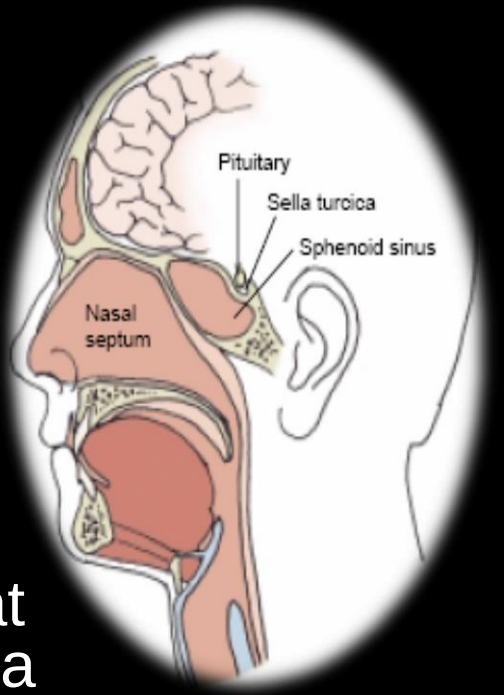
HYPOTHALAMIC AND HYPOPHYSEAL SYSTEM

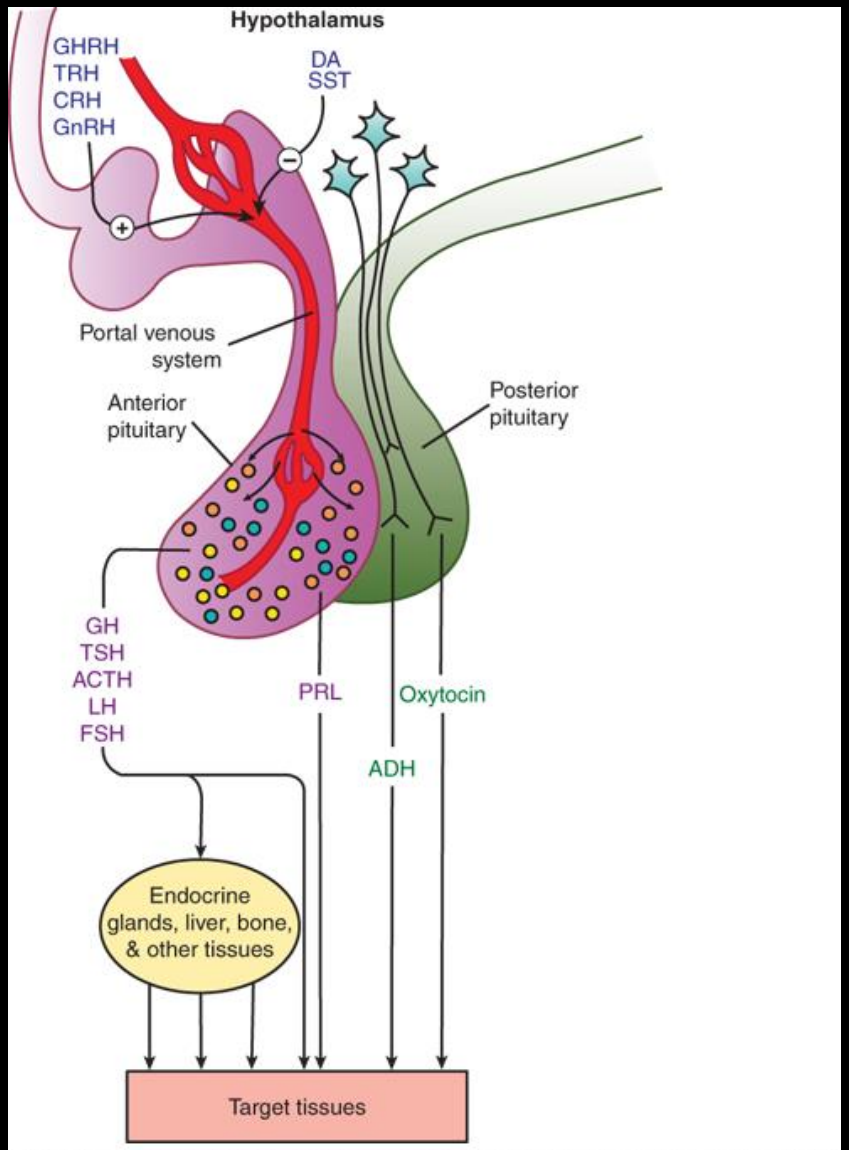
Dr. ZELİHA BAYRAM

- The hypothalamus and pituitary gland function cooperatively as master regulators of the endocrine system.

- Together, hormones secreted by the hypothalamus and pituitary gland control important homeostatic and metabolic functions, including reproduction, growth, lactation, thyroid and adrenal gland physiology, and water homeostasis.

- The pituitary weighs about 0.6 g and rests at the base of the brain in the bony sella turcica near the optic chiasm and the cavernous sinuses.





- The pituitary consists of an anterior lobe (adenohypophysis) and a posterior lobe (neurohypophysis)
- It is connected to the overlying hypothalamus by a stalk of neurosecretory fibers and blood vessels, including a portal venous system that drains the hypothalamus and perfuses the anterior pituitary.
- The portal venous system carries small regulatory hormones from the hypothalamus to the anterior pituitary.

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	—

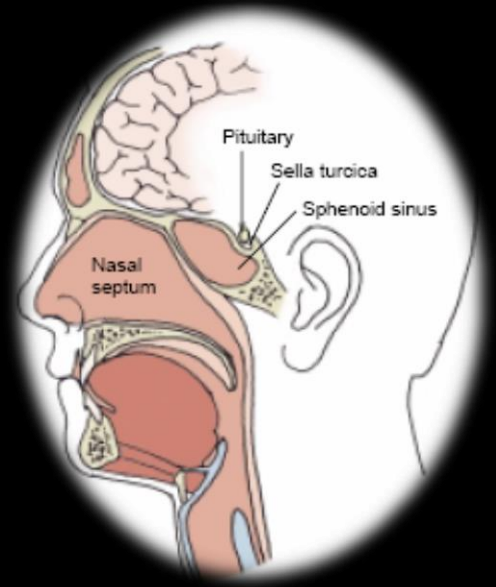
[1]All of these hormones act through G protein-coupled receptors except GH and PRL, which act through JAK/STAT receptors.

