

# Pharmacology of Growth hormone and Pituitary Adenomas

Dr. Ishfaq Bukhari

Dr. Aliah Alshanwani

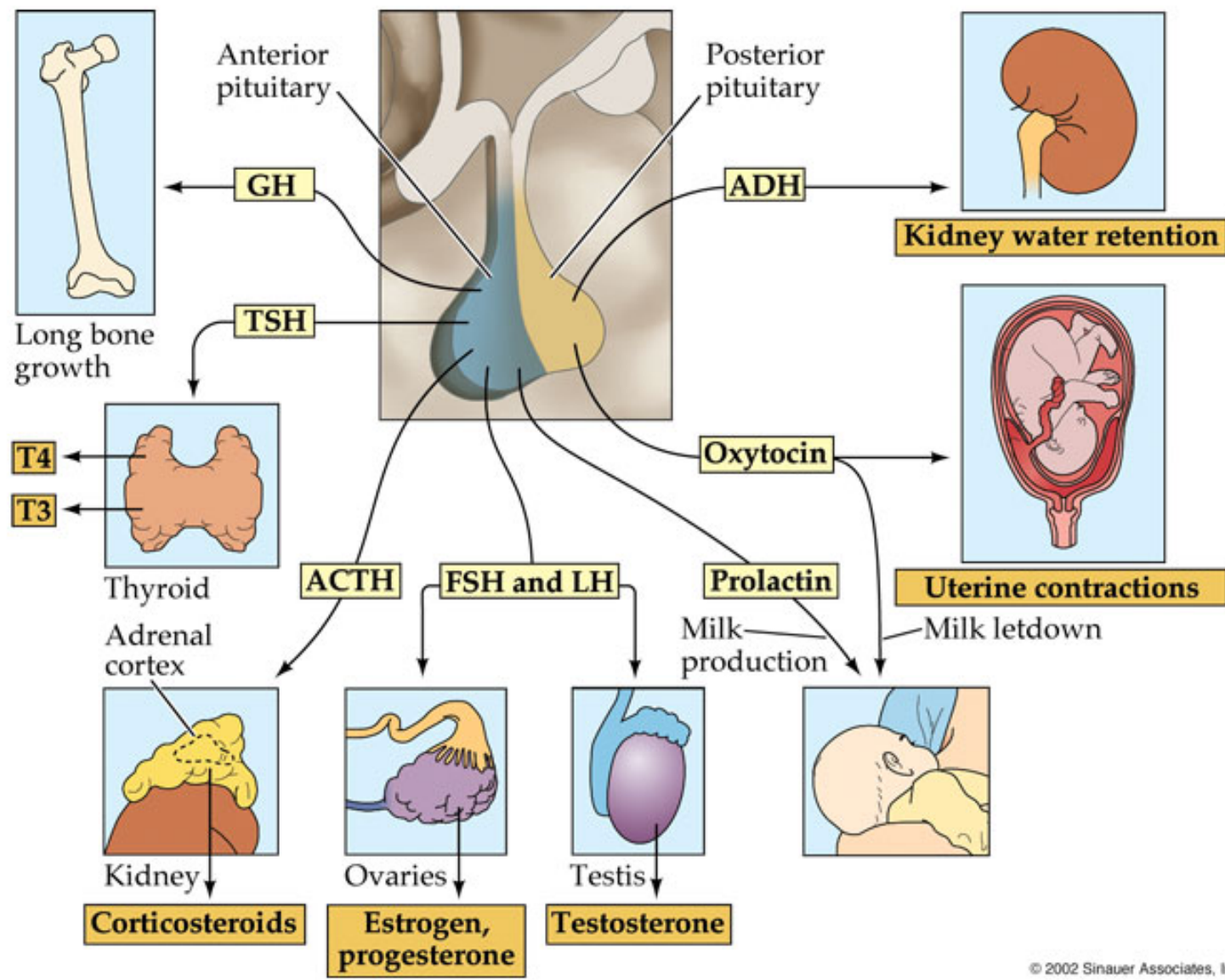
# Pituitary and Hypothalamus

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

Hypothalamus is also 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 behavior.

