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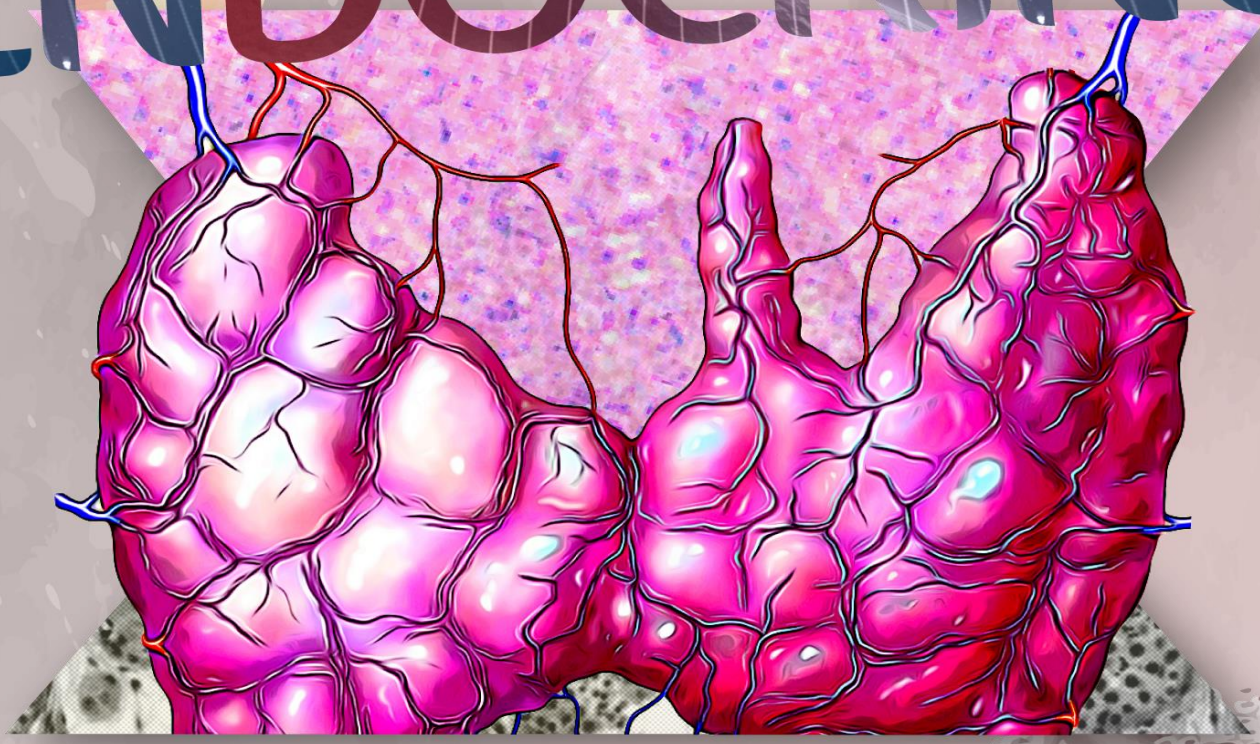
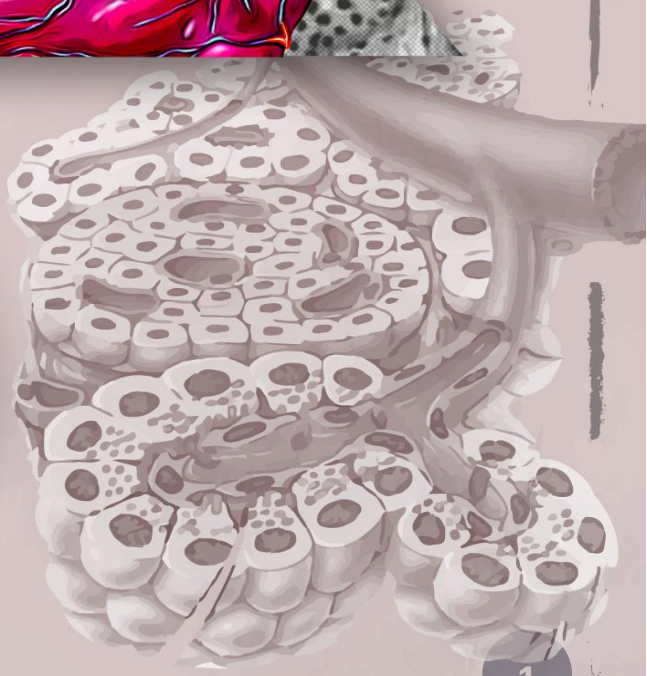
ENDOCRINE





