Lectures (4+5)

In this lecture we are going to talk about drugs acting on the uterus but before that we are going to discuss the Posterior pituitary hormones

Posterior pituitary hormones

ADH (AVP) and Oxytocin
They are called posterior pituitary hormones because they are stored and released from the posterior pituitary gland

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 (Antidiuretic hormone) , Also known as vasopressin

The main job for ADH is to conserve body water and regulate tonicity of body fluids ; thus , it is regulated by osmotic and volume stimuli (Water deprivation increases osmolality of plasma which activates hypothalmic osmoreceptors to stimulate ADH release
It works by :-

1-Vasoconstriction & ↑ platelet aggregation (V1a receptors)

2-↑ reabsorption of H2O from collecting ducts (V2 receptors)

3-↑Synthesis of certain clotting factors (VIII, Von Willebrand) (V2 receptor)

A-Factors / Drugs that ↑ ADH release :-

The most important are the first two

1-Hypovolemia : Decrease in blood volume
2-Hyperosmolarity
3-Stress , pain , nausea , fever , hypoxia

4-Angiotensin II
It works naturally to induce the secretion of ADH and increase body fluid's volume which will eventually increase the blood pressure .
5-Certain Prostaglandins
6-Nicotine , cholinergic agonists , B-adrenergics
7-Tricyclic antidepressants
8-Insulin , morphine , vincristine….
Insulin and morphine induces the release of ADH from the posterior pituitary hormone

B-Factors/drugs ↓ ADH release

1-Hypervolemia : increase in blood volume
2-Hypoosmolarity
3-Alcohol
4-Phenytoin
5-Cortisol
6-Anticholinergics , a-adrenergics , GABA

Disorders affecting ADH release
A. Excess production (inappropriate ADH secretion) → Dilutional hyponatremia
Dilutional hyponatremia, also known as water intoxication, occurs when a person consumes too much water without an adequate intake of electrolytes

Causes:-
Head trauma, encephalitis Meningitis, oat cell carcinoma...

Treatment :-
Water restriction (Treatment of choice)
Hypertonic saline solution
Loop diuretics (Furosemide)
ADH antagonists

ADH antagonist :-
-Conivaptan , a non peptide antagonist given IV
-Tolvaptan ; Lixivaptan and Satavaptan , a non-peptide orally effective selective V2R antagonists

B. Deficiency of ADH polyuria —> Diabetes insipidus (DI) —> Polyuria

Associated with:-

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

Treatment :-
ADH preparations (HRT) ; preparations that work like the normal hormone

ADH preparations :-

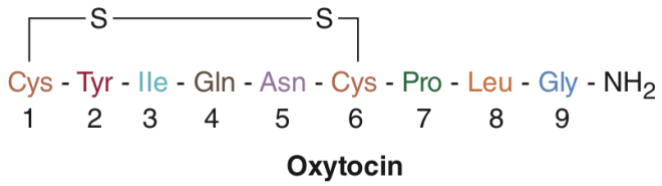
-Natural human ADH (Pitressin) , Given I.M, S.C, has short half-life (15min)
-Lypressin (synthetic, porcine source) , Given intranasally, I.V, I.M, has short DOA (4hrs)
-Desmopressin (synthetic ADH-like drug = analogue) , given intranasally , S.C
Most widely used preparations , has long DOA (12hrs) BEST ONE .

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
A-Uterine stimulants

1-Oxytocin
Structure
Nanopeptide = 9 amino acid peptide



Oxytocin

Pharmacodynamics (MOA : Mechanism Of Action)

1-It binds to specific surface receptors —> stimulates voltage-sensitive Ca++ channels —> depolarization of uterine muscles —> contractions
2- It increases intracellular Ca++
3- It increases prostaglandin release

So , it contracts the myoepithelial cells of the breast —> milk letdown; milk ejection . The major stimuli for its release is baby cry and suckling . And it also 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 . Finally it has slight ADH - like activity.

