The Endocrine System

☑ Sheet ☐ Slide ☐ Handout

Number:	4
Subject:	hypothalamic & pituitary hormones
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Salam to you all….

NOTE1: This sheet was written according to sec2.record.and it will cover slide2.

NOTE2 : To accomplish this sheet quickly , study it with love ☺

Lecture topics:

1- general Physiology and pharmacology of the pituitary gland hormones.

2- growth hormone therapy.

3- Insulin Like Growth Factor (IGF-1)agonist.

4- Growth hormone antagonist.

Let's Start^-^

First: general Physiology and pharmacology of the pituitary gland hormones.

Today we will talk about pharmacology of the endocrine system…we will start with hypothalamus and pituitary gland.

As we now the regulation of the endocrine system starts from the the hypothalamus which you can consider the master of pituitary gland which will secrete its hormone to affect target organs (ie,target glands)which will secrete hormones that will then return to the hypothalamus or the pituitary by feed back loops .

NOW what is the application of that in pharmacology "what is the effect of Drugs that mimic or block the effects of hypothalamic or pituitary hormones"??

1-Replacement therapy for hormone deficiency states:

If there was any defecincy state in the hypothalamus and the pituitary ,we don't give hypothalamic and pituitary hormone ...what we do is that we give the target gland hormone that is regulated by the deffecincy

.Ex.1if you have a deficeincy in TRH or TSH we dont give the patient any of these hormone instead you give them thyroxineT4 "target hormone for TRH and TSH".

.Ex.2 if you have a deficiency in ACTH hormone you give cortisol.

-so we use replacement therapy for hormone deficiency states.

However ,some hormones secreted from the pituitary gland cannot be replaced by the target gland hormone, such as Growth hormone which cannot be replaced by a target gland hormone because it has an effect on every cell of the body in addition to its effect in stimulating Somatomedin hormone. So the best treatment for growth hormone deficiency is growth hormone replacement.

2-Diagnostic tools for identifying several endocrine disorders.

-We know that drugs in general are used in diagnosis ,prevention and treatment of the disease .

- we can use these drugs for diagnosis by stimulation or suppression test.

3-Antagonists for diseases resulting from excess production of pituitary hormones.

-in cases of ecesses or more production you can use the antagonist of the hormone to treat this disease .

** **To sum up :because of the great ease in administration of target endocrine gland hormones or their synthetic analogs, the related hypothalamic and pituitary hormones (TRH, TSH, CRH, ACTH &**

GHRH) are either not used clinically or used rarely for specialized diagnostic testing.
*means that replacement therapy is not valid for these hormone except in extreme cases.

Second: Growth hormone therapy

GH(somatotropin) structure and pharmacokinetics

Note: the growth hormone therapy uses the same endogenous structure of growth hormone produced in the body of a healthy indivual , accordingly the therapeutic growth hormone and the endogenous growth hormone have the same structure and composition.

-You know it is a 191-amino acid peptide with 2 sulfhydryl bridges.

-The available form for therapeutic use is known as ***Recombinant human GH(rhGH)(somatropin).*** Which is administrated **subcutaneously**.
if you look at the **half life of the circulating growth hormone you will find it is**(25-30)min** and their action stay for **36h** .

→DOES this clicked in your mind!! WHY the action is 36h while the half life is only(25-30).

-because the action is not always direct ; sometime its indirect .
-also after binding the receptor you have a sequence that needs time"postreceptor signaling pathway".so when you just stimulate the receptor , the action induced by receptor

stimulation will take a long time to induce a response"even if the hormone is not there".

