In the name of GOD

Hypothalamus pituitary Hormones

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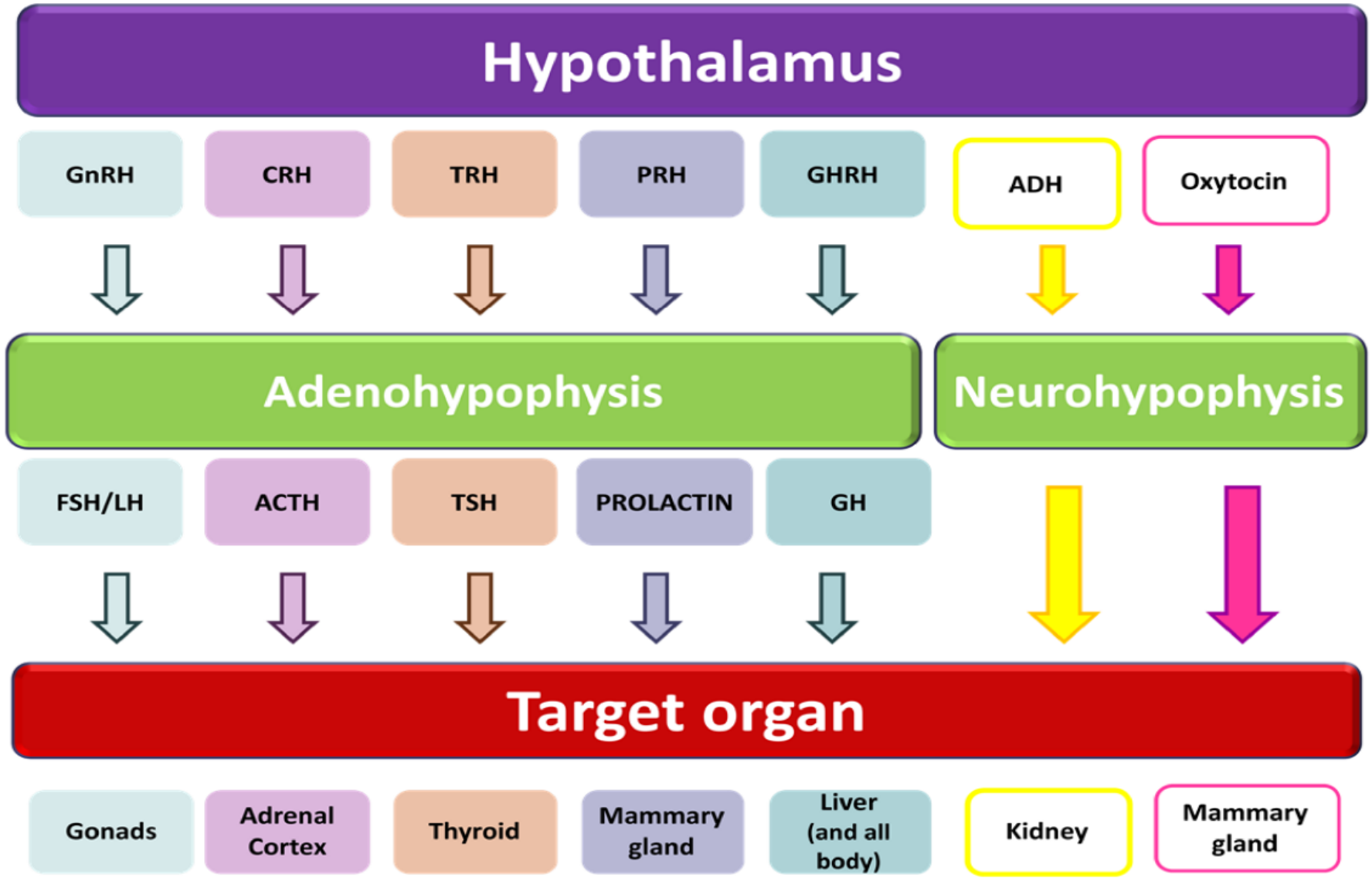
Hypothalamus pituitary regulatory Hormones

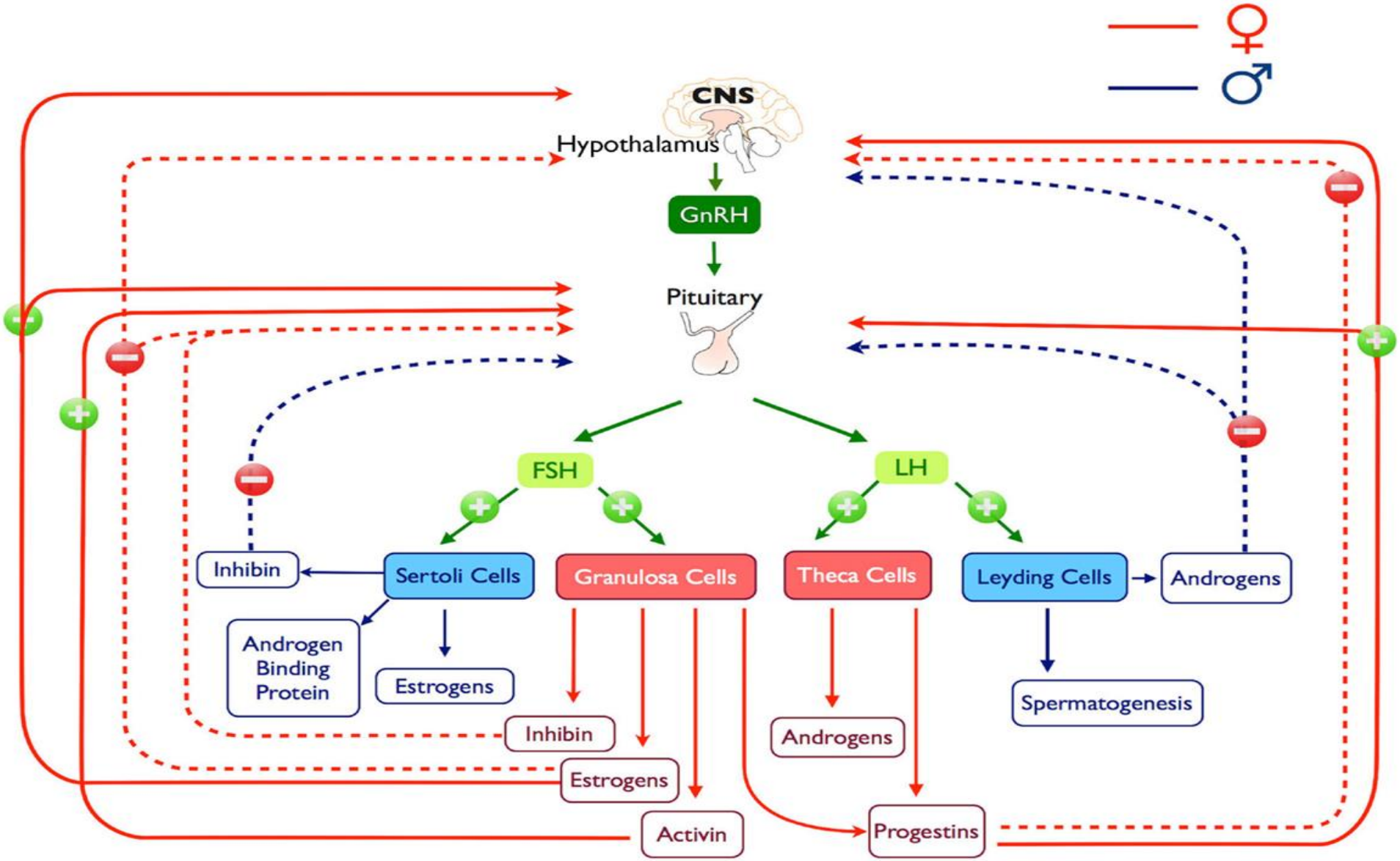
Hypothalamo pituitary regulatory target organ axes



Hypothalamic-pituitary axis

- GnRH - gonadotrophin releasing hormone;
- CRH - Corticotrophin releasing hormone;
- TRH - Tirotrophin releasing hormone;
- PRH – Prolactin releasing hormone;
- GHRH - Growth hormone releasing hormone

GnRH - Gonadotrophin Releasing Hormone



GnRH - Gonadotrophin Releasing Hormone

- **Synthetic:** ***Gonadorelin***
- **Analogues** including *Buserelin, Deslorelin, Goserelin, Histrelin, Leuprorelin, Nafarelin, & Triptorelin*
- **Antagonists** *Abarelix, Cetrorelix, & Ganirelix*

GnRH Synthetic *Gonadorelin / Lutrepulse*

- Half life 10-40 **min**

GnRH - Gonadotrophin Releasing Hormone

GnRH Analog	Amino Acid Position (C to N terminal) 1 pGlu	2 His	3 Trp	4 Ser	5 Tyr	6 Gly	7 Leu	8 Arg	9 Pro	10 Lys-NH_2
Agonists (inhibition of gonadotropin hormone levels due to feedback inhibition of high levels of LH and FSH when maintained at constant GnRH levels)										
Lupron	–	–					-	–	NEt	X
Zoladex	–	–					-	–	–	AzGly
Supprelin	–	–	–	–	–	(D)His-Bzl	–	–	–	–
Synarel	–	–	–	–	–	(D)Nal	–	–	–	–
Tryptorelin	–	–	–	–	–	(D)Trp	–	–	–	–
Buserelin	–	–	–	–	–	(D)Ser tBu	–	–	NEt	X
Antagonist (inhibition of LH/FSH surges when given every 24 hr as a bolus dose)										
Cetrotide	Ac-(D)Nal	(D)Cpa	(D)Pal	–	–	(D) Cit	–	–	–	(D)Ala
Antagon	Ac-(D)Nal	(D)Cpa	(D)Pal	–	–	(D)hArg-$(Et)_2$	–	(D)hArg-$(Et)_2$	–	(D)Ala
Ganirelix	Ac-(D)Nal	(D)Cpa	(D)Pal	–	–	(D)hArg-$(Et)_2$	–	(D)hArg-$(Et)_2$	–	(D)Ala
Firmagon	Ac-(D)Nal	(D)Cpa	(D)Pal	–	Aph (Hor)	(D)Aph-(Cba)	–	Lys (iPr)	–	(D)Ala

