Revised & Approved

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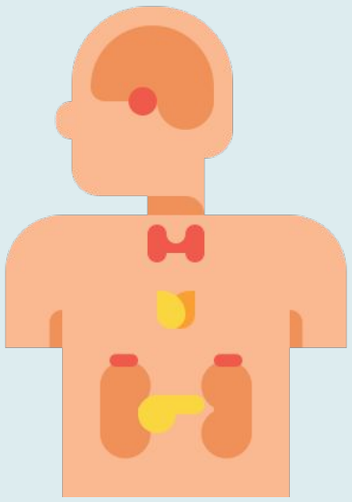
Pharmacology 439

MED439
KING SAUD UNIVERSITY



Endocrine Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Growth hormone & Drugs used in Pituitary Adenoma

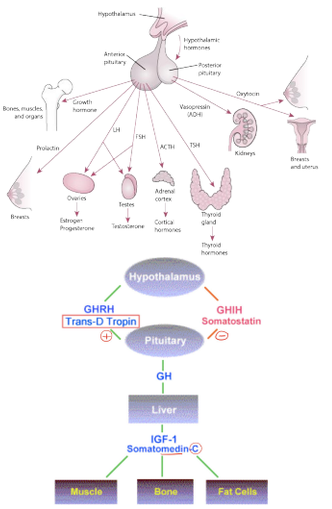
Editing file | Summary

Hypothalamic Pituitary Functions

Not important for exam

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 emotional behaviors, motivation, and learning.



Mechanism of Action of GH

01

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

Once the hormone binds to it, phosphorylation will start and it will activate the downstream signal transduction pathway to activate IGF and produce effect

02

The effects of GH are primarily mediated by **insulin-like growth factor 1 (IGF-1)** released by liver in response to GH.

Anterior Pituitary: Growth Hormone (GH) = Somatotropin

Stimulates increase In **size & mitotic rate of body cells**, increase **fat utilization** (use of fat, not storage)

Promotes **long bone growth**

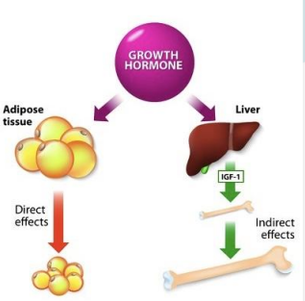
GHRH stimulates secretion of GH; **Somatostatins** inhibits secretion of GH

Enhances amino acid movement through membranes & promotes protein synthesis

EFFECTS OF GH

DIRECT EFFECT

1. Binds to adipocytes & causes them to break down triglycerides & prevents them from accumulating fat in the blood.
2. Releases insulin-like growth factor-1 (IGF-1) from the liver.



INDIRECT EFFECT through IGF

Stimulates:

1. Bone growth
2. Cartilage cells (chondrocytes) growth.
3. Myoblasts growth & differentiation
4. Amino Acid uptake & protein synthesis.

Abnormalities of GH

Abnormalities	Leads to	Example
Deficiency or absence of somatotroph cells	Underproduction of growth hormone	**Pituitary Dwarfism, primary.** **(Laron Syndrome)** Delayed skeletal growth & retarded sexual development but **alert, intelligent, well proportioned child.**
Overactivity (or tumor) of somatotroph cells	**Overproduction of growth hormone** which will increase IGF-1 (Stimulates protein synthesis, Influenced CHO and fat metabolism, Mitosis of all cell types)	**Gigantism in children** Onset before bony epiphysis have closed at puberty. Because excess IGF-1 causes excessive bone growth **Acromegaly in adults** Onset after puberty, bones increase in size (hands, feet, face).
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 (in adult) or gigantism (in children) b. **Prolactin excess** leads to galactorrhoea, menstrual abnormalities and infertility (prolactinoma) c. **Adrenocorticotropic hormone (ACTH)** cause Cushing disease d. **Thyroid stimulating hormone (TSH)** excess lead to Hyperthyroidism.	