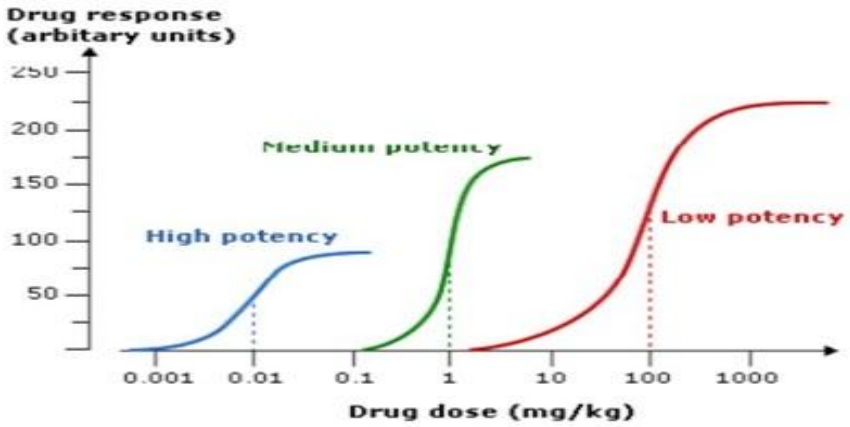
يعني: الهرمون اوصل الرسالة لreceptorو بعد ذلك انفصل عنه ولكن اثره ما زال مستمرا حتى بعد زواله:P

→when you say that the half life is 25min ,HOW LONG the hormone will stay in he circulation??

100min~2hours →4 half life→the drug that has dissolved is 95% and the remanant of drug is 5%which can't be detectable in our circulation.

*SO at the end the drug will not disappear in the circulation, it will be not detectible by our blood test technique.which means that there is a still small percentage of it in the circulation SO if the drug is highly potent it can produce effect even in the absence of detectable drug in the circulation.

Note: high potency drugs is the drug that can do its effect in low concentration..mean that we need small dose of this drug to produce the effect . for this we can note that there is a shift in the drug response curve toward the left because small dose can cause effect.



**Mechanism of Action:

-GH act on a surface receptor of JAK\STAT cytokine receptor superfamily.although it is not cytokine.ex of cytokine : interleukin-1 ,interferon,TNF..etc .

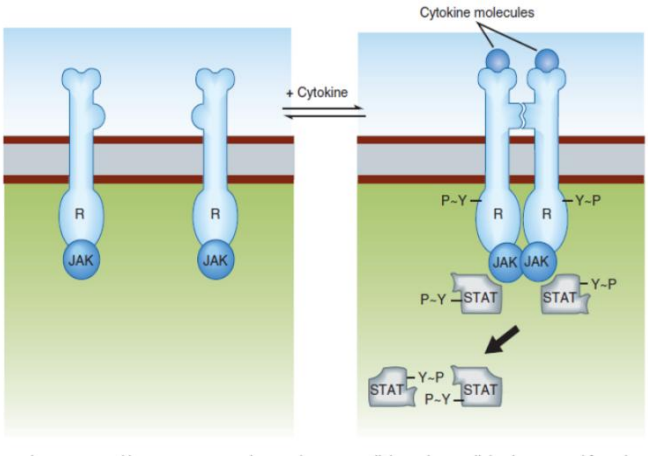
-The difference between GH and cytokines is that in cytokine we need 2molecule in order to activate dimerization ,but the GH only one molecule is needed .

-After binding of hormone to their receptors ,dimerazation of the two receptor will occurs.

-there is a kinase in each receptor(JAK) , the kinase that found on first receptor will phosphorylate the second receptor ,and visa versa.

-once the 2 JAKS are phosphorylated they attract the (STAT) which will form a dimer that enter the nucleus where they willstimulate the transcribtion of gene , so their activity is will mediated by synthesing of different proteins like Insulin Like Growth Factor.

the action of GH is mediated through production of **insuln-like growth factor(IGF-1) mainly by the liver,and in others tissue.
**So.. IGF-7 is the target organ hormone for GH , T3-T4 is the targt organ for the TSH , cortisol is the target organ hormone for ACTH ….and so on..



****JAK : juanse kinase …**

- it means "just another kinase"which is the first name for this kinase when it was discover ed.

-also mean (ذو الوجهين بالوثنية) ::
Cause this kinases can **produce**d their action by phosphorylation AND **regulate** their action.