Glp–His–Trp–Ser–Tyr–**Gly**–Leu–Arg–Pro–**Gly**–NH_2

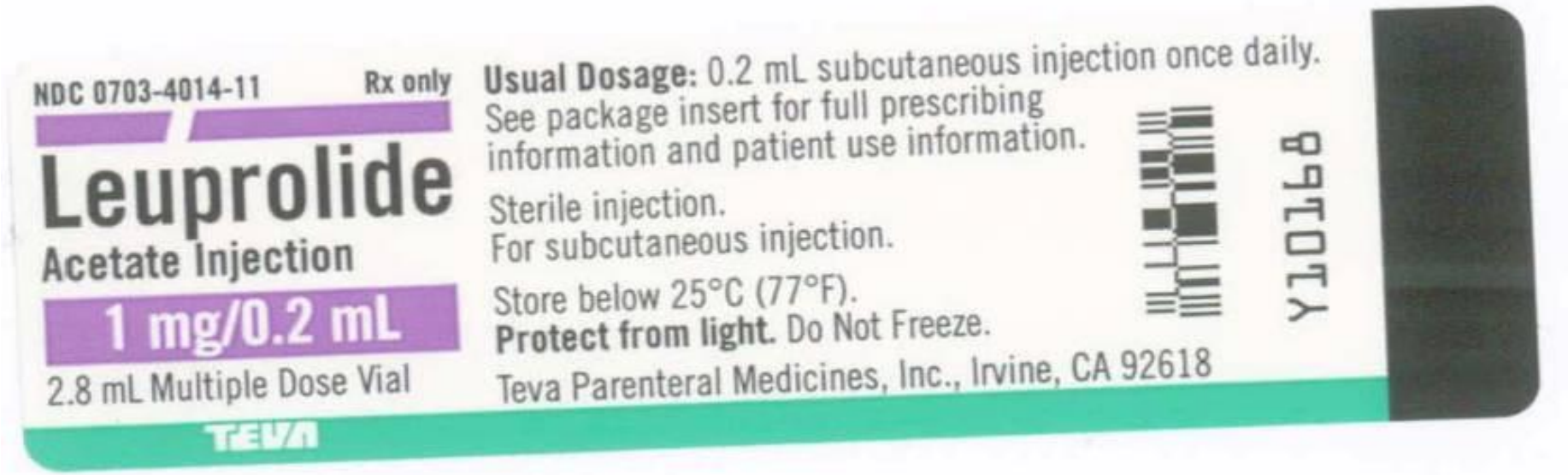
luteinizing hormone-releasing factor (LH-RH)
(gonadorelin)

GnRH –Agonist *Goserelin /Zoladex*

GnRH –Agonist *Goserelin /Zoladex*

- **Palliative treatment of advanced carcinoma of the prostate**
- *Zoladex should be administered* as a **subcutaneous implant** at the anterior abdominal wall below the navel line.
- Continuous release biodegradable 1.5 mm diameter cylinder implant containing either 3.6 or 10.8 mg goserelin acetate.
- Goserelin acetate is useful for *in vitro fertilization and is possibly effective in controlling* precocious puberty and early puberty.

GnRH –Agonist *Leuprolide / Lupron*



GnRH –Agonist *Leuprolide / Lupron*

- Palliative treatment of **advanced prostate cancer** *Lupron (leuprolide acetate)* **SC** ***Injection*** *3.75 mg and Lupron Depot (7.5, 22.5, 30, and* 45 mg)
- **management of endometriosis** *Lupron Depot (3.75 mg and 11.25 mg)*
- *Lupron Depot-PED (7.5, 11.25, 15, 30 mg) is indicated* in the treatment of children with **central precocious puberty**.

GnRH –Agonist *Triptorelin / Trelstar / Diphereline?*

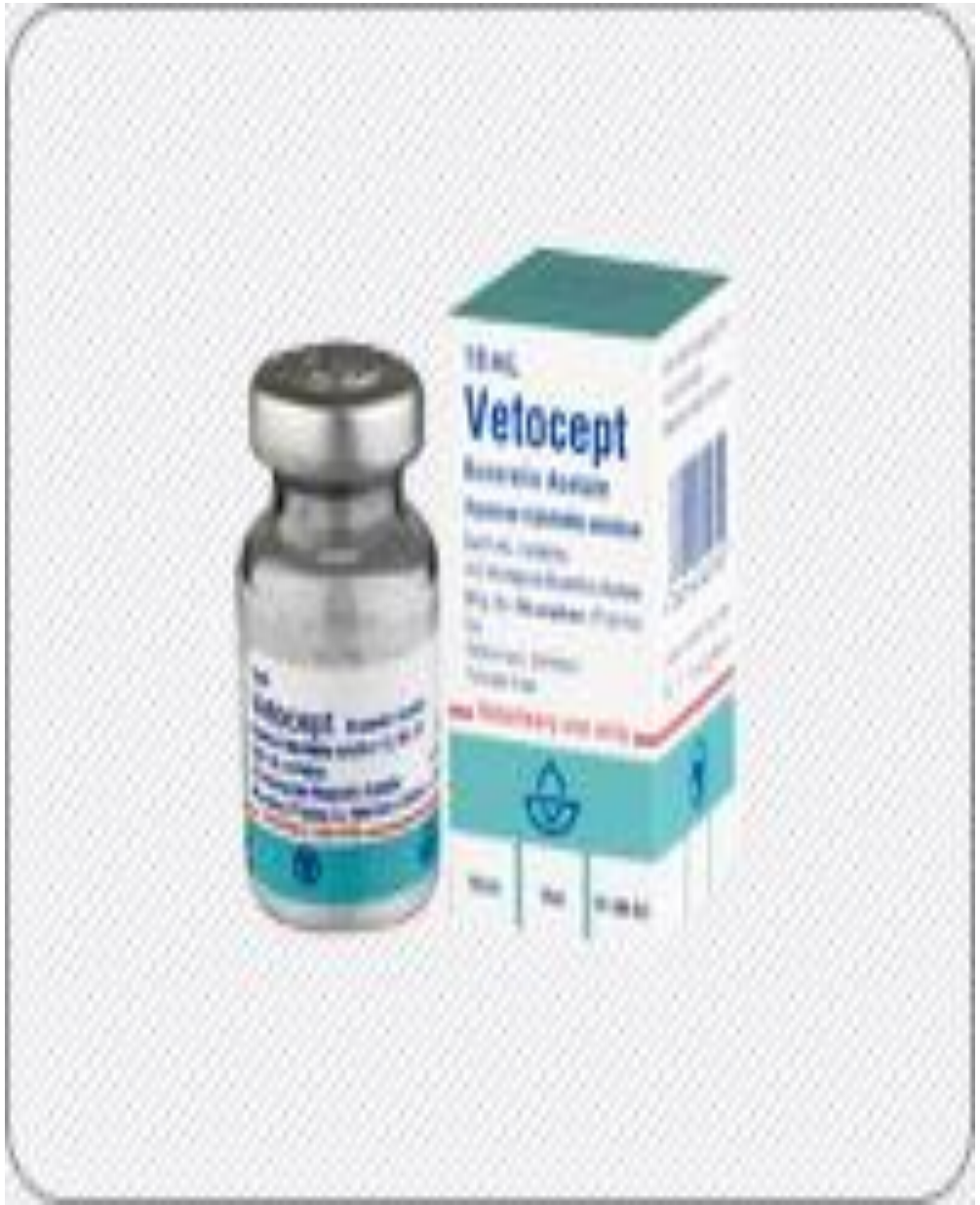
GnRH –Agonist *Triptorelin / Trelstar / Diphereline?*

- Palliative treatment of **advanced prostate cancer**
- It is available at 3.75, 11.25, and 22.5 mg **intramuscular** injection
- The recommended dose is 3.75 mg every 4 weeks, 11.25 mg every 12 weeks, or 22.5 mg every 24 weeks.
- The evidence favors efficacy for use of triptorelin pamoate to treat **CPP** (50 microg/Kg) , **endometrial hyperplasia** (0.1 mg/day) , **endometriosis** (3.75 every 4 weeks) , fibrocystic breast changes, *in vitro fertilization, and uterine leiomyoma.*

GnRH –Agonist *Nafarelin / Synarel*

- Management of **endometriosis** 400 µg/day
- Treatment of **central precocious puberty** 1600 µg/day
- 8 mL *Synarel* ***Nasal*** *Solution 2 mg/mL (*one spray is equal to 200 µg).

GnRH –Agonist *Busereline/ Supprelin*



GnRH –Agonist *Busereline/ Supprelin*

- In advanced **prostatic carcinoma** doses of 500 micrograms are injected ***subcutaneously*** every 8 hours for 7 days. On the eighth day treatment is changed to the ***nasal*** route; 100 micrograms is sprayed into each nostril 6 times daily
- In **endometriosis** a dose of 150 micrograms is sprayed into each nostril three times daily. The usual duration of therapy is 6 months, which should not be exceeded.
- In **infertility**, pituitary desensitisation before ovulation induction → Therapy should be continued until pituitary downregulation occurs, which normally takes 1 to 3 weeks. 150 micrograms intranasally four times daily, beginning either in the early follicular phase (day 1) or midluteal phase (day 21) of the menstrual cycle. Alternatively, 200 to 500 micrograms may be given daily as a subcutaneous injection.

GnRH –Antagonist Cetrorelix/Cetrotide

GnRH –Antagonist Cetrorelix/Cetrotide

- Cetrorelix is given by subcutaneous injection as the acetate
- The half-life after a subcutaneous injection of 3 mg is about 60 hours
- Controls the release of LH and FSH in a dose-dependent manner
- Prevent LH surges and premature ovulation (infertility) 250 micrograms daily on day 5, and continued until ovulation induction.
- It has also been tried in benign prostatic hyperplasia, malignant neoplasms of the prostate, endometriosis, and for uterine fibroids.

GnRH –Antagonist *Ganirelix*

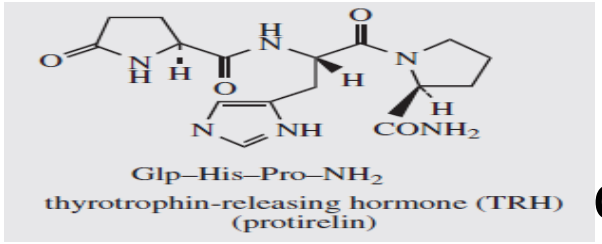
- **It is used as a component of ovarian stimulation regimens for assisted reproduction in infertility**
- 250 micrograms is given once daily, starting on day 6 of ovarian stimulation and continued until ovulation induction.

