Pharmacology of Growth hormone and Pituitary Adenomas

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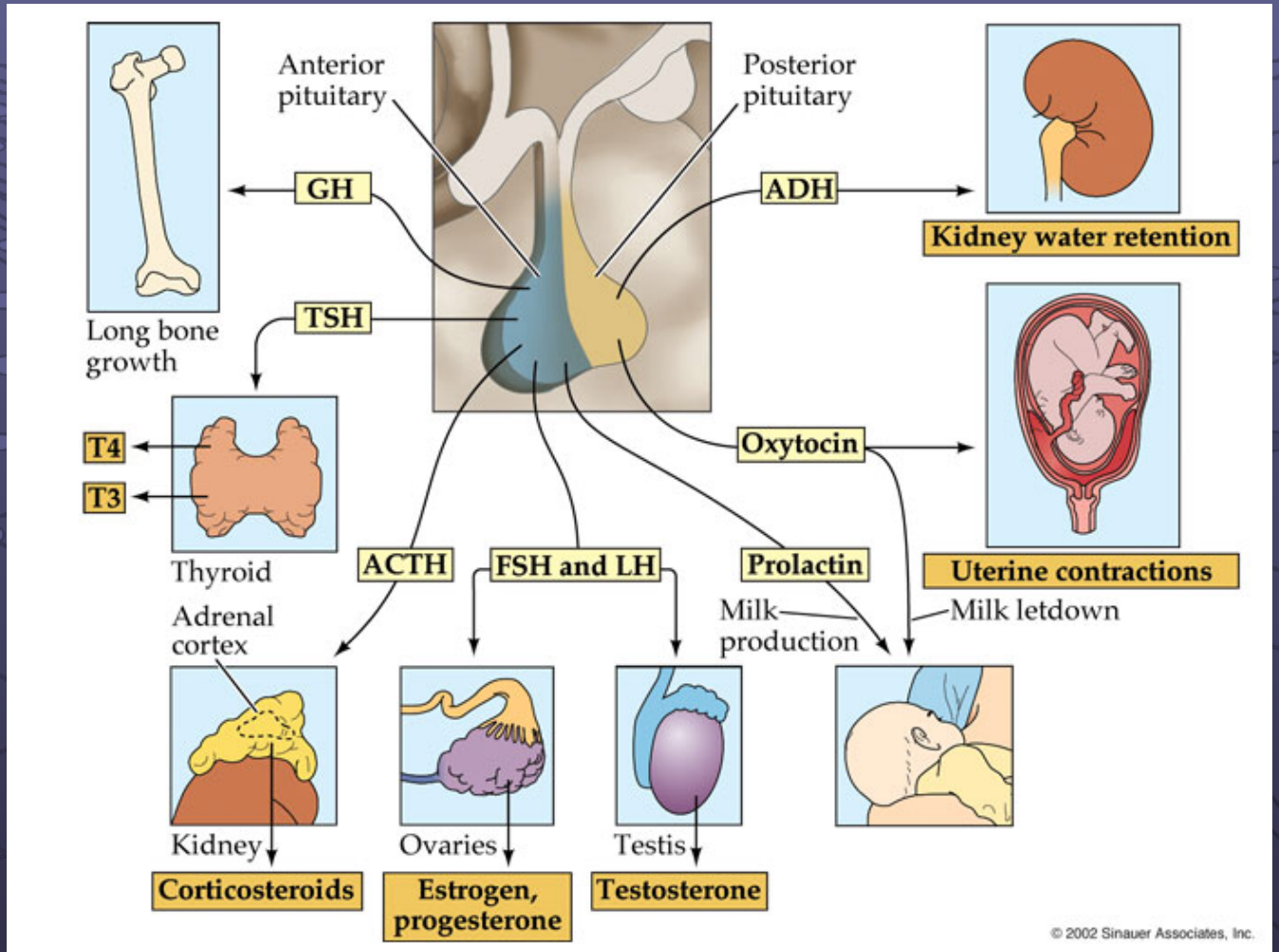
Pituitary and Hypothalamus