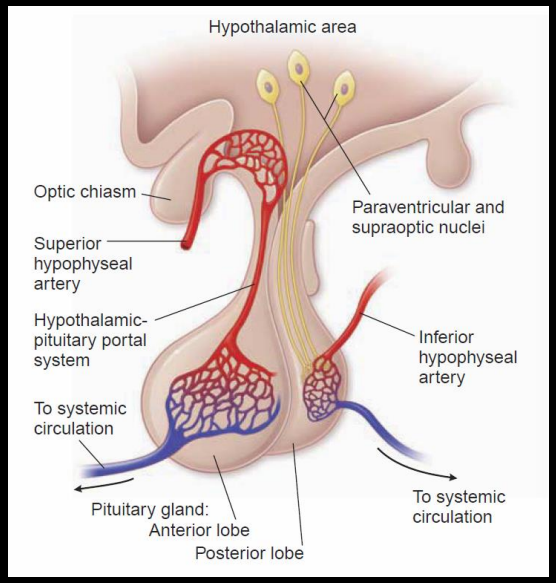
[2]Endogenous GnRH, which is released in pulses, stimulates LH and FSH release. When administered continuously as a drug, GnRH and its analogs inhibit LH and FSH release through down-regulation of GnRH receptors.

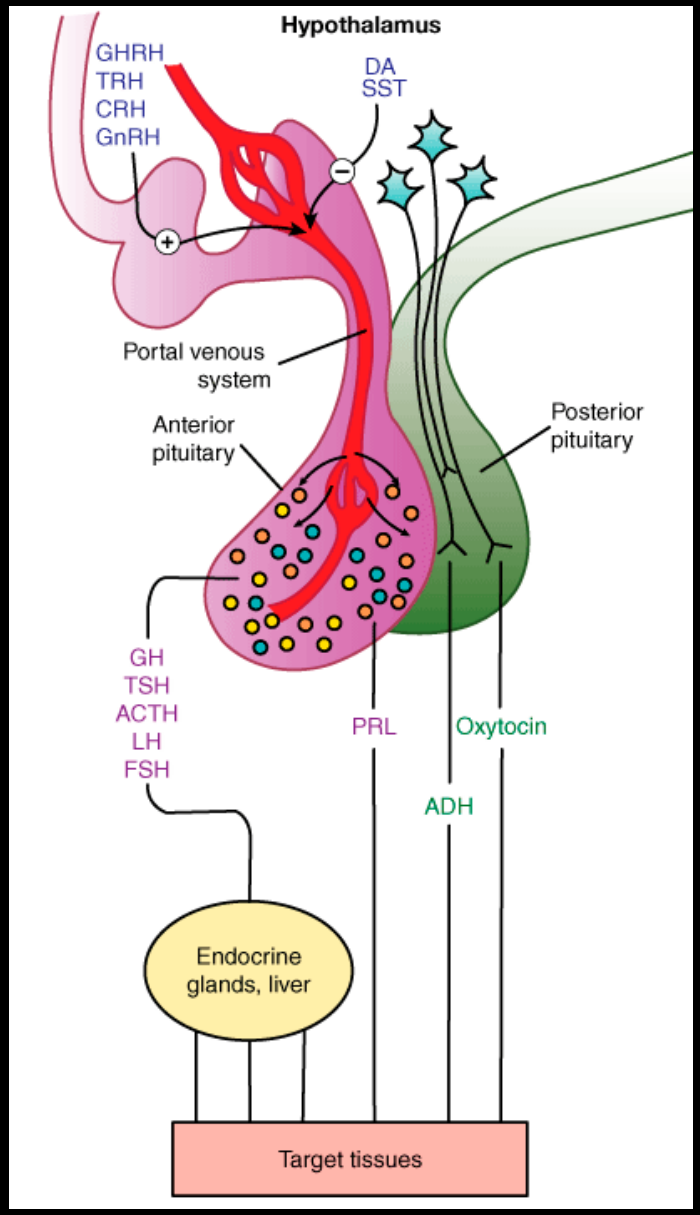
(+), stimulant; (–), inhibitor.

- Drugs that mimic or block the effects of hypothalamic and pituitary hormones have pharmacologic applications in three primary areas:
  1. as replacement therapy for hormone deficiency states
  2. as antagonists for diseases caused by excess production of pituitary hormones
  3. as diagnostic tools for identifying several endocrine abnormalities

ANTERIOR PITUITARY HORMONES & THEIR HYPOTHALAMIC REGULATORS







- The anterior pituitary hormones can be classified according to hormone structure and the types of receptors that they activate.
- **Growth hormone (GH)** and **prolactin (PRL)**, single-chain protein hormones → activate receptors of the JAK/STAT superfamily.
- **Thyroid-stimulating hormone (TSH, thyrotropin), follicle-stimulating hormone (FSH),** and **luteinizing hormone (LH)**—are dimeric proteins → activate G protein-coupled receptors.
- **Adrenocorticotropic hormone (ACTH)**, a single peptide cleaved from a larger precursor, pro-opiomelanocortin (POMC), that can be cleaved into various other biologically active peptides like α-melanocyte-stimulating hormone (MSH) and β-endorphin.
- ACTH → acts through a G protein-coupled receptor.

Table 37–1 Links between Hypothalamic, Anterior Pituitary, and Target Organ Hormone or Mediator.[1]

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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	—

Growth hormone (GH) and **prolactin (PRL)** activate receptors of the JAK/STAT superfamily.

Except from GH and PRL the other hormones activate G-protein coupled receptors

Table 37–1 Links between Hypothalamic, Anterior Pituitary, and Target Organ Hormone or Mediator.[1]

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The hypothalamic hormonal control of GH and prolactin differs from the regulatory systems for TSH, FSH, LH, and ACTH.

The hypothalamus secretes two hormones that regulate GH; **growth hormone-releasing hormone (GHRH)** stimulates GH production, whereas the peptide **somatostatin (SST)** inhibits GH production. GH and its primary peripheral mediator, **insulin-like growth factor-I (IGF-I)**, also provide feedback to inhibit GH release. Prolactin production is inhibited by the catecholamine **dopamine** acting through the D subtype of dopamine receptors.

