I. Growth Hormone (somatotropin):

Growth hormone (GH) is a **191 amino acid single chain polypeptide** (MW 22,000 daltons).

Growth hormone is synthesized as a preprohormone by somatotrophs of the **anterior pituitary** and released in a **pulsatile** manner.

The half life of growth hormone in circulation is about 20 minutes.

Growth hormone has about 83% sequence homology with the human placental lactogen hormone (hPL) and about 16% sequence homology with prolactin.

Growth hormone is **species** specific

Plasma level: adult 3ng/mL, child 5ng/mL.

Daily secretion in an adult human is approximately 500 micrograms.

A. Physiological action

1. Promotes linear growth (gain in height), maintains lean body mass.
2. Increases protein, RNA and DNA synthesis in most tissues (anabolic).
3. Increases fat utilization (lipolytic) and decreases carbohydrate utilization (hyperglycemia).
4. Increases calcium and phosphate retention.
5. Growth hormone stimulates release of somatomedin ‘C’ or **insulin-like growth factor I (IGF-I)**, from the liver, fibroblasts, muscle etc.
   a. IGF-1 with GH stimulates skeletal (cartilage) growth by stimulating chondrocyte mitosis, collagen synthesis and matrix synthesis.
   b. IGF-1 production is decreased with low insulin and low dietary intake.

B. Secretion of GH:

**Release of GH:** - Release of GH is generally greater in **women** than in men, presumably due to **estrogen**.

1. During slow wave sleep (stage IV of sleep)
2. Stress
3. Exercise
4. Arginine infusion
5. Hypoglycemia (fasting)
6. High serum amino acids levels
7. Cortisol and thyroid hormones (physiological concentration)
8. Neurotransmitters GABA, serotonin, acetylcholine etc.
9. Ghrelin (28 amino acid peptide), synthesized in oxyntic gland of the stomach
10. Growth hormone-releasing hormone (GHRH)

Failure to increase GH after such stimulation is evidence of deficiency.

**Inhibition of GH release by:**

1. Hyperglycemia (high serum sugar levels)
2. Increase in free fatty acids
3. Cortisol (pharmacological doses)
4. Obesity
5. Somatostatin
6. Aging

**Wakeful GH release:**

Is great in **puberty** (seems to increase before sex steroids) and declines after puberty.

**Sleep-induced GH release:**

Provides a major part of the diurnal quotient of growth hormone and is maximal at puberty, diminishing progressively in later years.

**C. Control of GH Secretion (Fig.1):**

Two hypothalamic hormones appear to regulate the release of growth hormone.

1. **GHRH** (growth hormone-releasing hormone, a polypeptide of 44 amino acids) stimulates growth hormone release.
2. **Somatostatin** (a polypeptide of 14 amino acids) inhibits growth hormone release.

**IGF-I stimulates** the secretion of somatostatin from hypothalamus and also acts directly on the anterior pituitary to **inhibit GH.**
Figure 1: Feedback control of GH secretion. The dashed arrows indicate inhibitory effects and the solid arrows stimulatory. IGF-I stimulates somatostatin secretion from hypothalamus and acts directly on ant. pituitary to inhibit GH secretion.

D. **Mechanism of GH Action (Fig. 2):**

The binding of growth hormone to the extracellular domain of its receptor results in the dimerization of the receptor with rapid phosphorylation and activation of Janus kinases on the cytoplasmic domain. These result in phosphorylation of STAT, IRS, GRB2, and PLC pathways and stimulation of gene expression.
E. **Growth hormone abnormalities:**

GH excess (such as pituitary tumor):

1. Childhood growth hormone excess leads to **gigantism** characterized by abnormally tall stature.
2. Growth hormone excess in adults leads to **acromegaly**. In acromegaly patients, the head, soft tissues, and many body organs enlarge in size. These changes lead to enlarged sinus cavities in the skull, and widened hands and feet. Height is not increased in adults because the epiphyses of the long bones are closed. Treated with somatostatin analogue octreotide.

Excess growth hormone can also be **diabetogenic**. The high levels of blood glucose induced by excess growth hormone stimulate excessive insulin release and can eventually lead to pancreatic β-cell “burn out”.

**Kwashiorkor** is a disease associated with starvation (particularly protein...
deficiency) and is characterized by high growth hormone levels (possibly due to hypoglycemia) and protein depletion.