CRH - Corticotrophin releasing hormone

- **41 amino acids**: Ser–Gln–Glu–Pro–Pro–Ile–Ser–Leu–Asp–Leu–Thr–Phe–His–Leu–Leu–Arg–Glu–Val–Leu–Glu–Met–Thr–Lys–Ala–Asp–Gln–Leu–Ala–Gln–Gln–Ala–His–Ser–Asn–Arg–Lys–Leu–Leu–Asp–Ile–Ala–NH2
- with only the **C-terminal blocked** as an **amide**.
- it acts via the cAMP second messenger system
- **Corticorelin** ➔ A single dose of 100 micrograms, or of 1 microgram/kg, is given by intravenous injection over 30 seconds ➔ differential diagnosis of **Cushing's syndrome**

TRH - Tirotrophin releasing hormone

- TRH is a tripeptide with an N-terminal pyroglutamyl residue and a C-terminal prolineamide



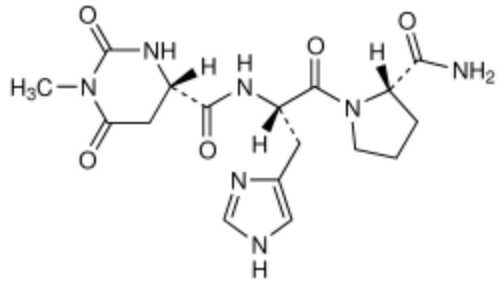
- Acts directly on the anterior pituitary t of thyroid-stimulating hormone (TSH), prolactin, and growth hormone (GH).
- Synthetic material (known as Protirelin**) is used to assess thyroid function and TSH reserves.**

TRH - Protirelin

- The **diagnosis** of mild hyperthyroidism or hypothyroidism is given **intravenously**, usually in doses of 200 to 400 micrograms
- **Intranasal** protirelin has been tried for stimulation of **lactation**, and in any case mechanical stimulation is preferable to drug treatment
- **Neonatal respiratory distress syndrome?**

TRH - Taltirelin

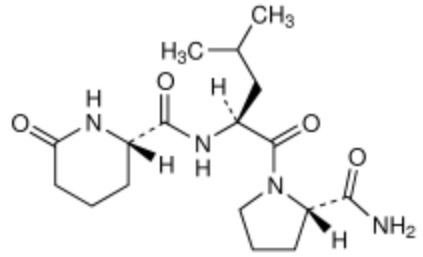
- **Taltirelin** is claimed to have Beneficial effects on CNS function.
- **Taltirelin** is used in the treatment of spinocerebellar degeneration.



Chemical Structure of Taltirelin

TRH - Posatirelin

- It is claimed to have beneficial effects on CNS function, and has been investigated in the **management of dementia** of various causes.



Chemical Structure of Posatirelin

PRH – Prolactin releasing hormone

- Dopamine is an inhibitor of prolactin secretion
- Dopamine works by stimulating the pituitary lactotroph D2 receptor to inhibit adenylate cyclase and consequently inhibits both prolactin synthesis and secretion.
- Several neuropeptides, including TRH, have prolactin-releasing properties, but there is little evidence for a physiologic role

GHRH - Growth hormone releasing hormone

- Synthesized as a **108 aa precursor** and the **active GHRH contains 44 aa** residues (**Somatorelin**).
- the 44-amino acid form may possibly be converted to the smaller forms (40-, and 37-aa) but all are reported to be active, the activity residing in the **first 29 amino-acid residues**.
- Regulates receptor-mediated **pulsatile release** of growth hormone

GHRH - Growth hormone releasing hormone

- GHRH was originally used **as a diagnostic test** to determine whether GH deficiency in children was a pituitary (GH release) or hypothalamic (GHRH) defect.
- Those children **deficient in GHRH** at the hypothalamic level can benefit from GHRH treatment.
- Due to the discovery that GHRH has a great effect on fat redistribution; **lipolytic effect**; (fat reduction)
- The **lack** of or **lower effects** on **glycemic indices V.S. the GH**

GHRH- **Somatorelin; Sermorelin**

GHRH- Somatorelin; Sermorelin

- **Sermorelin** is a synthetic peptide corresponding to the 1–29 amino acid sequence of **somatorelin**.
- Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2 acetate hydrate
- Synonyms: GRF(1-29)NH_2 (sermorelin); Growth Hormone-releasing Factor (Human)-(1-29)-peptide Amide (sermorelin);

GHRH- Sermorelin

- the **diagnosis** of growth hormone deficiency. The usual dose is the equivalent of sermorelin **1 microgram/kg** by **intravenous injection** in the morning after an overnight fast.
- the treatment of growth hormone deficiency in children; doses equivalent to **30 micrograms/kg**, as the acetate, may be given once daily at bedtime by subcutaneous injection
- Sermorelin has also been tried as an adjunct to gonadotrophin therapy in the induction of ovulation
- sermorelin **1 mg twice daily subcutaneously** for 12 weeks in patients with **HIV-related lipodystrophy**

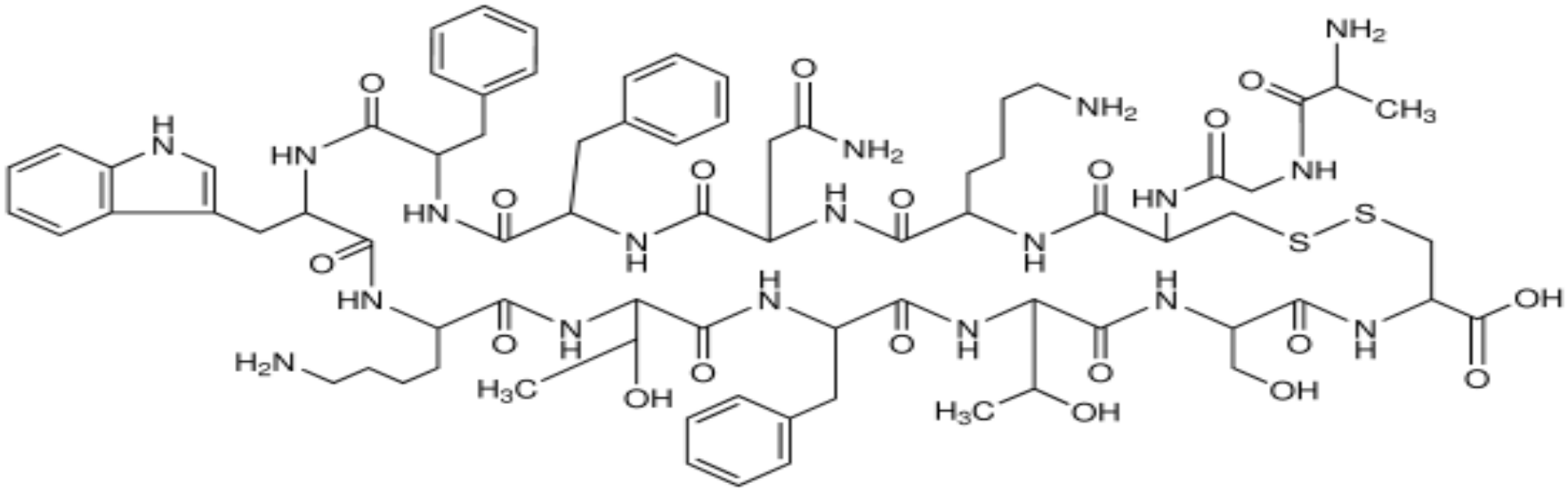
GHRH analog- *Egrifta (tesamorelin)*

GHRH analog- *Egrifta (tesamorelin)*

- **Synthetic GHRH** that is composed of 29 N-terminal aa residues of endogenous 44 aa GHRH.
- half-life of approximately 26–38 minutes.
- *Egrifta is believed to cause* pituitary somatotroph cells to synthesize and **pulsatile** release endogenous GH, which is both **anabolic** and **lipolytic**, and thus reduces lipodystrophy in HIV patients

Growth-hormone-release-inhibiting Hormone

- GH-RIF; GHRIH; **Somatostatin**



- G protein-coupled mechanisms that involve **c-AMP**

Growth-hormone-release-inhibiting Hormone

- GH-RIF; GHRIH; **Somatostatin**
- It is synthesized as a **92-aa precursor** and proteolytically cleaved into two active forms, SST-14 aa in hypothalamus and SST-28 aa in other tissues.
- Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys **cyclic** (3→14) **disulphide (**cyclic tetradecapeptide)
- Intra-disulfide bridge exposes the active biding epitope, **Phe-Trp-Lys-Thr**.
- G protein-coupled mechanisms that involve **c-AMP**

