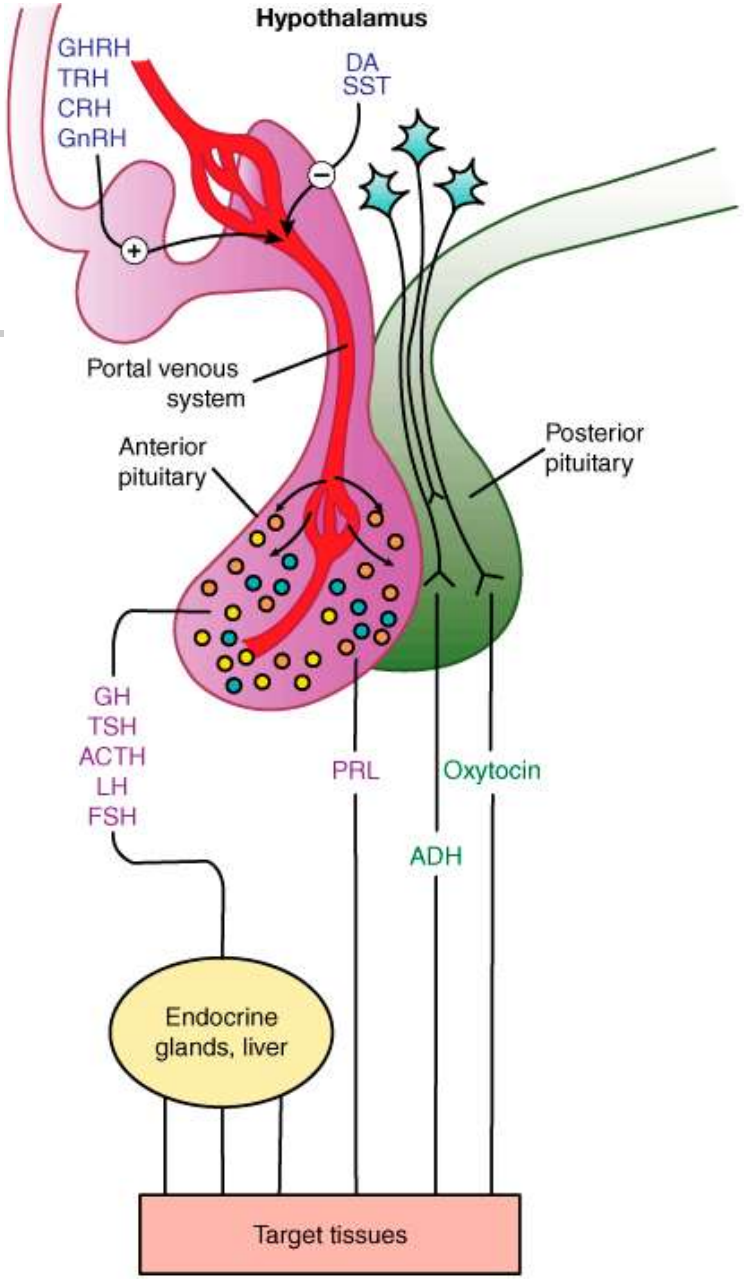
# Hypothalamic &Anterior pituitary hormones

# The hypothalamic-pituitary endocrine system

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# hypothalamic, anterior pituitary, and target organ hormone

| Anterior Pituitary Hormone | Hypothalamic Hormone | Target Organ | Primary Target Organ Hormone or Mediator |
|---|---|---|---|
| Growth hormone (GH, somatotropin) | Growth hormone-releasing hormone (GHRH) (+) Somatostatin (-) | Liver, muscle, bone, kidney, and others | Insulin-like growth factor-1 (IGF-1) |
| Thyroid-stimulating hormone (TSH) | Thyrotropin-releasing hormone (TRH) (+) | Thyroid | Thyroxine, triiodothyronine |
| Adrenocorticotropin (ACTH) | Corticotropin-releasing hormone (CRH) (+) | Adrenal cortex | Glucocorticoids, mineralocorticoids, androgens |
| Follicle-stimulating hormone (FSH) Luteinizing hormone (LH) | Gonadotropin-releasing hormone (GnRH) (+)[2] | Gonads | Estrogen, progesterone, testosterone |
| Prolactin (PRL) | Dopamine (-) | Breast | — |

(+), stimulant; (-), inhibitor.

