Lecture 4
Anterior pituitary hormones
Growth hormone

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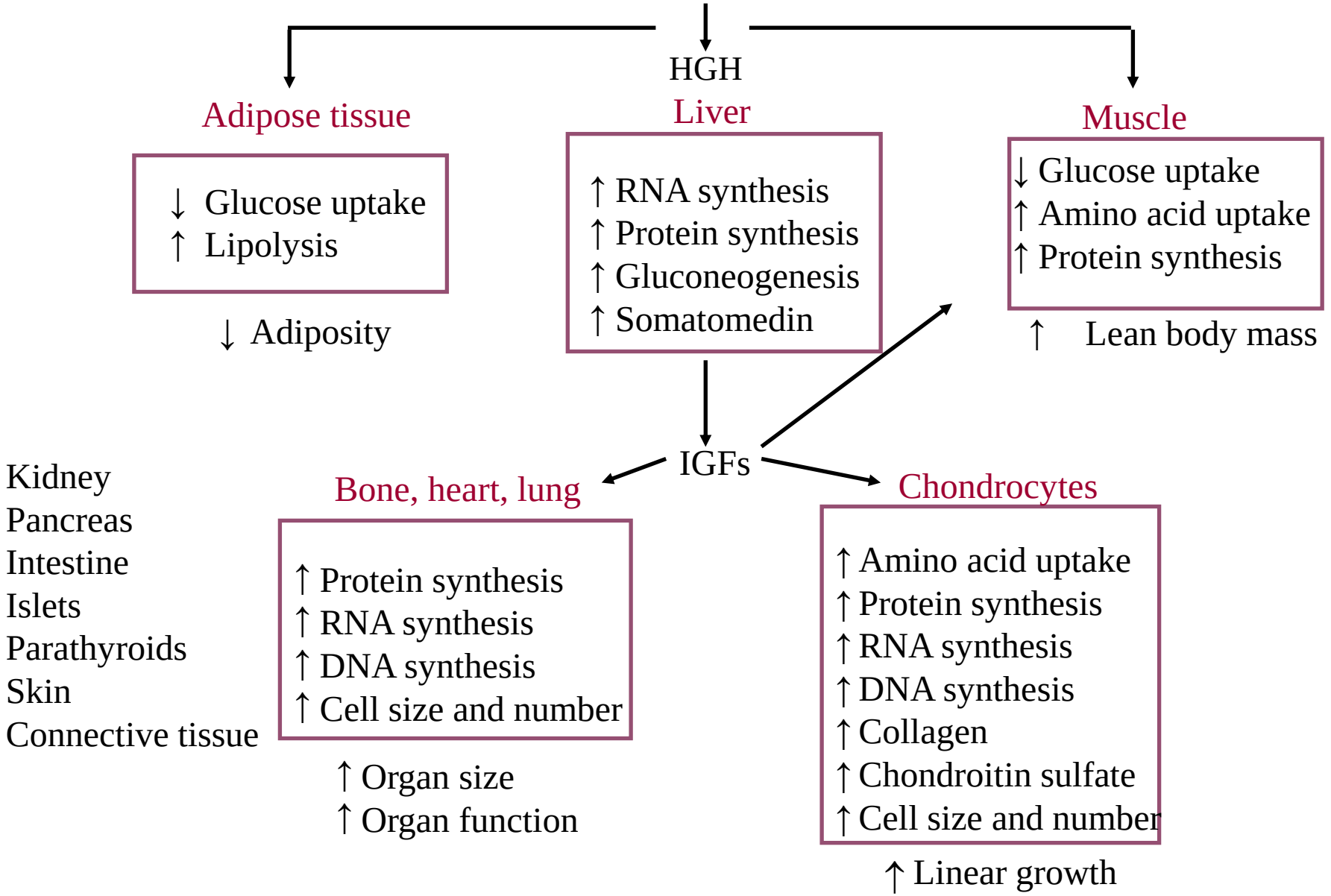
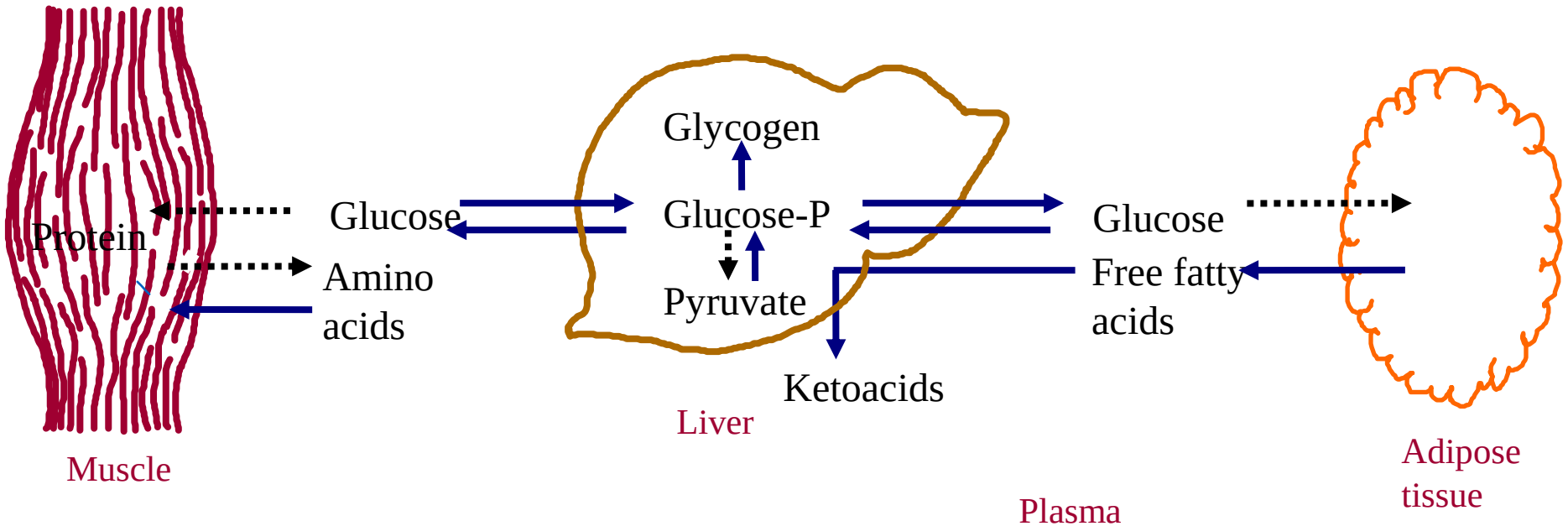
Growth hormone(called somatotropic hormone or somatotropin)