Growth-hormone-release-inhibiting Hormone

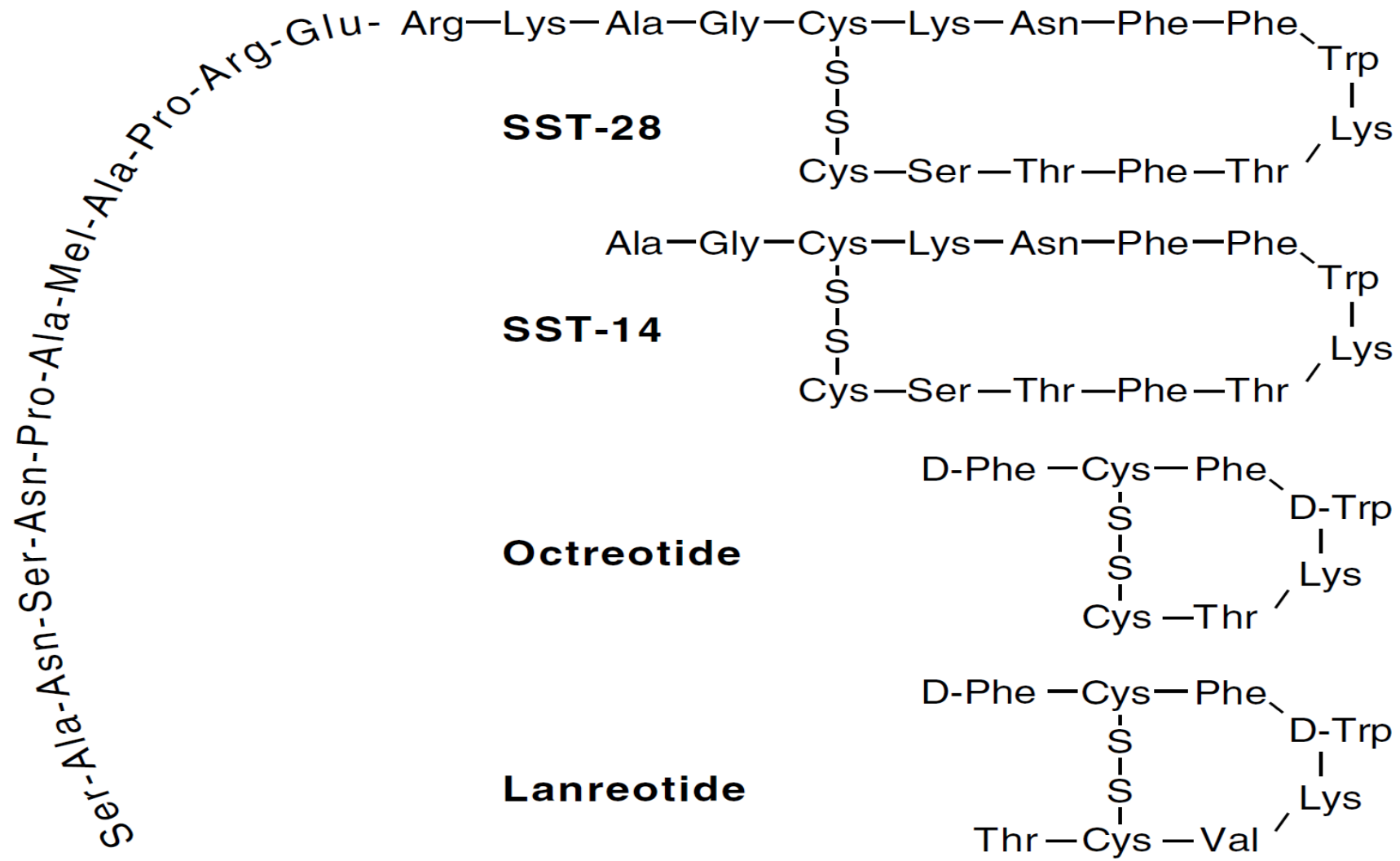
- GH-RIF; GHRIH; **Somatostatin**
- Somatostatin inhibits the release of
  - **Growth Hormone**
  - **Thyrotrophin**
  - **Corticotropin**
  - **Glucagon & Insulin**
- appears to have a role in the **regulation of duodenal and gastric secretions**.
- appears to play a role in the perception of **pain in CNS**.

GH-RIF; GHRIH; Somatostatin

GH-RIF; GHRIH; Somatostatin

- IV , or slow bolus Injection (**250 mcg and 3 mg**) can be used to provide relieve in the following condition:
  - Severe acute haemorrhage from oesophageal varices.
  - Severe acute haemorrhage from gastric or duodenal ulcers.
  - Adjuvant treatment in pancreatic, biliary and intestinal fistulae.
  - Prophylaxis and treatment of postoperative complications following pancreatic surgery.
  - Adjuvant treatment in diabetic ketoacidosis.
  - Treatment of acute pancreatitis.

GHRIH- analogues: Octreotide; Lanreotide



GHRIH- analogues: Octreotide; Lanreotide

- SST also blocks secretion of other **hormones** and **cytokines** in a number of tissues and cells
- Is used to treat cancer patients with **metastatic carcinoid** tumors to inhibit the severe diarrhea and flushing symptoms
- to treat cancer patients with **vasoactive intestinal peptide (VIP) tumors** that elicit profuse watery diarrhea associated with **intestinal tumors**

Lanreotide Acetate

Lanreotide Acetate

- ***Somatuline Depot***
- Synthetic cyclical octapeptide analog of the natural hormone, somatostatin. Its Mw is 1.09 kDa.
- It is used to reduce **growth hormone** (GH) and **insulin growth factor 1** (IGF-1) levels to normal.
- For the long-term treatment of **acromegalic** patients who have had an inadequate response to surgery and/or radiotherapy
- deep subcutaneous (SC) injection
- It is available at 60, 90, and 120 mg strengths

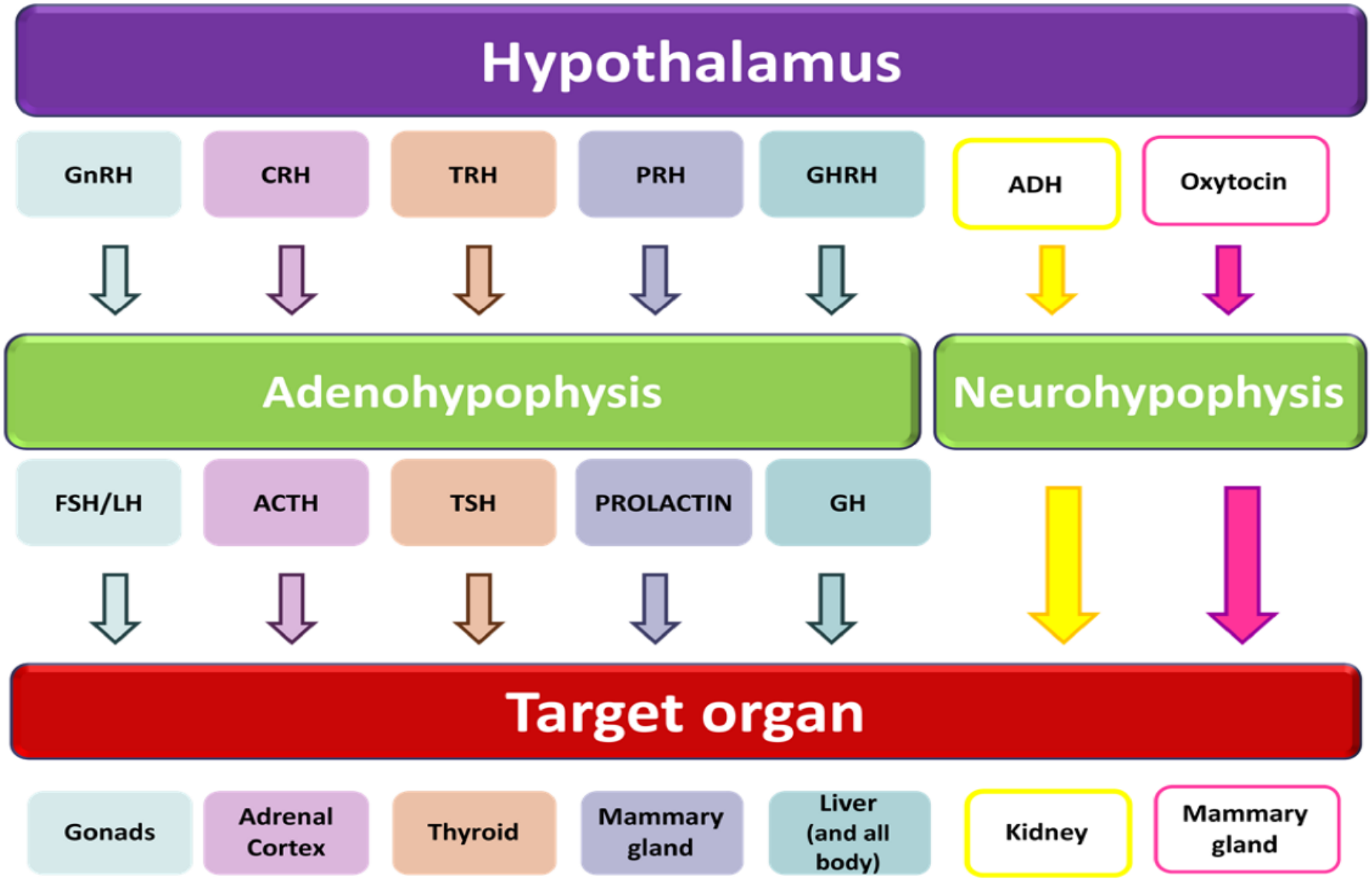
Octreotide Acetate

- ***Sandostatin, Sandostatin LAR Depot***

Octreotide Acetate

- ***Sandostatin, Sandostatin LAR Depot***
- **Octreotide acetate** is a long acting cyclic octapeptide (Mw 1 kDa)
- Reduction of blood levels of **growth hormone** and **insulin-like growth factor 1** (IGF-I) in **acromegaly** patients, symptomatic treatment of **metastatic carcinoid** tumors, and treatment of profuse water diarrhea associated with **intestinal tumors**
- 1 mL ampules / 50, 100, or 500 µg, and
- 5 mL multidose vials / 200 and 1,000 µg/mL.