SUBJECT: Pharmacology

DONE BY: Assem Al Refaei

CORRECTED BY: Hadi Al Refaei

DOCTOR: Malik

The Dr started the lecture talking about the anti-aging effect of GH, he said that all the reviews based on human and animal researches proved that there's no anti-aging effect for GH. So, we conclude that nothing can make life longer except for Ibrahim Al Zoraiqi interrupting the angel of death with some questions.

Last lecture, we talked about multiple topics Including the agonism of GH, while for today here's the checklist:

1- The Antagonism of GH.

2- Somatostatin and Octreotide.

3- Octreotide (usages and side effects)

4- Pegvisomant

5- Bromocriptine

6- Prolactin

The antagonism of GH.

- When do we use them?

When we have hypersecretion of GH, obviously.

- What are the diseases treated with these antagonists?

In Acromegaly and Gigantism.

- We've three options for GH antagonism, what are they?
- 1. Somatostatin analogs, octreotide .
- 2. Dopamine receptor agonists, bromocriptine.
- 3. GH receptor antagonists, pegvisomant.

The First Option, Somatostatin And Octreotide.

- Remember, how does Somatostatin work?
- Somatostatin inhibits GHRH from binding to its receptor on somatotropes of the anterior pituitary which leads for less GH stimulation.

	Somatostatin	Octreotide
Structure	14 AAs peptide	Analog* of somatostatin
Endogenous secretion	Hypothalamus, GIT, Pancreas and CNS	None
Function and potency	inhibits the release of GH, TSH, glucagon,insulin and gastrin.	45 times more potent than somatostatin in inhibiting GH release but only twice as potent in reducing insulin secretion.
Half life	1-3 mins	80 mins
Administration method	Not used clinically.	Subcutaneous
Metabolism	Metabolized and excreted mainly by the kidney.	Not mentioned. Multiple actors and sites (internet).

- Why we don't give Somatostatin?

  1- It's a short half life (1-3 mins)

  2- Poor selectivity as it has multiple functions like inhibiting TSH, Insulin, Glucagon, TSH and GH (which is the only one I aim toward)

- *What's an analog?

  Is a compound having a structure similar to that of another compound, but differing from it in respect to a certain component affecting is metabolism, activity and half life. So is octreotide to Somatostatin.

- What is the significance of octreotide function and potency mentioned in the table?

  It's highly potent against GH, and much less against insulin. As a result, no hyperglycemia shall develop and effective treatment for my GH hypersecretion is there.

Octreotide

Remember, Octreotide is an analog of Somatostatin with a half life of 80 mins. It's 45 times more potent than somatostatin in inhibiting GH release but only twice as potent in reducing insulin secretion and is injected subcutaneously.

- What are the therapeutic uses?
  (TDE – Tumors, Diarrhea, Esophagheal varices bleeding)

1- Reduces symptoms caused by a variety of hormone-secreting **tumors**: acromegaly, carcinoid syndrome, gastrinoma, VIPoma, glucagonoma, insulinoma, and ACTH-secreting tumor. (**MOA: reducing hormone release)**

2- **Diarrhea**— secretory, HIV associated, diabetic, chemotherapy, or radiation induced. (**MOA: secretin inhibition)**

3- Acute control of bleeding from **esophageal varices** (portal hypertension). (**MOA: unknown)**

- What are the adverse effects? (HPV GS)
- 1.**Hyperglycemia (M:Inhibits insulin and glucagon secretion)** – rare, and may be transient, the drug is more selective than Somatostatin but it still has some activity as we said.
  Note: hyperglycemia is established because insulin is the only hypoglycemic hormone while there're multiple hyperglycemics.