# A 'global' view of hypothalamic pituitary functions



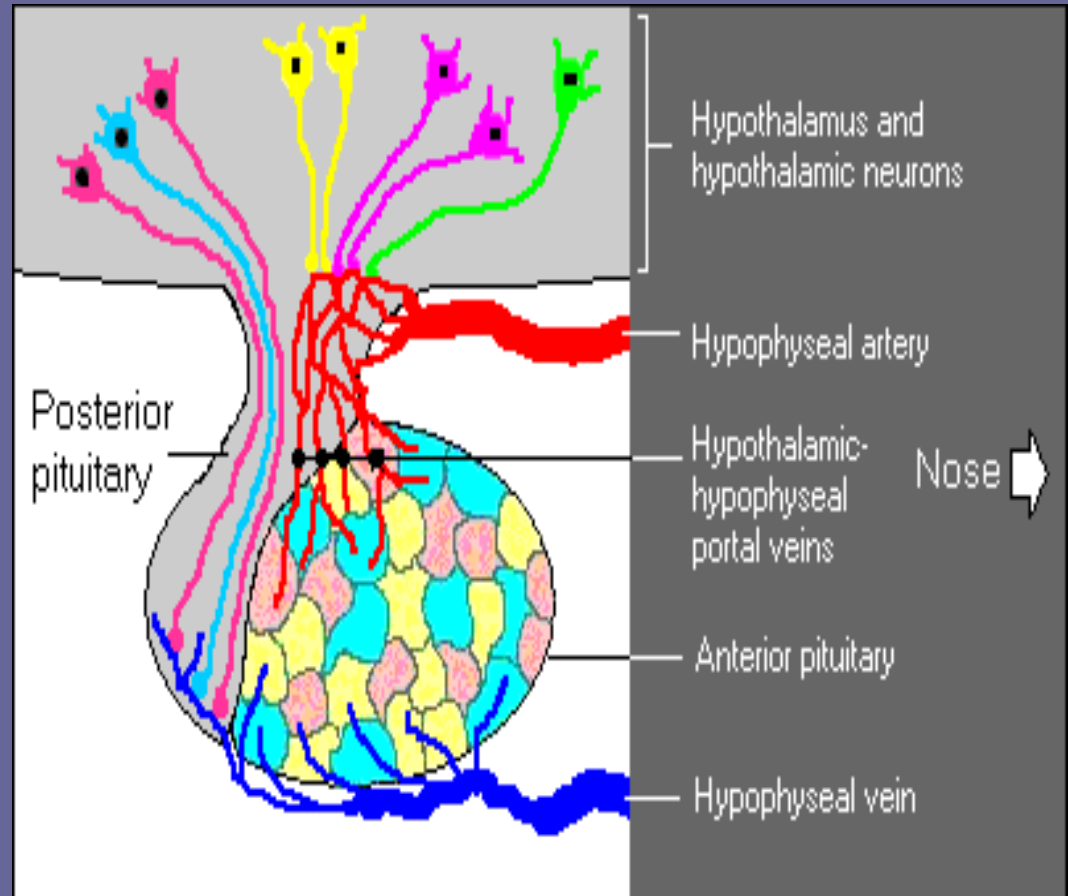
# Function

## ● Anterior Lobe:

- FSH
- LH
- ACTH
- TSH
- Prolactin
- GH

## ● Posterior Lobe:

- ADH
- Oxytocin





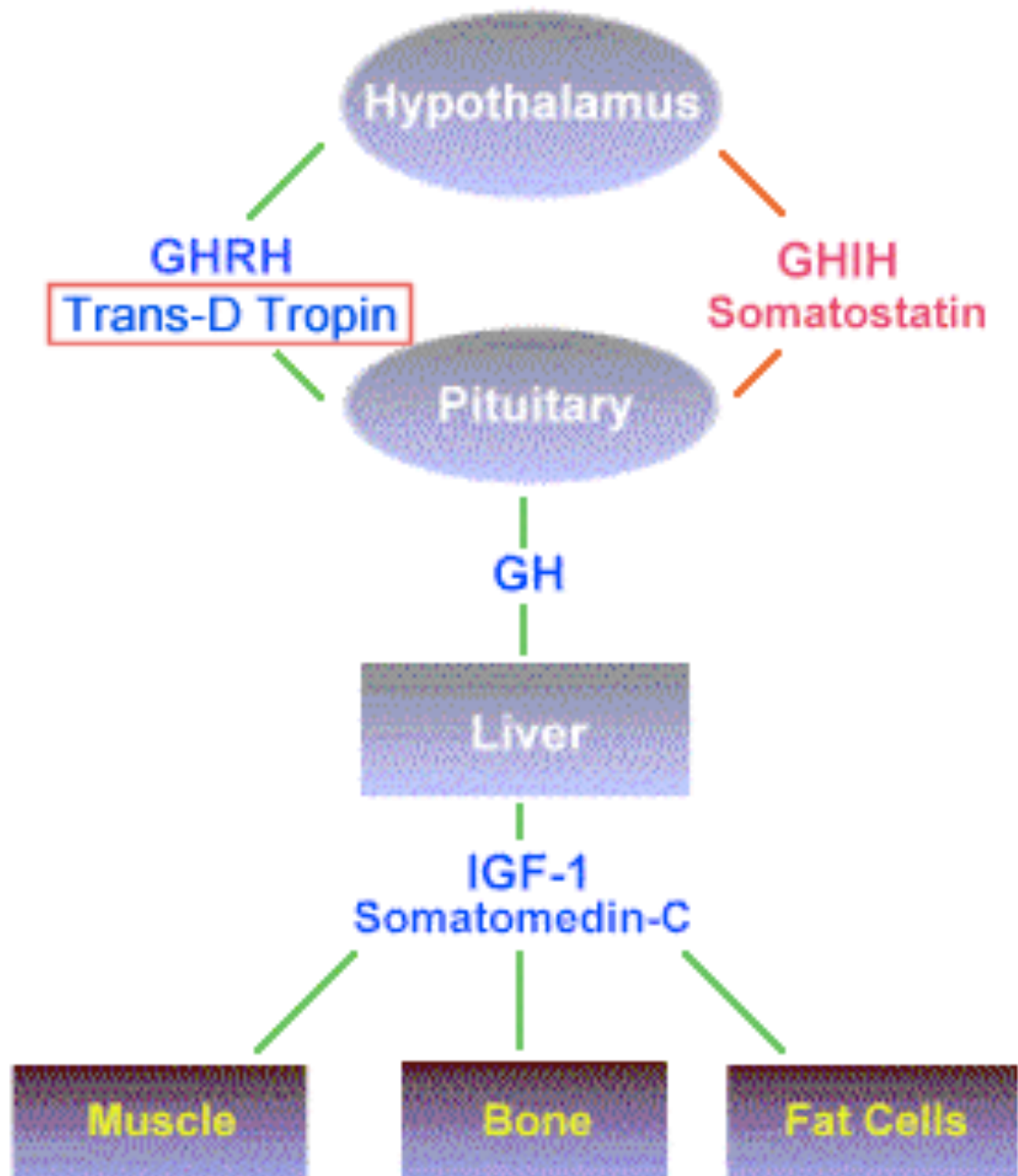
## **Mechanism of Action:**

Binding of GH to its 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.

# Anterior Pituitary: Growth Hormone (GH)= SOMATOTROPIN

- **Stimulates increase in size & mitotic rate of body cells, increases fat utilization**
- **Enhances amino acid movement through membranes & promotes protein synthesis**
- **Promotes long bone growth**
- Hypothalamic growth hormone releasing hormone (**GHRH**) stimulates secretion of GH; **Somatostatin (SS)** inhibits secretion of GH



Deficiency or absence of  
**somatotroph** cells



Underproduction of  
growth hormone



**PITUITARY DWARF, primary**

(Laron syndrome)

Delayed skeletal growth & retarded  
sexual development but alert,  
intelligent, well proportioned child.

Functional overactivity (or tumour) chiefly of the **SOMATOTROPH** cells of the anterior pituitary leads to **GIANTISM** in the CHILD: **ACROMEGALY** in the ADULT.

↓  
Overproduction of *growth Hormone*

↓  
↑ *IGF-1 (somatomedin C)*

↓  
Stimulates protein synthesis.  
Influences carbohydrate and fat metabolism and mitosis of **ALL CELLS** of the body