Drugs Used in Case of GH Deficiency (GH Agonist)

	Sermorelin	Somatropin	Somatrem	Mecasermin
Drug	**Synthetic** growth hormone releasing hormone **(GHRH)** from hypothalamus	**Recombinant human growth hormone.** **Somatropin:** A 191-amino acid peptide, identical to the native form of hGH. (commonly used)		**Recombinant IGF-1**, administered S.C.
Uses	Used if a patient possesses **defective hypothalamic releasing of GHRH** BUT normally functioning anterior pituitary somatrophs.	• Documented Growth failure in pediatric patients associated with **GH deficiency** and **Turner syndrome** (chromosomal condition affects development in female-short stature) (to increase height in girls by 10-15 cm). • Idiopathic short stature. • Wasting muscle in patients with AIDS. Catabolism is usually high in aids patient • Short bowel syndrome in patients who are also receiving specialized nutritional support.		Used for children with **severe IGF1 deficiency** due to **mutations** in the GH receptor (**Laron dwarfism**) or development of **neutralizing antibodies against GH.**
ADRs **Children** can tolerate **better**, whereas in **adult** it's **worse**.	-	• **Leukemia.** Due to overstimulation of cell division • Rapid growth of melanocytic lesions (pigmentation) can cause melanoma.. • Contraindication in patient with ACTIVE malignancy because it is increases mitotic rate • Hypothyroidism. Because thyroid gland uses the same hypothalamic pituitary axis • Insulin resistance, since it works on insulin receptor • Arthralgia. • Increase in cytochrome P450 activity.		The common ADR is **Hypoglycemia**: **can be avoided** by consumption of meal 20 min before or after the administration of drug.

Drugs Used in Case of GH Overproduction (GH Antagonist)

Drug	Octreotide	Lanreotide	Pegvisomant
	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 (few minutes) Octreotide: ● **Mainly Inhibit GH secretion.** ● Partially inhibits GH-induced IGF-1 generation. ● Reduce GHRH release. Dr Ishfaq: edit this to "Reduce the function of GHRH"		Normally: ● GH has 2 distinct receptor binding sites, initiates cellular signaling cascades by **dimerizing** (conformational changing) 2 GH receptors. Pegvisomant: ● A long-acting derivative of a mutant GH that is able to cross-link GH receptors (bind to the receptor) but is incapable of inducing the conformational changes required for receptor activation. **Basically**, it just binds to the receptor and **blocks** it from binding to a real GH (that can actually make conformational changes).
P.K	● numbers not important ● Very expensive. ● Synthetic long-lasting peptide ● 45 times more potent. ● 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.
Uses	**Treatment of acromegaly & gigantism**		
ADRs	● Significant GI disturbances. ● Gallstones. ● **Cardiac conduction abnormalities.**		-

- **Dopamine agonists** can be used as primary and adjuvant treatment but their response rate is low.
  - Bromocriptine up to 20 mg/day
  - Cabergoline 1-2 mg/week

Comparison between the drugs and their effect on GH and IGF-1

	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%** Good if patient has IGF production problem	**10%**	**35%**

Dr Ishfaq: The only important thing to know in this table is that in case of GH overproduction we don't use Pegvisomant we use Somatostatin analogues, and in case of IGF-1 overproduction we use Pegvisomant"

Dopamine D2 receptor Agonist

- **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, they are only used in high doses
- In case of ★ **Prolactinoma** (pituitary adenoma with excess release of prolactin) the initial therapy is generally dopamine agonists.

Safe for Baby during pregnancy

	Bromocriptine 2-bromo-α- ergocryptine mesylate	**Cabergoline**	**Pergolide Mesylate**
Drug	**Ergot derivatives** (#CNS: vasoconstrictors used for treatment of migraine)		Long-acting **ergot derivatives** with dopaminergic properties but strong **vasospasm and uterotonic**
MOA	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 say: Dopaminergic agonists. The downstream mechanism will ultimately inhibit synthesis and release of PRL**		
P.K	• inhibiting prolactin secretion **without the uterotonic, vasospastic** properties of other ergots. • Doesn't cause tumor shrinkage • **safe in pregnancy.** Only one safe • 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 effective than bromocriptine for tumor shrinkage.** By promoting apoptosis and autophagic cell death • Well tolerated but **not safe in pregnancy.** • more expensive. • given once or twice a week with a starting dose of 0.25 mg 2 x week. • Titrate these based on prolactin levels & tolerability	contraindicated during pregnancy
ADRs	–	Orthostatic hypotension, nausea, dizziness and CVS side effects; can be avoided by beginning with low dose (gradual therapy)	–
	• GI intolerance, postural hypotension, constipation, nasal stuffiness		