****STAT : (signal transducers and activators of transcription).**

**** CLINICAL CASE:**

-diabetic women will have large baby's !!

since mother have hyperglycemia , high glucose will stimulate insulin to reduce that glucose. Glucose of the mom will cross the placenta to the fetus but insulin will not s cause is a larg protein to fetus. This glucose will stimulate the fetal insulin to take care of glucose that is coming from mom. But it will act in (IGF-7).and by activating these receptors this will stimulate growth in the fetus .HOWEVER it also cause hypoglycemia in the fetus because after the baby is born glucose e fetus , in this case doctos should give this baby glucose directly.

Pharmacodynamics of GH:

**GH has complex effects its not only affects the growth ,it also has a metabolism effect on protein , carbohydrates,lipids, and body composition.

1-Growth: the growth promoting effect of GH is not direct …it is mediated through an increase in the production of insuln-like growth factor(IGF-1) mainly by the liver,and in others tissue.

(IGF-1: is not an endocrine hormone , it is either paracrine or autocrine hormone.) .So GH stimulate longtidunal bone growth. any deficiency in GH in children will cause DWARFISM because during the childhood the epiphysis is still open but dwarfism can be treated if the epiphys is not closed and pateints can get normal or close to the normal growth.

3-Body composition : in both children and adults, it has anabolic effects in muscles and catabolic effects in adipose tissue ..this mean that GH will stimulate the synthesis of protein in muscle and lipolysis of lipid in adipose tissue. So this will cause an increase in muscle mass and a reduction in body fat→if there any deficiency in GH you will have low in muscle mass and obesity.

→Q:can we use it to treat obesity?
→A:No ,because is not the only causative agent ..its rarely cause obesity .

4- Carbohydrates,lipids, and protein metabolism : we will focus on carbohydrate metabolism. It's a mixed story because the action of GH in carbohydrates is different from the action of the IGF-1(which is the target hormone for GH). In other word**,** GH and IGF have opposite effects on insulin sensitivity. These difference are:

A- (GH**)** reduces insulin sensitivity →so it makes insulin resistince →if insulin increase→this will stimulate glucose. and whenever there is an increase in glucose level this will stimulate insulsin to reduse glucose but insulin is not working so insulin will accumulate resulting in "hyperinsulinemia", and increased blood glucose levels" hyperglycemia".
- At end This will cause insulin resistance diabetes.

B-(IGF-1) its like insulin it stimulates growth and decreases glucose so as result insulin concentration in the blood will be reduced also.

SO:

****Adults with growth hormone deficiency often have:**

- generilized obesity
- reduced muscle mass and this is a bad thing cause loss of muscle mass will develop asthenia.

  Asthenia : **abnormal physical weakness or lack of energy**

- diminished bone mineral density .
- **dyslipidemia** abnormality in lipid in general .

(dys:means **either** abnormal **OR** pain in latin)

- -reduced cardiac output

****children with growth hormone deficiency often have:**

- Short stature <u>after birth</u> because <u>prenatal</u> growth is not growth hormone dependent.
- Mild adiposity.
- Hypoglycemia.

**** <u>IMPORTANT NOTE</u>:**

If your patient have a GH deficiency ..and when giving him an exogenous GH he doesn't show any response !!

IN this case he will have <u>GH resistance</u> which is related to many causes:

1-GH receptors mutations **.**

2- post- receptor signaling mutations:

ex. JAK\STAT mutation doesn't give effects in cells.

3-GH antibodies**:**they act as blockers for GH receptors مهم.

→in these cases the treatment is by giving IGF-1 and we won't get hyperglycemia or hyperinsulinemia cause it have different action on carbohydrate than GH as we said previously.

**** Therapeutic uses of GH :**

As we said in the beginning of the sheet, drugs targeting the pituitary gland are mainly concerned with :replacement of some hormones (like growth hormone) / diagnosis of diseases/ antagonist for diseases resulting from excessive hormone secretion from the pituitary gland . So drugs concerned with growth hormone are mainly used in:

1)**Replacement therapy** :this is the main therapy which used in the case of growth hormone deficiency state, in both adults and children .

