical use: premature delivery (weeks 20-36) → improve the survival of the newborn.

	β-adrenergic agonists	Magnesium sulfate	Progesterone	Oxytocin competitive antagonists	Prostaglandin synthesis inhibitors	Nifedipine
Examples	1. Ritodrine 2. Terbutaline		Dydrogesterone	Atosiban	Indomethacin, Meloxicam	
Administration	1. I.V infusion 2. Oral, S.C, I.V (respectively)	I.V infusion	Oral, I.M			
Uses	Most widely used; highly effective	premature delivery and convulsions of pre- eclampsia				
Side effects	Sweating, tachycardia, chest pain.					