GnRH, LH, FSH

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- 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

So synthetic hormones are easy to make due to small number of* .amino acids

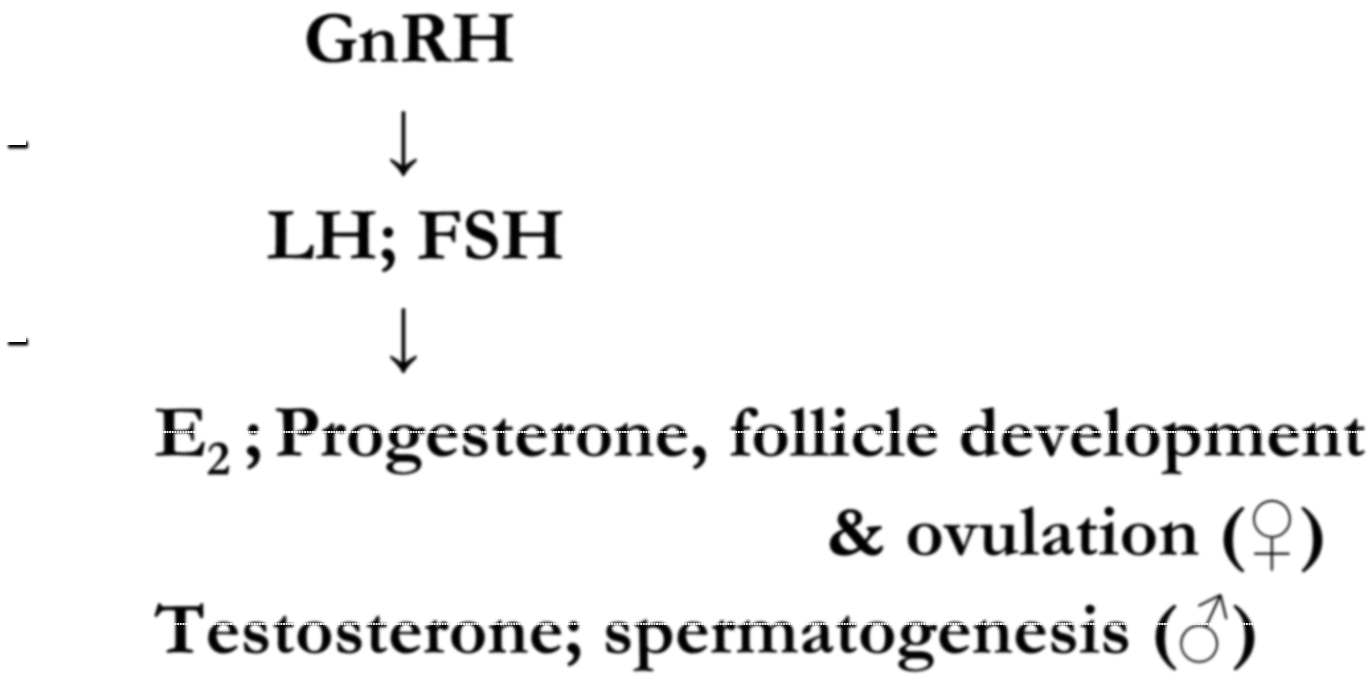
Females are more interesting regarding hormones because they go .menstrual cycle

Infertility is a major problem around the world and the hormonal problems are the major causes of infertility

.Cortisol used as very strong anti inflammatory agent

**Illustration of the figure

- Negative feedback mechanisms



This diagram is called (Hypothalamic Pituitary Gonadal axis)**

Hypothalamus produces GnRH

Ant. Pituitary produces LH & FSH

Ovary in.1 females
Testes in. 2 .males

In ovary of females (FSH) stimulate development of follicles in it then .the follicles themselves will release Estrogen

Now, Estrogen & progesterone has negative feedback effect on Hyopthalamus (means they inhibit release of GnRH When they become at high levels.) & Ant. Pituitary (means they inhibit release of FSH & LH when they become at high levels)

LH in ovary of females stimulate ovulation & has negative feedback .effect as mentioned above

In male LH & FSH stimulate testes to produce testosterone which plays .a role in spermatogenesis

:So how such hormones produce negative feedback effect

:There are 3 possible mechanisms

1 Direct effect on release (ex. When we have negative feedback) on LH & FSH from estrogen it prevents release of FSH & LH. . This is the major mechanism because release process is very quick , so drugs which act on release they have very rapid onset of action).immediately(