2)**others** : we are not in concern to talk about .

** Toxicity and contraindications of GH replacement therapy :

•Toxicity is not an adverse effect(they are not the same thing) ,it happens in the case of having high concentration of the drug so :

When the drug is in normal concentration (physiological range);it will produce adverse effects but when it is in high concentration (toxic range)it will produce toxicity.

•Its toxic effects in children are diferrent than those in adult,and it is relatively rare in childern.

→Some of the toxicity effects in children :

1-Idiopathic increase in intracranial pressue which is known as(psuedotumor cerebri) it is psuedo because it is not a mass occupying lesion means that there is no mass or collapse in the brain that causes the increase in intracranial pressure .

This psuedotumor cerebri will affect many things,mainly the optic nerve and so cause changes in vision,nausea,vomiting and headache.

2-Slipped capital femoral epiphysis (head of femur):

If a child has normal GH he will not suffer from abnormalities because the normal GH comes as response and equel the physiologic need of growth in the body.. regulated by its own ... But if the GH is exogenous (rhGH) and even though you control the dose ;it will not be withen the physiological range (the range that won't cause any side effect) ;some times there will be a little increase in the dose due to different metabolism of the drug between individuals which leads in some cases to a slight increase in the drug concentration (if you have a group of children with same disorder traditional therapy is by giving them the same dose but in it should be a personal therapy, because there body composition and structure are different so do their needs and responses. So maybe one of the children needs a little less dose and by giving him the common dose he will end up with excissive GH) ; the stimulation of the excessive GH in growing child will fasten the growth of the body as a result there will be an increase in the forces and stresses placed on the upped part of femur which can slip it .

3-Progression of scoliosis during rapid growth : GH increase the scoliosis But is not the cause of it.

4-others : pancreatitis, otitis media, gynecomastia,nevus (وحمة) growth, edema, hgperglycemia ,and increased risk of asphyxiation .

NOTE:

Hypothyroidism is commonly discovered during GH treatment : It is found that the patients who are treated with GH ,by time

they show hypothyroidism , But it is a coincidence which means that it dosen't happen as a result of GH therapy .the reason for the incidental finding is that the effects of GH deficiency was hiding and overwhelming the effect of hypothyroidism, so when a pateint starts to be supplemented by growth hormone the symptoms of hypothyroidism will start to manifest in the pateint . In conclusion, we have to be able to differentiate between the cause-result disorders and coincidence disorders.

→Toxicity effects in <u>adults</u> :

1- Peripheral edema ,myalgia,arthralgia(hands and wrists)

Myalgia : pain in the muscles.

Arthralgia : pain in the joints.

2-Carpal tunnel syndrome (compression of the medial nerve)

3-Increased activity of cytochrome p450 enzymes : that means that GH drugs increase the metabolism of other drugs and reduce their blood levels and to solve that we increase their doses & once we stop the GH treatment we have to decrease the doses of the other drugs otherwise they will produce toxicity .

4-Proliferative retinopathy :Gh cause proliferation of the tissue of retina and vascularization and then blindness.

5-Contraindicated in patients with active malignancies : GH induce the growth of malignancies .

6-Use in critically ill patients increases mortality :if some of the critically ill patients are given GH , GH will increase the body metabolism and this will demand an energy that can not be provided by an ill pateint and thus increasing the risk of mortality.

7-long acting rhGh (somatotropin)will cause: at the injection site will cause nodules,edema,arthralgia,fatigue,nausea, headache.

Third:IGF-1 aqonist.

****Now we talked about GH therapy as a treatment of GH deficiency But what if the body dosen't response to the exogenous GH !? What are the therapies available ?**

Mecasermin

✓ -Which is an insulin-like growth factor analog

✓ This drug is found in **two forms**:

- **Mecasermin:(the original form analog)** also known as recombinant human IGF-1 (rhIGF-1) .
- **Mecasermin rinfsbate**: is acomplex of rhIGF-1 and its binding proteins (rhIGFBP-3) the importance of the binding protein →is to increases the circularing half-life of rhIGF-1 so as to increaes the duration of action.