- is a small protein molecule that contains 191 amino acids
- Homologous with prolactin and human placental lactogen.
- Secreted by acidophilic somatotrophs (About 30 to 40) percent of the anterior pituitary cells are somatotrophs
- The basal plasma growth hormone level measured by radioimmunoassay in adult humans is normally less than 3 ng/mL.
- This represents both the protein-bound and free forms.
- Growth hormone is metabolized rapidly, probably at least in part in the liver.
- The half-life of circulating growth hormone in humans is 6–20 min

Actions of Growth Hormone



Metabolic Effects of Growth Hormone

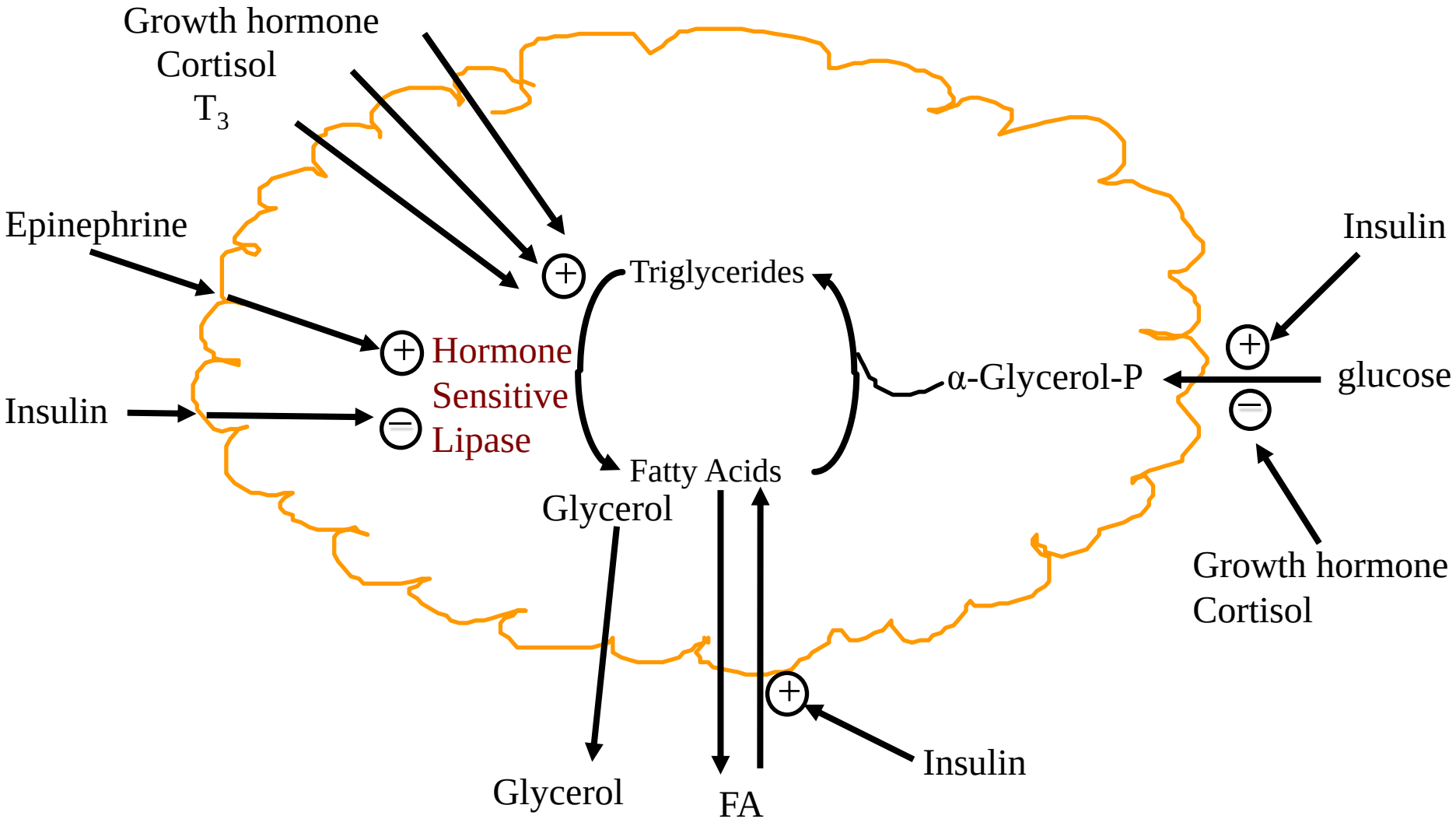


Stimulate
Inhibit

Plasma

↑ Glucose
↑ Free fatty acids
↑ Ketoacids
↓ Amino acids

Hormonal Effects on FFA Production



GH- Diabetogenic Effects

- Muscle-- ↓Glucose uptake
- Fat--↑ Lipolysis
- Liver--↑ Gluconeogensis; ↑ Glycogenolysis
- Muscle, liver, fat--Insulin resistance

