Growth hormone & Drugs used in pituitary Adenoma

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- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

No objectives

AMBOSS article on Hyperprolactinemia

Osmosis videos on Growth Hormone, Acromegaly & Prolactinomas

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Hypothalamus and Pituitary Gland

overview

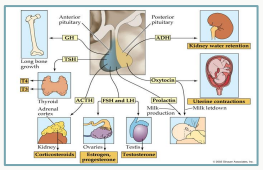
- Pituitary and hypothalamus are the link between the nervous system and the endocrine system.
- Hypothalamus is a major regulator of body homeostasis:

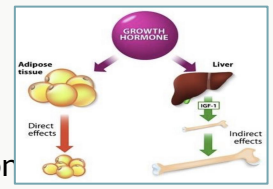
Homeostatic control includes regulating hunger, thirst, sex drive, sleep-wake cycles, body temperature, blood glucose.

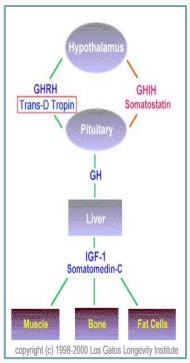
Endocrine control via regulating the release of pituitary hormones.

Autonomic control via descending pathways to sympathetic & parasympathetic preganglionic neurons.

Limbic function via connections to limbic system regulating emotion behaviors.



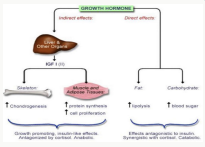


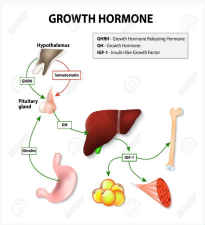


Functions

Anterior Pituitary GH/Somatotropin:

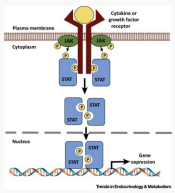
- Stimulates increase In size & mitotic rate of body cells, increase fat utilization
- Enhances amino acid movement through membranes & promotes protein synthesis
- Promotes **long bone growth** (The Most Important Function)





- **Hypothalamic GHRH** stimulates secretion of GH
- **Somatostatin** inhibits secretion of GH

Growth Hormone (GH)

MOA	○ Binding of GH to its cell surface receptor activates the signaling cascade mediated by receptor associated to **JAK tyrosine kinases.** ○ The effects of GH are primarily mediated by **insulin-like growth factor 1 (IGF-1)** released by liver in response to GH.	
effects	**Direct**	1. Binds to **adipocytes** & causes them to break down triglycerides & prevents them from accumulating fat in the blood. 2. Releases **IGF-1** from the liver.
	indirect	**Stimulates:** 1. **Bone** growth 2. **Cartilage** cells (chondrocytes) growth. 3. **Myoblasts** growth & differentiation 4. Amino Acid uptake & **protein** synthesis.

Abnormalities of GH

Abnormality	Leads to	Examples
Deficiency or **absence** of somatotroph cells	**Underproduction of GH**	• **Pituitary Dwarfism, primary.** • (Laron Syndrome) Which is known as Insensitivity to GH or Mutation in GH Receptor. • Delayed skeletal growth & retarded sexual development but alert, intelligent, well proportioned child.

Functional **Overactivity (or tumor)** of somatotroph cells	**Overproduction of GH** which will increase **IGF-1** (Stimulates protein synthesis, Influenced CHO and fat metabolism, Mitosis of all cell types)	Overgrowth of all body tissues
		• **Gigantism in children**
		  ○ Onset before bony epiphysis have closed at puberty
		  ○ ↑IGF-1 → longitudinal bone growth
		• **Acromegaly in adults**
		  ○ Onset after puberty
		  ○ bones ↑ in size, including hands, feet, and face + internal organs 

Pituitary Adenoma	A benign tumor of the anterior lobe of the pituitary that causes symptoms either by 1. **Underproduction:** growth hormone deficiency, major problem in children's growth, hypothyroidism. 2. **Overproduction** of the pituitary hormones: a. **Growth hormone excess** resulting in acromegaly or gigantism b. **Prolactin excess** leads to galactorrhoea (increase in milk production that is not related to pregnancy of lactation), menstrual abnormalities and impotence, infertility (prolactinoma) c. **Adrenocorticotropic hormone (ACTH)** cause Cushing disease d. **Thyroid stimulating hormone (TSH)** excess lead to Hyperthyroidism.	