✓ - the **adverse effects** of these drugs(the same if there was an excess in IGF-1)?

- .Hypoglycemia (it is the most important) and can cause brain damage.
- .Increased intracranial pressure which can cause blindness
- .Adenotonsillar hypertrophy :hypertrophy in the tonsils and adenoids.
- .Elevation of liver enzymes.

Fourth: growth factor antagonist.

❖ **When do I need GH antagonists ?**

- when there is an excissive GH in the whole body as in the case of pituitary gland adenoma .

❖ Remember : in the case of adenoma the defenitive treatment is removal surgery But until that time we treat the pateints temporarily with drugs.

❖ excessive GH produce Acromegaly in adult and Giantism in children even though they have common causative agent they differes from each other in The manifestations .

- Gigantism happens in children whose epiphysis is still not closed so produces longitudinal growth of bones plus the growth of other tissues .
- Acromegaly appears as thickening of every thing so the growth of adults is more in width unlike the growth of the children which is more in length because of the opened epiphysis .

NOW these antagonists are:

1- somatostatin

2- somatostatin analogs (Octreotide)

3- Pegvisomant

-Somatostatin :

• somatostatin is the endogenous inhibitor of growth hormone in the body but it can be provided as an exogenous form to inhibit excessive secretion of growth hormone in pateints

•It is a 14-amino acid peptide found in the hypothalamus, CNS, pancreas, GIT,.. -> lack of specificity.
• It is an inhibitory paracrine factor.
• It inhibits the release of GH, TSH, glucagon, insulin and gastrin.
• Half-life 1-3 min -> which limites its therapeutic uses .
• Metabolized and excreted mainly by the kidney.

-Octreotide:

• Is an analog of somatostatin .
• 45 times more potent than somatostatin in inhibiting GH release (means that we need 45 times less concentration than somatostatin to inhibit GH production) but only twice as potent in reducing insulin secretion → so it has the same lack of specificity as

somatostatin and thus causes the same effects of somatostatin but with less concentration.

• Half-life is around 80 min -> longer and more useful practically.
• Given subcutaneously.

• Therapeutic Uses of Octreotide :

1.Reduces symptoms caused by a variety of Growth hormone-secreting tumors: acromegaly, carcinoid syndrome, gastrinoma, VIPoma, glucagonoma, insulinoma, and ACTH-secreting tumor.
2. Diarrhea (secretory diarrhea -not infective diarrhea- , HIV associated, diabetic, chemotherapy, or radiation induced)
3. Acute control of bleeding from esophageal varices (portal hypertension): used to stop bleeding from esophageal varices.

• Its adverse effects:

1.Hyper/Hypo glycemia ??(Inhibits insulin and glucagon secretion) – rare, and may be transient: as we said that Octreotide inhibits every thing (insulin and glucagon and others) and we cannot know which is the predominant ;it differ among patients and so you could see hypo or hyper /glycemia

2.Pain at site of injection.

3.GIT: nausea, vomiting, abdominal cramps, flatulence, steatorrhea with bulky bowel movements.

4. Vitamin B12 deficiency with long-term use (reduced absorption).

5. Biliary sludge(mixture of particulate solids that have precipitated from bile) and gall stones (20-30% of patients after 6 months of use) ;that is because of the loss of perstalsis in the gall bladder ,so in those people the bile dosen't go to the intestines and accordingly they will suffer of steatorrhea.