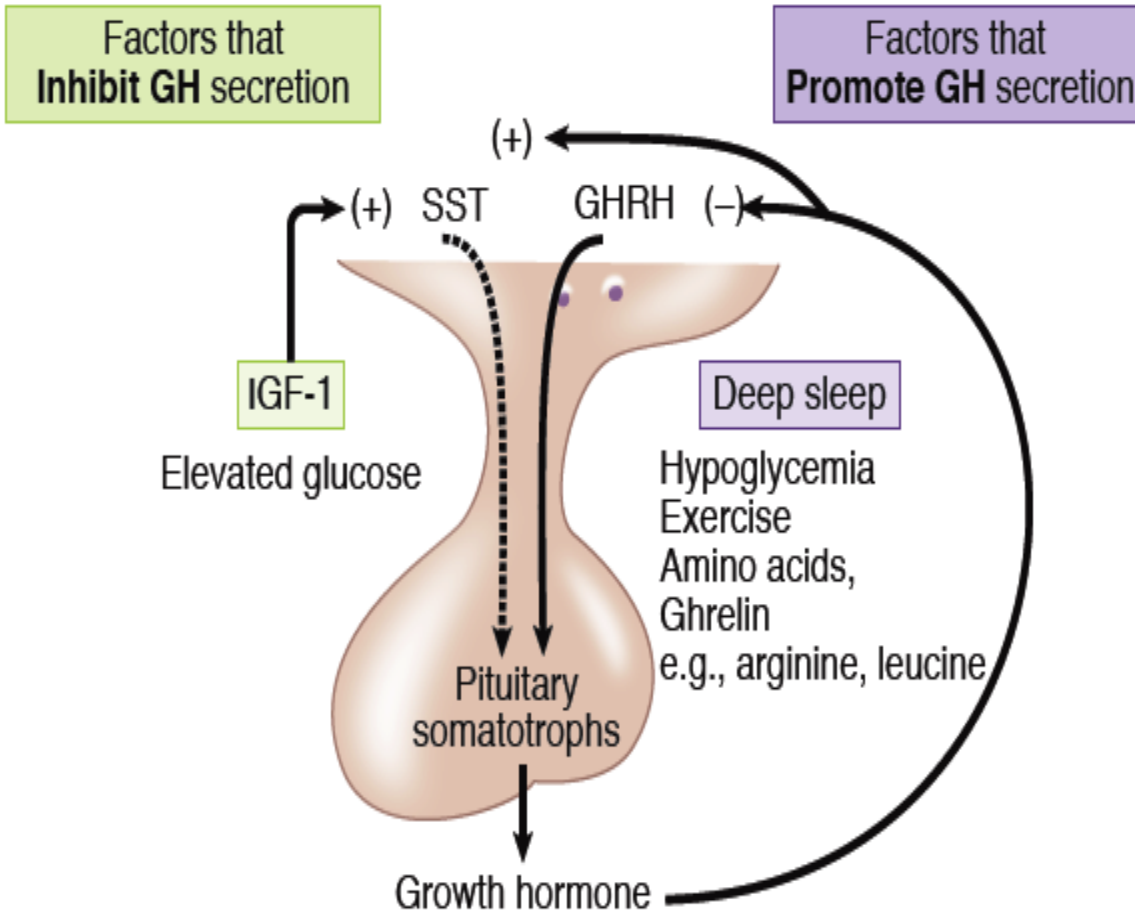
Specific Properties of the IGFs

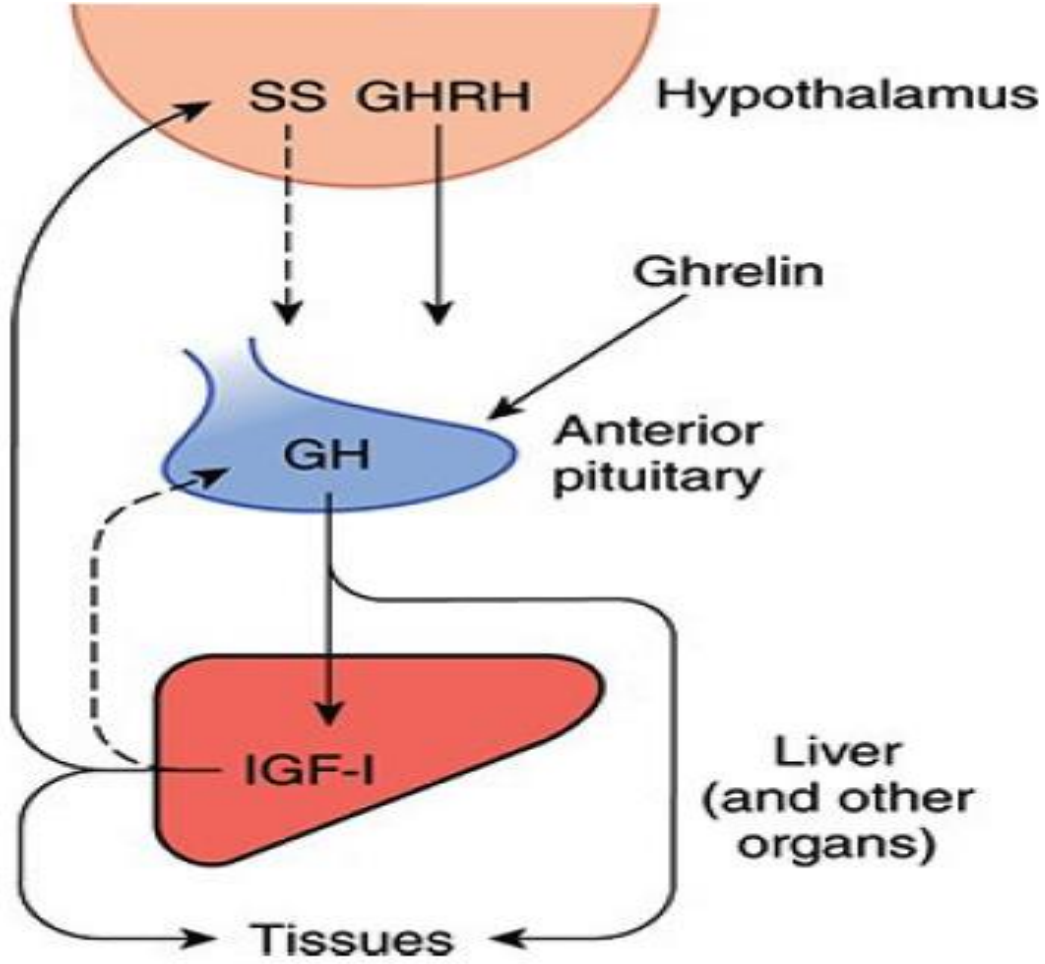
- IGF-I is a major anabolic growth factor produced in liver under the influence of GH
- Circulates peptide growth factor similar in structure to proinsulin and has some insulin-like activity
- Circulates in the blood tightly bound to a large protein, whose production is also dependent on growth hormone.
- Highly bound to plasma proteins-- $T_{1/2}$: IGF-I > GH
- Protein binding increases the half-life and thus serves as a better 24-hour marker of GH (half-life15–20 minutes). *This greatly prolongs the growth-promoting effects of the bursts of growth hormone secretion.*
- Inhibits GH secretion
- IGF-II is another growth factor, the importance of which is not well understood but may have a role in fetal development
- IGFs also decrease in catabolic states, especially protein-calorie malnutrition.

