Hypothalamic & Pituitary Hormones

Yacoub M. Irshaid, MD, PhD, ABCP

Department of Pharmacology, FOM, UJ

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Reference

Basic & Clinical Pharmacology

BG Katzung, SB Masters, AJ Trevor

McGraw Hill LANGE

12th edition pp 662-666; 672-673 , or 13th edition pp 643-649; 655-656

Hypothalamic & Pituitary Hormones

Pharmacologic Applications:

Drugs that mimic or block the effects of hypothalamic or pituitary hormones have the following applications:

1. **Replacement therapy for hormone deficiency states.**
2. **Antagonists for diseases resulting from excess production of pituitary hormones.**

Hypothalamic & Pituitary Hormones

3. **Diagnostic tools for identifying several endocrine disorders.**

TABLE 37–1 Links between hypothalamic, anterior pituitary, and target organ hormone or mediator.[1]

Anterior Pituitary Hormone	Hypothalamic Hormone	Target Organ	Primary Target Organ Hormone or Mediator
Growth hormone (GH, somatotropin)	Growth hormone-releasing hormone (GHRH) (+) Somatostatin (–)	Liver, bone, muscle, kidney, and others	Insulin-like growth factor-I (IGF-I)
Thyroid-stimulating hormone (TSH)	Thyrotropin-releasing hormone (TRH) (+)	Thyroid	Thyroxine, triiodothyronine
Adrenocorticotropin (ACTH)	Corticotropin-releasing hormone (CRH) (+)	Adrenal cortex	Cortisol
Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)	Gonadotropin-releasing hormone (GnRH) (+)[2]	Gonads	Estrogen, progesterone, testosterone
Prolactin (PRL)	Dopamine (–)	Breast	—

[1] All of these hormones act through G protein-coupled receptors except growth hormone and prolactin, which act through JAK/STAT receptors.

[2] Endogenous GnRH, which is released in pulses, stimulates LH and FSH release. When administered continuously as a drug, GnRH and its analogs inhibit LH and FSH release through down-regulation of GnRH receptors.

(+), stimulant; (–), inhibitor.

Hypothalamic & Pituitary Hormones

- **Because of the greater ease of administration of target endocrine gland hormones or their synthetic analogs, the related hypothalamic and pituitary hormones (TRH, TSH, CRH, ACTH & GHRH) are either not used clinically or used rarely for specialized diagnostic testing.**
- **This lecture will be limited to growth hormone.**

Growth Hormone (Somatotropin)

- **Is a 191-amino acid peptide with 2 sulfhydryl bridges.**
- **Recombinant human GH (rhGH) is available for clinical use (Somatropin).**

Growth Hormone (Somatotropin)

Pharmacokinetics:

- **Circulating GH has a half-life of 20-25 min, and is predominantly cleared by the liver.**
- **Active blood levels persist for 36 hours.**
- **rhGH is administered subcutaneously.**

Growth Hormone (Somatotropin)

Mechanism of Action:

- **Effects are mediated through binding to a cell surface receptor of the JAK/STAT cytokine receptor superfamily.**
- **Dimerization of 2 GH receptors by a single GH molecule activates signaling cascades mediated by receptor-associated JAK (Janus-kinase) tyrosine kinases and STATs (signal transducers and activators of transcription).**