- 2.**Pain at site of injection**. **(M: it's a subcutaneous injection)**
- 3.**GIT**: nausea, vomiting, abdominal cramps, flatulence, steatorrhea with bulky bowel movements. **(M: inhibition of secretin)**
- 4. **Vitamin B12** deficiency with long-term use. (**M: reduced absorption)**
- 5. **Biliary sludge and gall stones** (20-30% of patients after 6 months of use).
- 5. **Sinus bradycardia** (25%) and conduction disturbances in the heart (10%). **(M: GH inhibition as it increases heart rate, so no GH leads for sinus bradycardia)**

Pegvisomant

- Why is it used?

  To avoid side effects of octreotide in some patients, imagine having a patient with preexisting bradycardia or GI problems or Vit B12 deficiency, definitely his state will be worse. That's why we use pegvisomant.

Description	GH Receptor Antagonist
Structure	PEG* derivative of mutant GH*
Usage	Acromegaly

• Pegvisomant is synthesized from a mutant GH gene which yields us a mutant GH, after that we add polyethylene glycol to it in a process known as pegylation.

• Polyethylene glycol (PEG) reduces its clearance and improves its overall clinical effectiveness.

Note: It has increased affinity for one site of the GH receptor and reduced affinity at the second binding site. (The Dr didn't focus on it and said it's just molecular stuff).

- What's the MOA?

  It binds to the receptor and allow dimerization to take place but because of it being a mutant GH, it'll not lead for the conformational changes that lead for the JAK-STAT pathway, so no activation of intracellular signaling.

- What are the adverse effects?

1. May lead to increased GH levels and possible adenoma growth.
2. Elevation of liver enzymes. **(M: it's metabolized there)**

- How it can lead for somatotropes adenoma?

  • Remember in patients with acromegaly, we will be having high GH level and high GH signaling in our cells including our hepatocytes leading for high IGF production. Now, giving pegvisomant will reduce GH signaling, thus reducing and normalizing the level of IGF.
  • Also, remember that IGF increases Somatostatin that decreases GH. Thus, exhibiting negative feedback over GH.
  • From these two points we can see that pegvisomant will decreas GH signaling and decrease IGF production normalizing it after it was high and this will lead for decreased negative feedback which can lead for more proliferation of the cells secreting GH and more GH secretion and adenomas…

  Is that Ok? Absolutely not.

  The man suffering from acromegaly may have an adenoma at the first place!!!

- So, what's is the drug of choice?

  It's either pegvisomant or octreotide according to the patient, you either give him pegvisomant and monitor him or octreotide making sure that the side effects don't make a preexisting condition worse, Bromocriptine is given as an add on drug.

Bromocriptine

Briefly speaking, it's a D2 (dopamine receptor) agonist that can reduce GH and prolactin secretion but is not effective alone so it can be given as an add on drug to the regimen you chose.

Prolactin

General Info

• 198 AAs peptide from anterior pituitary ,similar in structure to growth hormone.

• Principal hormone responsible for **lactation** in the presence of estrogens, progestins, corticosteroids, and insulin.

• The prolactin-inhibiting hormone is dopamine.

Hyperprolactinemia

It's a state of prolactin hypersecretion, what are its features?

It leads for hypogonadism **(M: it inhibits GnRH (gonadotropin releasing hormone and this is an aspect (not the main one) in why there's no menstrual cycle during pregnancy)**

So, it'll inhibit GnRH leading for less sex hormones and no spermatogenesis or ovulation and eventually:

• infertility, oligomenorrhea or amenorrhea, and

galactorrhea in premenopausal women

• loss of libido, erectile dysfunction and infertility in men.

The Therapy

As we know dopamine is a natural Inhibitor for prolactin release, so if we administer dopamine agonists (especially D2) we will decrease prolactin.

The Drugs:

	Half life	**Administration**	**Site of administration**	**Class**
Bromocriptine (The oldest)	**7 hours**	**Three times daily**	**Orally or vaginally**	**Ergot derivative**
Cabergoline	**65 hours**	**Twice weekly**	**Orally or vaginally**	**Ergot derivative**
Quinaglolide	**20 hours**	**Once daily**	**Orally or vaginally**	**NonErgot**

Note: We prefer using cabergoline because of its long half life and infrequent administration (twice weekly)

Therapeutics uses for these D2 agonists

1. Hyperprolactinemia **(M: already explained)**

• Shrink pituitary prolactin-secreting tumors, due to inhibition.