CONTROL OF GROWTH HORMONE (GH) SECRETION

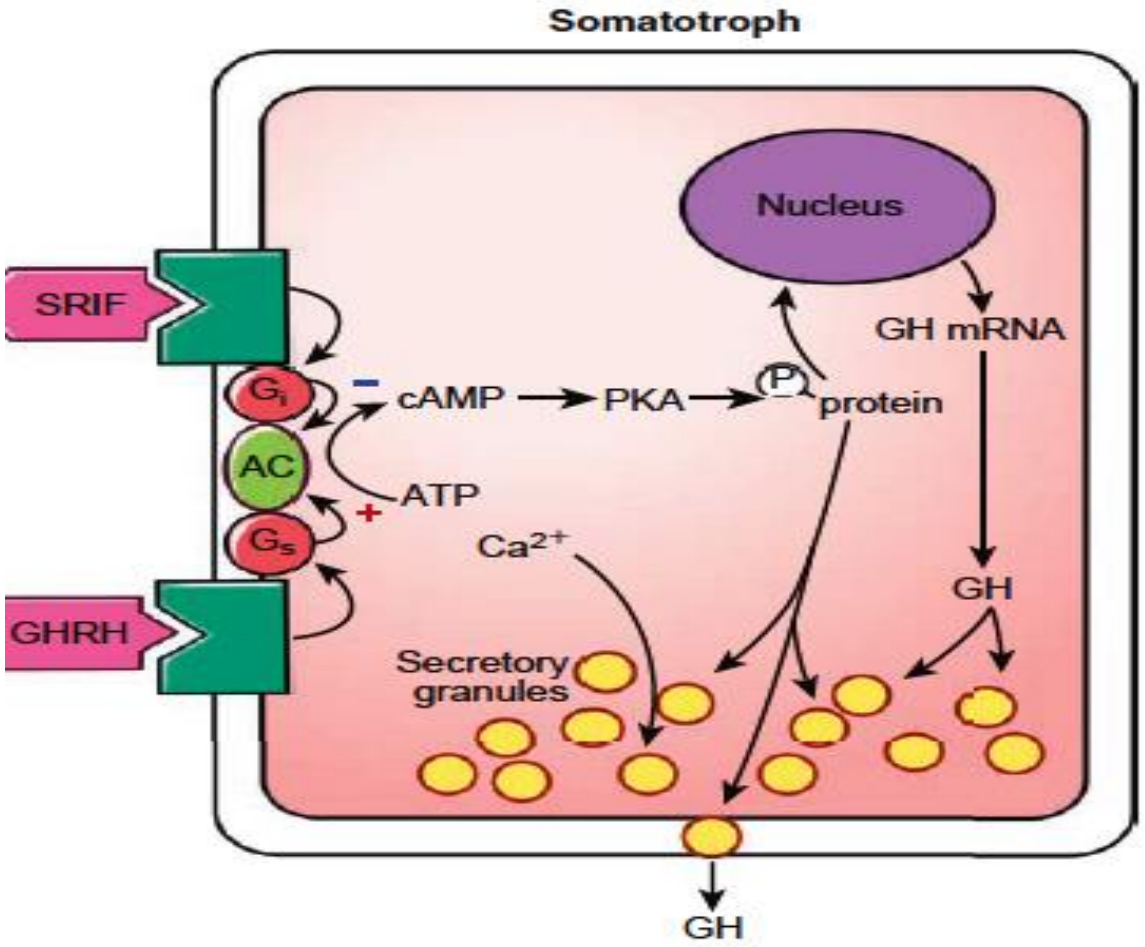
- GH secretion is pulsatile.
- The secretory pulses are much more likely to occur during the night in stages III and IV (non-REM) of sleep than during the day.
- Secretion of GH requires the presence of normal plasma levels of thyroid
- Hormones. GH secretion is markedly reduced in hypothyroid individuals.
- **Changes occurring with ageing** During the sixth decade of life and later, GH secretion diminishes considerably in both men and women. What initiates this decrease is unknown. (increased wrinkling of the skin, diminished rates of function of some of the organs, and diminished muscle mass and strength) may be all due to physiological decrease in GH release.

Feedback Control of growth hormone secretion





The actions of growth hormone releasing hormone (GHRH) and somatostatin (SRIF)



