Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Growth hormone and Pituitary Adenomas

Color index:
Important
Note
Extra

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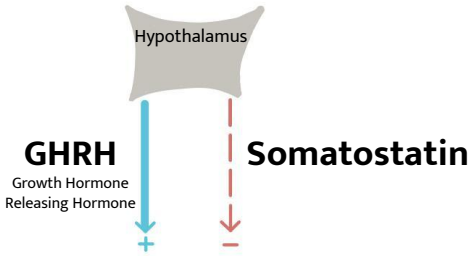
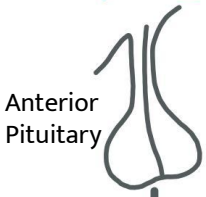
Editing File

Growth Hormone Physiology

Physiology isn't part of the exam





GH

Binds to adipocytes and causes them to break down triglycerides and prevents them from accumulating fat in the blood

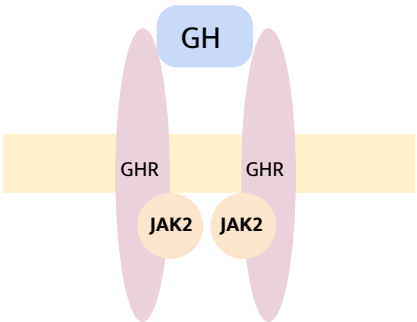
IGF-1
Insulin-like growth factor-1

↑ Myoblasts growth and differentiation
↑ Amino Acid uptake
↑ Protein synthesis

↑ Cartilage cells (chondrocytes) growth

Cellular Mechanism

Binding of GH to its receptor activates the signaling cascade mediated by receptor associated to JAK tyrosine kinases



Pituitary Adenoma

Pituitary adenoma is a benign tumor of the anterior lobe of the pituitary that causes symptoms either by

♦ **Underproduction**:
Growth hormone deficiency, major problem in children's growth, hypothyroidism,

♦ **Overproduction**:

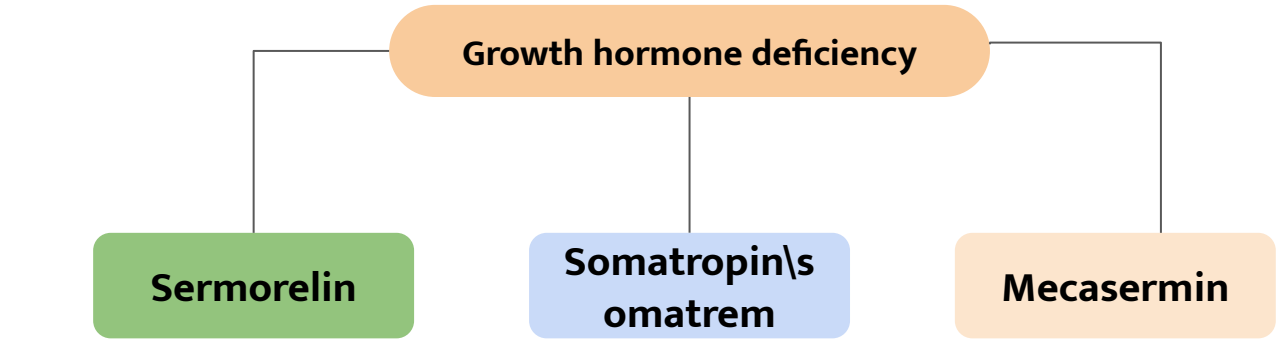
Growth hormone excess resulting in **Acromegaly** or **Gigantism**

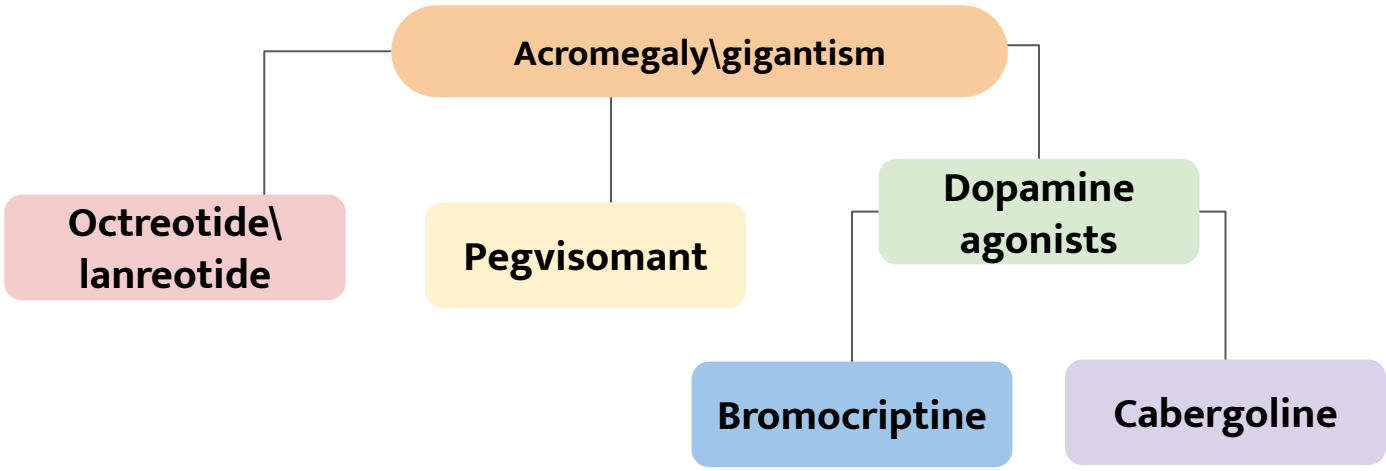
Prolactin excess leads to galactorrhoea, menstrual abnormalities and infertility