2 Synthetic machinery ; has delayed onset of action (remember) .synthesis takes time)

3 On the receptors (ant. Pituitary GnRH RECEPTORS) “Down) ”. regulation

** Structure-activity relationship:

** -His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly

** Pattern of release and MOA: ***

- Pulsatile (Ca^{++} second messenger) → ↑ LH & FSH
- Large doses or continuous administration (down regulation of pituitary GnRH receptors) → ↓ LH & FSH

.The first 3 amino acids are essential for AGONISTIC activity **

Any chemical modifications (ex. Replacement ,change…) in these

. amino acids will end up with specific ANTAGONIST to the GnRH

Amino acids from 4-10 especially GLYCINE residues at 6 & 10

position are essential for binding characteristics of the hormone to its receptors. Any chemical modifications in these amino acids will result with different agonists with different strengths & pharmacokinetics properties . This will result (especially glycine on .position 6 & 10) with what is known as (SUPER AGONIST)

:***PATTERN OF RELEASE & MECHANISMS OF ACTION

: General rules

When we said (Pulsatile manner =Small doses) we give GnRH in pulsatile manner in order to increase release of FSH & LH THUS increase estrogen , progesterone , testosterone.

BUT when we said(continuous manner= large doses =super agonist We give GnRH in order to reduce excessive amount of estrogen ,progesterone , testosterone . This happen by down regulation of the ant. Pituitary GnRH RECEPTORS.

- GnRH synthetic preparations:

Notice all end with suffix relin

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) **

Although GnRH agents are designed to use GnRH as contraceptive . but failure rate is high

Compound estrogen progestrone oral pills are better contraceptive as compared to GnRH . However , GnRH agents have LESS SIDE . EFFECT

***

- **Leuprolide acetate** ✓
  pGlu-His-Trp-Ser-Tyr-Leu-Leu-Arg-Pro-NHEt
- **Busereline** ✓
  pGlu-His-Trp-Ser-Tyr-Ser(tBu)-Leu-Arg-Pro-NHEt
- **Nafarelin** ✓
  pGlu-His-Trp-Ser-Tyr-2Nal-Leu-Arg-Pro-Gly-NH2
- **Triptorelin** ✓
  pGlu-His-Trp-Ser-Tyr-Trp-Leu-Arg-Pro-Gly-NH2
- **Goserelin** ✓
  pGlu-His-Trp-Ser-Tyr-Ser(tBu)-Leu-Arg-Pro-NHNHCONH2
- **Histrelin** ✓
  pGlu-His-Trp-Ser-Tyr-His(1-Bn)-Leu-Arg-Pro-NHEt

***

The previous slide is not for memorization just take an idea which is

(In such AGONIST the first 3 amino acids are the same in all synthetic GnRH .such as the natural GnRH .)

BUT for antagonists first 3 amino acids are different from .natural GnRH agents

- **GnRH clinical uses:**

a. Pulsatile administration

- Diagnostic use

- GnRH deficiency (Kallman's syndrome)

R_x of ♂ & ♀ hypogonadism; induction of ovulation (infertility), delayed puberty, amenorrhea, cryptorchidism…

When we give GnRH in pulsatile manner we said it increases LH .& FSH

AS Diagnostic use (we give LH & FSH if LH & FSH DONOT increase after administration then the problem is either .pituitary or hypothalamic

R Means treatment

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

- Ca prostate; Ca breast **
- Endometriosis
- IVF
- Precocious puberty
- Uterine fibroids or uterine leiomyomas, polycystic ovarian syndrome (PCOS)
- ?? Contraceptive

- 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

- GnRH specific antagonist: ****

  Ganirelix; given SC (IVF) (histamine release)

Ac-D-Nal[1]-(p-Cl)-D-Phe[2]-D-Pal[3]-Ser[4]-Tyr[5]-D-Cit[6]-Leu[7]-Arg[8]-Pro[9]-D-Ala[10]-NH_2

**

.Prostate cancer & Breast cancer are highly sensitive to androgens
In prostate cancer continuous administration is considered superior
.to other modalities of treatment even surgery

Sweating, facial flushing , hot flushes are estrogen dificiency***
.manifestations
. Osteoporosis is the major side effect of GnRH agents

Ganirelix is highly effective in management of prostate cancer****
.