# Clinical uses of hypothalamic hormones and their analogs

| Hypothalamic Hormone | Clinical Uses |
|---|---|
| Growth hormone-releasing hormone (GHRH) | Used rarely as a diagnostic test for GH responsiveness |
| Thyrotropin-releasing hormone (TRH, protirelin) | Used rarely to diagnose hyper- or hypothyroidism |
| Corticotropin-releasing hormone (CRH) | Used rarely to distinguish Cushing's disease from ectopic ACTH secretion |
| Gonadotropin-releasing hormone (GnRH) | Used rarely in pulses to treat infertility caused by hypothalamic dysfunction |
| | Analogs used in long-acting formulations to inhibit gonadal function in men with prostate cancer and women undergoing assisted reproductive technology (ART) or women who require ovarian suppression for a gynecological disorder |
| Dopamine | Analogs used for treatment of hyperprolactinemia |

# Diagnostic uses of thyroid-stimulating hormone and adrenocorticotropin

| Hormone | Diagnostic Use |
|---|---|
| Thyroid-stimulating hormone (TSH; thyrotropin) | In patients who have been treated surgically for thyroid carcinoma, to test for recurrence by assessing TSH-stimulated whole-body $^{131}$I scans and serum thyroglobulin determinations |
| Adrenocorticotropin (ACTH) | In patients suspected of adrenal insufficiency, to test for a cortisol response. |
| | In patients suspected of congenital adrenal hyperplasia, to identify 21-hydroxylase deficiency, 11-hydroxylase deficiency, and 3$\beta$-hydroxy-$\Delta^5$ steroid dehydrogenase deficiency, based on the steroids that accumulate in response to ACTH administration |

# Pharmacologic Applications of hypothalamic and pituitary hormones

- Replacement therapy for hormone deficiency states
- Antagonists for diseases that result from excess production of pituitary hormones
- Diagnostic tools for identifying several endocrine abnormalities

# GROWTH HORMONE (SOMATOTROPIN)

# Introduction

- Peptide hormones
- Important effects on lipid and carbohydrate metabolism
- Its effects are primarily mediated via
  - **insulin-like growth factor 1 (IGF-1, somatomedin C)**
  - **insulin-like growth factor 2 (IGF-2)**.

# Chemistry & Pharmacokinetics

- STRUCTURE:
  - is a 191-amino-acid peptide with two sulfhydryl bridges
- rhGH
  - **Somatropin** has a 191-amino-acids
  - **Somatrem** has 192 amino acids

# Pharmacodynamics

- Mediates its effects via cell surface receptors of the JAK/STAT cytokine receptor superfamily
- Has complex effects on
  - growth, body composition
  - carbohydrate, protein, and lipid metabolism
- The growth-promoting effects are mediated through IGF-1
- GH has anabolic effects in muscle and catabolic effects in lipid cells

# Clinical Pharmacology

- GROWTH HORMONE DEFICIENCY
- PEDIATRIC PATIENTS WITH SHORT STATURE
- Other Uses of Growth Hormone

# Clinical uses of recombinant human growth hormone

| Primary Therapeutic Objective | Clinical Condition |
|---|---|
| Growth | Growth failure in pediatric patients associated with:<br>Growth hormone deficiency<br>Chronic renal failure<br>Prader-Willi syndrome<br>Turner syndrome |
| | Small for gestational age with failure to catch up by age 2 |
| | Idiopathic short stature in pediatric patients |
| 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 AIDS |
| Improved gastrointestinal function | Short bowel syndrome in patients who are also receiving specialized nutritional support |

# Toxicity & Contraindications

- A rarely reported side effect is intracranial hypertension, which may manifest as vision changes, headache, nausea, or vomiting