Overgrowth of all body tissues

Onset before bony epiphyses have closed at puberty

Onset after puberty

# Direct Effects of GH

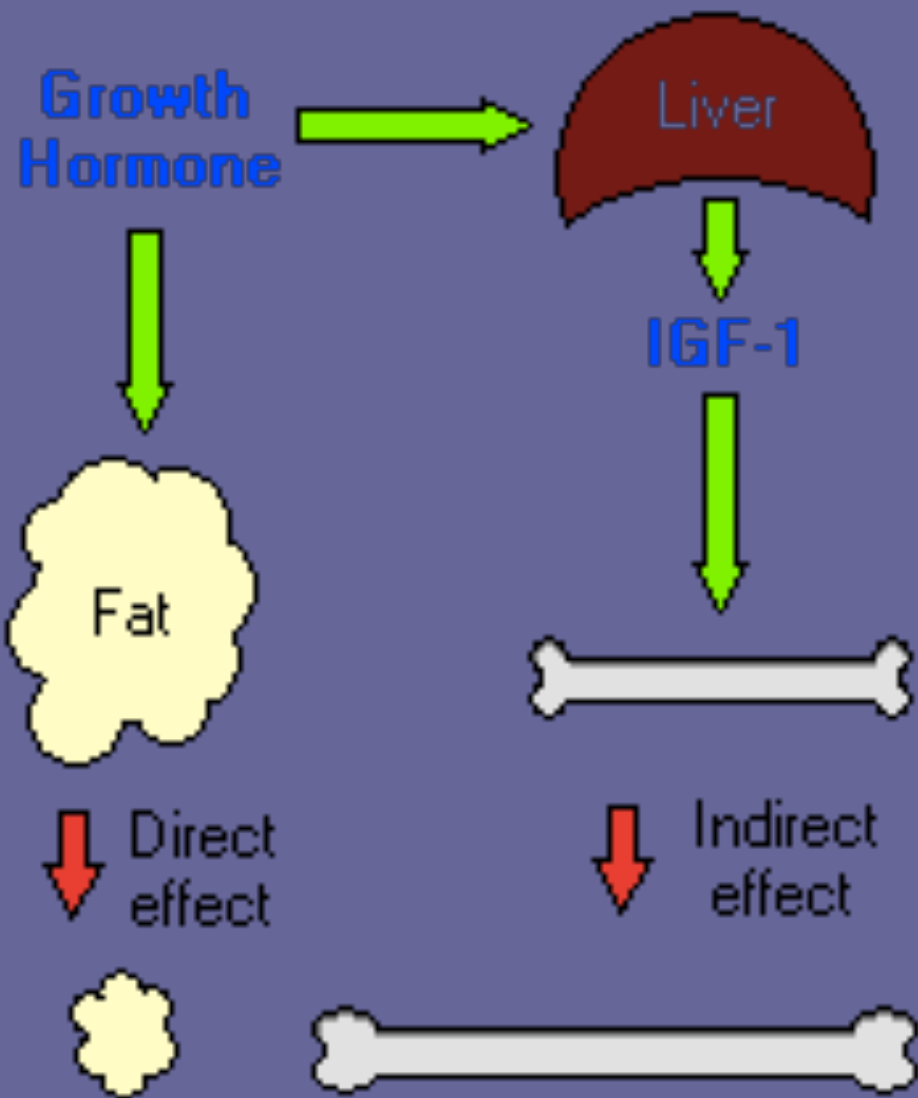
- Binds to adipocytes & causes them to break down triglycerides & prevents them from accumulating fat in the blood
- Releases IGF-1 from the liver

# Indirect Effects of GH

## ● Stimulates:

- Bone growth
- Cartilage cells (chondrocytes) growth
- Myoblasts growth & differentiation
- Amino Acid uptake & protein synthesis





# 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.

or **overproduction** of the pituitary hormones

**Growth hormone excess resulting in acromegaly or gigantism.**

**Prolactin excess** leads to galactorrhoea, menstrual abnormalities & infertility

Cushing's disease resulting from adrenocorticotrophic hormone (ACTH).

# Clinical Presentation Of overproduction

- Prolactin – Amenorrhea, galactorrhea, impotence
- Growth hormone – Gigantism & acromegaly
- Corticotropin – Cushing's disease
- TSH – Hyperthyroidism.

# Pharmacology of Growth Hormone Deficiency

## Drugs Used:

- Synthetic GHRH (Sermorelin)
- Recombinant human growth hormone (Somatropin, Somatrem)
- Recombinant IGF-1 (Mecasermin)

**Sermorelin:** It is used if a patient possesses defective hypothalamic release of GHRH but normally functioning anterior pituitary somatotrophs

Treatment with Recombinant Human Growth Hormone (**Somatropin, Somatrem**); **Somatropin** (synthetic growth hormone), which is a 191-amino acid peptide, identical to the native form of hGH.