The hypothalamus does not produce a hormone that specifically stimulates prolactin secretion, although TRH can stimulate prolactin release, particularly when TRH concentrations are high in the setting of primary hypothyroidism.

Whereas all the pituitary and hypothalamic hormones described previously are available for use in humans, only few are of major clinical importance.

Table 37–2 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 gynecologic disorder
Dopamine	Dopamine agonists used for treatment of hyperprolactinemia

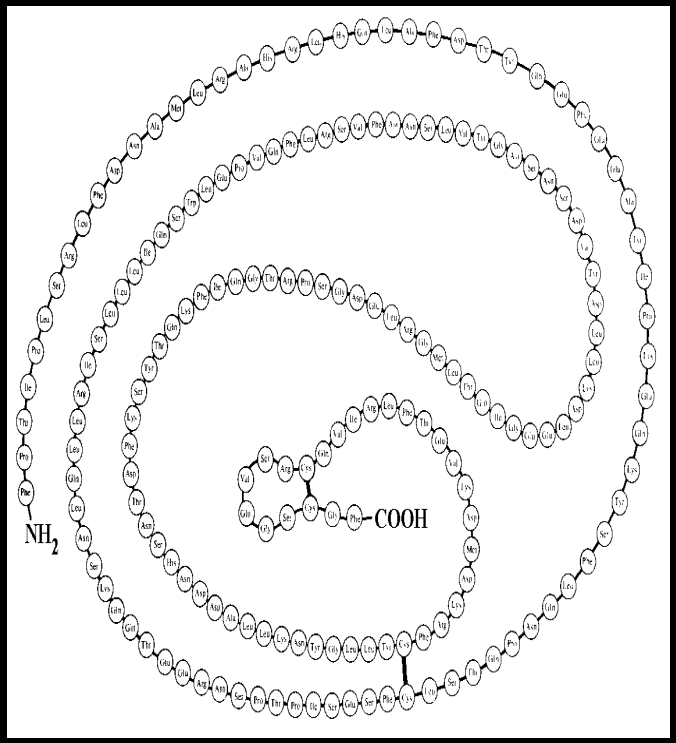
Table 37–3 Diagnostic Uses of Thyroid-Stimulating Hormone and Adrenocorticotropin.

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 3β-hydroxy-Δ^5 steroid dehydrogenase deficiency, based on the steroids that accumulate in response to ACTH administration (see Figure 39–1 and Chapter 39)

GROWTH HORMONE: PHYSIOLOGY AND PATHOPHYSIOLOGY

secreted by the acidophil cells in the anterior pituitary.

- Single chain
- 191 amino acids
- 2 intramolecular disulfide bonds
- Similar to:
- prolactin
- placental lactogen



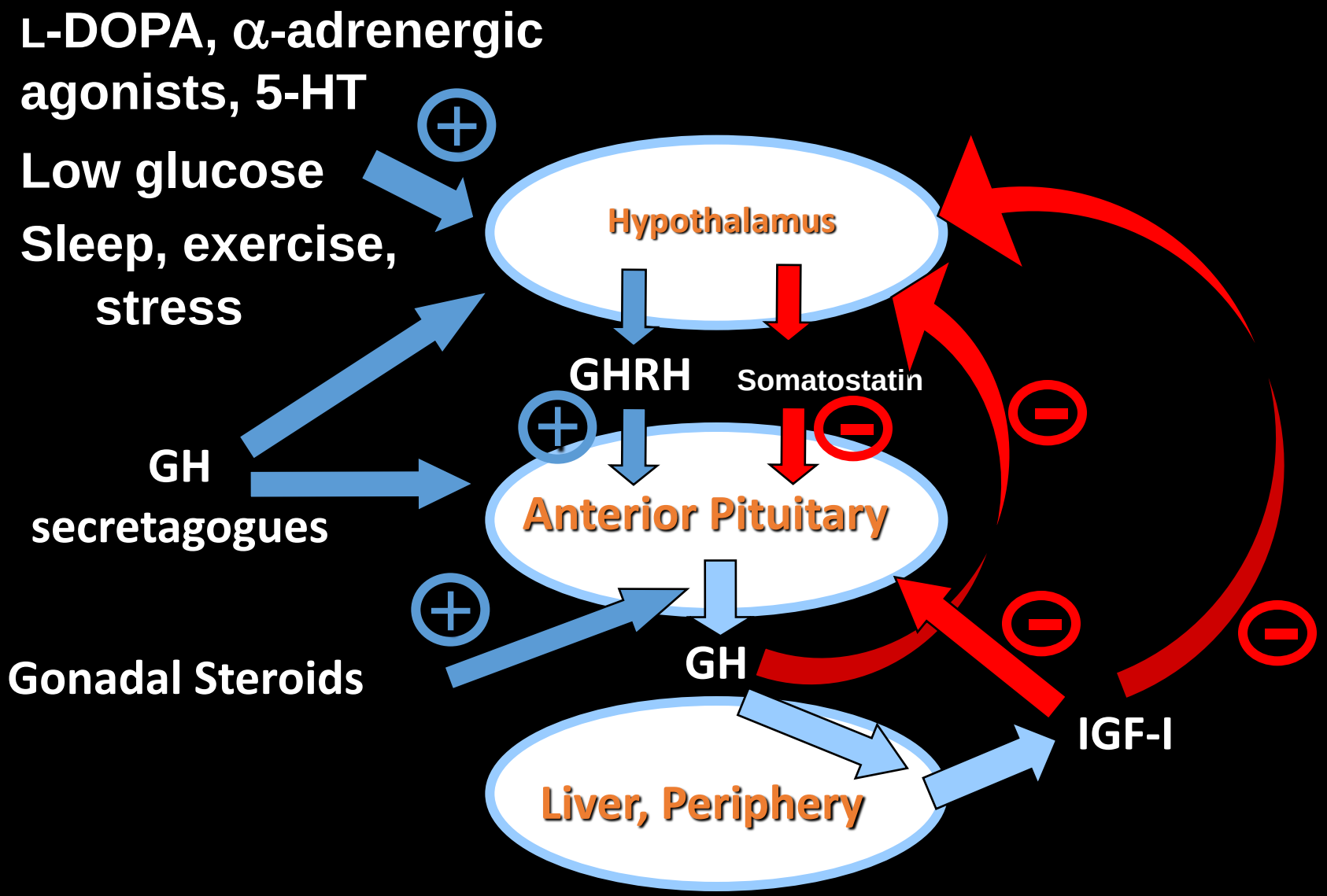
- Secretion occurs in brief pulses, with a slower underlying diurnal variability, and is greatest during sleep. Secretion is much greater during growth than in older individuals.

