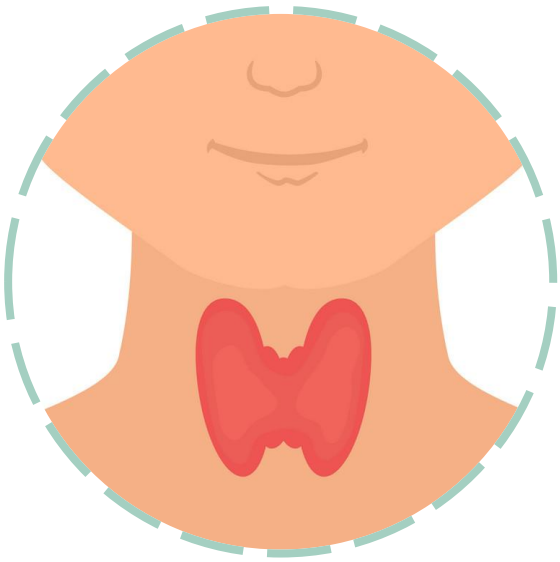
Editing File

Mnemonic File



Endocrine Block

Pharmacology team 438

Growth Hormone & Drugs used in Pituitary Adenoma

Objectives:

By the end of the lecture , you should know:

- بمناسبة دخولنا ما يسمى "ربيع الطب", نود أن نعلن عن مسابقة mnemonics
- طريقة المسابقة:

1- كتابة mnemonics من إنشاء الطالب في الرابط المخصص لذلك.
2- كتابة بجانب الmnemonics إسم مستعار (Nickname).

سيتم التصويت على أفضل mnemonics وإعلان الإسم المستعار الذي يفوز نهاية البلوك.

تمنياتنا لكم بربيع طب موفق
الإدارة العليا لتيم الفارما

Color index:

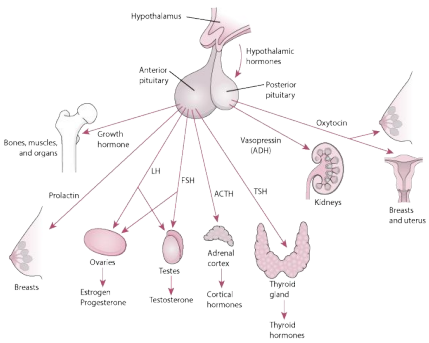
Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Hypothalamic Pituitary Functions

Pituitary and hypothalamus are the link between the nervous system and the endocrine system.

Hypothalamus is a **major regulator of body homeostasis:**

1. **Homeostatic control** includes regulating hunger, thirst, sex drive, sleep-wake cycles, body temperature, blood glucose.
2. **Endocrine control** via regulating the release of pituitary hormones.
3. **Autonomic control** via descending pathways to sympathetic & parasympathetic preganglionic neurons.
4. **Limbic function** via connections to limbic system regulating emotional behaviors.



Mechanism of Action of GH

1. Binding of GH to its receptor activates the signaling cascade mediated by receptor associated to **JAK tyrosine kinases**.
2. The effects of GH are primarily mediated by **insulin-like growth factor 1 (IGF-1)** released by liver in response to GH.

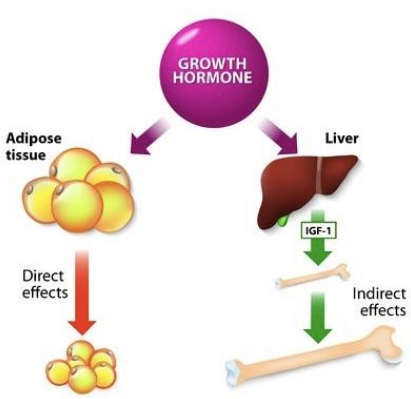
Anterior Pituitary: Growth Hormone (GH)

- Stimulates increase in **size & mitotic rate of body cells**, increases **fat utilization**
- 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 [1]

Stimulates:

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

1. Through IGF

Abnormalities of the GH

1

Deficiency or absence of somatotroph cells → Leads to → Underproduction of growth hormone → Example → **Pituitary Dwarfism, primary. (Laron Syndrome/Lorain dwarfism)** Delayed skeletal growth & retarded sexual development but **alert, intelligent, well proportioned child.**

2

Overactivity (or tumor) of somatotroph cells → Leads to → Overproduction of growth hormone which will increase IGF-1 (Stimulates protein synthesis + Influenced CHO and fat metabolism + Mitosis of all cell types) → Example →

Gigantism in children
Onset before bony epiphysis have closed at puberty.

Acromegaly in adults
Onset after puberty.