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

Hypothalamus is also ***major regulator of body homeostasis***

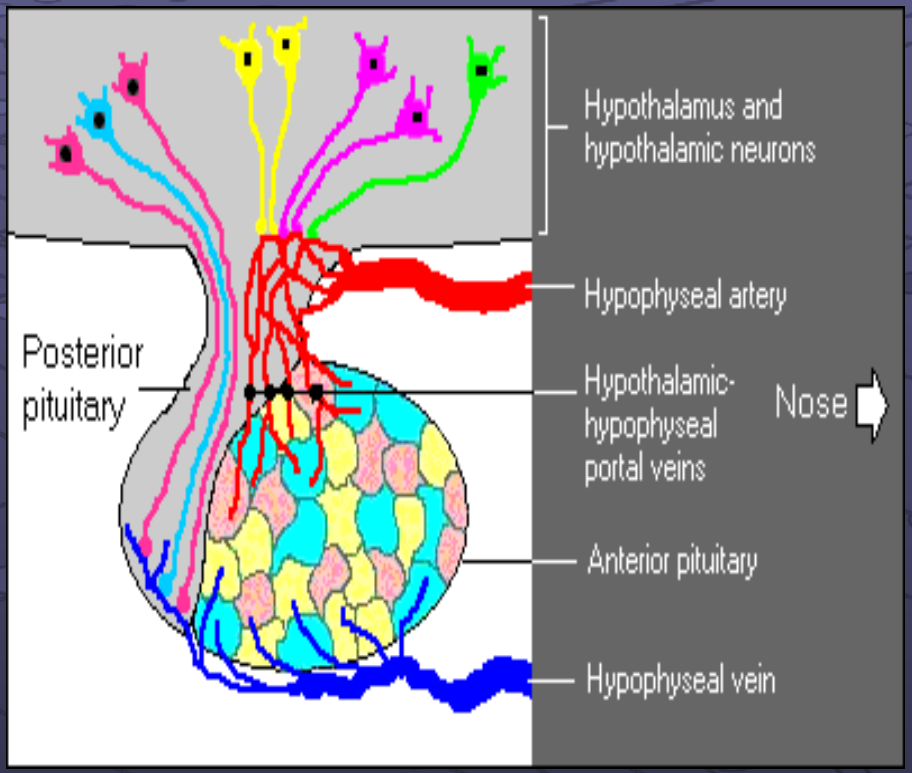
1. **Homeostatic control** includes regulating hunger, thirst, sex drive, sleep-wake cycles, body temperature, blood glucose
2. **Endocrine control** via regulating the release of pituitary hormones
3. **Autonomic control** via descending pathways to sympathetic & parasympathetic preganglionic neurons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