★ GH Deficiency: *GH Agonists*

Drug	Sermorelin	Somatropin	Somatrem	Mecasermin
Overview	**Synthetic** growth hormone releasing hormone **(GHRH)**	**Recombinant** (Genetically engineered) **human GH.** **Somatropin:** A 191-amino acid peptide, **identical** to the native form of hGH.		**Recombinant IGF-1**, administered S.C.
Uses	Used if a patient possesses **defective hypothalamic release of GHRH** BUT **normally** functioning anterior pituitary somatotrophs. (central defects)	• Documented Growth failure in pediatric patients associated with **GH deficiency** and **Turner syndrome** (chromosomal condition that affects development in female → short stature & infertility) (to increase height in girls by 10-15 cm). • Idiopathic short stature. • Wasting of muscles in patients with AIDS. • Short bowel syndrome in patients who are also receiving specialized nutritional support. E.g. TPN		Used for children with **severe IGF1 deficiency** due to mutations in the GH receptor (**Laron dwarfism)** or development of neutralizing antibodies against GH. (recombinant hGH will be destroyed)
ADRs	-	• **Leukemia** Due to overstimulation of cell division • Rapid growth of melanocytic lesions can cause melanoma. • Hypothyroidism because thyroid gland uses the same hypothalamic pituitary axis • Insulin resistance, since it works on insulin receptor • Arthralgia. • ↑ in cytochrome P450 activity.		The common ADR is **Hypoglycemia** (Insulin like action)**: can be avoided** by consumption of meal **20 min** before or after the administration of drug.

GH overproduction: *GH Antagonists*

drug	Octreotide	Lanreotide	Pegvisomant
Overview	Somatostatin analogues		GH receptor antagonist
MOA	**Normally:** Somatostatin physiologically inhibits GH secretion, but is rarely used clinically, since it has a very short half-life (a few minutes) **Octreotide:** • **Inhibit GH secretion.** • Partially inhibits GH-induced IGF-1 generation. • Reduce GHRH release.		**Normally:** GH has 2 distinct receptor binding sites, initiates cellular signaling cascades by dimerizing 2 GH receptors. **Pegvisomant:** 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.
P.K.	• Very expensive. • Synthetic long-lasting peptide • 45 times **more potent** than somatostatin • Suppress GH levels for 6–12 h. • Half-life in plasma being 113 min. • Peak plasma. concentrations within 1 h. • Given every 4 weeks. • Given S.C / I.M	Given I.M	• Given S.C. • Check IGF-1 level every 4-6 weeks. • Monitoring GH not useful. Because it doesn't affect GH secretion from pituitary • Dose 10-40 mg/d
use	Treatment of acromegaly		
ADRs	• Significant GI disturbances. • **Gallstones**. "Decreases contraction of gallbladder → accumulation of bile → stone" • **Cardiac conduction abnormalities** (Sinus bradycardia)		-

drug	Dopamine agonists
Overview	• (only high doses) can be used as primary and adjuvant treatment but their response rate is low. (Not used unless other drugs are contraindicated) ○ Bromocriptine up to 20 mg/day (prescribed under **hyperprolactinemia**) ○ Cabergoline 1-2 mg/week

Comparison between the drugs

Numbers are NOT Important	Octreotide (S.C) 100 to 500 mic.gm TDS	Octreotide (I.M) at 28 days interval	Lanreotide (I.M) every 7-14 days	Pegvisomant	Bromocriptine	Cabergoline
GH reduction	47%	56%	50%	Not useful	20%	44%
IGF-1 reduction	46%	66%	48%	97%	10%	35%

Note: Best in lowering GH? IM Octreotide. Best in lowering IGF? Pegvisomant. Cabergoline is more effective than bromocriptine

Prolactinomas: *D2 receptor Agonists*

- **Overproduction** of Prolactin will lead to: 1-Amenorrhea 2-Galactorrhea 3-Impotence
- Dopamine D2 receptor agonists such as bromocriptine are more effective at inhibiting prolactin release than inhibiting GH release. (#CNS: used for parkinsonism along with levodopa)
- However, **high doses** of D2 receptor agonists have some efficacy in the treatment of small GH-secreting tumors.
- In case of ★ Prolactinoma (pituitary adenoma with excess release of prolactin) the initial therapy is generally dopamine agonists.