6. Sinus bradycardia (25%) and conduction disturbances in the heart (10%).

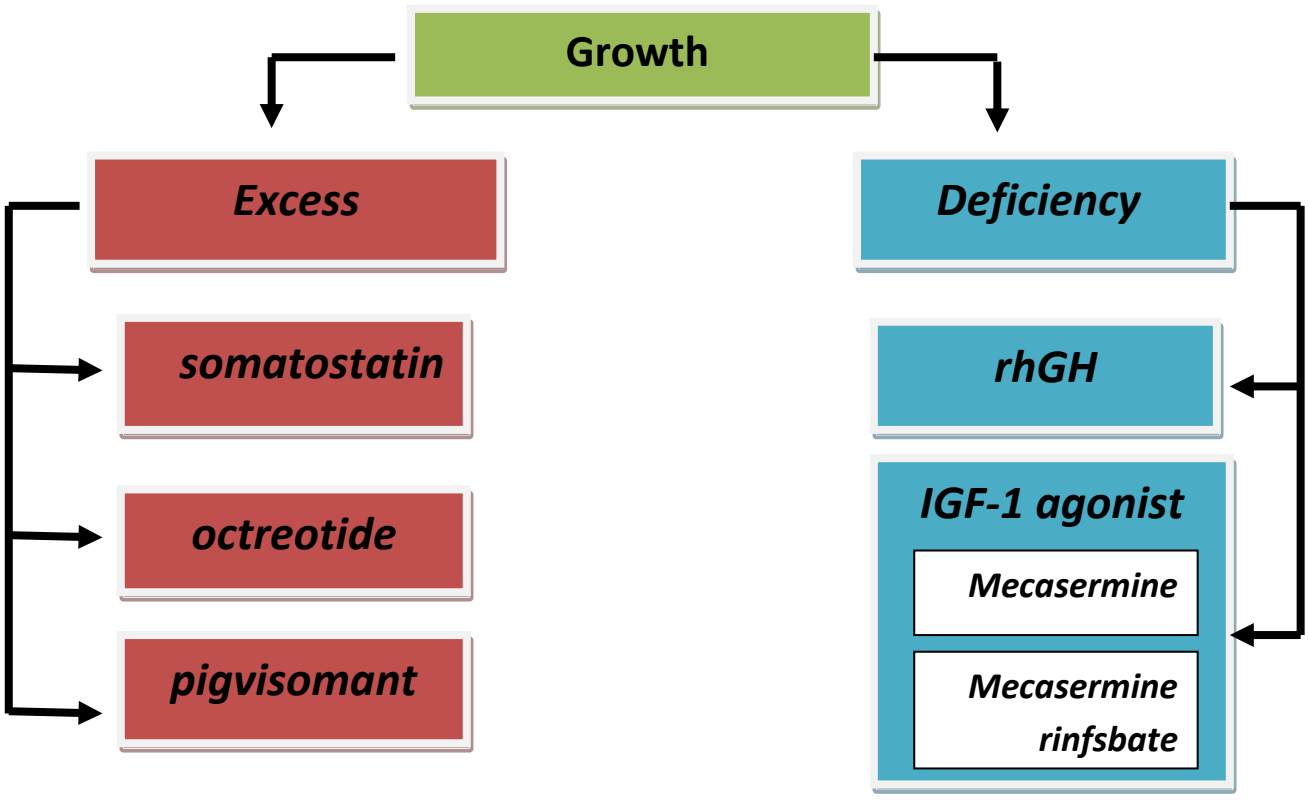
-Pegvisomant :

- ✓ GH receptor antagonist, Useful for treatment of acromegaly.
- ✓ Is a polyethylene glycol (PEG) derived from a mutant GH.
  Remember: Pegylation reduces its clearance and improves its overall clinical effectiveness.
- ✓ It has increased affinity for one site of the GH receptor and reduced affinity at the second binding site (as we said GH binding 2 receptors by

dimerization) and this will allow dimerization of the receptor but blocks the conformational changes required for signal transduction.

- ✓ Important note : Pegvisomant normalizes IGF-1 levels, but does not inhibit GH secretion ,so it could increase the secretion of GH because when you prevent the action of the hormone there will be an adaptation and increase of the hormone secretion throughout a negative feedback mechanism.
- ✓ Adverse effects:
  - **1.**May lead to increased GH levels and possible adenoma growth.
    2. Elevation of liver enzymes.

Summary



your patients are waiting you ; waiting for a perfect doctor….SO be up to their expectations☺

(Sorry for any mistakes)