Clinical indications for oxytocin :-
1-Induction of labor , drug of choice given in units in an I.V infusion

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

3-Breast engorgement , intranasally

4-Abortifacient , I.V infusion . >= 2o weeks of gestation , ineffective in early pregnancy

Side effects to oxytocin :-

1-Rupture of the uterus , major and most serious side effect
2-H 2 O intoxication and hypertension ; due to its ADH

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 (PGE2)
Vaginal pessaries , inserts and gel , tab
Abortifacient , induction of labor

Dinoprost (PGF2a)
I.V infusion , same uses as dinoprostone

Carboprost (PGF2a)
I.M
Abortifacient and postpartum hemorrhage

Gemeprost (PGE1)
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)

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

1.B- adrenergic agonists:
* Ritodrine
I.V infusion
Most widely used ; highly effective

*Terbutaline
Oral , S.C, I.V

Side Effects to B-adrenergics (Over sympathetic stimulation) :
Sweating, tachycardia, chest pain

2. Magnesium sulfate
I.V infusion

Uses: premature delivery and convulsions of pre-eclampsia

3.Progesterone
Naturally progesterone level is high during the natural pregnancy process.
Oral , I.M
Dyhdrogesterone

4.Oxytocin competitive antagonists
Antagonists will reverse the action of oxytocin (contraction of the uterus)
Atosiban

5.Prostaglandin synthesis inhibitors
Indomethacin , Meloxicam

6.Nifedipine

Now we are going to talk about GnRH , LH , FSH

Gonadotropins include :-

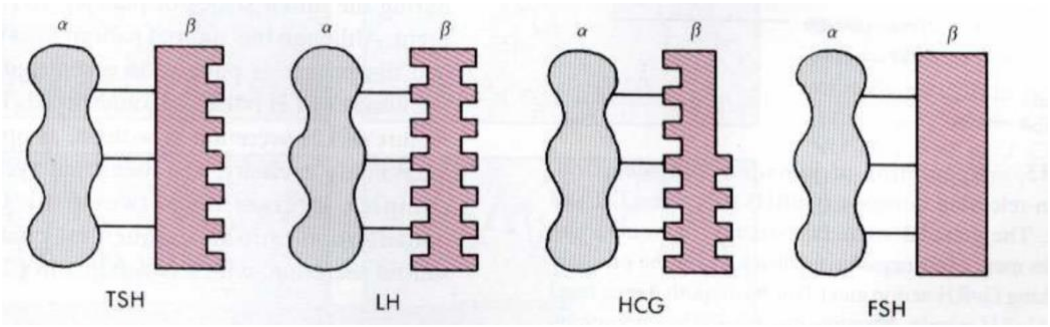
1• Follicle-stimulating hormone (FSH),
2• luteinizing hormone(LH),
3• human chorionic gonadotropin (hCG)
4• TSH

They have
a and b subunits , each subunit encoded by different gene

1-a subunit is identical for all hormones
2-b subunit are unique and provide biological specificity

Glycoprotein hormones

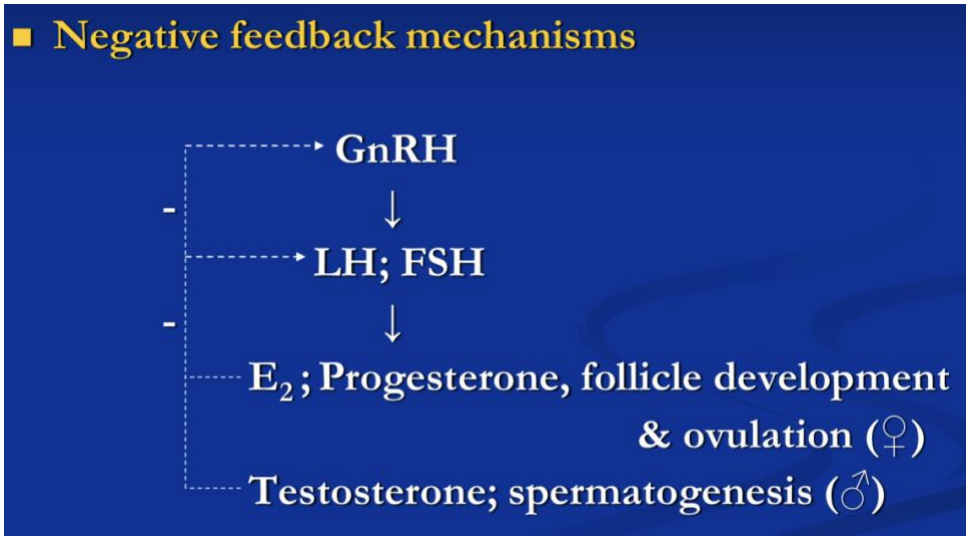
Glycoprotein hormones contain two subunits, a common a subunit and a distinct b subunit: TSH, LH, FSH and hCG.