## **GH Indications:**

Documented growth failure in pediatric patients associated with: GH deficiency & Turner syndrome (to increase height in girls by 10-15 cm)

Idiopathic short stature

Wasting in patients with AIDS

Short bowel syndrome in patients who are also receiving specialized nutritional support.



# GH Cont'

## Side Effects:

- Leukemia,
- rapid growth of melanocytic lesions
- Hypothyroidism
- Insulin resistance
- Arthralgia
- Increase in cytochrome P450 activity.

# Treatment with Recombinant IGF1 (**Mecasermin**)

**Mecasermin** is used for children with severe IGF1 deficiency due to mutations in the GH receptor (Laron dwarfism) or development of neutralizing antibodies against GH.

Its administered S.C, the common adverse effect is hypoglycemia, can be avoided by consumption of meal 20 min before or after the administration of drug.

# Features of Excess Growth Hormone

This usually results from benign tumor of the anterior pituitary.

(1) In children: It causes **gigantism**. Occurs before the closure of epiphyses, because excess IGF1 causes excessive longitudinal bone growth

(2) In adults: It causes **acromegaly** (bones increase in size, including those of hands, feet and face).

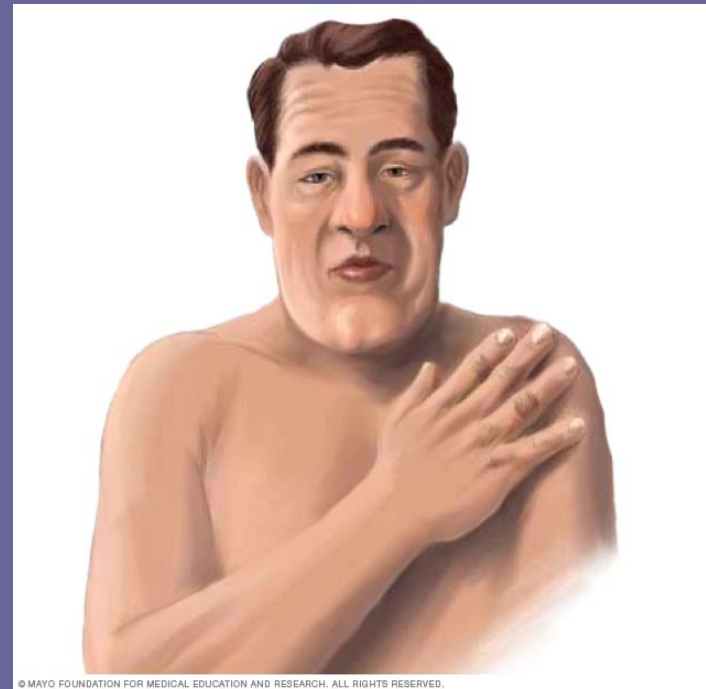
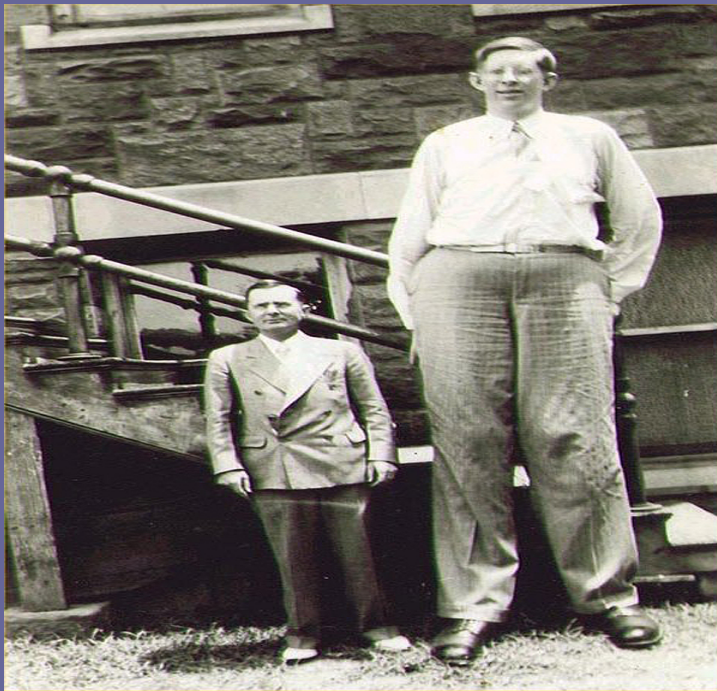
Growth retardation  
(dwarfism)



ADAM.