Elagolix its super agonist medication , effective particularly in
.endometriosis ,its orally effective so its non peptide

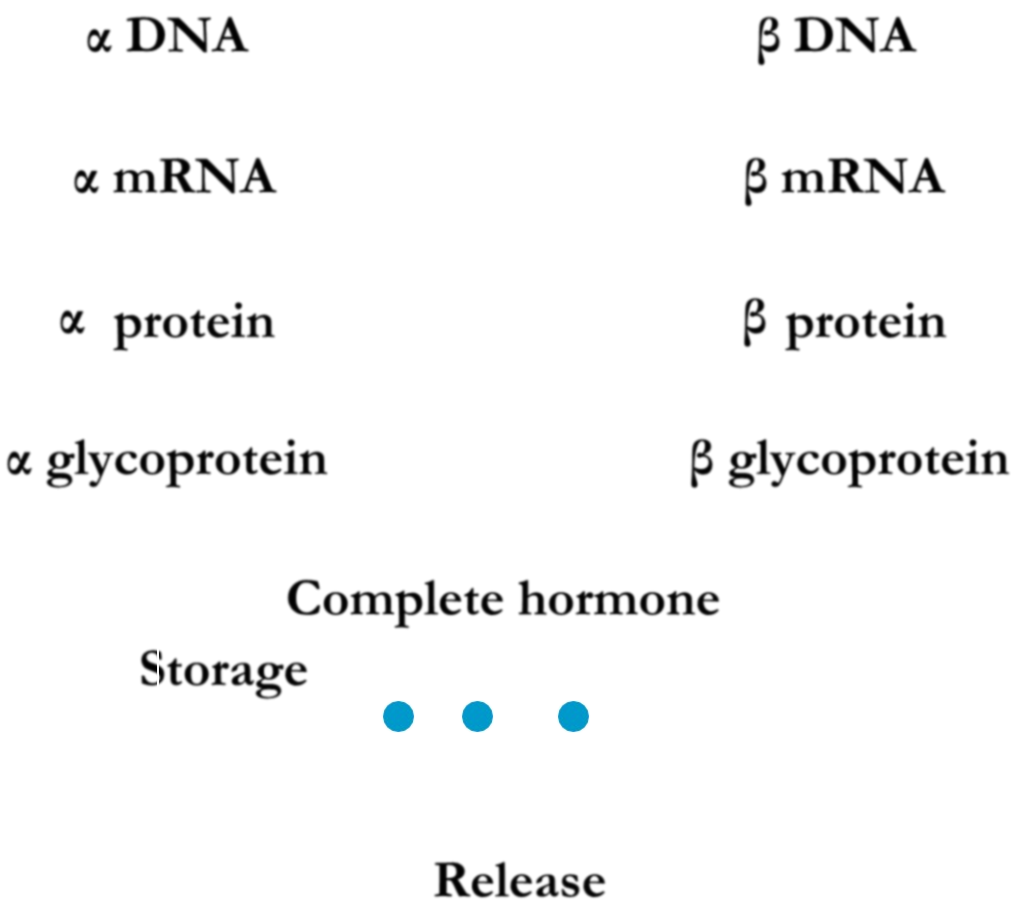
Gonadotropins: LH & FSH

Glycoproteins; under regulation by GnRH

LH FSH TSH hCG

These are the only 4th glycoproteins in your body meaning they share some characteristics .BUT There is no overlap between (LH , FSH) &(HCG , TSH)

Synthetic machinery : a-subunit & beta subunit are separately synthesized , negative feedback mechanism can affect any of these .steps , first process to be affected is the release



LH , FSH , TSH , hCG, all have alpha and beta subunits

The alpha subunit is similar in these hormones because all of them is encoded by the same gene.

Beta subunits are different because they are encoded by different genes , thus beta subunit is believed to produce the biological activity of the hormone

Both subunits are glycosylated.

- **MOA of LH & FSH:**

- 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 & FSH: *****

- Natural human source. Human menopausal gonadotropins (HMG; Menotropin) (Mainly FSH)
- rDNA preparations (rβ-FSH; rLH+FSH)

.Interact with G-protein coupled to adenylate cyclase*

Stimulate desmolase enzyme which is the first step in**
. steroidogenesis

The source of HMG is the urine of postmenopausal ladies***
,because they lose their ovarian function thus no estrogen progesterone negative feedback on ant. Pituitary thus level of FSH & LH in blood will increase then secreted through active secreted
.mechanism through kidney to get rid of by urine

hCG is more stable than LH because the metabolization of it has longer time in liver it needs around 8-10 hours.