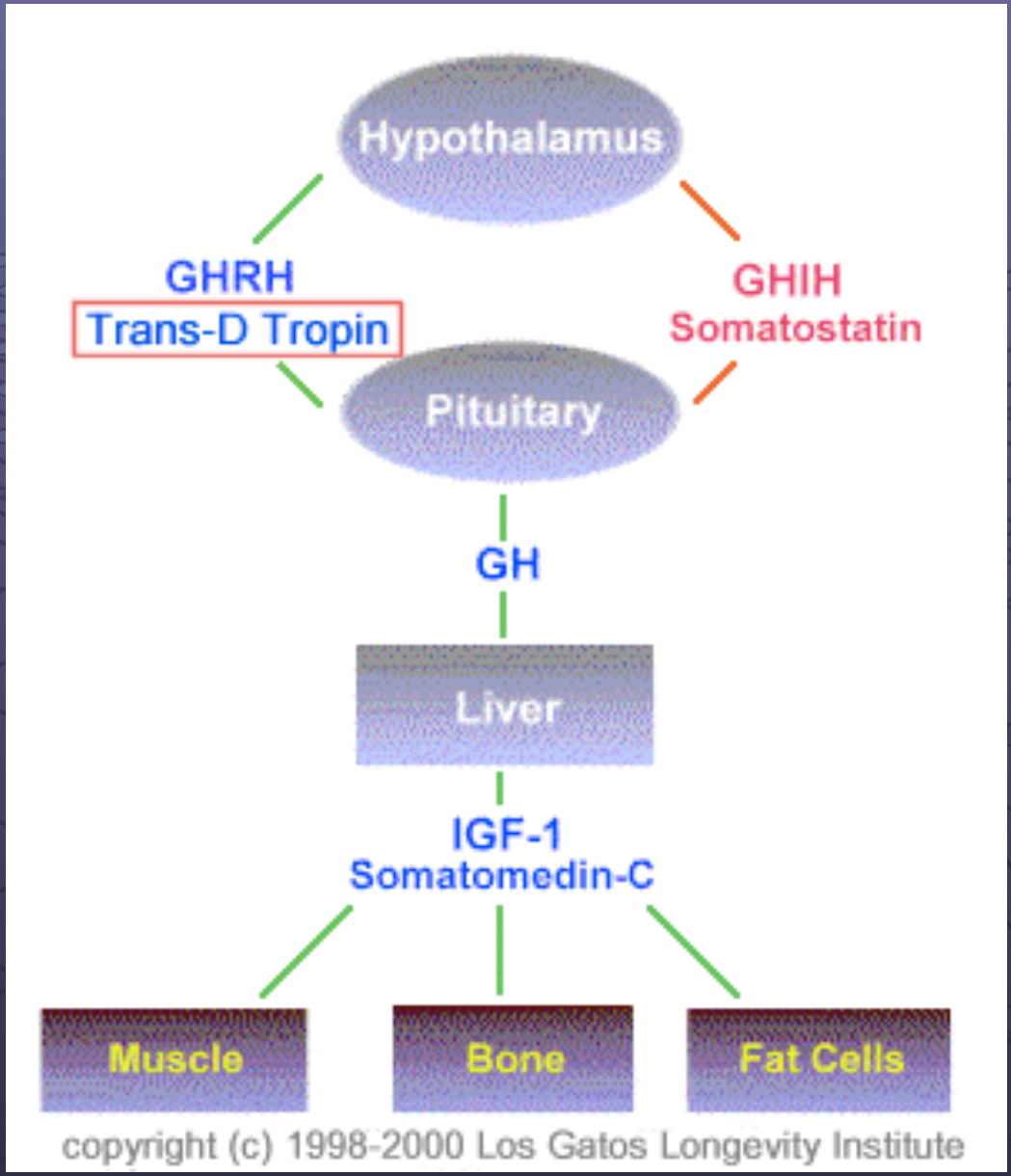
Anterior Pituitary: Growth Hormone (GH)= SOMATOTROPIN

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


Hypothalamus
GHRH
Trans-D Tropin
GHIH
Somatostatin
Pituitary
GH
Liver
IGF-1
Somatomedin-C
Muscle
Bone
Fat Cells
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Deficiency or absence of **somatotroph** cells