Mechanism of growth hormone action

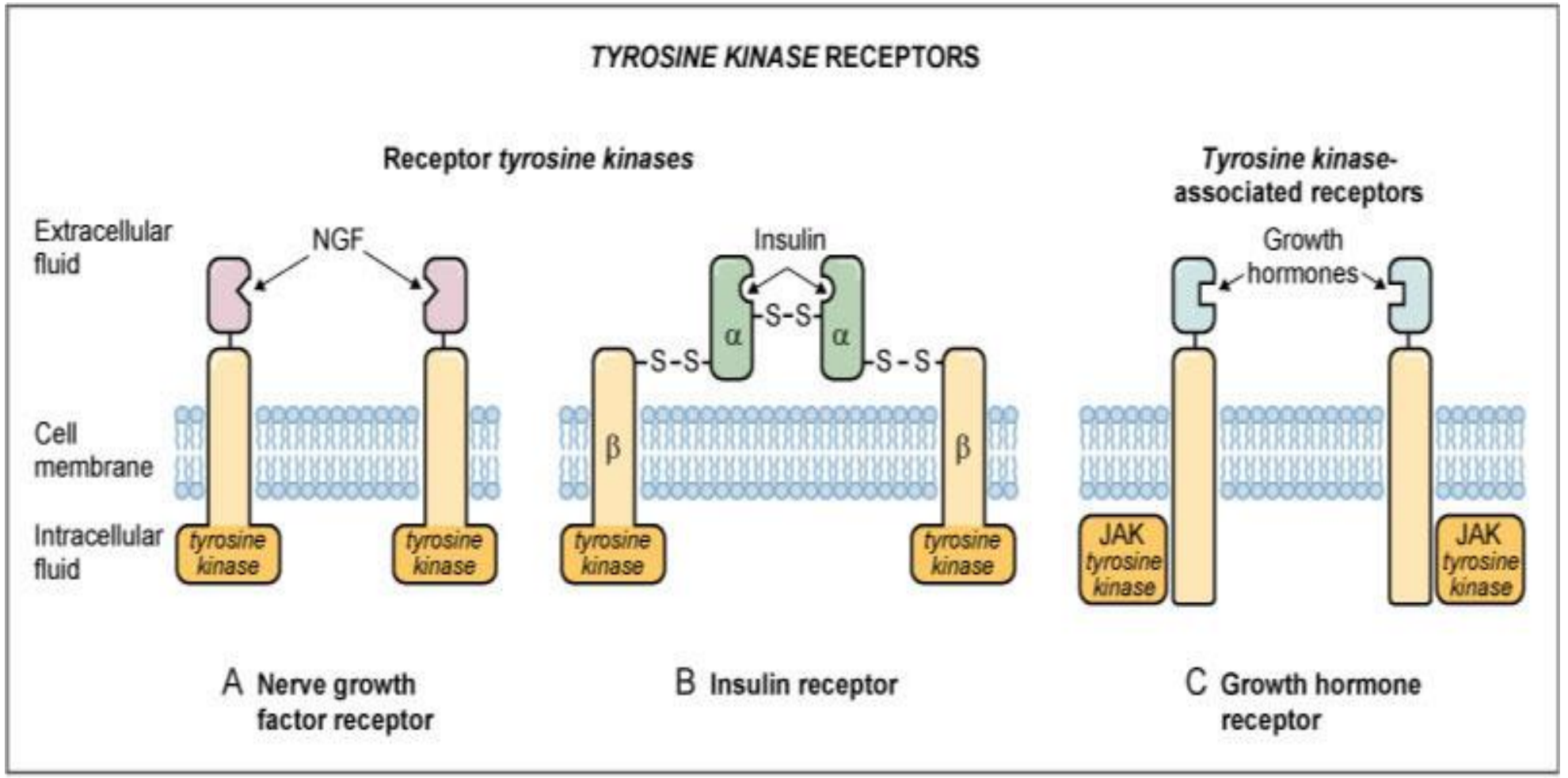


Fig. 9-6. **Tyrosine kinase receptors.** Nerve growth factor **(A)** and insulin **(B)** utilize receptor tyrosine kinases that have intrinsic tyrosine kinase activity. Growth hormone **(C)** utilizes a tyrosine kinase–associated receptor. NGF, nerve growth factor; JAK, Janus family of receptor-associated tyrosine kinase.

JAK2 and STAT

- JAK2 is a member of the Janus family of cytoplasmic tyrosine kinases.
- STATs (for signal transducers and activators of transcription) are a family of inactive cytoplasmic transcription factors that, upon phosphorylation by JAK kinases, migrate to the nucleus and activate various genes.
- JAK–STAT pathways are known to mediate the effects of prolactin , growth hormone and various other growth factors.

Stimulate Growth Hormone Secretion

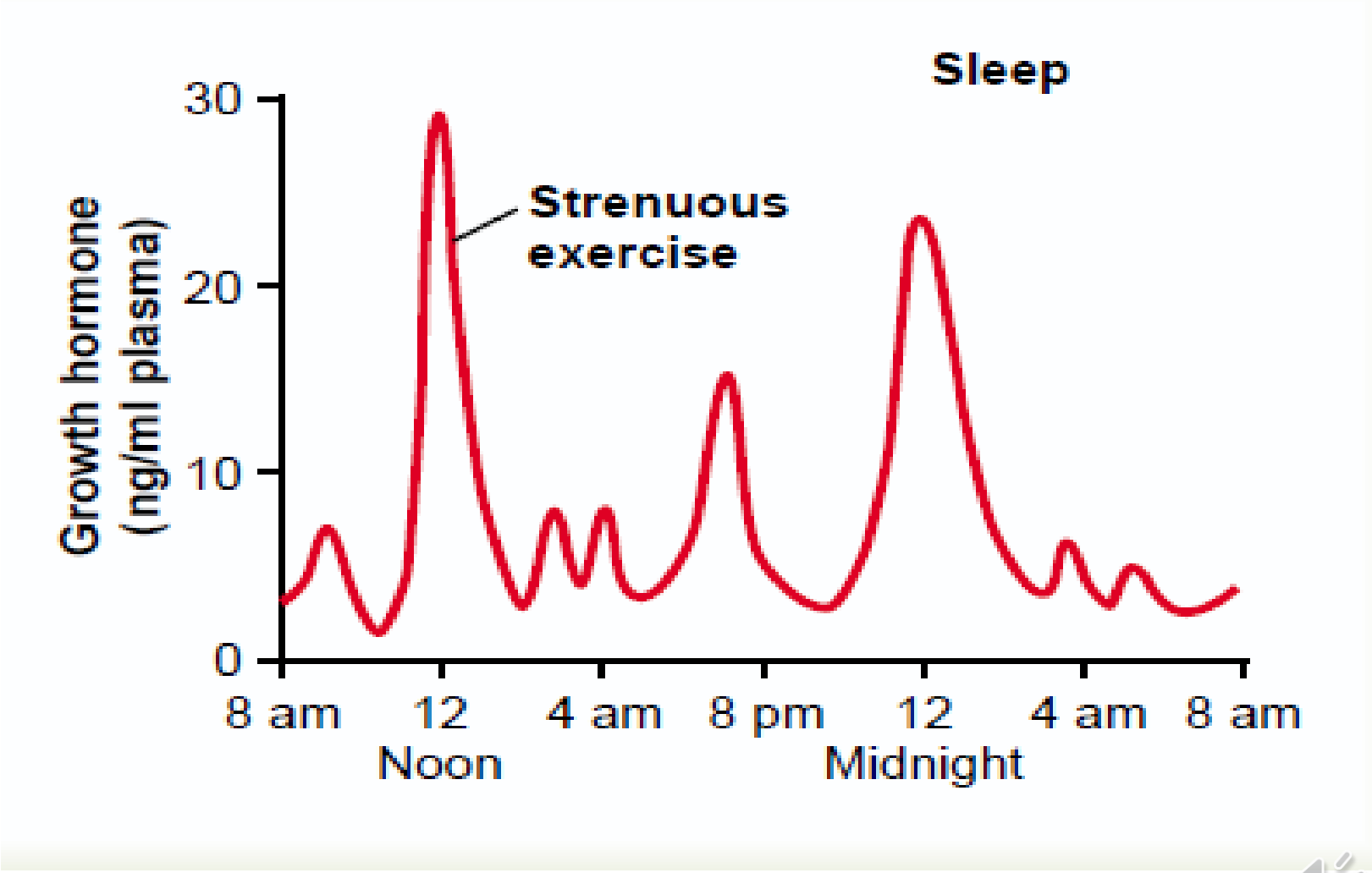
- Decreased blood glucose
- Decreased blood free fatty acids
- Increased blood amino
- acids (arginine)
- Starvation or fasting,
- protein deficiency
- Trauma, stress, excitement
- Exercise
- Testosterone, estrogen
- Deep sleep (stages II and IV)
- Growth hormone–releasing hormone
- Ghrelin