- 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 ♂'s and ♀'s due to LH & FSH deficiency
- I.V.F Will be discussed later
- Cryptorchidism (hCG; I.M)

sometimes multiple births could be****
.advantage but its still side effect

- Side effects to gonadotropins:

- Allergy
- Ovarian hyperstimulation syndrome (fever; abdominal pain, ovarian enlargement, ascites, pleural effusion, arterial thrombosis, hemoperitoneum, shock...)
- Multiple births ****
- Production of specific antibodies
- Precocious puberty and gynecomastia
- ? Ovarian tumors
- Failure of Rx (abortion)

Finally, leads to death and its very important side effect needs to check

*** If the problem is sexual function

Give estrogen or testosterone

*** If the problem is infertility:

- GnRH in pulses
- LH, FSH, hCG
- Estrogen (♀'s); testosterone (♂'s)
- Bromocriptine Dopamine agonist
- Clomiphene citrate or Tamoxifen (estrogen antagonists) in ♀'s & ♂'s

Excess prolactin in male & female made infertility (hyperprolactinemia)

.Prolactin is under inhibited by dopamine

In case of infertility due to strong negative feedback this means there is very high level of estrogen so we need to give estrogen antagonists .in order to reduce amount of estrogen

When testosterone is in high level you should give estrogen antagonists because what is responsible about testosterone negative feedback is estrogen , because testosterone is converted to estrogen . by aromatase enzyme

. Remember : estrogen is produced from testosterone

The main precursor is cholesterol then by desmolase enzyme its converted to pregnenolone which is converted to progesterone by .DHE. And this is the first progesterone synthesized in placenta

. from progesterone aldosterone , cortisol ,androgens are synthesized

- **MOA of estrogen antagonists as anti-infertility agents:**

X GnRH X -

- ↓ E_2

LH; FSH

- ↓ -

E_2 ; Progesterone (♀)

Testosterone (♂)

Estrogen antagonists are considered estrogen receptor modulator
The major side effect of estrogen loss is hot flushes and its treated .by small dosage of estrogen

E-antagonists (Clomiphene citrate or Tamoxifen) are highly effective in inducing ovulation in ♀'s and restoring fertility in ♂'s

Also E-antagonists are used with HMG and hCG to regulate ovulation in IVF

Major side effects: N:nausea V:vomiting

Menopausal manifestations in ♀'s, N & V, multiple birth, allergies, headache, insomnia, fatigue, ovarian enlargement and cyst formation

- IVF; GIFT; ZIFT; IVM

IVF : it is a procedure called in vitro fertilization in which sperm is combined with ova , to ensure success we have to over stimulate ovary to produce more than one ova by FSH & LH.

Before taking eggs from female we suppress GnRH thus FSH & LH thus ESTROGEN &progesterone totally suppressed in order to produce ovulation at the same time this is done be giving extensive hormonal therapy such as GnRH super agonist or GnRH antagonist (unpreferred)

Then we give female hormones from outside such as LH , FSH , along with hCG , bromocriptine by this lady ends up with formation at least 5-8 ova (we take them all through catheter) , then we combine all ova with sperm to produce zygote which is introduced to the uterus.

Success rate 25% (means around 70% of ladies may pregnant but eventually abortion happens.

GIFT :(gametocyte intra fallopian transfer) similar to IVF but here we introduce them to fallopian tube meaning its mimic the normal . physiology of the body

Success rate same as IVF 25% ,sometimes may become a little bit . better but it is more difficult procedure as compared to IVF

ZIFT :(zygote intra fallopian tube): fertilization takes place in vitro then .insert the zygote into fallopian tube

.Same success rate 25%

IVM : (In vitro maturation) : it is the most recent one , we take IMMATURE follicles from lady & mature them outside ,so lady is not exposed to hormones as compared to the previous procedures , thus it .is the best one

For some ladies who do not have appropriate production of the .follicles we give them small doses of LH & FSH

.This procedure used in infertility centers nowadays

Researches on it resemble researches on prostaglandins , they .considered hot area