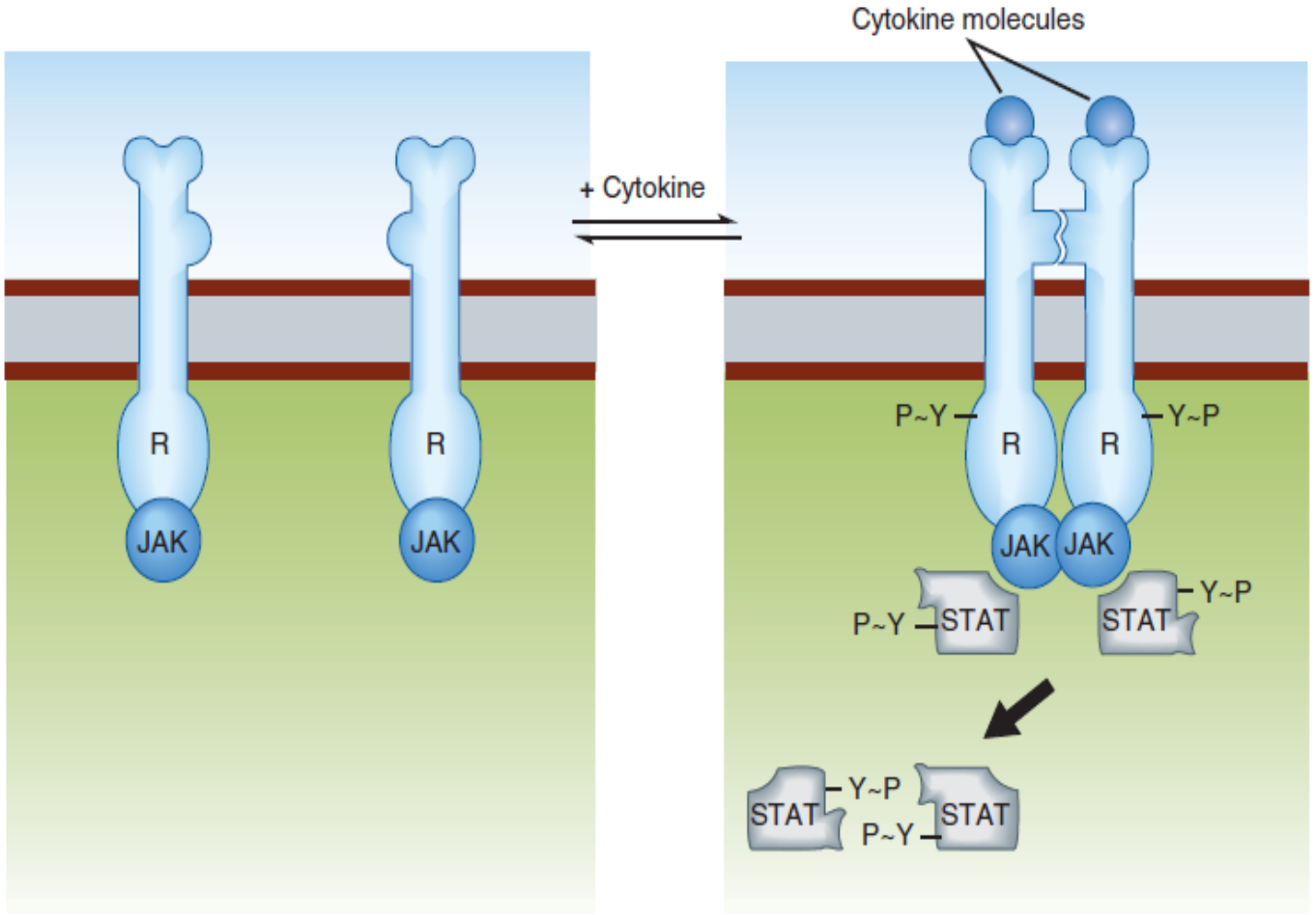

FIGURE 2–8 Cytokine receptors, like receptor tyrosine kinases, have extracellular and intracellular domains and form dimers. However, after activation by an appropriate ligand, separate mobile protein tyrosine kinase molecules (JAK) are activated, resulting in phosphorylation of signal transducers and activation of transcription (STAT) molecules. STAT dimers then travel to the nucleus, where they regulate transcription.

The difference is that a single GH molecule is needed to activate the 2 receptors

Growth Hormone (Somatotropin)

Pharmacodynamics:

- **GH has complex effects on growth, body composition and carbohydrate, protein and lipid metabolism.**

1. **The growth promoting effect is mediated mainly through production of insulin-like growth factor 1 (IGF-1), mainly by the liver, but also in bone, cartilage, muscle, kidney and other tissues, where it has autocrine or paracrine roles.**

Growth Hormone (Somatotropin)

2. **It stimulates longitudinal bone growth until the epiphyses close near the end of puberty.**
3. **In both children and adults, it has anabolic effects in muscles and catabolic effects in adipose tissue → shift the balance of body mass to an increase in muscle mass and a reduction in adiposity.**

Growth Hormone (Somatotropin)

4. **The direct and indirect effects of GH on carbohydrate metabolism are mixed, partly because GH and IGF-1 have opposite effects on insulin sensitivity:**

A. **GH reduces insulin sensitivity resulting in mild hyperinsulinemia, and increased blood glucose levels.**

B. **IGF-1 has insulin-like effects on glucose transport, lowers serum glucose and reduces circulating insulin.**

Growth Hormone (Somatotropin)

- ***In patients who are unable to respond to growth hormone because of severe resistance (caused by GH receptor mutations, post-receptor signaling mutations, or GH antibodies), the administration of recombinant human IGF-I may cause hypoglycemia because of its insulin-like effects.***

Growth Hormone (Somatotropin)

- ***Adults with GH deficiency often have generalized obesity, reduced muscle mass, asthenia, diminished bone mineral density, dyslipidemia, and reduced cardiac output.***
- ***Growth hormone-deficient adults who have been treated with GH experience reversal of many of these manifestations.***

Growth Hormone (Somatotropin)

Therapeutic Uses:

1. **Replacement therapy for growth hormone deficiency states, in both adults and children.**
2. **Others…..**

TABLE 37–4 Clinical uses of recombinant human growth hormone.