Inhibit Growth Hormone Secretion

- Increased blood glucose
- Increased blood free fatty acid
- Aging After adolescence, secretion decreases slowly with aging, finally falling to about 25% of the adolescent level in very old age.
- Obesity
- somatostatin
- Growth hormone(exogenous)
- Somatomedins (insulin-like growth factors)

Pulsatile release of GH

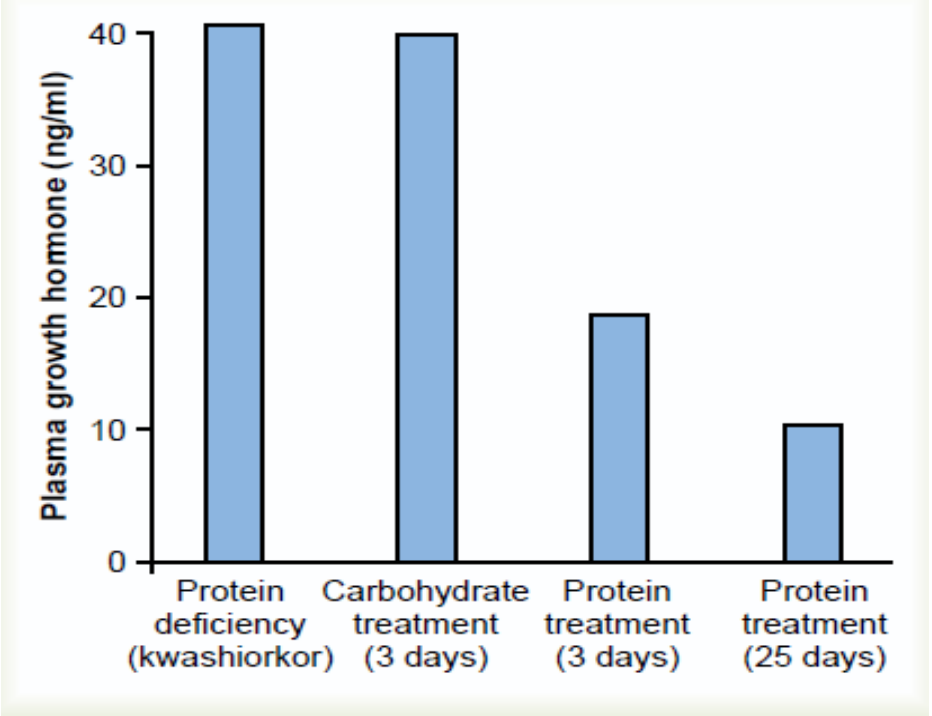
Typical variations in growth hormone secretion throughout the day, demonstrating the especially powerful effect of strenuous exercise and also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.



Growth hormone release during protien depletion In Kwashiorkor

In **acute** conditions **hypoglycemia** effect is most powerful, while in **chronic** conditions, it is **protein depletion** or degradation the most important (as in starvation).

The high level of Growth hormone *(stimulated by chronic protein deficiency)* is not suppressed by CHO diet but with protein diet in Kwashiorkor



Pathophysiology of growth hormone

Prepubertal Growth Hormone Deficiency

- *Growth hormone deficiency*
- Congenital
  - mutations in genes for factors that are important in pituitary gland development
  - IGF recptors deficiency or resistance
  - in receptors and factor
  - Failure to generate IGF in the liver
  - idiopathic (low GHRH)
- Acquired :
  - hypothalamic-pituitary tumor, head trauma, radiation therapy

Prepubertal Growth Hormone Deficiency
Growth hormone deficiency (GHD), also known as dwarfism or pituitary dwarfism

- A deficiency causes dwarfism, which is characterized by: short stature, immature facial appearance, delayed skeletal maturation, and tendency to episodes of hypoglycemia.
- Children with GHD have abnormally short stature with normal body proportions mild obesity, and delayed puberty.
- Isolated growth hormone deficiency in children abnormalities of their growth hormone secreting cells leading to short stature with normal sexual development and reproduction

Dwarfism due to receptors defect or IGF production

- Laron Dwarfism (Laron syndrome)
  - The plasma growth hormone synthesis and secretion is normal
  - Gene mutations in receptors (Tissue resistance) to GH
  - Hormonal assay shows (↑ growth hormone, ↓ IGF-I)
  - This results Laron syndrome
- Pygmies of Central Africa
- Hereditary inability to produce somatomedin C (IGF) : Plasma IGF-I is markedly reduced
- Have normal plasma growth hormone levels and a modest reduction in the plasma level of growth hormone-binding protein.
- Their plasma IGF-I concentration fails to increase at the time of puberty,

Hormonal testing and management

- Stimulation test is with an arginine infusion.
- Growth hormone deficiency following puberty decreases lean body mass, and replacement therapy is now considered an acceptable treatment.
- Treatment of GH deficiency is simple replacement of GH.
- Treatment of Laron dwarfism (lack of GH receptor) is synthetic IGF.
- If treatment is commenced promptly in childhood, almost normal stature can often be attained.