GnRH (Gonadotropin Releasing Hormone; Gonadorelin) :-

-A small peptide (decapeptide= 10 a.a peptide)
-Stimulates synthesis and release of two different complex glycoprotiens (LH & FSH)
-Has unique pattern of release from hypothalamus
-Has interesting structure activity relationship
-Has many clinical uses

This figure shows the relationship between GnRH and other hormones that are affected by it :-
From the figure we can see that GnRH induces the release of FSH and LH , and these two hormones induce the release of Progesterone (in



females) [which is responsible for follicular development and ovulation] and Testosterone (in males) [which is responsible for spermatogenesis]
Structure - activity relationship:-

pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH2

form the hormone's structure which contains 10 amino acids , the first 3 amino acids are stable meanwhile the rest there will be changes in their structure ; this is a description of the modified structures which are synthesized later on in order to be used in similar function of GnRH

Pattern of release and MOA (Mechanism Of Action)

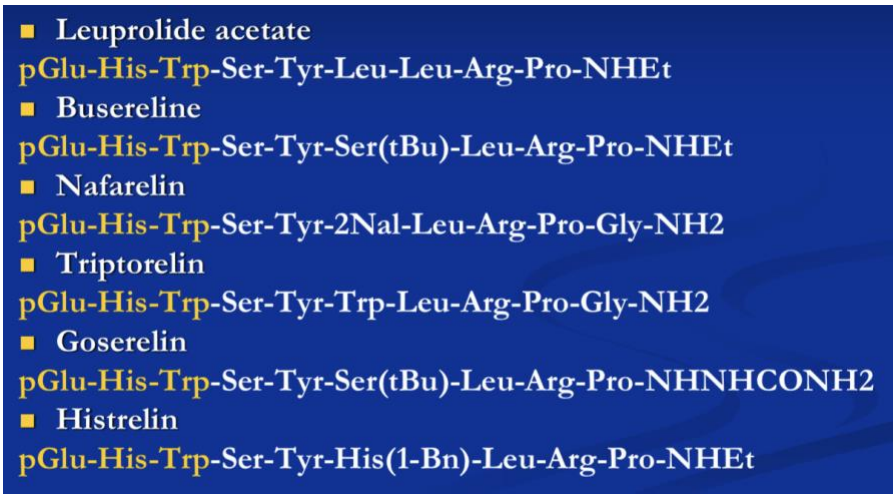
Pulsatile (Ca ++ second messenger) —> ↑LH and FSH

Large doses or continuous administration (down regulation of pituitary GnRH receptors) which is not naturally occurring situation it is done by specific clinical interference for specific purposes —> ↓ LH and FSH

GnRH synthetic preparations:
Leuprolide acetate, Triptorelin, Goserelin, Histrelin,
Nafarelin, Busereline...