- The hypothalamus controls GH secretion from the pituitary by secreting a GH-releasing hormone (GHRH), somatorelin and a GH-release-inhibiting hormone, somatostatin, which is also synthesized in D cells of the islets of Langerhans in the pancreas.

- GH-secreting pituitary adenomas cause acromegaly in adults (gigantism in children), whereas GH deficiency in children causes growth retardation and short stature.

Li CH and Graf L, *Proc Nat Acad Sci USA* 71: 1197-1201, 1974

Growth hormone secretion



- GH increases cell growth and protein synthesis in all tissues (somatotrop hormone)
- Excess release of GH: Gigantism in children

  Acromegali in adults
- GH deficiency in children: hypophysial dwarfism
- Anabolic effects in muscle and catabolic effects in adipose cells →increase in muscle mass and a reduction in adiposity

- Indirect effect primarily mediated via somatomedins (sulphation factors) that are produced in liver and the other tissues.
  - Insulin like growth factor-1 (IGF-1; also known as somatomedin C) → most important
  - GH increases blood glucose levels (reduces insulin sensitivity),
  - IGF-1 reduces insülin and blood glucose levels
- In the past, medicinal GH was isolated from the pituitaries of human cadavers. However, this form of GH was found to be contaminated with prions that could cause Creutzfeldt-Jakob disease.
- Recombinat preparations are used now: **Somatropin and Somatrem**
- **3-7 times per week, SC.**

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

Use of Somatotropin

- Half-life :
  - Endogenous GH: 20 to 30 minutes
  - Recombinant human GH (rhGH) is administered subcutaneously 6–7 times per week.
  - Peak levels: 2–4 hours and active blood levels persist for approximately 36 hours.
  - duration: up to 36 hours
  - 25 - 30 % bound to GH-binding protein in plasma
- Adverse effects
  - Few in children
  - Rarely; intracranial hypertension, with papilledema, visual changes, headache, nausea, and/or vomiting
  - In adults: peripheral edema, myalgias, arthralgias, carpal tunnel syndrome
    Hyperglycemia not a frequent side effect
- Drug interactions
  - Increased cytochrome P450 isoforms → increased clearance of steroids, anticonvulsants, cyclosporine

MECASERMIN

Complex of recombinant human IGF-1 and a combination of recombinant human IGF-1 with its binding protein (IGFBP-3)

Indications: for patients with impaired growth secondary to mutations in the GH receptor or postreceptor signaling pathway, patients with GH deficiency who develop antibodies against GH

Dose: 40-80 g/kg per dose twice daily by subcutaneous injection

Side effexts: hypoglycemia and lipohypertrophy

intracranial hypertension in some patients

GH ANTAGONİSTS

- 1. SOMATOSTATIN ANALOGUES
- 2. DOPAMINE RECEPTOR AGONISTS
- 3. PEGVISOMANT

Patients with microadenomas releasing GH

Treatment:

- SOMATOSTATIN ANALOGUES
- DOPAMINE RECEPTOR AGONISTS

GH receptor antagonist

- PEGVISOMANT

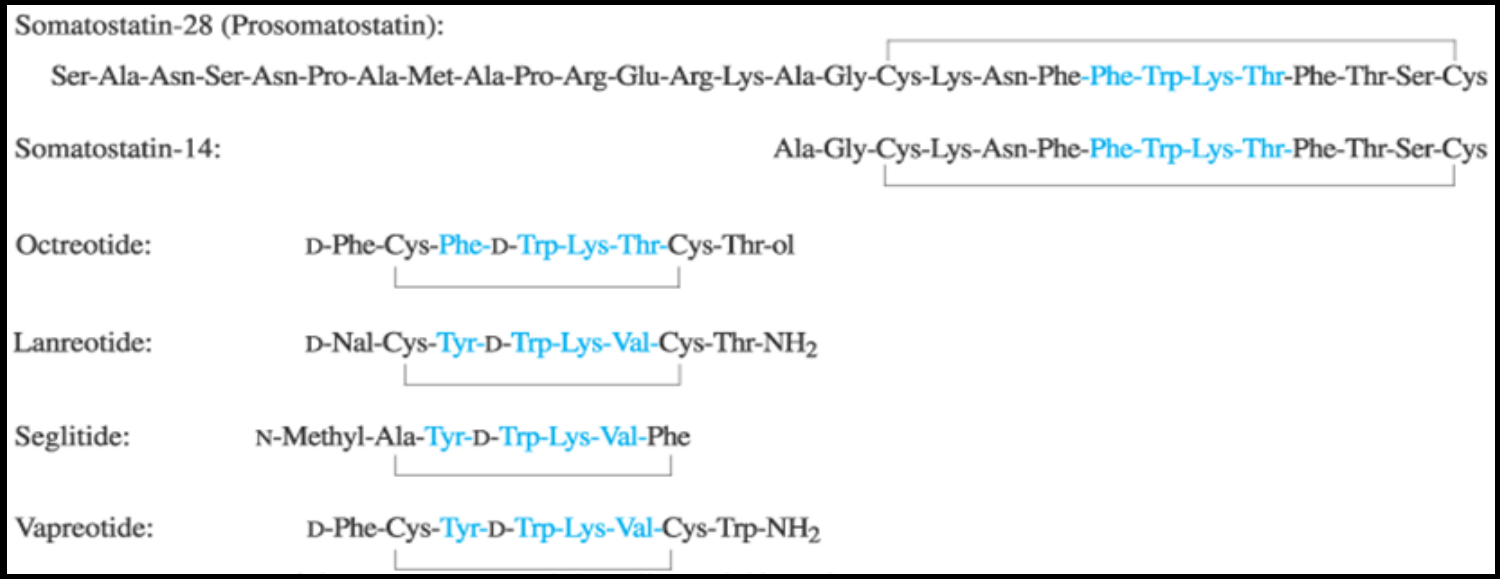
Patients with macroadenomas

- Excessive GH production, visual defects, CNS defects

Treatment: Transphenoidal surgery, radiation

SOMATOSTATIN

- It is released from hypothalamus.
- Inhibits GH release from pituitary.
- 14 aa peptide (**Somatosatin-14**)



SOMATOSTATIN ANALOGUES

- Somatostatin → short duration of action ($t_{1/2}$: 1-3 minute)

- A series of longer-acting somatostatin analogs that retain biologic activity have been developed.