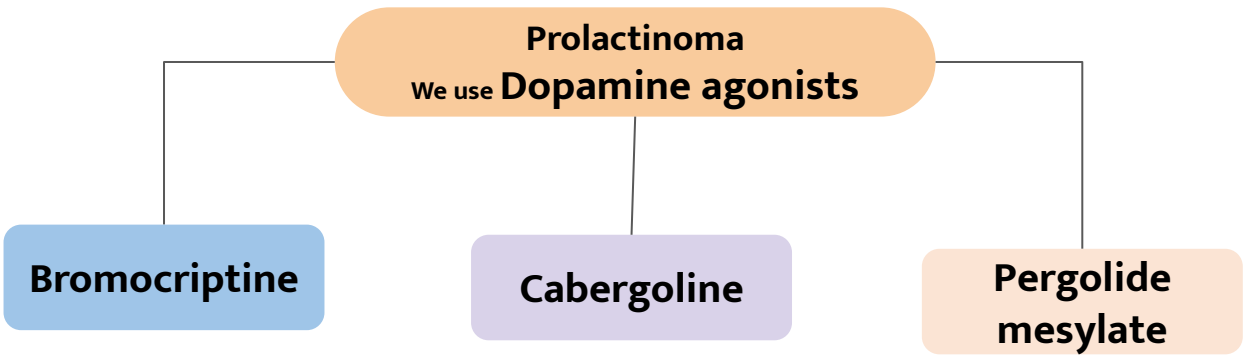
Cushing disease resulting from adrenocorticotropic hormone (ACTH).

Clinical Presentation :
- Amenorrhea
- galactorrhea
- impotence

Mind maps


Growth hormone deficiency
Sermorelin
Somatropin\s omatrem
Mecasermin


Acromegaly\gigantism
Octreotide\ lanreotide
Pegvisomant
Dopamine agonists
Bromocriptine
Cabergoline


Prolactinoma
We use Dopamine agonists
Bromocriptine
Cabergoline
Pergolide mesylate

Treatment of growth hormone deficiency

Sermorelin

Synthetic GHRH used if a patient possesses **defective hypothalamic release** of GHRH but normally functioning anterior pituitary somatotrophs

Somatropin	Somatrem

Recombinant (synthetic) Human Growth Hormone
which is a 191-amino acid peptide, identical to the native form of hGH

Indications	-Documented **Growth failure in pediatric** patients associated with: **GH deficiency** and **Turner syndrome** (increase height in girls) -Idiopathic short stature **-Wasting** in patients with **AIDS** **-Short bowel syndrome** in patients who are also receiving specialized nutritional support patients who undergo intestinal surgery and receive total parenteral nutrition (TPN) have defect in GH and mitosis and anabolic action thus we might give them GH
Side Effects more in adults and less in kids bc kids are more tolerable to GH	- Leukemia - rapid growth of melanocytic lesions - Hypothyroidism - Insulin resistance - Arthralgia pain in the joint - Increase in cytochrome P450 activity

Mecasermin

Recombinant IGF1 , administered S.C

Indications	used for children with severe IGF1 deficiency due to mutations in the GH receptor (Laron dwarfism) or development of neutralizing antibodies against GH
Side Effects	- **Hypoglycemia** : can be avoided by consumption of meal 20 min before or after the administration of drug.

Treatment of Acromegaly / Gigantism :

	Octreotide	Lanreotide
is a synthetic long-lasting peptide analogue of somatostatin		
P.K	➢ very expensive ➢ 45 times more potent. than somatostatin ➢ half-life in plasma being 113 min ➢ peak plasma concentrations within 1 h ➢ suppress GH levels for 6–12 h ➢ Given every 4 weeks	
MOA	**1- Inhibit GH secretion** **2- partially inhibits GH-induced IGF-1 generation** 3- reduce GHRH release	
ADRs	- Significant Gastrointestinal disturbances - Gallstones - Cardiac conduction abnormalities ECG is very important	

Pegvisomant

GH receptor antagonist

MOA	a long-acting derivative of a mutant GH that is able to cross-link GH receptors but is incapable of inducing the conformational changes required for receptor activation. approved for treatment of acromegaly
P.K	• Pegvisomant given s.c: • Check IGF 1 level every 4-6 weeks • Monitoring GH not useful {Only reduce IGF-1 (does not affect GH level)} • Dose 10-40 mg/d