-Could be given S.C, I.M, I.V . Mainly given S.C
-Ineffective orally
-Available in intranasal, suppositories, subdermal implants and vaginal pessaries dosage forms (? contraceptive)

This slide is just to show you that the first 3 amino acids are constant in all of them but the difference is in the rest .
NOT FOR MEMORIZING



GnRH clinical uses :-

a. Pulsatile administration , simulation of the normal release process .
1-Diagnostic use , to know if the problem in this hormone or in the other hormones that are affected by it .
2-GnRH deficiency (Kallman's syndrome)
Treatment of female and male hypogonadism (hypogonadism means diminished functional activity of the gonads—the testes or the ovaries) , delayed puberty , amenorrhea , cryptorchidism (Cryptorchidism is the absence of one or both testes from the scrotum)

b. Continuous administration or large doses or the use of a GnRH superagonists:-

1-Prostate cancer , breast cancer
2-Endometriosis *(Endometriosis is a condition in which cells similar to those in the endometrium, grow outside of it)*
3-IVF
4-Precocious puberty *(precocious puberty is puberty occurring at an unusually early age)*
5-Uterine fibroids *(Uterine fibroids benign smooth muscle tumors of the uterus)* , polycystic ovarian syndrome (PCOS)
6-Contraceptives

Side effects to GnRH :-

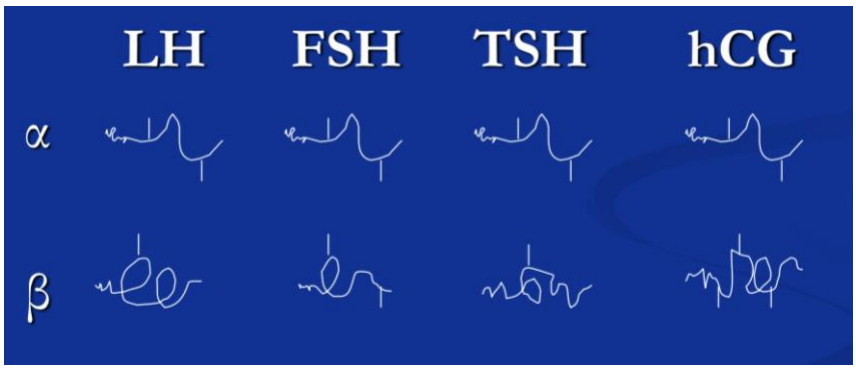
-Production of GnRH Abs → resistance to treatment
-Headache and abdominal pain (tolerance develops to these side effects) , Sweating, facial flushing, hot flushes
-Osteoporosis

When these side effects occur , GnRH specific antagonists could be used

GnRH specific antagonist :-
Ganirelix ; (IVF, SC) ; Degarelix (prostate cancer , SC) ; Elagolix (endometriosis , oral)

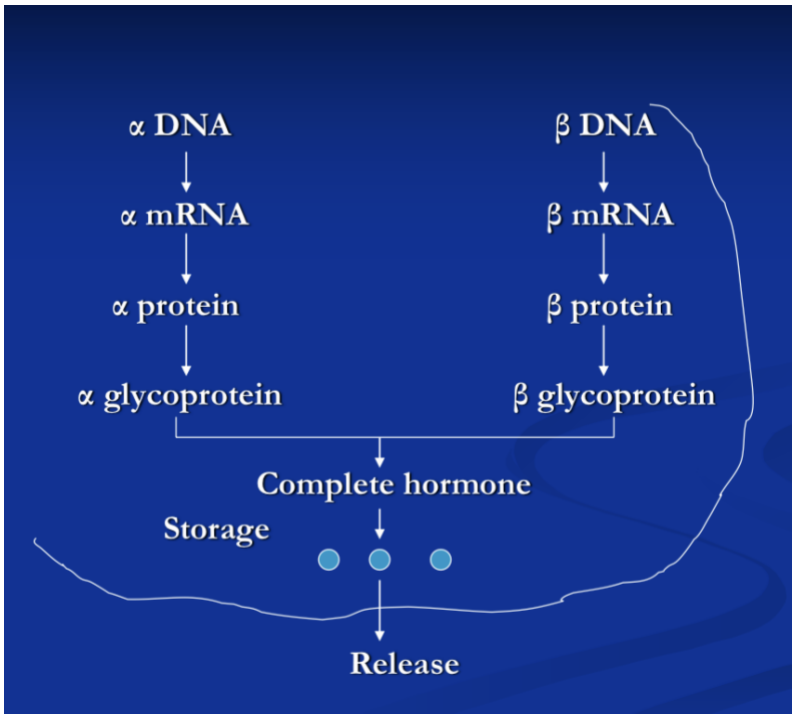
Gonadotropins : LH and FSH , they are glycoproteins which are under regulation by GnRH

As we said before that they have a common subunit which is the alpha subunit , and they differ in the Beta subunit .