Octreotide

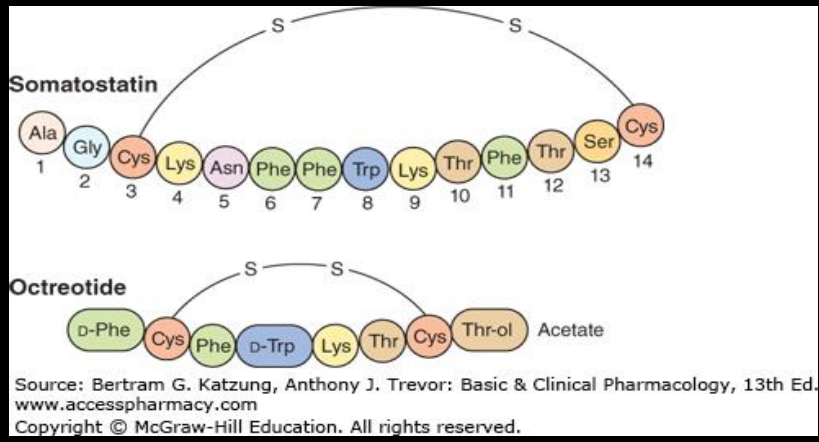
$t_{1/2}$: 80 minute
45 times more potent than somatostatin in inhibiting GH release
50–200 mcg given subcutaneously every 8 hours
Indications:

- acromegaly,
- carcinoid syndrome, gastrinoma, glucagonoma,
- insulinoma, VIPoma, and ACTH secreting tumor

Octreotide acetate injectable long-acting suspension

- a slow-release microsphere formulation
- IM, 4-week intervals in doses of 10–40

Lanreotide
long acting somatostatin analog
Treatment of acromegaly

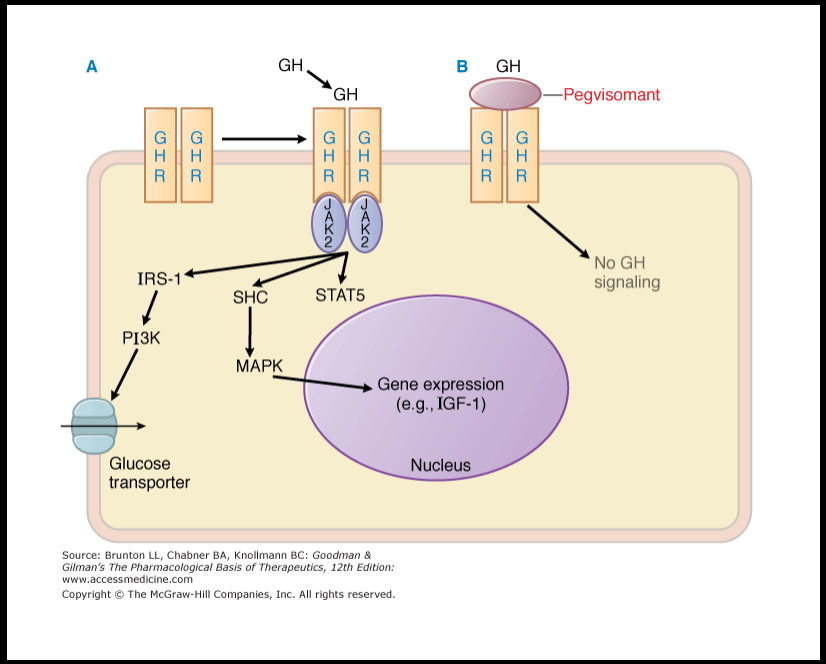


Advers Effects

- abdominal cramps, flatulence,
- Steatorrhea
- Biliary sludge and gallstones:
  - after 6 months of use in 20–30% of patients
  - the yearly incidence of symptomatic gallstones is about 1%.
- sinus bradycardia (25%)

Pegvisomant

- GH receptor antagonist
- Indication:acromegaly with an inadequate response to surgery, radiotherapy and somatostatin analogues
- polyethylene glycol (PEG) derivative of a mutant GH



SUMMARY

Growth hormone (GH, somatropin)

- Somatropin (recombinant GH) is used to treat short stature due to:
  - GH deficiency;
  - Turner's syndrome;
  - Prader–Willi syndrome;
  - chronic renal impairment;
  - children who were born small for gestational age.
- Somatropin is also used for adults with severe symptomatic GH deficiency.
- GH secretion is controlled physiologically by:
  - somatorelin (stimulates GH secretion);
  - somatostatin (inhibits GH secretion).
- Somatostatin is secreted by D cells in the islets of Langerhans, as well as centrally, and inhibits the secretion of many gut hormones in addition to GH.
- Octreotide is a somatostatin analogue used:
  - in acromegalics with persistent raised GH despite surgery/radiotherapy;
  - in functional neuroendocrine tumours (e.g. carcinoid, VIPomas, glucagonomas);
  - to reduce portal pressure in variceal bleeding (unlicensed indication).
- Pegvisomant is a specific GH receptor antagonist: it is used for acromegaly when conventional treatment has failed.