Hand comparison of twins - one on the left has acromegaly.  
R Gagel, IE McCutcheon. Pituitary Gigantism. NEJM  
1999;340:524. 1999.



© MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH. ALL RIGHTS RESERVED.



# Growth Hormone Antagonists

Drugs Used:

Somatostatin analogues (Octreotide S.C, IM,  
Lanreotide (I.M))

GH receptor antagonist (Pegvisomant)

Dopamine receptor agonist **only high doses**  
(Bromocriptine - described under  
hyperprolactinemia)

# Growth Hormone Antagonists

## Somatostatin analogues:

Somatostatin physiologically inhibits GH secretion, but is rarely used clinically, since it has a very short half-life (a few minutes)

**Octreotide** is a synthetic long-lasting peptide analogue of somatostatin (45 times more potent)

**Side effects** : Octreotide & lanreotide cause significant gastrointestinal disturbances, gallstones, & cardiac conduction abnormalities.



# Somatostatin analogues:

- **Octreotide (very expensive):** 45x more potent.
  - half-life in plasma being 113 min
  - peak plasma concentrations within 1 h
  - suppress GH levels for 6–12 h
  - Given every 4 weeks

## Mechanism of action

- Inhibit GH secretion
- Partially inhibits GH-induced IGF-1 generation
- Reduce GHRH release.

	Octreotide (S/C) 100 to 500 mic.gm TDS	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%

Freda PU:clinical review 150:somatostatin analogs in acromegaly.j clin endocrinol metab 87:3013-3018,2002

# Dopamine agonists :

- Used both as primary & adjuvant treatment
  - Bromocriptine up to 20 mg/day
  - Cabergoline 1–2 mg/week
- Response rate low

# Dopamine agonists :

	Bromocriptine	Cabergoline
GH REDUCTION	20%	44%
IGF1 REDUCTION	10%	35%

Freda PU:clinical review 150:somatostatin analogs in acromegaly.j clin endocrinol metab 87:3013-3018,2002

# GH-Receptor Antagonist :

- Pegvisomant given s.c:
- Check IGF 1 level every 4-6 weeks
- Monitoring GH not useful
- Dose 10-40 mg/d

# Growth Hormone Antagonists

## Pegvisomant

**Pegvisomant** is a GH receptor antagonist approved for treatment of acromegaly.

Normally, GH, which has 2 distinct receptor binding sites, initiates cellular signaling cascades by dimerizing 2 GH receptors.

**Pegvisomant** is 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.

## Dopamine D<sub>2</sub> Receptor Agonists

**Dopamine** D<sub>2</sub> receptor agonists such as **bromocriptine** are more effective at inhibiting prolactin release than inhibiting GH release. However, high doses of D<sub>2</sub> 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.

**Bromocriptine**, a dopamine agonist, is generally given orally, ergot derivatives.

- **Cabergoline** is given once or twice weekly. Better tolerated & more effective than bromocriptine for tumor shrinkage but more expensive.

### Side effects:

Orthostatic hypotension, nausea, & dizziness; avoided by beginning with low-dose therapy.

- Other compounds include **pergolide mesylate**, a long-acting ergot derivative with dopaminergic properties but strong vasospasm & uterotonic.

## Dopamine agonists:

- Bromocriptine
- Cabergoline
- Pergolide mesylate

## Side effects—

GI intolerance, postural hypotension, constipation, nasal stuffiness.

# Mechanism of action of Dopamine agonist

Selective activation of D2 receptors located on lactotroph cell surface (PRL-producing cells)



Decrease adenylate cyclase activity



Decrease in c.AMP level



Inhibition of **PRL synthesis & release.**

## Bromocriptine:

- (2-bromo- $\alpha$ -ergocryptine mesylate)
- Developed by Flückiger and colleagues in the late 1960s
- Purpose was inhibiting prolactin secretion without the uterotonic, vasospastic properties of **other ergots**
- **Bromocriptine is safer in pregnancy**

## Bromocriptine:

- The absorption rate from the GI tract is 25-30%
- Very high first-pass effect, with 93.6% of a dose being metabolized & 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) :

- more effective
- Well tolerated but not safer 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.

THANK YOU