• Lower circulating prolactin levels.

• Restore ovulation in ~ 70% of women with microadenomas and ~ 30% of those with macroadenomas.

2. Suppression of physiologic lactation to prevent breast engorgement when breast- feeding was not desired. (discouraged use!)*****

3. Acromegaly. **(As we said, bromocriptine can be used as an add on drug to reduce GH)**

4. Parkinsonism. **(In Parkinsonism, low amounts of dopamine are present in the brain, so the balance between the main three chemicals of the CNS (Dop, Ser, NEP) is lost leading for multiple symptoms, administration of dopamine agonists will reduce the dose of levodopa (precursor of dopamine) administered to these patients.)**

******* for number 2**

Milk is the only thing an infant can take in his first 6 months, so it's vital and important. For lactogenesis, the process starts during pregnancy as Prolactin increases, but why isn't there milk? Because of the high estrogen levels that block that activity BUT it doesn't affect Prolactin effect over gene expression through the JAK-STAT pathway leading for proteins synthesis,proliferation and growth of the alveolar ducts in the breast (preparing for postpartum breastfeeding). As the woman gives birth, حليب اللبى will be secreted and it's protein rich and important for the infant (proteins that are there all the time), estrogen will decrease in 3 days and this will lead for Prolcatin full activity to show up leading for opening up of all the channels (IGA, Carbs, AAs and many nutrients, THE OPTIMAL MEAL FOR THE INFANT, hence we say eat good so your milk becomes good for mothers).

It's also important that the child starts to suck after birth, as sucking activates neuroendocrine reflexes that increase prolactin, and more milk for the baby.

Some women prefer to don't feed their babies because she has no time or whatever so she use these drugs to decrease prolactin and this is highly discouraged for the health of the newborn, and in some cases the newborn doesn't breastfeed or shouldn't because of metabolic disease like phenylketonuria. As a result in these cases where the baby won't breastfeed, milk will crystalize and engourge in the breast and to get rid of this, moms must use D2 agonists.

Adverse Effects of these D2 agonists:

1. Nausea, vomiting, headache, fatigue and lightheadedness. **(Remember in antiemetic drugs we used dopamine antagonists so the opposite will produce vomits)**

2. Orthostatic hypotension. **(When we studied ANS (BIG LOL), some of our vessels(ex: kidney) have D2 receptors as a part of ANS, when they're stimulated by dopamine, they vasodilate, so giving these drugs will lead for vasodilation and minimal hypertension (not extreme) and as a result it's orthostatic and only shows up when you stand up and change your position)**

3.. Psychiatric manifestations even at lower doses, and may take months to resolve. **(As we know, dopamine is one of the happiness hormones and alone NEP and Serotonin, they play major roles in our CNS, so any drug that affects this balance will lead for psychiatric effects as in schizophrenia, where they have dopaminergic overstimulation)**

Recall: Dopamine agonists in low dose (nickname: kidney dose) act over the D2 receptors leading for vasodilation, hypotension and is used in oliguria (decreased kidney output) while at a moderate dose it affects alpha 1 and at a high one beta 1 (nickname: cardiac dose).

4. Erythromelalgia (paroxysmal throbbing and burning pain in the skin, affecting one or both legs and feet, sometimes one or both hands). **(Idiopathic)**

5. Pulmonary infiltrates with chronic high dose therapy.

7. No apparent increase in spontaneous abortion or congenital malformations if given during pregnancy for macroadenomas.

8. Stroke or coronary thrombosis in postpartum women taking bromocriptine to suppress postpartum lactation.

If you're studying this sheet befoe the exam, stay postive. Don't think of what you should've done better, think of what you should do now and what to do better in the future. Give up your phone and any source of attraction or time wasting. Focus on your mission, make a reasonable studying course for whatever left for the exam and get into it. It won't determine your future, but it's a step in it and every step and word counts.

GOOD LUCK, FUTURE DOCTOR