Gonadotropins

- Luteinizing hormone (lutropin, LH) - 115 aa
- Follicle stimulating hormone (follitropin, FSH)- 115 aa
- The human anterior pituitary gland secretes follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
- Chorionic gonadotropin (choriogonadotropin, CG)- 145 aa
  - Placental, same receptor as LH but longer half-life

Mechanism of action: Specific G protein-coupled receptors, activation of adenylate cyclase

Gonadotropins: Actions

In the female:

- FSH→stimulates development of ovarian follicles
- LH → stimulates production of estrogen and progesterone, induces ovulation

In the male:

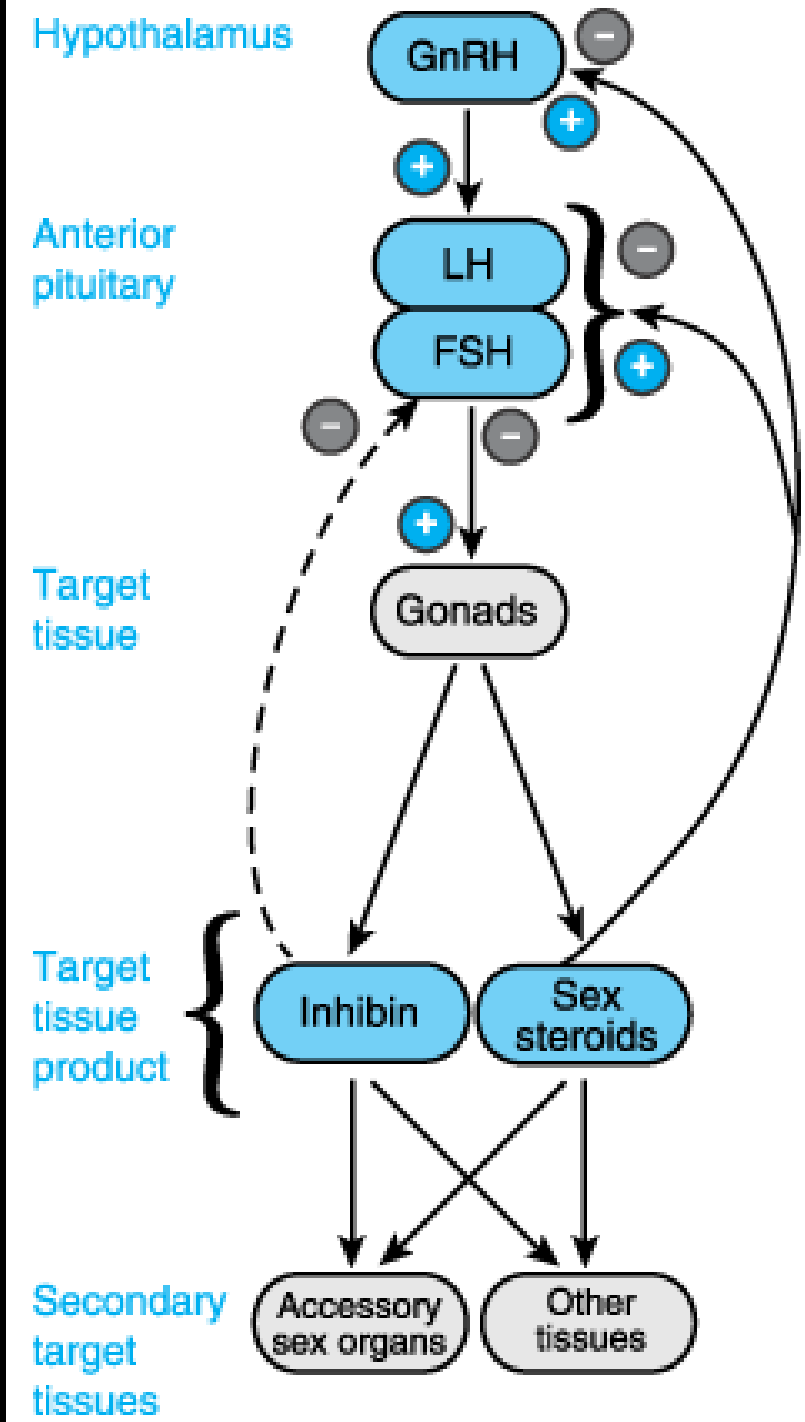
- FSH →stimulates production of androgen-binding globulin
  - •maintains high testosterone levels in the seminiferous tubules required for spermatogenesis
- LH → stimulates production of testosterone

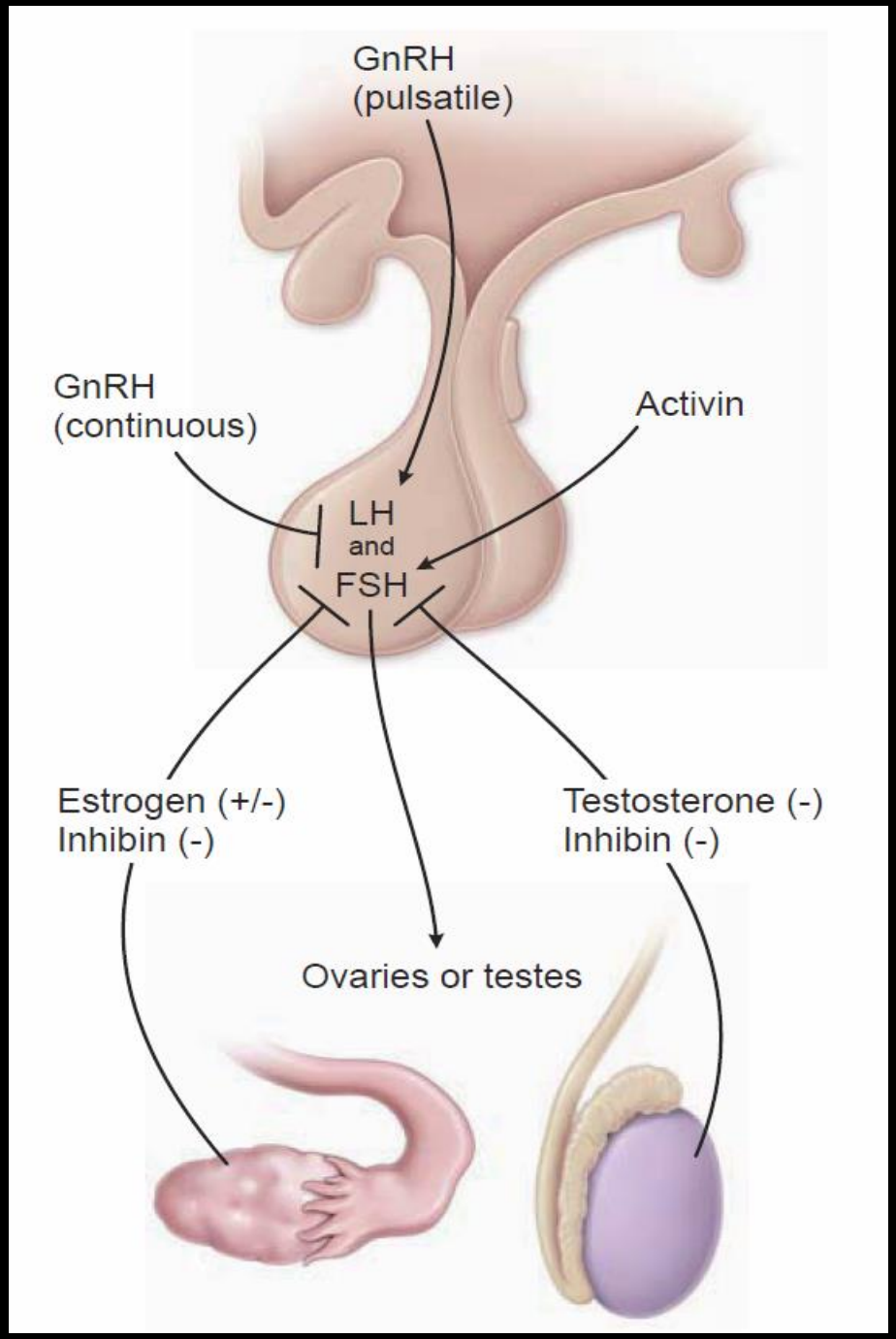
Human Chorionic gonadotropin (hCG)