Hypothalamo pituitary regulatory target organ axes



Hormones produced by the pituitary gland and their functions

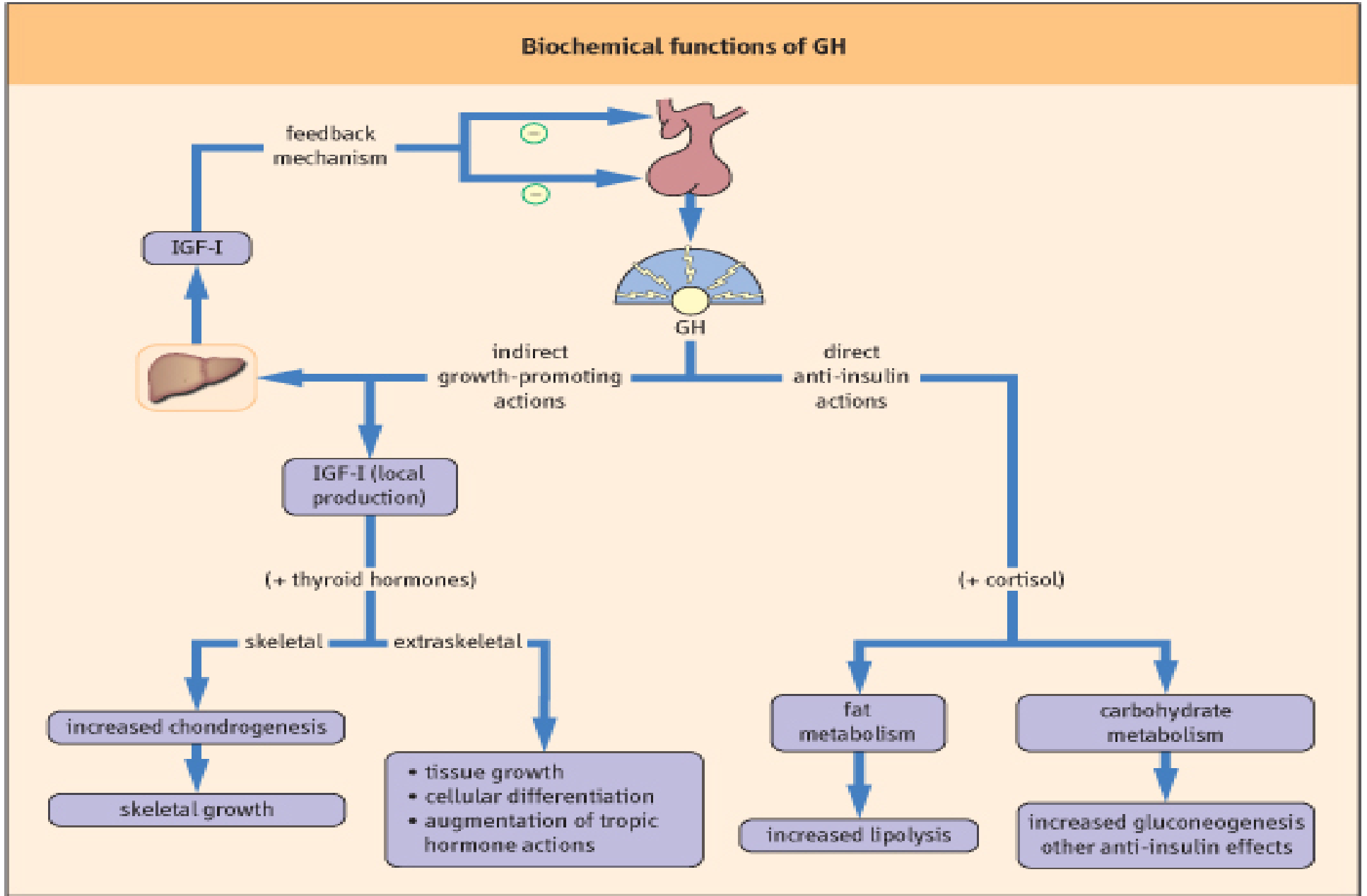
Endocrine gland	Hormone	Function	Secretion control is made by
Pituitary – Anterior	GH	Stimulates liver to produce growth factors that stimulate bone and cartilage growth	GHRH (Hypothalamus)
	Prolactin	Stimulates mammary gland growth and milk production	---------
	ACTH	Stimulates adrenal cortex to produce hormones (glucocorticoids and mineralocorticoids)	CRH (Hypothalamus)
	FSH	♀- Stimulates development of follicles ♂- Stimulates the production of sperm in the seminiferous tubules of the testes	GnRH (Hypothalamus)
	LH	Stimulates development of ovaries	Oestrogen secreted by Graafian follicles
	ICSH	Stimulates testosterone production by the interstitial cells of the testes	GnRH (Hypothalamus)
	TSH	Stimulates thyroid gland to produce hormones (T3, T4, calcitonin)	TRH (Hypothalamus)
	MSH	Promotes distribution of melanin granules	---------
Pituitary – Posterior	ADH	Stimulates retention of water, increasing its permeability at distal convoluted tubules and collecting ducts of the nephrons	Status of the extracelular fluid and bood plasma
	Oxytocin	Stimulates uterine contractions during parturition and promotes milk ejection reflex in the mammary glands	Suckling by the neonate initiates a reflex arc

Clinical conditions associated with pituitary hormone disorders.

Pituitary hormone disorders		
Hormone	**Deficiency**	**Excess**
TSH	hypothyroidism	thyrotoxicosis
ACTH	hypoadrenalism	Cushing's disease
FSH/LH	hypogonadism	precocious puberty
GH	short stature	gigantism/acromegaly
prolactin	none	galactorrhea/infertility

Hormone	Molecular Weight (Da)	Number of Peptide Chains	Amino Acid Length	Carbohydrate (%)
Somatotropic Hormones				
Growth hormone (GH)	22,000	1	191	0
Prolactin (Prl)	23,000	1	199	0
Placental lactogen (PL)	22,125	1	190	0
Growth hormone releasing hormone (GHRH)	(11,000 precursor) 5,039	1	(108) 44	0
Keratinocyte growth factor (KGF)	16,300	1	140	0
Glycoprotein Hormones[a]				
Luteinizing hormone (LH)	29,400	2	α-92 β-121	23
Follicle-stimulating hormone (FSH)	32,600	2	α-92 β-111	28
Human chorionic gonadotropin (hCG)	38,600	2	α-92 β-145	33
Thyroid-stimulating hormone (TSH)	28,000	2	α-92 β-112	22
Pro-opiomelanocortin (POMC)-Derived Hormones				
Corticotropin (ACTH)	4,500	1	39	0
α-Melanocyte-stimulating Hormone	1,650	1	13	0
β-Melanocyte-stimulating hormone (β- MSH)	2,100	1	18	0
ββ-Lipotropin (β-LPH)	9,500	1	91	0
γ-Lipotropin (γ-LPH)	5,800	1	58	0

Growth Hormone



Growth Hormone

- It promotes growth of skeletal, muscular, and other tissues, stimulates protein anabolism, and affects fat and mineral metabolism. The hormone has a diabetogenic action on carbohydrate metabolism.
- Secretion is **pulsatile** and dependent on neural and hormonal influences including a **Somatostatin**, and **Somatorelin**. Sleep, hypoglycaemia, and physical or emotional stress result in increased secretion of growth hormone.
- The effects of growth hormone on skeletal growth are mediated by the somatomedins

GH lipolytic effect

- by interacting with specific receptors on a wide range of target cells, including myocytes, chondrocytes, osteoblasts, hepatocytes, and adipocytes, leading to the targeted lipolytic (fat reduction) effects.

GH glycemic effects

- Weekly dosing of hGH (~ 3-hour half-life) that produces sufficient GH levels that could interfere with glycemic control.
- Lower glycemic effects of GHRH are likely due to pulsatile release of GH in response to a daily subcutaneous dose of a GHRH analog that is cleared with a half-life of approximately 26–38 minutes.

Growth Hormone

- 191 aa; 22,000 Da; **polypeptide hormone**
- Initially purified from human cadaver pituitary glands
- First recombinant hGH *E. coli* has an **S-adenosyl methionine** at the N-terminus (**soma-*trem***)
- Without **S-adenosyl methionine** (**soma-*tropin***)
- *Humatrope, Genotropin, Omnitrope, and Tev-Tropin in* ***E. Coli***
- *Valtropin is synthesized in* a strain of ***S. cerevisiae***
- *Saizen, Serostim, and Zorbtive are produced* by a **mammalian cell line**

Growth Hormones (GH)

used for intestinal disorder (short bowel syndrome)

Growth Hormones (GH)

- **Somatropin**
- Genotropin, Humatrope, Norditropin, Nutropin, Serostim, Zorbtive
- SC or IM
- Used for the treatment of Growth failure
- Used for growth hormone deficiency
- Used for intestinal disorder (short bowel syndrome)
- HIV-related weight loss or wasting

Growth Hormones (GH) Somatropin

- ***Humatrope*** *and* ***Saizen*** should be administered by **SC or IM** injection.
- ***Genotropin***, ***Nutropin***, ***Serostim***, ***Tev-Tropin***, ***Omnitrope***, *and* ***Zorbtive*** *should be administered* by **SC** injection.
- ***Norditropin*** *and* ***Valtropin*** are intended for **SC** injection in the thighs after reconstitution.
- ***Nutropin Depot*** *should be administered* by **SC** injection once or twice a month

Growth Hormone

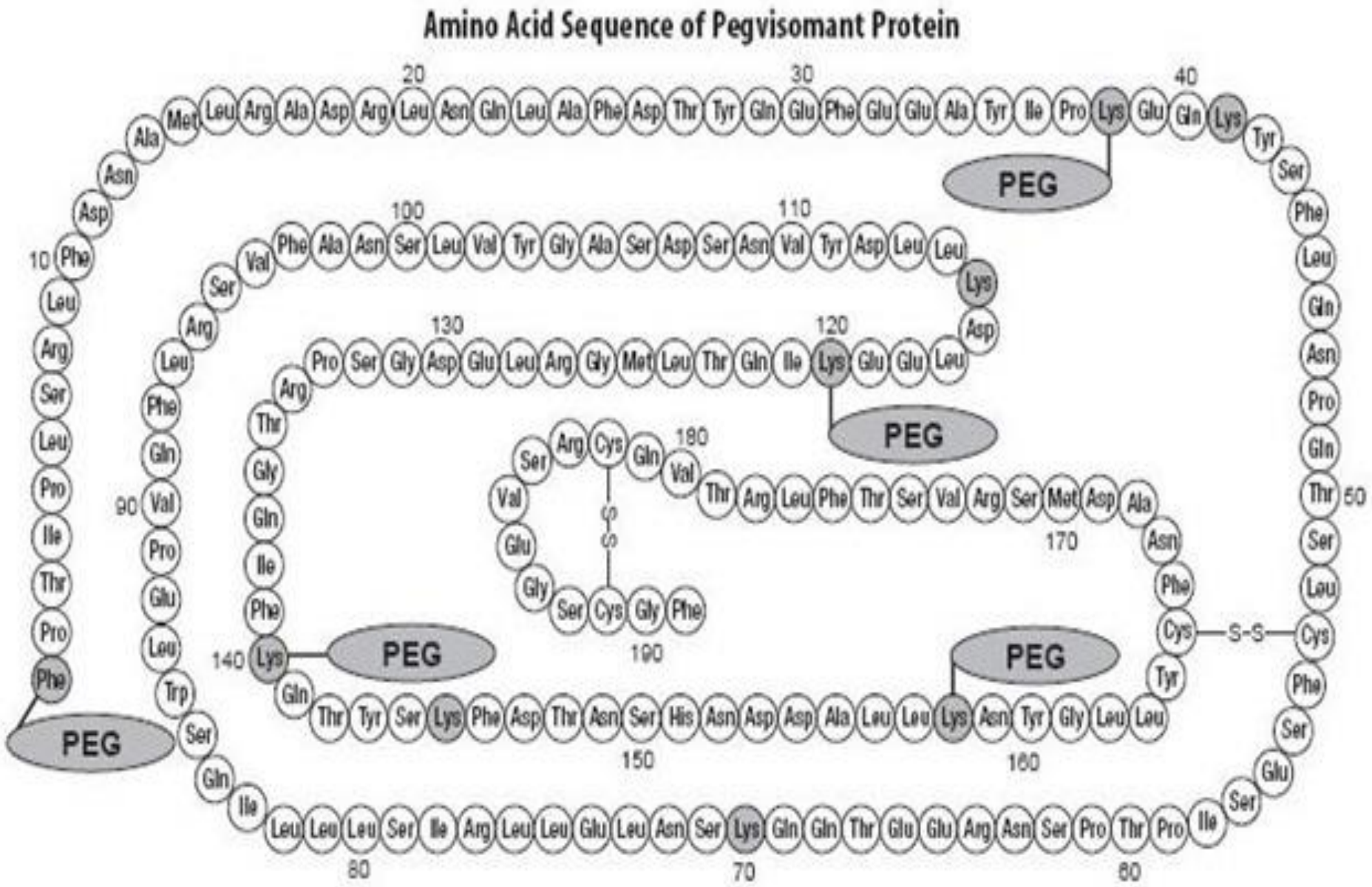
- **Used in including growth failure** due to
  - ➢ Growth hormone deficiency
    - Children (25 to 35 micrograms/kg) Adult: (6 micrograms/kg)
  - ➢Prader-Willi syndrome, (35 micrograms/kg)
  - ➢ Chronic renal insufficiency, (45 to 50 micrograms/kg)
  - ➢Turner syndrome (gonadal dysgenesis) (45 to 50 micrograms/kg)
- Used in the **management of wasting or cachexia** associated with **AIDS**
- In **short bowel syndrome**, to increase intestinal **absorption** of water, electrolytes, and nutrients