Important note: 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.**

Summary

Class	Drug	M.O.A	Uses	ADRs
GH Deficiency (GH Agonist)	**Sermorelin**	Synthetic growth hormone releasing hormone (GHRH) from hypothalamus	**Defective hypothalamic releasing of GHRH** BUT normally functioning anterior pituitary somatotrophs.	-
	Somatropin	Recombinant human growth hormone which is a 191-amino acid peptide, **identical** to the native form of hGH. (commonly used)	- Documented Growth failure in pediatric patients associated with **GH deficiency** and **Turner syndrome** - Wasting muscle	- Hypothyroidism **- Leukemia** - Insulin resistance
	Somatrem	Recombinant human growth hormone		
	Mecasermin	Recombinant IGF-1	children with **severe IGF-1 deficiency**	**Hypoglycemia**
GH Overproduction (GH Antagonist)	**Octreotide**	**Somatostatin analogues** Inhibit GH secretion.	**Treatment of acromegaly & gigantism**	- Significant GI disturbances. - Gallstones. - Cardiac conduction abnormalities.
	Lanreotide			
	Pegvisomant	**GH receptor antagonist** mutant GH that is able to cross-link GH receptors (bind to the receptor) but is incapable of inducing the conformational changes required for receptor activation.	**Treatment of acromegaly**	-
D2 receptor Agonist	**Bromocriptine** 2-bromo-α- ergocryptine mesylate **(only one safe in pregnancy)**	**Dopaminergic agonists. The downstream mechanism will ultimately inhibit synthesis and release of PRL**	Inhibiting **prolactin release** In case of **★Prolactinoma**	- GI intolerance - postural hypotension - Constipation - nasal stuffiness
	Cabergoline			
	Pergolide Mesylate			

MCQs

Q1: 32-year-old pregnant woman in the second trimester presented to your clinic complaining of Galactorrhea, which of the following is the best treatment			
A- Sermorelin	B- Bromocriptine	C- Pegvisomant	D- Surgery
Q2: Which of the following works by mainly inhibiting GH secretion?			
A- Somatropin	B- Mecasermin	C- Cabergoline	D- Lanreotide
Q3: A child presents to the clinic with abnormally short stature, investigations point to the issue originating from the hypothalamus, which of these would be the best treatment option?			
A- Sermorelin	B- Somatropin	C- Somatrem	D- Mecasermin
Q4: A child presents to the clinic with abnormally short stature, blood work shows abnormally high antibody titer, which of these would be the best treatment option?			
A- Sermorelin	B- Somatropin	C- Somatrem	D- Mecasermin
Q5: Which of these has no effect in reducing GH?			
A- Octreotide (S.C)	B- Octreotide (I.M)	C- Lanreotide (I.M)	D- Pegvisomant
Q6: A patient came to you complaining of getting lightheaded whenever they stand up, which of the following may be the cause of his complaint?			
A- Somatrem	B- Octreotide	C- Cabergoline	D- Mecasermin
Q7: Which of the following drugs may cause cardiac conduction abnormality?			
A- Pegvisomant	B- Octreotide	C- Sermorelin	D- Mecasermin
Q8: Which of the following drugs increases risk of abortion and is therefore contraindicated?			
A- Bromocriptine	B- Pergolide Mesylate	C- Cabergoline	D- Pegvisomant

1	2	3	4	5	6	7	8
B	D	A	D	D	C	B	B

SAQ

Case1: A 15-year-old girl presented at the endocrinology clinic complaining of short stature compared with her siblings and peers. There was no history of bone fractures. The rest of patient and social history was not significant. Physical examination revealed a young woman with short stature: height: 1.20 m, weight: 37 kg, temperature: 36.7°C, pulse rate: 86 beats per minute, blood pressure: 115/68 mm Hg. Doctor suspected of growth hormone deficiency. He will investigate further to know the exact cause of deficiency.

Q1) Mention 3 drugs that can be used to treat GH deficiency

1)
2)
3)

Q2) Mention the MOAs of drugs mentioned in Q1

1)
2)
3)

Q3) Mention the possible indicated uses for each drug mentioned in Q1

1)
2)
3)

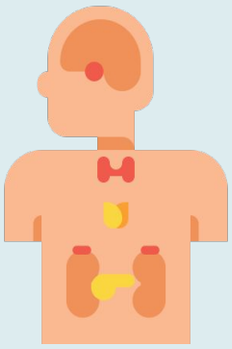
Answers

1. **Drug one:**
   Name: Sermorelin
   MOA: Synthetic growth hormone releasing hormone (GHRH)
   Use: Defective hypothalamic releasing of GHRH BUT normally functioning anterior pituitary somatotrophs.

2. **Drug two:**
   Name: Somatropin
   MOA: Recombinant human growth hormone
   Use: GH deficiency and Turner syndrome

3. **Drug 3:**
   Name: Mecasermin
   MOA: Recombinant IGF-1
   Use: Severe IGF-1 deficiency due to mutations in the GH receptor (Laron dwarfism), or in development of neutralizing antibodies against GH.

Feedback Form



Endocrine Block

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