- produced by the placenta in pregnant women

Functions

- promotes the maintenance of the pregnancy
- Secretes estrogen and progesterone from placenta


Hypothalamus
GnRH
Anterior pituitary
LH
FSH
Target tissue
Gonads
Target tissue product
Inhibin
Sex steroids
Secondary target tissues
Accessory sex organs
Other tissues


GnRH (pulsatile)
GnRH (continuous)
Activin
LH and FSH
Estrogen (+/-)
Inhibin (-)
Testosterone (-)
Inhibin (-)
Ovaries or testes

Gonadotropins used clinically

- Administration: generally daily, (SC or IM)
- t1/2: 10-40 hours

Equivalent LH and FSH activity (FSH + LH):

- Human menopausal gonadotropin (hMG; menotropin)
  - extracted from the urine of postmenopausal women
  - FSH (75 Ü) + LH (75 Ü) (İM)

FSH

- Ürofolitrofin:
  - Menotropin with LH component removed
  - 75 Ü FSH/ampül (SC)
- Recombinant human FSH (rFSH): follitropin alfa and follitropin beta (differ from each other in the composition of carbohydrate side chains)

LH

- Human chorionic gonadotropin (hCG)
  - extracted from the urine of pregnant women; 500, 1000, 1500, 5000 Ü (İM)
- Choriogonadotropin alfa (rhCG): a recombinant form of hCG
- Rekombinant human LH (rLH): Lutropin

Gonadotropin Releasing Hormone (GnRH)

Chemistry: single chain 10 amino acid peptide

Pyro-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly

Hormone preparations used clinically:

Synthetic GnRH (gonadorelin hydrochloride)

Used for pulsatile administration

Long-acting synthetic agonists

Leuprolide acetate

Nafarelin acetate

Histrelin acetate

Goserelin acetate

Table 42.1: GnRH analogues

Drug	Use and additional comments
Goserelin	Used to treat endometriosis, prostate cancer and advanced breast cancer
Leuprorelin	Used to treat endometriosis and prostate cancer
Buserelin	Used to treat endometriosis. Prostate cancer. Induction of ovulation prior to IVF

GnRH: Adverse effects

Long acting agonists induce symptoms of hypogonadism, including detrimental effects on bone mineralization and lipids

GnRH Receptor Antagonists

Abareliks (USA)

Ganireliks, Setroreliks

- SC, IM
- Abareliks: approved for men with advanced prostate cancer.
- Ganireliks ve Setroreliks :approved for use in controlled ovarian stimulation procedures

Adverse effects

Nausea and headache

Hypotension and syncope

Prolonged the QT interval

Signs and symptoms of androgen deprivation

SUMMARY

Gonadotrophins and GnRH analogues

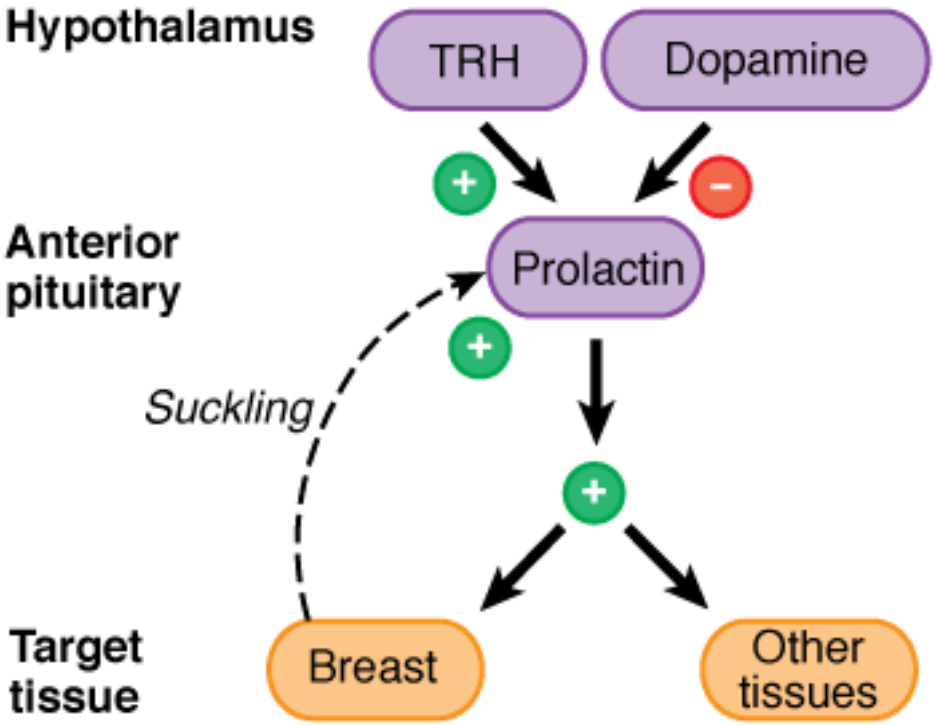
- FSH and LH are secreted in pulses and stimulate gonadal steroid synthesis.
- GnRH analogues initially stimulate, but then downregulate the release of FSH and LH.
- GnRH analogues (e.g. goserelin, buserelin) are used in the treatment of :
  - endometriosis;
  - female infertility;
  - prostate cancer;
  - advanced breast cancer.
- Side-effects of GnRH analogues include:
  - menopausal symptoms;
  - reduced bone density (by reducing oestrogen secretion).