↓

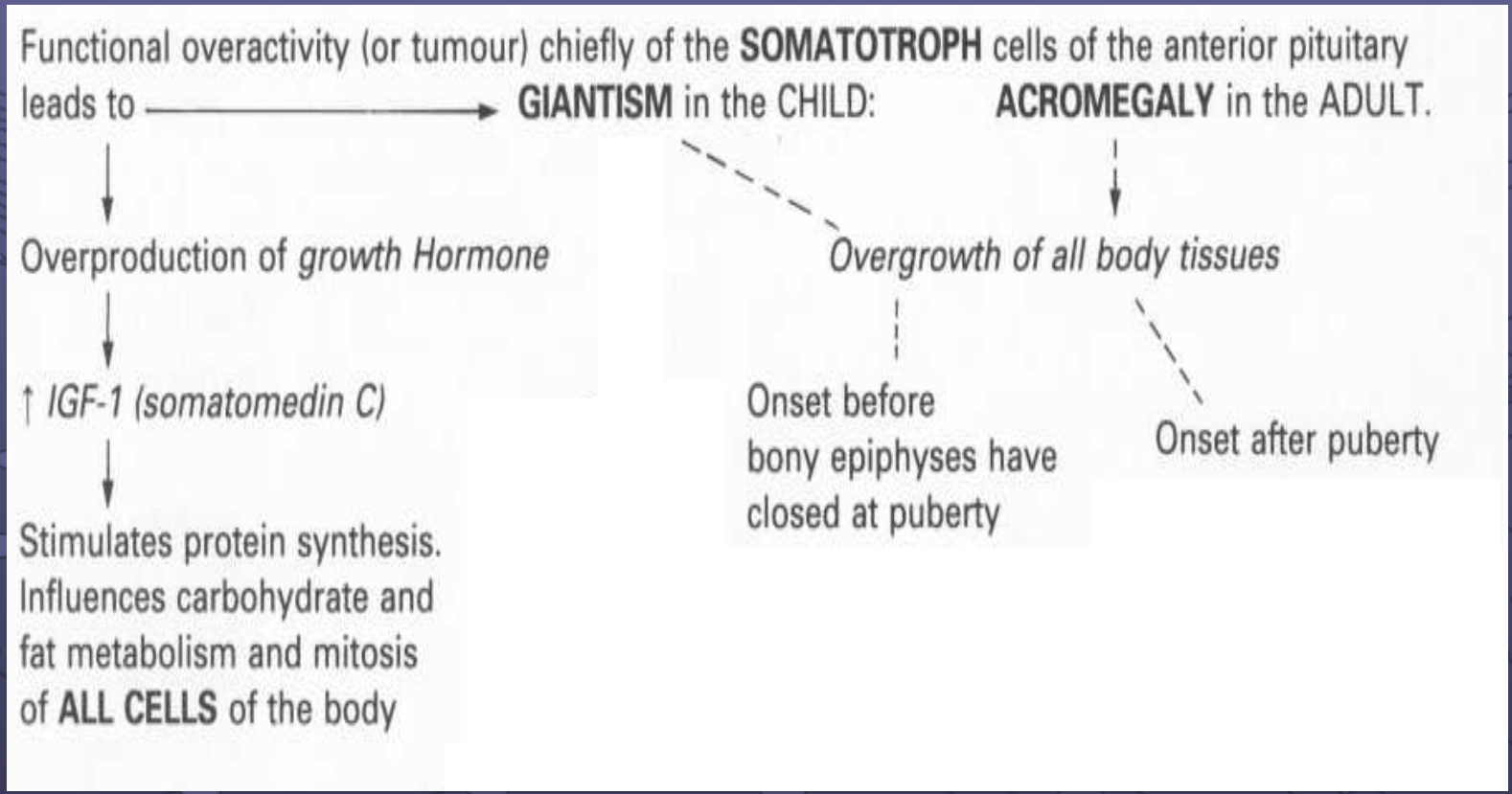
Underproduction of growth hormone (somatotrophin)

↓

PITUITARY DWARF

(Lorain Dwarf)