Drug	**Bromocriptine** 2-bromo-α- ergocryptine mesylate	**Cabergoline**	**Pergolide Mesylate**
Source	**Ergot derivatives** (#CNS: vasoconstrictors used for treatment of migraine)		Long-acting **ergot derivatives**
M.O.A.	Selective activation of D2 receptors located on lactotroph cell surface (PRL-producing cells) → decrease adenylate cyclase activity → decreasing in cAMP level → **inhibition of prolactin (PRL) synthesis & release.** *"You can simply say: Dopaminergic agonists, dopamine, has a Negative feedback mechanism on Prolactin that will ultimately inhibit its synthesis and release"*		
P.K.	• The absorption rate from the GI tract is 25-30%. • Given orally. • 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.	• **more expensive**. • given once or twice a week with a starting dose of 0.25 mg 2 x week.	-
	Titrate (Adjust the dose) based on prolactin levels & tolerability		
Actions	• More effective in inhibiting prolactin release than inhibiting GH release • Inhibiting prolactin secretion **without the uterotonic, vasospastic** properties of other ergots. • **Safe in pregnancy.**	• **more effective** than bromocriptine for **tumor shrinkage** by promoting apoptosis and autophagic cell death • **Well tolerated (less side effects at regular doses) but not safe in pregnancy.**	• dopaminergic properties • strong **vasospasm and uterotonic**
ADRs	-		# during pregnancy
	GI intolerance, postural hypotension, constipation, nasal stuffiness, dizziness - avoided by beginning with low dose therapy		

Adenomas of the pituitary gland which cause hyperprolactinemia are called **Prolactinomas.** If the patient is pregnant, The best choice is bromocriptine. Otherwise, **Both Bromocriptine and Cabergoline are considered first line.**

MCQ

1. Which of the following used if the patient have defective hypothalamiv release of GHRH but normal anterior pituitary somatotrophs

A. Sermorelin	B. Somatropin	C. Somatrem	D. Mecasermin

2. Which of the following used if the patient have growth failure associated with GH deficiency

A. Sermorelin	B. Somatropin	C. Somatrem	D. Mecasermin

3. Which of the following is used in children with severe IGF1 deficiency

A. Sermorelin	B. Somatropin	C. Somatrem	D. Mecasermin

4. Which of the following drugs can cause gallstones?

A. Octreotide	B. Pegvisomant	C. Dopamine antagonists	D. None

5. Which of the following drugs is the drug of choice for treating prolactinoma in pregnancy

A. Bromocriptine	B. Cabergoline	C. Pergolide Mesylate	D. None

6. Which of the following drugs can cause hypoglycemia

A. Somatrem	B. Octreotide	C. Mecasermin	D. Bromocriptine

1:A ,2:B+C ,3:D ,4:A ,5:A ,6:C

SAQ

1

★ A patient presented with **dwarfism**. after investigations the condition was found to associated with GH deficiency

A. What class of drugs would you prescribe?
B. Give two examples to the previously mentioned class?
C. Mention four side effects associated with the drug?

A. Recombinant human GH
B. Somatropin and Somatrem
C. Leukemia, hypothyroidism, insulin resistance, arthralgia

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★ A patient presented with **dwarfism**. after investigations the condition was found to be associated with IGF1 deficiency

A. What class of drugs would you prescribe?
B. Give an example to the previously mentioned class?
C. Mention the main side effect associated with the drug?

A. Recombinant IGF1
B. Mecasermin
C. Hypoglycemia

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A 34 year old female patient presented with **prolactinoma**. after taking history it was found that the patient is 4 months pregnant

A. What class of drugs would you prescribe?
B. Give an example to the previously mentioned class?
C. briefly explain its mechanism of action
D. Mention the main side effect associated with the drug?
E. Which drugs are contraindicated in her case?

A. Dopamine agonists (D2 receptor)
B. Bromocriptine
C. Selective activation of D2 receptors located on lactotroph cell surface (PRL-producing cells) → decrease adenylate cyclase activity → decreasing in cAMP level → inhibition of prolactin synthesis & release.
D. GI intolerance, postural hypotension, constipation, dizziness
E. Cabergoline

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