PROLACTIN

- 198-amino-acid peptide hormone produced in the anterior pituitary
- Prolactin like hormone in pregnant women: Human placental laktogen (**human chorionic somatomammotropin (HCS)**

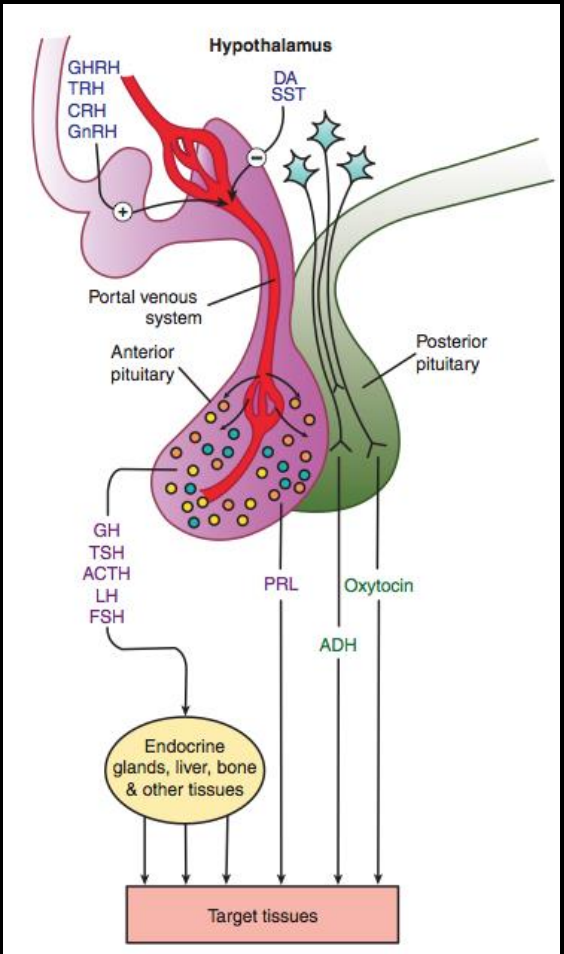
Functions:

- Plasma levels increase during pregnancy, breastfeeding and reach maximum after pregnancy.
- Principal hormone responsible for lactation: Stimulates milk production, induces enzymes which are related to synthesis of lactose.
- In Hyperprolactinemia;
  - Inhibition of GnRH release and then FSH and LH synthesis.
    - In women: contraceptive effect and galactorrhea
    - In man:decrease libido, impotence, infertility



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

POSTERIOR PITUITARY HORMONES



The two posterior pituitary hormones—vasopressin and oxytocin— are synthesized in neuronal cell bodies in the hypo- thalamus and transported via their axons to the posterior pituitary, where they are stored and then released into the circulation. Each has limited but important clinical uses.

OXYTOCIN

Functions

- Participates in labor and delivery
- Elicits milk ejection in lactating women.
- During the second half of pregnancy, uterine smooth muscle shows an increase in the expression of oxytocin receptors and becomes increasingly sensitive to the stimulant action of endogenous oxytocin.
- Pharmacologic concentrations of oxytocin powerfully stimulate uterine contraction.

Absorption, Metabolism, Excretion

- i.v. for initiation and augmentation of labor.
- i.m. for control of postpartum bleeding.

- Not bound to plasma proteins
- Eliminated by the kidneys and liver
- T ½ = 5 min.

OXYTOCIN ANTAGONIST

Atosiban

- For treatment of preterm labor (tocolysis).

- Administered by i.v. infusion for 2–48 hours.

VASOPRESSIN (ANTIDIURETIC HORMONE, ADH)

- Released in response to rising plasma tonicity or falling blood pressure.
- Antidiuretic and vasopressor properties.
- Deficiency → diabetes insipidus (DI)
- Desmopressin acetate is a long-acting synthetic analog of vasopressin

Absorption, Metabolism, Excretion

Vasopressin

- i.v. or i.m.
- T ½ = 15 min.
- Renal and hepatic metabolism.

Desmopressin

- i.v., s.c., intranasal, oral.
- T ½ = 1.5 - 2.5 hours.

VASOPRESSIN RECEPTOR AGONISTS

• Desmopressin	Relatively selective vasopressin V_2 receptor agonist	Acts in the kidney collecting duct cells to decrease the excretion of water • acts on extrarenal V_2 receptors to increase factor VIII and von Willebrand factor	Pituitary diabetes insipidus • pediatric primary nocturnal enuresis • hemophilia A and von Willebrand disease	Oral, IV, SC, or intranasal • *Toxicity:* Gastrointestinal disturbances, headache, hyponatremia, allergic reactions

• *Vasopressin: Available for treatment of diabetes insipidus and sometimes used to control bleeding from esophageal varices*

Toxicity & Contraindications

- Rarely: Headache, nausea, abdominal cramps, agitation, allergic reactions.
- Overdosage can result in hyponatremia and seizures.
- Vasopressin (but not desmopressin) can cause vasoconstriction and should be used cautiously in patients with coronary artery disease.
- Nasal desmopressin may be less effective when nasal congestion is present.

VASOPRESSIN RECEPTOR ANTAGONIST

• Conivaptan	Antagonist of vasopressin V_{1a} and V_2 receptors	Reduced renal excretion of water in conditions associated with increased vasopressin	Hyponatremia in - hospitalized patients	IV infusion • *Toxicity:* Infusion site reactions

• *Tolvaptan: Similar but more selective for vasopressin V_2 receptors; oral administration; treatment course limited to 30 days due to risk of hepatotoxicity*

Thank you for your attention