3

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, menstrual abnormalities and infertility
   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 [1]	Somatrem	Mecasermin
Drug	Synthetic growth hormone releasing hormone (GHRH)	Recombinant human growth hormone which is a 191-amino acid peptide, **identical** to the native form of hGH.	Recombinant human growth hormone	Recombinant[2] 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**[3] (to increase height in girls by 10-15 cm). • Idiopathic short stature. • Wasting muscle in patients with AIDS. • Short bowel syndrome[4] 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 [5]	-	★ **Leukemia.** • Rapid growth of melanocytic lesions.(pigmentation) • Hypothyroidism. • Insulin resistance. • Arthralgia. ★ Increase in cytochrome P450 activity.		The common ADR is **Hypoglycemia**[6]: can be avoided by consumption of meal 20 min before or after the administration of drug.

1. Somatropin is more commonly used compared to Somatrem.
2. Recombinant DNA is a technology used to synthesize proteins and hormones by inserting a specific DNA into the plasmid, forcing the plasmid to synthesize a target hormone.
3. Chromosomal condition that affects development in females causing short stature.
4. Bowel resection and intestinal bypass.
5. Children can tolerate the ADR of GH agonists.
6. Due to its insulin-like effect

Drugs Used in Case of GH Overproduction (GH Antagonist)

Drug	Octreotide	Lanreotide	Pegvisomant
	synthetic long-lasting peptide **analogue of somatostatin.**		**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.	-	**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.
P.K	• Very expensive • 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.** • Dose 10-40 mg/d.
Uses	• Treatment of acromegaly & gigantism.		
ADRs	• Significant Gastrointestinal 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[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%**	**10%**	**35%**

1: explanation of the table:
- Note that the efficacy of Octreotide can increase by changing the route of administration.
- D2 receptor agonists are not very effective, but Cabergoline shows more efficacy than Bromocriptine.

Dopamine D2 receptor Agonist

- 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, **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.**

Drug	Bromocriptine 2-bromo-α- ergocryptine mesylate	Cabergoline
	Ergot derivatives	
MOA	Selective activation of D2 receptors located on lactotroph cell surface (PRL-producing cells) ⟶ decrease adenylate cyclase activity ⟶ decreasing in cAMP level ⟶ **inhibition of PRL synthesis & release.**	
P.K	★ inhibiting prolactin secretion **without the uterotonic, vasospastic** properties of other ergots ★ **safe in pregnancy** • 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 ★ 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
ADR	-	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**	

Drug	Pergolide Mesylate
	Long-acting ergot derivatives with dopaminergic properties but **strong vasospasm and uterotonic** [1] **.**
MOA	• Same as Btomocriptein and cabergoline
ADR	• GI intolerance, postural hypotension, constipation, **nasal stuffiness**

1. contraindicated during pregnancy.
   - Generally speaking, Pregnant? Bromocriptine. Not pregnant? Cabergoline.

Quiz

MCQ

1- Which of the following have no effect on GH reduction?

A- Pegvisomant B- Octreotide C- Cabergoline D- Bromocriptine

2- Which of the following medications can be used safe in pregnancy?

A- Pergolide Mesylate B- Bromocriptine C- Cabergoline D- Trimethoprim

3- Which of the following drugs can't be used with cardiac patients due to cardiac conduction abnormalities?

A- Pergolide Mesylate B- Octreotide C- Cabergoline D- Somatrem

4- Which of the following have a hypoglycemic side effect?

A- Lanreotide B- Somatropin C- Cabergoline D- Mecasermin

5- Which of the following can be used in treating turner syndrome?

A- Lanreotide B- Somatropin C- Bromocriptine D- Pegvisomant

SAQ

1- A 32 years old pregnant woman was taking medication for back pain for a long time, later she developed galactorrhea and amenorrhea and was diagnosed with prolactinoma after looking to her PRL concentration in her blood that showed increase amount of the prolactin caused by a tumor.

Q1-What is the best drug to be used in this case?

Q2- What is the M.O.A of the drug?

2- A 39 years old male was diagnosed before by acromegaly, he uses his medication regularly. After while, he visited the clinic complaining of abdominal pain. Based on physical and laboratory finding he was diagnosed with gallstones.

Q3-What is the drug he use?

Q4-List 2 other side effect of those drugs.

Answers:

MCQ

Q1	A
Q2	B
Q3	B
Q4	D
Q5	B

SAQ

Q1	Bromocriptine
Q2	Selective activation of D2 receptors located on lactotroph cell surface
Q3	Octreotide, Lanreotide
Q4	GI disturbances & Cardiac conduction abnormalities

pharmacology
Team 438

Thank you for all your love and support.

Good luck future doctors!

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