Primary Therapeutic Objective	Clinical Condition
Growth	Growth failure in pediatric patients associated with:
	Growth hormone deficiency
	Chronic renal insufficiency pre-transplant
	Noonan syndrome
	Prader-Willi syndrome
	Short stature homeobox-containing gene (SHOX) deficiency
	Turner syndrome
	Small for gestational age with failure to catch up by age 2 years
	Idiopathic short stature
Improved metabolic state, increased lean body mass, sense of well-being	Growth hormone deficiency in adults
Increased lean body mass, weight, and physical endurance	Wasting in patients with HIV infection
Improved gastrointestinal function	Short bowel syndrome in patients who are also receiving specialized nutritional support

Growth Hormone (Somatotropin)

Toxicity & Contraindications:

In children (are relatively rare):

1. **Increase in intracranial pressure in children (psuedotumor cerebri) manifested as changes in vision, headache, nausea and vomiting.**
2. **Slipped capital femoral epiphysis.**
3. **Progression of scoliosis during rapid growth.**

Growth Hormone (Somatotropin)

4. **Hypothyroidism is commonly discovered during GH treatment.**
5. **Others: pancreatitis, otitis media, gynecomastia, nevus growth, edema, hyperglycemia, and increased risk of asphyxiation.**

Growth Hormone (Somatotropin)

In adults (more than children):

1. **Peripheral edema, myalgia, arthralgia (hands and wrists).**
2. **Carpal tunnel syndrome.**
3. **Increased activity of cytochrome P450 enzymes → increased metabolism of some drugs and reduction of their blood levels.**
4. **Proliferative retinopathy.**

Growth Hormone (Somatotropin)

5. **Contraindicated in patients with active malignancies.**
6. **Use in critically ill patients increases mortality.**
7. **Long-acting somatropin: injection site nodules, edema, arthralgia, fatigue, nausea, headache.**

Mecasermin

- A small number of children with growth failure have severe IGF-I deficiency that is not responsive to exogenous GH.
- May be caused by mutations in GH receptor and in the GH receptor signaling pathway, neutralizing antibodies to GH, and IGF-I gene defects.
- Mecasermin and mecasermin rinfabate may be used for treatment of this condition.

Mecasermin

- **Mecasermin is rhIGF-I alone, administered subcutaneously.**
- **Mecasermin rinfabate is a complex of rhIGF-I and recombinant human insulin-like growth factor-binding protein-3 (rhIGFBP-3).**
- **This binding protein significantly increases the circulating half-life of rhIGF-I.**

Mecasermin

Adverse effects:

1. **Hypoglycemia (is the most important).**
2. **Increased intracranial pressure.**
3. **Adenotonsillar hypertrophy.**
4. **Elevation of liver enzymes.**

Growth Hormone Antagonists

- **Antagonists of GH are used to reverse the effects of GH-producing cells (somatotrophs) in the anterior pituitary that tend to form GH-secreting tumors.**
- **Hormone-secreting pituitary adenomas occur most commonly in adults.**

Growth Hormone Antagonists

Growth hormone excess produces:

1. **Acromegaly in adults: Abnormal growth of cartilage, bone, skin, muscle, heart, liver and GIT,.. And affect metabolism.**
2. **Gigantism in children before long bone epiphyses close.**

Growth Hormone Antagonists

Drug treatment:

GH antagonists, which include:

1. **Somatosatin analogs, octreotide .**
2. **Dopamine receptor agonists, bromocriptine.**
   - **Both reduce the production of GH.**
3. **GH receptor antagonists, pegvisomant.**

Somatostatin & Octreotide

Somatostatin:

- **It is a 14-amino acid peptide found in the hypothalamus, CNS, pancreas, GIT,..→ lack of specificity.**
- **It is an inhibitory paracrine factor.**
- **It inhibits the release of GH, TSH, glucagon, insulin and gastrin.**
- **Half-life 1-3 min → limited therapeutic uses.**
- **Metabolized and excreted mainly by the kidney.**

Octreotide

Octreotide:

- **Is an analog of somatostatin.**
- **45 times more potent than somatostatin in inhibiting GH release but only twice as potent in reducing insulin secretion.**
- **Half-life is around 80 min.**
- **Given subcutaneously.**

Octreotide

Therapeutic Uses:

1. Reduces symptoms caused by a variety of hormone-secreting tumors: acromegaly, carcinoid syndrome, gastrinoma, VIPoma, glucagonoma, insulinoma, and ACTH-secreting tumor.

2. Diarrhea — secretory, HIV associated, diabetic, chemotherapy, or radiation induced.

3. Acute control of bleeding from esophageal varices (portal hypertension).

Octreotide

Adverse effects:

1. Hyperglycemia (? Inhibits insulin and glucagon secretion) – rare, and may be transient.
2. Pain at site of injection.
3. GIT: nausea, vomiting, abdominal cramps, flatulence, steatorrhea with bulky bowel movements.

Octreotide

4. Vitamin B_{12} deficiency with long-term use (reduced absorption).
5. Biliary sludge and gall stones (20-30% of patients after 6 months of use).
5. Sinus bradycardia (25%) and conduction disturbances in the heart (10%).

Pegvisomant

- **GH receptor antagonist, Useful for treatment of acromegaly.**
- **Is a polyethylene glycol (PEG) derivative of a mutant GH.**
- **Pegylation reduces its clearance and improves its overall clinical effectiveness.**
- **It has increased affinity for one site of the GH receptor and reduced affinity at the second binding site.**

Pegvisomant

- **This allows dimerization of the receptor but blocks the conformational changes required for signal transduction.**
- **Normalizes IGF-1 levels, but does not inhibit GH secretion.**

Adverse effects:

1. **May lead to increased GH levels and possible adenoma growth.**
2. **Elevation of liver enzymes.**