Abnormalities of growth hormone hypersecretion

Gigantism:

Occurs when over secretion during postnatal growth period and before adulthood

can be caused in GH secreting tumor cells

10% od the patients will develop DM.

Eventually if the patient is not treated he develops panhypopituitarism (the destroys the gland) and death in early adulthood.

Acromegaly:

It is caused by a post pubertal excessive secretion of growth hormone.

ACROMEGALY

- It is caused by a post pubertal excessive secretion of growth hormone.
- It is almost always due to macroadenoma of the anterior pituitary and second in frequency to prolactinomas.
- There is a slow onset of symptoms, and the disease is usually present for 5 to 10 years before diagnosis.
- Some tumors contain lactotrophs, and elevated prolactin can cause hypogonadism and galactorrhea.
- Increased IGF-I causes most of the deleterious effects of acromegaly but growth hormone excess directly causes the hyperglycemia and insulin resistance.
- There is characteristic proliferation of cartilage, bone and soft tissue, visceral, and cardiomegaly.
- Observable changes include enlargement of the hands and feet (acral parts) and coarsening of the facial features, including downward and forward growth of the mandible. increased hat size and kyphosis
- .

Clinical Features of Acromegaly

- **Local tumor effects**
  - ↑ pituitary size , visual field defects, headache
- hypogonadism and galactorrhea. : Some tumors contain lactotrophs, and elevated prolactin
- **Somatic systems**
  - Acral enlargement, prognathism, carpal tunnel syndrome :
    - enlargement of the hands and feet (acral parts) and coarsening of the facial features, including downward and forward growth of the mandible.
  - Mostly induce by increase IGF-I
- **CV system**
  - Ventricular hypertrophy, cardiomyopathy,
  - **Pulmonary system**
  - Sleep disturbances, sleep apnea
- **Visceromegaly**
  - Tongue, thyroid gland, liver, spleen, liver, kidney, prostate
- **Metabolic**
  - Insulin resistance, fasting hyperglycemia mainly due to increased GH secretion

ACROMEGALY

Diagnosis tests:

- Elevated IGF level
- measure and confirms diagnosis with the lack of growth hormone suppression by oral glucose
- MRI shows lesion in brain in pituitary