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

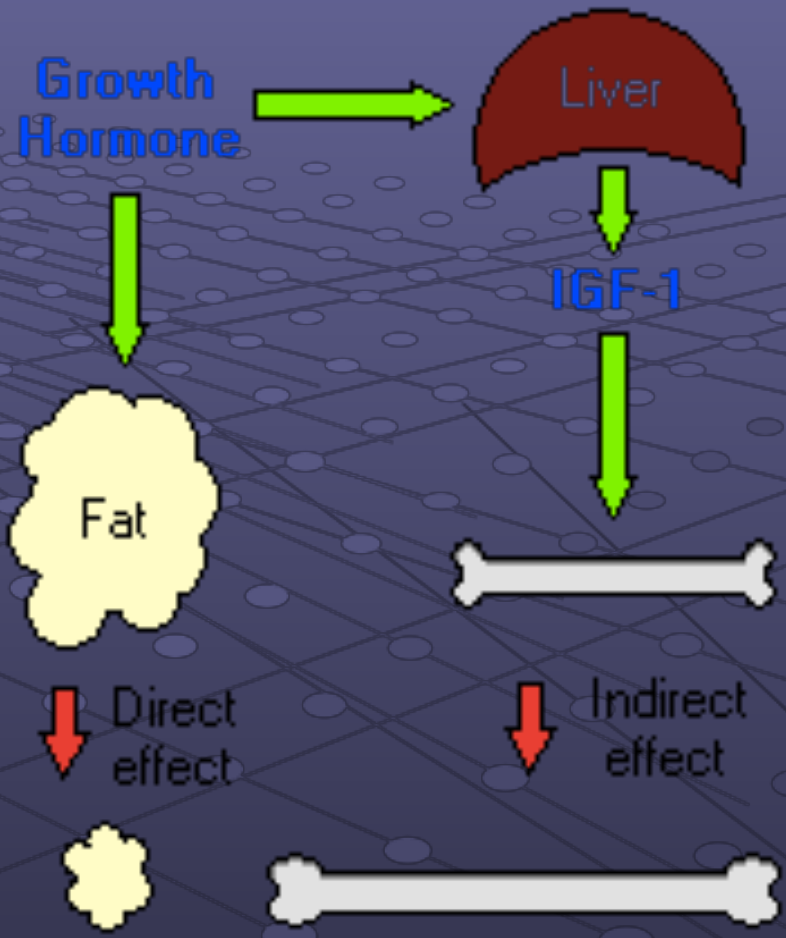

Functional overactivity (or tumour) chiefly of the SOMATOTROPH cells of the anterior pituitary
leads to
GIANTISM in the CHILD:
ACROMEGALY in the ADULT.
Overproduction of growth Hormone
Overgrowth of all body tissues
↑ IGF-1 (somatomedin C)
Onset before bony epiphyses have closed at puberty
Onset after puberty
Stimulates protein synthesis. Influences carbohydrate and fat metabolism and mitosis of ALL CELLS of the body

Direct Effects of GH

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

Indirect Effects of GH

- Stimulates:
  - Bone growth
  - Cartilage cells (chrondrocytes) growth
  - Myoblasts growth & differentiation
  - Amino Acid uptake & protein synthesis


Growth Hormone
Liver
IGF-1
Fat
Direct effect
Indirect effect

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 adrenocorticotropic 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

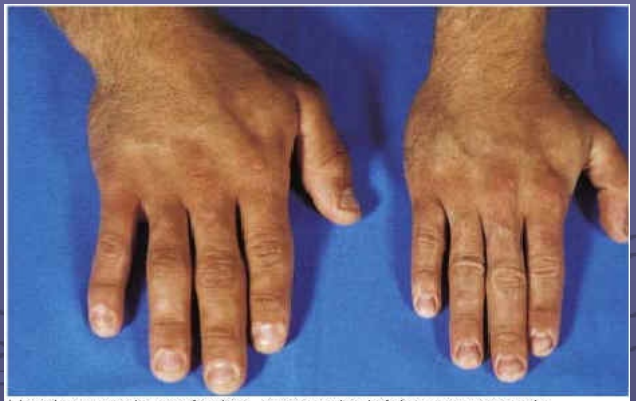
This usually results from benign tumor of the anterior pituitary.

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

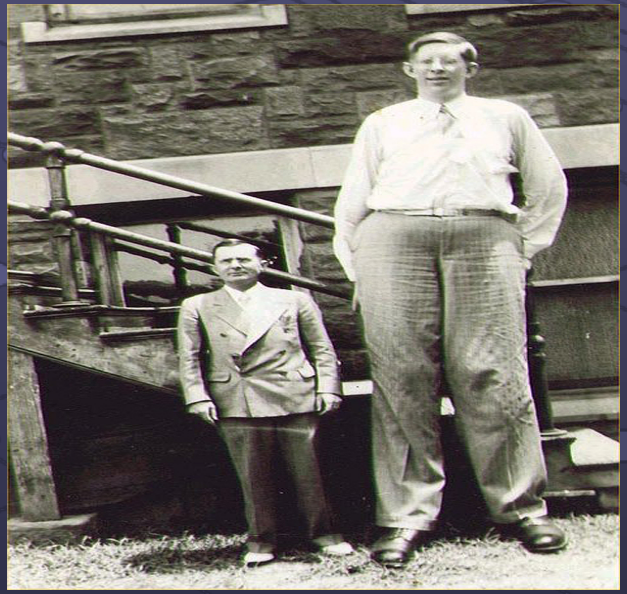
(2) In adults: It causes **acromegaly** (bones increase in size, including those of hands, feet and face).

Growth retardation
(dwarfism)

A.D.A.M.



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



Growth Hormone Antagonists

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 and lanreotide cause significant gastrointestinal disturbances, gallstones, & cardiac conduction abnormalities.

Somatostatin analogues:

Octreotide (very expensive): 45 times 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 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. **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-α-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