**GH Deficiency:**

Growth hormone deficiency may result from damage to or malformation of either the hypothalamus or the pituitary gland.

1. Low GH levels in **adults** can result in hypoglycemia.
2. In **children**, growth hormone deficiency leads to **dwarfism**, characterized by abnormally short stature, mild obesity and delayed puberty (sexual dysfunction), excess fat and reduced lean body mass.

**State of end-organ resistance to GH (Laron dwarfism).**
Mutation or gross deletions in the gene coding:

1. Growth hormone receptor (high plasma GH levels, low IGF-I levels).
2. IGF-I receptor (high plasma GH levels, high IGF-I levels).

II. **Somatostatin** (14 amino acid and also 28 amino acid peptide):

A. **Sources of somatostatin:**

Hypothalamus, D cell of pancreatic islet, GI-tract.

Somatostatin can act as an autocrine, paracrine or endocrine regulator.

B. **Physiological Action:**

1. Inhibits release of **growth hormone, prolactin, TSH, insulin, glucagon, gastrointestinal hormones (gastrin, secretin, motilin, vasoactive intestinal peptide, cholecystokinin).**
2. Decreases GI blood flow and motility, and inhibits secretion of gastric acid and pepsin.
3. Increases GI water and electrolyte absorption.

C. **Mechanism of action of somatostatin:**

Somatostatin binds to a plasma membrane receptor and decreases intracellular cAMP and calcium levels.

↑ somatostatin, ↓ intracellular calcium, ↓ cAMP and blockade of potassium channel.

Half-life of somatostatin in blood is approximately **one minute.**
This leads to the development of analogs with prolonged duration and potency of action such as Octreotide.

In clinical studies, octreotide is effective in reducing the hormonal hypersecretion of acromegaly, insulinoma, TSH and VIP secreting adenoma.

III. **Prolactin:**

- Polypeptide of **199 amino acids** (MW 23,000 daltons).
- Prolactin is produced by **mammotrophs** of the anterior pituitary as a preprohormone.
- The circulatory half life of prolactin is 30-50 min.

A. **Physiological action of prolactin:**

1. Initiates and maintains milk production (stimulates synthesis of milk proteins casein and lactoalbumin), development of breast.
2. Influences immune responses and reproductive function.

- Levels are higher in women (and during pregnancy) than men: a direct consequence of estrogen.

B. **Stimuli which enhance prolactin secretion:**

1. TRH
2. Nursing-suckling in the post-partum period leads to PRL secretion.
3. Sleep
4. Opioids, serotonin
5. Estrogen
6. Stress
7. Pregnancy

C. **Inhibition of prolactin release:**

1. **Bromocriptine mesylate**, specific therapy for female infertility associated with hyperprolactinemia in the absence of a demonstrable pituitary tumor.
2. **Dopamine**
3. GABA
4. Somatostatin

D. **Prolactin Regulation (Fig.3):**

1. The predominant effect of the hypothalamus is to suppress synthesis and release of prolactin by secreting dopamine and somatostatin.
2. Hypothalamic thyrotropin hormone (TRH) promotes prolactin release. TRH also increases TSH release as described in thyroid hormone lecture.
E. **Mechanism of prolactin action:**

The cell membrane receptor for prolactin which is, very similar in structure and function to growth hormone receptor has been identified in adrenal, breast, ovary, liver, prostate, and immune cells.

Prolactin binds to plasma membrane receptors and activates cytoplasmic Janus kinases. These phosphorylate STAT proteins that stimulate expression of genes such as milk proteins casein, lactoalbumin etc.

F. **Abnormality of prolactin secretion :**

*Prolactin deficiency* leads to decreased milk production.

*Prolactin excess* (such as pituitary tumors) can result in the following:

1. May produce **impotency and impair testicular function** in males (↑ plasma prolactin, ↓ testosterone secretion, ↓ sperm production).
2. **Galactorrhea and amenorrhea (depression of secretion of gonadotrophin releasing hormone (GnRH))**, thereby impeding secretion of luteinizing hormone (LH) and (FSH) or by **directly blocking the action of FSH and LH at the ovaries** in women.

**Special note:**

Estrogen **can decrease PRL-binding in breasts** (↑ estrogen, ↓ prolactin receptor in breasts), but increase PRL-binding in liver.