Growth Hormone inhibitor

Growth Hormone inhibitor

- *Somavert (pegvisomant) is a PEGylated* rhGH designed to compete with endogenous rhGH for binding to its receptor.
- With four to six PEG molecules (MW = 5 kDa each) conjugated to each rhGH (22 Kda), binding of *Somavert blocks the ability of endogenous rhGH to* bind to its receptor and interferes with the GH signal transduction that stimulates IGF-1.
- Intended for normalizing high levels of IGF-1 in **acromegaly patients** who have had an inadequate response to surgery, radiation therapy, or other medical therapies

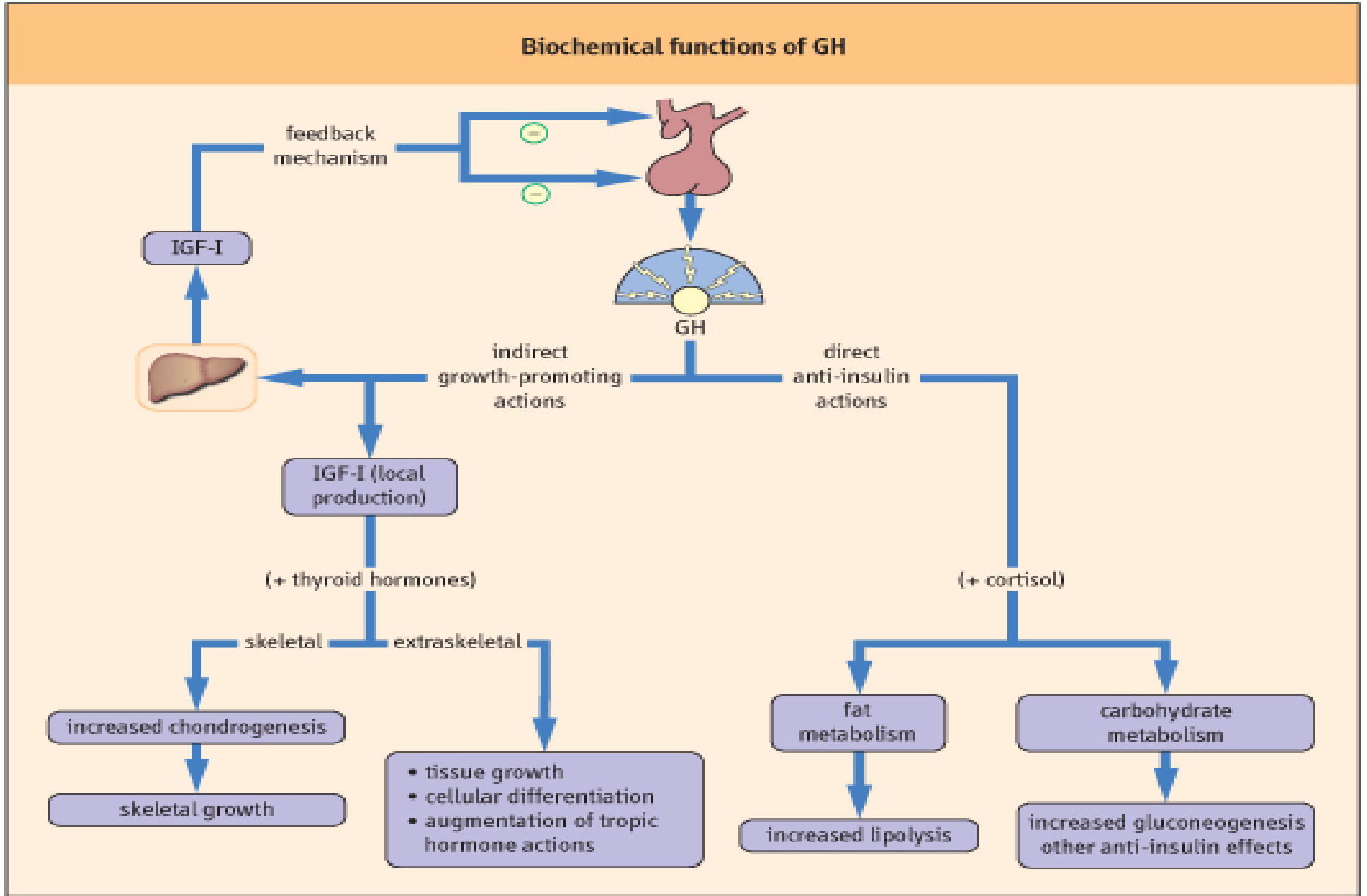
Growth Hormone inhibitor



Somatomedins

- The somatomedins are a group of polypeptide hormones, some of which are involved in mediating the effects of growth hormone in the body.
- IGF-I (mecasermin) as below
- IGF-II is thought to play an important role in fetal growth,

Growth Hormone



Insulin-like Growth Factor 1

Insulin-like Growth Factor 1

- IGF-I (**mecasermin**) (**somatomedin-C**) is a **70-aa** single-chain basic peptide with three intramolecular **disulfide bridges** and has a Mw of 7.6 kDa ; it has homology with proinsulin.
- It is secreted primarily by the **liver**, regulated principally by **growth hormone** and **insulin** secretion. In response to tropic hormones like GH, IGF-I is produced in many tissues & acts as a **parahormone.**
- IGF-I is believed to be responsible for many of the **anabolic effects** of growth hormone.
- IGF-I, which is structurally related to insulin, also has **potent hypoglycaemic properties**.
- Type 1 IGF receptor with **tyrosine kinase** activity.

Insulin-like Growth Factor 1

- stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues
- treatment of growth failure in children with severe primary **IGF-I deficiency**
- who have developed neutralising **antibodies to growth hormone**.
- Mecasermin is also being investigated in the management of **diabetes mellitus** and **insulin resistance**
- It is **not** intended for **treatment of GH deficiency**

IGF-1 Mecasermin

- *Increlex*
- The rhIGF-1 protein is synthesized in *E. coli.*
- Sterile solution in a multiple-dose glass vial at a concentration of 10 mg/mL; for **SC** injection
- The recommended starting dose is 0.04– 0.08 mg/kg twice daily
- Stimulate the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues.
- Mecasermin should be given within 20 minutes before or after food, to minimise hypoglycaemia

Hormones produced by the pituitary gland and their functions

Endocrine gland	Hormone	Function	Secretion control is made by
Pituitary – Anterior	GH	Stimulates liver to produce growth factors that stimulate bone and cartilage growth	GHRH (Hypothalamus)
	Prolactin	Stimulates mammary gland growth and milk production	---------
	ACTH	Stimulates adrenal cortex to produce hormones (glucocorticoids and mineralocorticoids)	CRH (Hypothalamus)
	FSH	♀- Stimulates development of follicles ♂- Stimulates the production of sperm in the seminiferous tubules of the testes	GnRH (Hypothalamus)
	LH	Stimulates development of ovaries	Oestrogen secreted by Graafian follicles
	ICSH	Stimulates testosterone production by the interstitial cells of the testes	GnRH (Hypothalamus)
	TSH	Stimulates thyroid gland to produce hormones (T3, T4, calcitonin)	TRH (Hypothalamus)
	MSH	Promotes distribution of melanin granules	---------
Pituitary – Posterior	ADH	Stimulates retention of water, increasing its permeability at distal convoluted tubules and collecting ducts of the nephrons	Status of the extracelular fluid and bood plasma
	Oxytocin	Stimulates uterine contractions during parturition and promotes milk ejection reflex in the mammary glands	Suckling by the neonate initiates a reflex arc

Prolactin

- Prolactin is a 23 kDa protein, which is homologous to GH.
- Prolactin may assist **breast growth & milk formation** in association with other pregnancy-related hormones
- Prolactin exerts its effects on female reproductive function by **blocking the action of FSH** on follicular estrogen secretion and by **enhancing progesterone levels** by inhibiting steroid-metabolizing enzymes.

Prolactin

- There are no known prolactin deficiency syndromes but **hyperprolactinemia** is very common
- In women, the presenting features of hyperprolactinemia include menstrual irregularity and galactorrhea (discharge of milk from the breast).
- In men, hyperprolactinemia can cause impotence and prostatic hyperplasia
- Treatment options include **long-acting dopamine agonist** drugs or surgery.

Hormones produced by the pituitary gland and their functions

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Corticotropin (ACTH) Structure

- ACTH is synthesized as a **241-aa precursor molecule** pro-opiomelanocortin (POMC).
- POMC is cleaved at multiple sites to release several hormonally active peptides, including the **endorphins, melanocyte stimulating hormones,** and **Corticotropin** (ACTH)
- ACTH itself is comprised of 39 aa (4,500 Da) with the biological activity residing in the *N*-terminal 24 aa moieties.