And also we said that each subunit is encoded by different genes .

Form the figure :-
1-each subunit comes form different origin in the DNA
2- DNA will be copied into mRNA
3- mRNA will be translated into protein to produce glycoprotein
4- now these two subunits will unite to produce the complete hormone
5- The complete hormone will be stored and released upon specific stimulation (which is the GnRH)



MOA of LH and FSH :-
They will bind to specific surface receptors; cAMP 2nd messenger

☺ LH stimulates desmolase enzyme —> ↑ steroidogenesis in gonads , LH helps in the descent of testes during fetal life .

Source of LH and FSH
Natural human source

Human Chorionic Gonadotropin (hCG)
A product of the placenta
Has similar pharmacological properties to LH Obtained from the urine of pregnant ladies Recombinant preparations are also available.

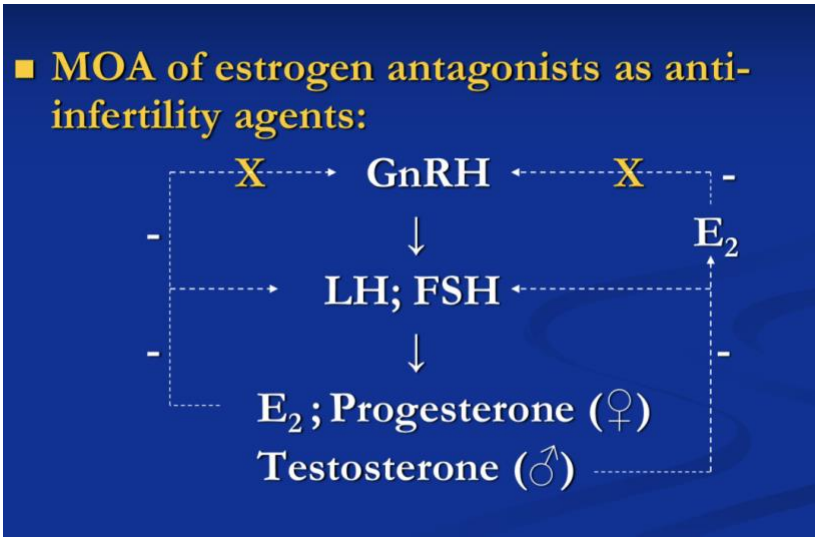
Clinical uses to gonadotropins :-
-Infertility in females and males due to LH and FSH deficiency
-IVF
-Cryptorchidism

Side effects
-Allergy
-Ovarian hyperstimulation syndrome (fever; abdominal pain, ovarian enlargement, ascites, shock…)
- Multiple births
-Production of specific antibodies
-Precocious puberty
-Ovarian tumors
-abortion

In general :-
☺ If the problem is sexual function —> Give estrogen or testosterone
☺ If the problem is infertility:-
-GnRH in pulses
-LH, FSH, hCG
-Estrogen (females) ; Testosterone (males)
-Clomiphene citrate or Tamoxifen(estrogen antagonists) in females and males

Estrogen antagonists (E-antagonists)
They block the negative feedback to GnRH ; which in turn will inducing the release of Progesterone and Testosterone.

E-antagonists (Clomiphene citrate or Tamoxifen) are highly effective in inducing ovulation in females and restoring fertility in males .



Major side effects :-

Menopausal manifestations in females , Nausea , Vomiting , Multiple birth , allergies , Headache , insomnia , fatigue , ovarian enlargement and cyst formation .