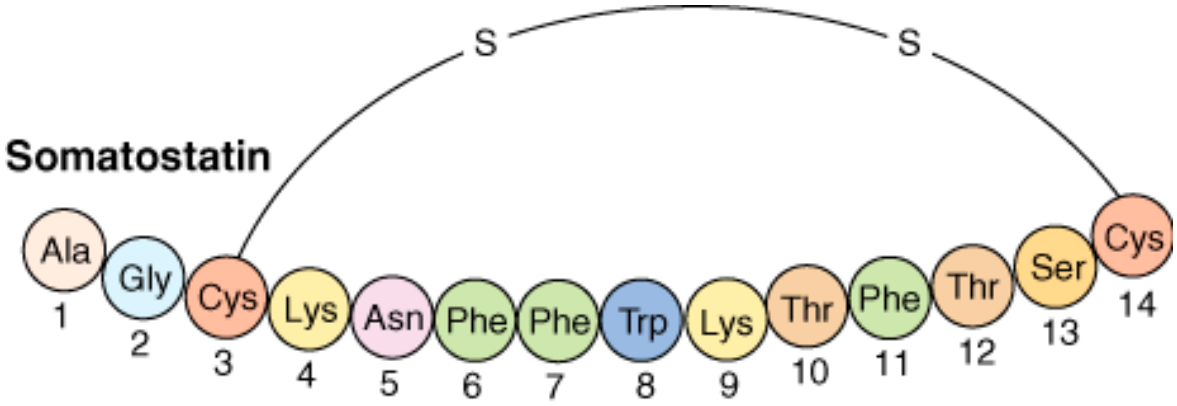
# MECASERMIN

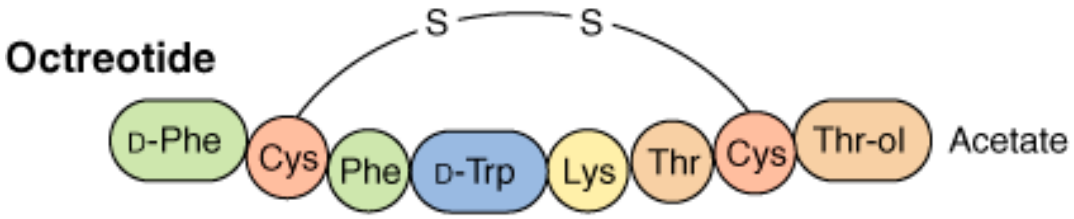
- Is a complex of
  - recombinant human IGF-1 (rhIGF-1)
  - recombinant human insulin-like growth factor-binding protein-3 (rhIGFBP-3)
- For treatment of severe IGF-1 deficiency
- The most important adverse effect is hypoglycemia

# GROWTH HORMONE ANTAGONISTS

- **Somatostatin**
  - **It inhibits the release of GH, glucagon, insulin, and gastrin**
  - **has limited therapeutic usefulness**
- **Octreotide**
  - reduces symptoms caused by a variety of hormone-secreting tumors
    - acromegaly; the carcinoid syndrome; gastrinoma; glucagonoma; nesidioblastosis
    - the watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome; and diabetic diarrhea.

# Amino acid sequence of somatostatin and its analog

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# Pegvisomant

- Is a GH receptor antagonist
- Useful for the treatment of acromegaly
- The polyethylene glycol (PEG) derivative of a mutant GH, B2036,

# THE GONADOTROPINS

- FSH
- LH
- human Chorionic Gonadotropin (hCG)
- Are dimers that share
  - an identical $\alpha$ chain
  - in addition to a distinct $\beta$ chain