Numbers aren't important	**Octreotide** (S/C) 100 to 500 mic.gm three times a day	**Octreotide** (I/M) at **28 days interval**	**Lanreotide** (I/M) every 7-14 days	**Pegvisomant**
GH REDUCTION	47%	56%	50%	Not useful
IGF1 REDUCTION	46%	66%	48%	97% very selective

- **Octreotide and Lanreotide are** Both equally effective no difference clinically
- Increasing the intervals between doses will make the treatment more effective with less side effects

Dopamine agonists	
Bromocriptine	**Cabergoline** Has stronger effect
- described under **hyperprolactinemia** - more effective at inhibiting prolactin release	- More effective in GH and **IGF1** reductions
used as a last choice if all the previous drugs didn't have any action	
Indications	-Used both as primary and adjuvant treatment -only high doses -Response rate low
Bromocriptine up to 20 mg/day	Cabergoline 1–2 mg/week

	Bromocriptine	**Cabergoline** better than bromocriptine
GH REDUCTION	20%	44%
IGF1 REDUCTION	10%	35%

Numbers aren't important

Dopamine D2 Receptor Agonists

Dopamine D2 receptor agonists such as bromocriptine are more effective at inhibiting **prolactin release** than **inhibiting GH release.** However, high doses of D2 receptor agonists have **some** efficacy in the treatment of small GH-secreting tumors

Prolactinoma

(pituitary adenoma with excess release of prolactin)

Initial therapy is generally **Dopamine agonists.**

Mechanism of action of Dopamine agonists

Selective activation of **D2** receptors located on lactotroph cell surface

↓

Decrease **adenylate cyclase** activity

↓

Decrease in **C- AMP** level

↓

Inhibition of PRL synthesis and release.

Bromocriptine

(2-bromo-α-ergocryptine mesylate)

A dopamine agonist the Purpose of it was **inhibiting prolactin secretion** without the uterotonic, vasospastic properties of other **ergots**.
Bromocriptine is **safer in pregnancy**

P.K	• The absorption rate from the GI tract is 25-30%. • Very high first-pass effect, with 93.6% of a dose being metabolized and only 6.5% of an absorbed dose reaching the systemic circulation unchanged • Excreted via the biliary route into the feces • start low dose at 2.5 mg day at night before increasing to 2.5 – 10 mg per day in divided doses • Take with food to reduce side effects

Cabergoline

Ergot drug

	❑ Given once or twice a week with a starting dose of 0.25 mg 2 x week ❑ More effective ❑ Well tolerated but not safer in pregnancy ❑ More expensive Better tolerated and more effective than bromocriptine for tumor shrinkage but more expensive.
ADR	Orthostatic hypotension, Nausea, and Dizziness; avoided by beginning with low-dose therapy.

Pergolide mesylate	
ADR	**ADRs for all dopamine agonists** :GI intolerance, postural hypotension, constipation, nasal stuffiness - ➡➡ Must **not** be used in pregnancy

QUESTIONS

What's the mechanism of action of Bromocriptine ?

A. GH Antagonist
B. Synthetic IGF-1
C. Dopamine Agonist

Which of the following is a side effect of mecasermin ?

A. Arthritis
B. HyperGlycemia
C. HypoGlycemia

Which of the Following is the most effective in treating Acromegaly ?

A. Pegvisomant
B. Pergolide mesylate
C. Somatropin

Which of the following Drugs is safer during Pregnancy ?

A. Bromocriptine
B. Cabergoline
C. Pergolide mesylate

Which of the following has no effect on GH reduction ?

A. Pegvisomant
B. Octreotide
C. Cabergoline

Answers:
C - C - A - A - A

Treatment of Growth hormone deficiency		
Sermorelin Synthetic GHRH	**Somatropin** Somatrem Synthetic hGH	**Mecasermin** Synthetic IGF1
	- Used in **Growth failure** **- ADRS :** Leukemia rapid growth of melanocytic lesions Hypothyroidism	ADRs: Hypoglycemia

Treatment of Acromegaly / Gigantism :		
Octreotide Synthetic somatostatin	**Pegvisomant** GH receptor antagonist	**Bromocriptine / Cabergoline** Dopamine agonists
- very expensive - Given every 4 weeks - ADRs: GI disturbances Gallstones Cardiac conduction abnormality	- Only Reduce **IGF-1** - Does not Reduce GH	- Cabergoline is More effective in **GH** and **IGF1** reductions than Bromocriptine - Only high doses

Treatment of Prolactinoma :		
Bromocriptine Dopamine agonists	**Cabergoline** Dopamine agonists	**Pergolide mesylate** Dopamine agonists
- Bromocriptine is safer in pregnancy - Take with food	- Better tolerated and more effective - ADR : Orthostatic hypotension	- ADRs: : Nasal stuffiness - Should Not be used in pregnancy

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Thanks for those who worked on the lectures :

Mohammed abdulsalam

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References:

- ✓ Doctors' slides and notes

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