Corticotropin (ACTH) Regulation

- Two hypothalamic peptides are regulators of **pituitary ACTH release**, corticotropin-releasing hormone (CRH) and vasopressin.
- Also Regulated by a **negative feedback mechanism** involving concentrations of circulating glucocorticoids.
- Conditions of **stress** may also stimulate secretion.

Corticotropin (ACTH) function

- ACTH stimulates the **synthesis** and **release** of **glucocorticoid hormones (**cortisol (hydrocortisone) and mineralocorticoids**)** by interacting with cell-surface receptors on the adrenal cortex that stimulate the production of intracellular cAMP.
- Acute increases in the adrenal synthesis of cortisol (hydrocortisone), occur within 3 minutes, principally by stimulating the **activity of cholesterol esterase**.
- Chronic effects of ACTH include **induction of transcription** of the genes that encode steroidogenic enzymes

Corticotropin (ACTH)

- Plain injection SC, IM, IV
- long-acting depot; **viscose gelatin;** SC, IM
- **Used diagnostically** to investigate adrenocortical insufficiency. **10 to 25 units in 500 mL of glucose 5% infused intravenously over 8 hours.**
- **Used therapeutically** in systemic corticosteroid therapy (with the exception of the adrenal deficiency & adrenocortical over activity). **20 units four times daily by the SC or IM, and for the depot preparation about 20 to 80 units every 24 to 72 hours by the Sc or IM.**
- Corticotropin may be used in certain neurological disorders such as **infantile spasms** and **multiple sclerosis**.

Corticotropin (ACTH) analogues

- The synthetic polypeptide **Tetracosactide** first 24 residues of human corticotropin

  Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro

- The synthetic polypeptide **Tosactide**

  first 28 residues of human corticotropin

  Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-Asp-Ala-Gly-Glu

Tetracosactide

- Diagnostically to investigate adrenocortical insufficiency (**250 micrograms** per 1.73 m^2)
- is rarely used for the conditions in which systemic corticosteroid therapy is indicated: **IM** injection as the long-acting depot preparation(1 mg daily) (or 1 mg every 12 hours in acute cases)

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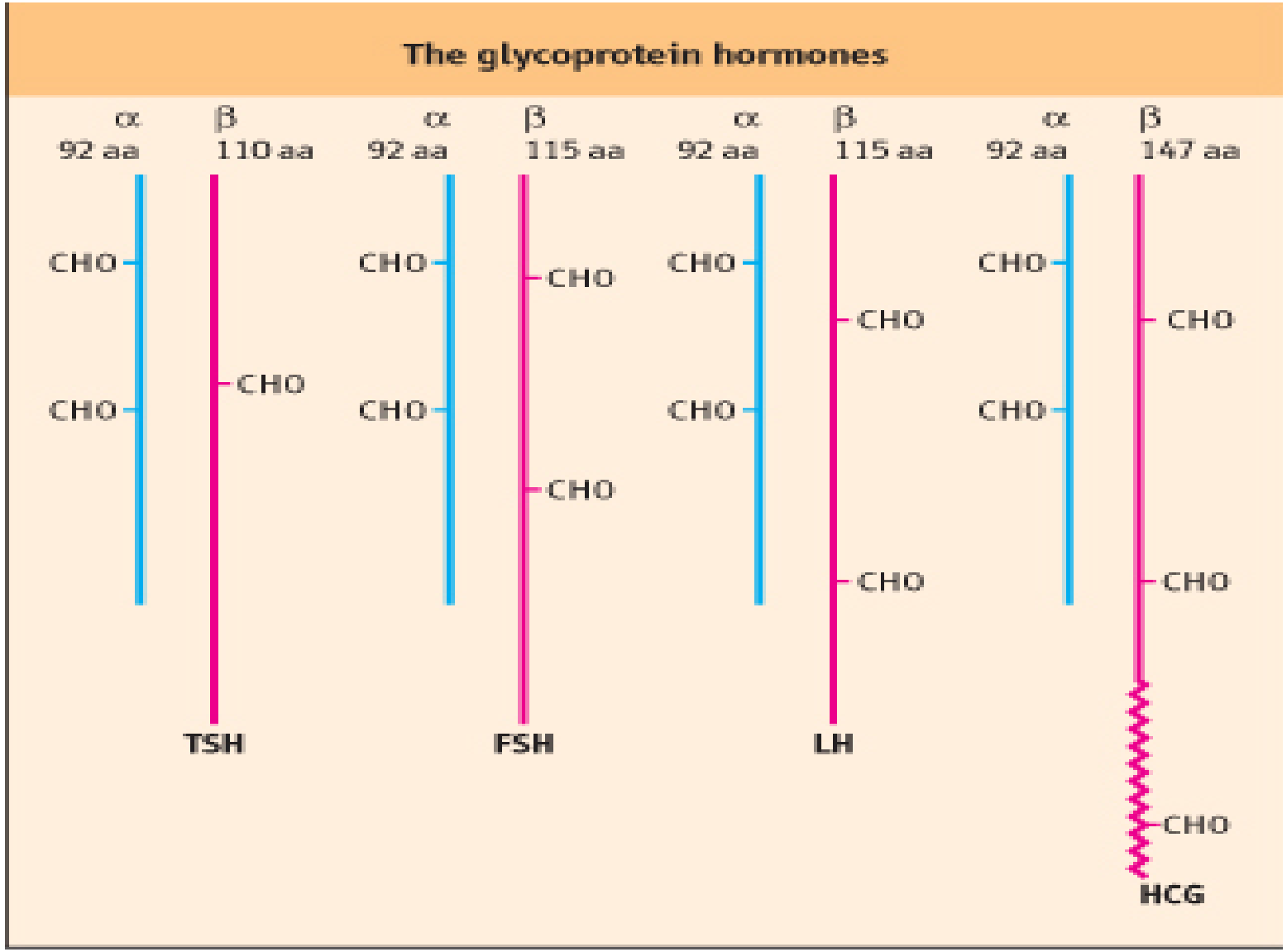
Relative structures of glycoprotein hormones



Gonadotropins

- luteinizing hormone (LH),
- Follicle-stimulating hormone (FSH), and
- Human chorionic gonadotropin (hCG)

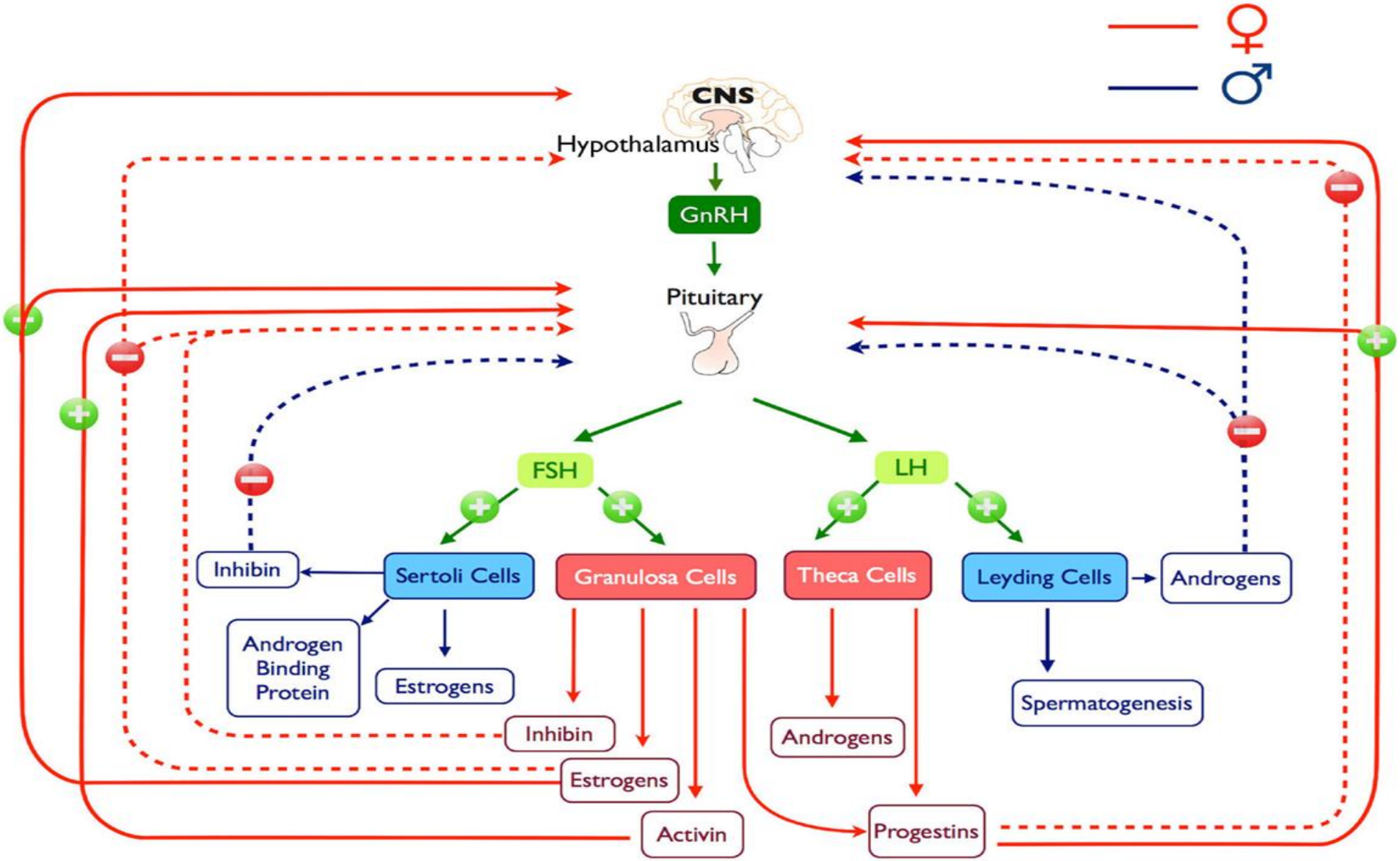
➢ Originally extracted from the urine of pregnant women

- recombinant glycoprotein hormones:
- **rFSH** (follitropin-alfa, or *Gonal F, and follitropin beta,* or *Follistim),*
- ***rLH*** *(lutropin alfa, or Luveris), and*
- **rhCG** (choriogonadotropin-alfa, or *Ovidrel).*