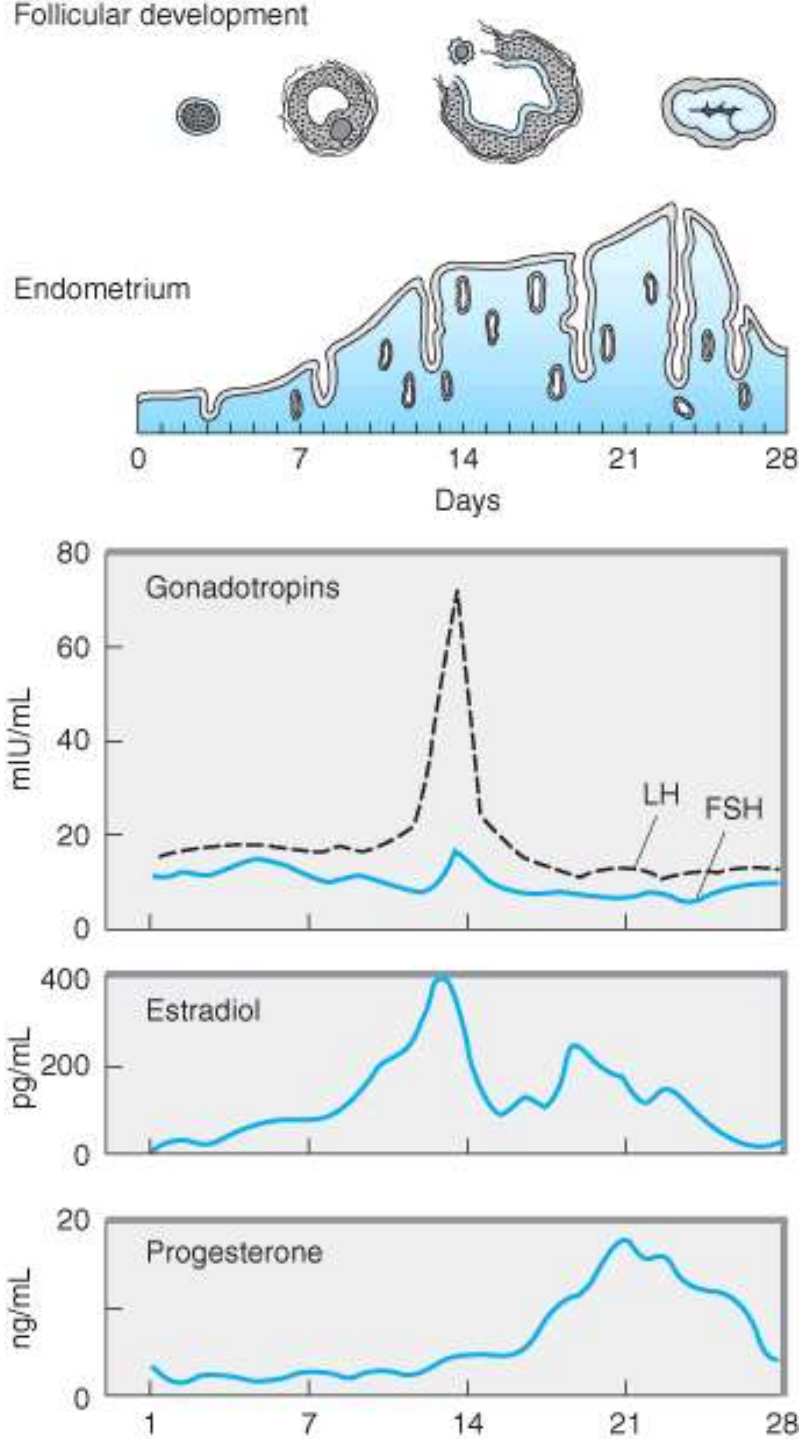
# Chemistry & Pharmacokinetics

- MENOTROPINS
- FOLLICLE-STIMULATING HORMONE
  - **Urofollitropin**,
  - **follitropin alfa** and **follitropin beta**
- LUTEINIZING HORMONE
  - **Lutropin**,
- HUMAN CHORIONIC GONADOTROPIN

# Pharmacodynamics

- Effects through G protein-coupled receptors

# The menstrual cycle



# Clinical Pharmacology

- OVULATION INDUCTION
  - to induce ovulation in women with anovulation due to:
    - hypogonadotropic hypogonadism
    - polycystic ovary syndrome
    - obesity
- MALE INFERTILITY

# Toxicity & Contraindications

- **ovarian hyperstimulation syndrome**
- **multiple pregnancies**
- Headache, depression, edema, precocious puberty

# GONADOTROPIN-RELEASING HORMONE & ITS ANALOGS

- *Pulsatile* GnRH secretion is required to stimulate the gonadotroph cell to produce and release LH and FSH
- Sustained, *nonpulsatile* administration of GnRH or GnRH analogs *inhibits* the release of FSH and LH by the pituitary

# Chemistry & Pharmacokinetics

- **STRUCTURE**
  - GnRH is a decapeptide found in all mammals
  - **Gonadorelin** is an acetate salt of synthetic human GnRH
  - Synthetic analogs include **goserelin, histrelin, leuprolide, nafarelin**, and **triptorelin**.
- **PHARMACOKINETICS**
  - GnRH analogs can be administered subcutaneously, intramuscularly, via nasal spray or as a subcutaneous implant

# Pharmacodynamics

- GnRH exhibit complex dose-response relationships that change dramatically from the fetal period through the end of puberty.

# Clinical Pharmacology

- STIMULATION
  - Female infertility
  - Male infertility
  - Diagnosis of LH responsiveness
- SUPPRESSION
  - Controlled ovarian hyperstimulation
  - Endometriosis
  - Uterine leiomyomata (uterine fibroids)
  - Prostate cancer
  - Central precocious puberty
  - Other
    - advanced breast and ovarian cancer

# Toxicity

- Headache, light-headedness, nausea, and flushing
- Contraindications to the use of GnRH agonists in women include
  - pregnancy and breast-feeding

# GNRH RECEPTOR ANTAGONISTS

- **Ganirelix** and **cetrorelix**
  - Pharmacokinetics
    - absorbed rapidly after subcutaneous injection
  - Clinical Pharmacology
    - preventing the LH surge during controlled ovarian hyperstimulation
  - Toxicity
    - nausea and headache

# PROLACTIN

- Is a 198-amino-acid peptide hormone
- Its structure resembles that of GH

# DOPAMINE AGONISTS

- **Bromocriptine , cabergoline, pergolid and Quinagolide**
- **Pharmacokinetics**
  - All available dopamine agonists are active as oral preparations
- **Clinical Pharmacology**
  - HYPERPROLACTINEMIA
  - PHYSIOLOGIC LACTATION
  - ACROMEGALY
- **Toxicity & Contraindications**
  - **nausea, headache, light-headedness, orthostatic hypotension, and fatigue**