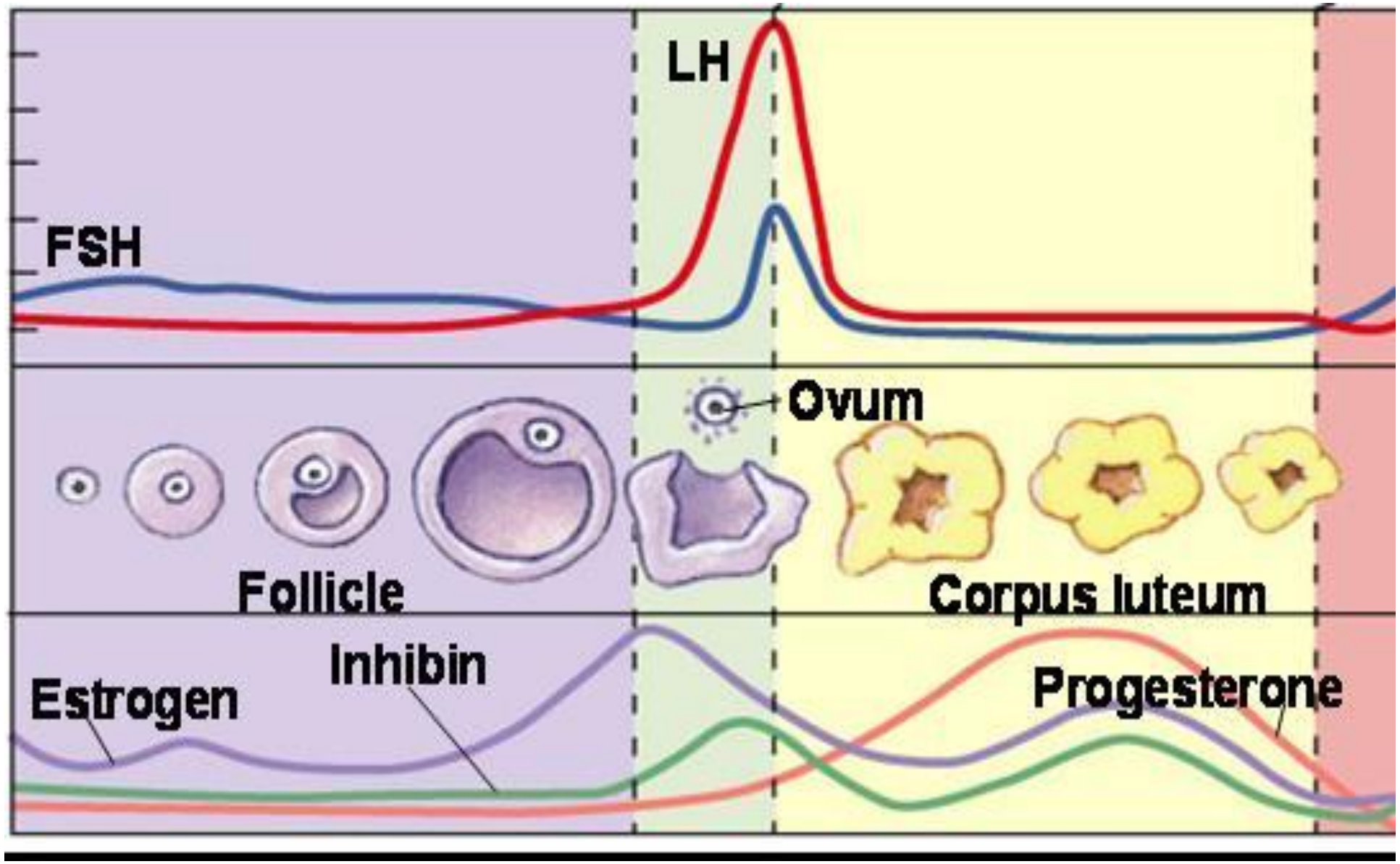
Gonadotropins

Gonadotropin	Half-Life (hr)	Vss (L)
hCG	29	5.9
LH (lutropin-α)	11	10
FSH (follitropin-α)	24–32	10
FSH (follitropin-β)	44	8

FSH & LH


♀
♂
CNS
Hypothalamus
GnRH
Pituitary
FSH
LH
Inhibin
Sertoli Cells
Granulosa Cells
Theca Cells
Leyding Cells
Androgens
Androgen Binding Protein
Estrogens
Inhibin
Estrogens
Activin
Androgens
Progestins
Spermatogenesis

FSH & LH


LH
FSH
Ovum
Follicle
Corpus luteum
Inhibin
Estrogen
Progesterone

Follicle-stimulating hormone

- a mixture of LH and follicle- stimulating hormone (FSH) isolated from urine.
- Recombinant: **follitropin-alfa, or *Gonal F***, *and* ***follitropin beta, or Follistim***

- In women, follicle-stimulating hormone stimulates the development and **maturation of the follicles and ova**
- In men it has a role in **spermatogenesis**
- Follitropins are also used as part of **IVF** or other assisted reproductive technologies

Follicle-stimulating hormone

- In the treatment of female infertility due to **anovulation**, in women who have not responded to **clomifene** therapy.
- Treatment is usually begun with **75 to 150 units** daily by **SC** or **IM** injection for 7 or 14 days; if there is no response, dosage is increased at 7- or 14-day intervals until an adequate but not excessive response is achieved.
- Treatment is then stopped and followed after 1 or 2 days by a single dose of **Chorionic Gonadotrophin 5000 to 10 000 units** to induce ovulation.

Luteinizing hormone (LH)

- extracted from human placenta
- **Lutropin alfa** is a recombinant human LH used to induce **ovulation** in women with severe deficiency of luteinising and follicle-stimulating hormones.
- **It is used at the same time as a preparation with follicle-stimulating activity, usually follitropin alfa.**

luteinizing hormone (LH)

- Treatment is usually begun with **75 units of lutropin alfa** daily by **SC** injection for 7 to 14 days, **accompanied by FSH**.
- If there is no response, the FSH dosage may be increased at 7- or 14-day intervals until an adequate but not excessive response is achieved.
- **A treatment cycle of up to 5 weeks may be needed.**
- Treatment is then stopped and followed after 1 or 2 days by a single dose of **Chorionic Gonadotrophin 5000 to 10 000 Units** to induce ovulation

Human Chorionic Gonadotropin (hCG)

- Produced by the placenta and obtained from the urine of pregnant women
- **Choriogonadotropin alfa** is a **recombinant** form

- Its effects are mainly those of the LH, which is responsible for **triggering ovulation** and formation of the corpus luteum in women, and **stimulates the production of testosterone** by the testes in men.

Thyrotrophin (TSH)

- Its main actions are to increase iodine uptake by the thyroid and the formation and secretion of the thyroid hormones. It may produce hyperplasia of thyroid tissue.
- Thyrotrophin increases the uptake of radio-iodine by the thyroid and has been used as a **diagnostic tool** and as an adjunct in the **treatment of certain types of thyroid cancer**.

Thyrotrophin (TSH)

- The usual dose is 10 units daily by IM or SC injection; depending upon the indication this dose may be given for between 1 and 8 days.
- **Thyrotropin alfa** is a recombinant form of thyrotrophin used in the follow-up of patients with thyroid cancer. The usual dose is 900 micrograms intramuscularly, every 24 hours for two doses, or every 72 hours for three doses, given before serum-thyroglobulin testing with or without radio-iodine imaging

Biopharmaceutical	Trade Name	Molecular Description[b]	Indication for Use[c]	Page Number
Cetrorelix acetate	*Cetrotide*	GnRH	Premature luteinizing hormone surges	320
Choriogonadotropin alfa	*Ovidrel*	rh-CG	Induction of ovulation and pregnancy	321
Degarelix	*Firmagon*	GnRH	Advanced prostate cancer	322
Exenatide	*Byetta*	GLP-1	Glycemic control, type 2 diabetes	323
Follitropin alfa	*Gonal-F*	rh-FSH	Ovulation, pregnancy, spermatogenesis	324
Follitropin beta	*Follistim*	rh-FSH	Follicle development, ovulation induction	325
Ganirelix acetate	*Ganirelix*	GnRH	Premature luteinizing hormone surges	327
Glucagon	*GlucaGen, Glucagon*	r-Glucagon	Hypoglycemia, diagnostic aid	328
Goserelin acetate	*Zoladex*	GnRH	Carcinoma of the prostate	329
Histrelin acetate	*Supprelin, Vantas*	GnRH	Central precocious puberty, prostate cancer	330
Human insulin	*Humulin, Novolin*	rh-Insulin	Glycemic control for diabetes	331
Insulin aspart	*NovoLog*	rh-Insulin	Glycemic control for diabetes, rapid-acting	332
Insulin detemir	*Levemir*	rh-Insulin	Glycemic control for diabetes, long-acting	334
Insulin glargine	*Lantus*	rh-Insulin	Glycemic control for diabetes, long-acting	335
Insulin glulisine	*Apidra*	rh-Insulin	Glycemic control for diabetes, rapid-acting	336
Insulin lispro	*Humalog*	rh-Insulin	Glycemic control for diabetes, rapid-acting	337
Lanreotide acetate	*Somatuline Depot*	Somatostatin	Acromegaly	339
Leuprolide acetate	*Lupron*	GnRH	Prostate cancer, endometriosis, UL, CPP	340
Lutropin alfa	*Luveris*	rh-LH	Follicular development in LH deficiency	342
Mecasermin	*Increlex*	rh-IGF-1	Severe primary IGF-1 deficiency	343
Nafarelin acetate	*Synarel*	GnRH	Endometriosis, central precocious puberty	344
Octreotide acetate	*Sandostatin*	Somatostatin	Acromegaly, diarrhea in VIPomas	345
Oxytocin	*Pitocin*	Oxytocin	Labor induction, postpartum bleeding	347
Pegvisomant	*Somavert*	rh-GH	Refractory acromegaly	348
Pramlintide acetate	*Symlin*	Amylin	Glucose control for diabetes	349
Somatropin	*Genotropin*[a]	rh-GH	Growth failure, AIDS wasting, SBS	350
Teriparatide	*Forteo*	rh-PTH	Osteoporosis, low bone mass	353
Tesamorelin	*Egrifta*	h-GRF	HIV-associated lipodystrophy	354
Triptorelin pamoate	*Trelstar*	GnRH	Palliation for advanced prostate cancer	355

[a]Somatropin (recombinant) trade names: *Genotropin, Humatrope, Norditropin, Nutropin, Nutropin Depot, Omnitrope, Tev-Tropin, Saizen, Serostim, Valtropin, Zorbtive*.