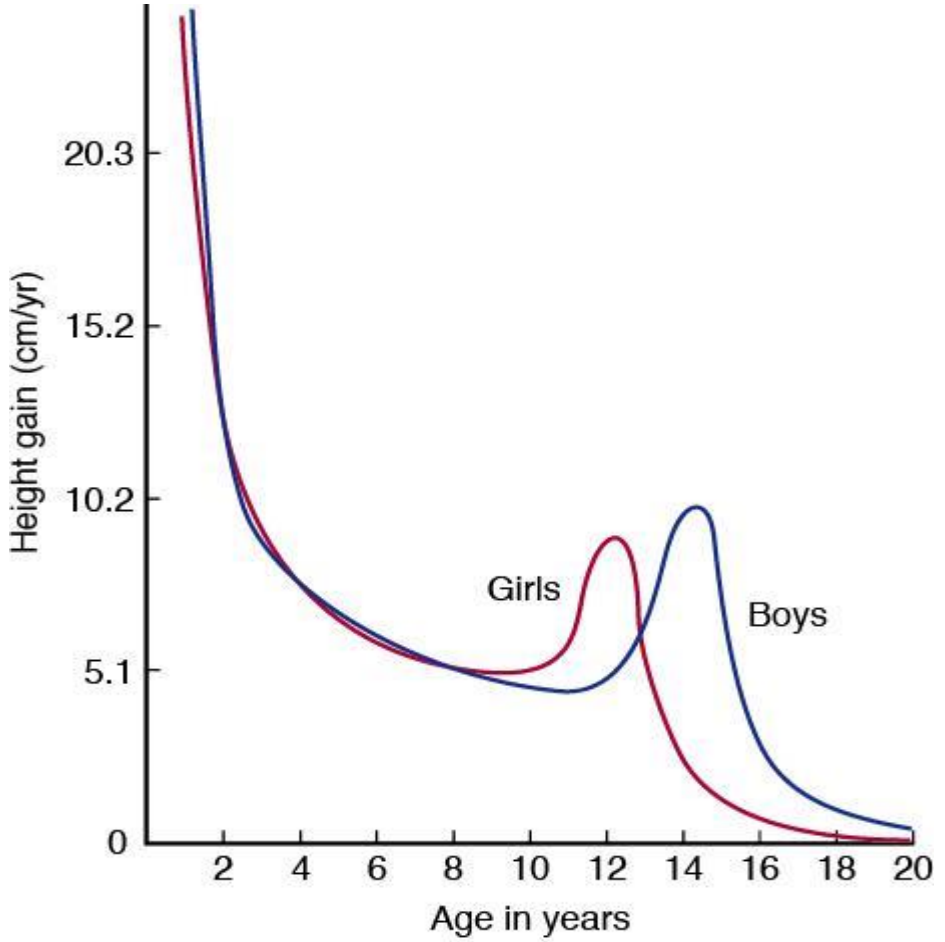
Therapies for Gigantism- Acromegaly

- Hypophysectomy
- Radiation
- Somatostatin analogues
- GH antagonists

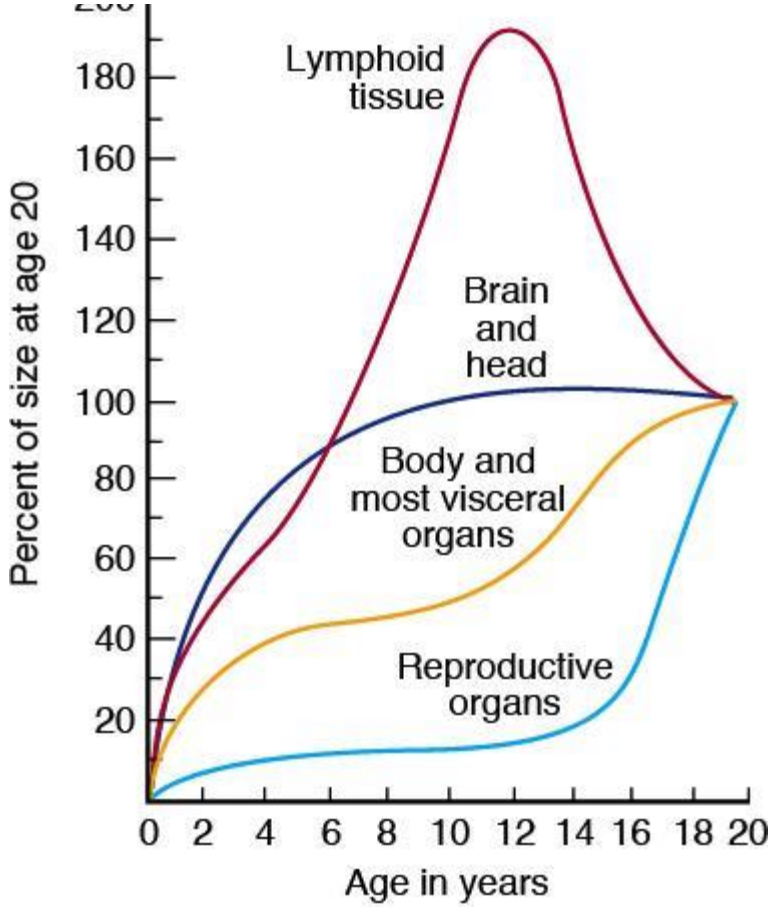
Characteristics of human growth

- The first period of accelerated growth occurs in infancy and is continuation of the fetal growth period.
- The second growth spurt, at the time of puberty, is due to growth hormone, androgens, and estrogens
- the subsequent cessation of linear growth is due in large part to closure of the epiphyses in the long bones by estrogens
- After this time, further increases in height are not possible.
- Because girls mature earlier than boys, growth spurt appears earlier in girls.

Rate of growth in boys and girls from birth to age 20.



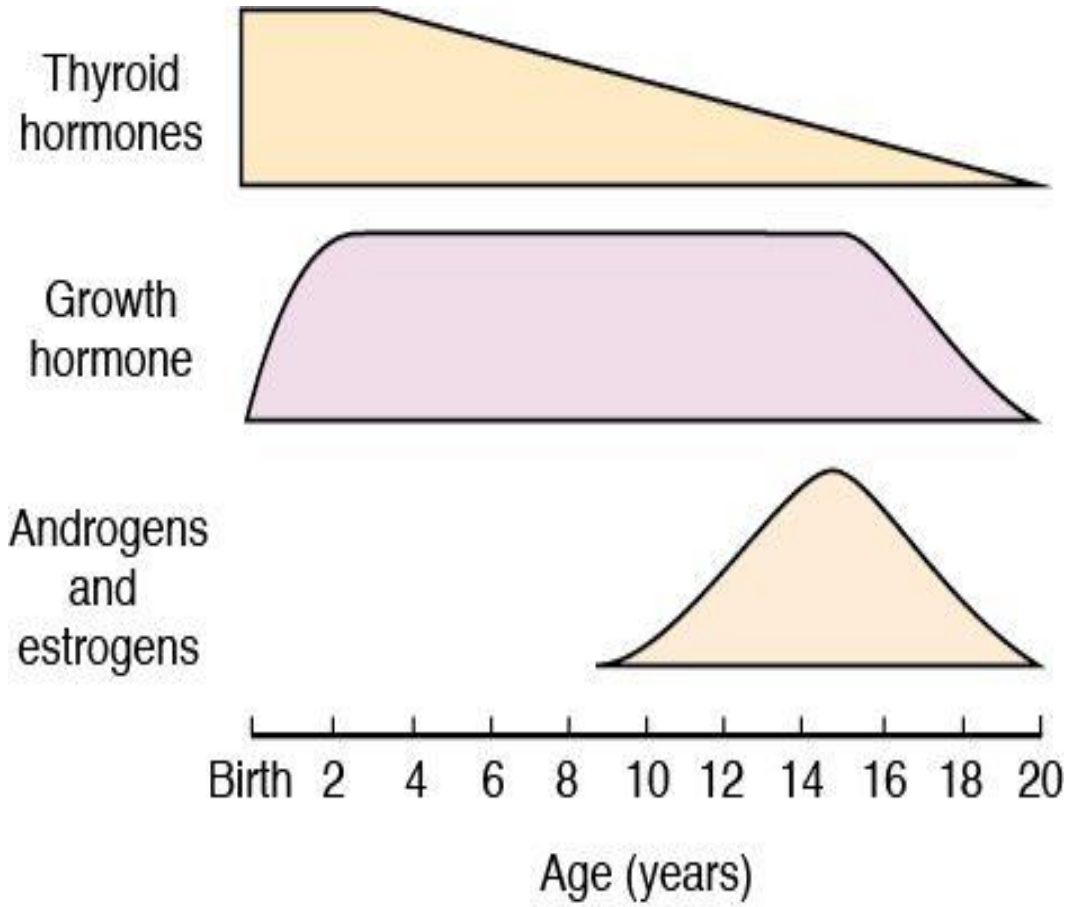
Growth of different tissues at various ages as a percentage of size at age 20



Hormones that contributes to human growth

- Growth hormone
- Insulin and Insulin like growth factors
- Thyroid hormones
- Androgens and estrogens
- Glucocorticoids ?
- Other factors : genetic factors, and adequate nutrition.

Relative importance of different hormones in human growth at various ages



Stages of growth and hormones

Intrauterine Growth

- Growth hormone, insulin, and thyroid hormone play major are needed for normal fetal growth.
- IGF-II (early in gestation), IGF-I (later in gestation).
- Untreated hypothyroidism of mothers during pregnancy can affect fetal development and maternal health of the fetus.
- Hypothyroidism during prenatal stages causes irreversible abnormalities in nervous system maturation, which in turn lead to mental retardation and growth retardation(cretinism)
- Infants of diabetic mothers have increased insulin levels and are large.

Postnatal Growth

- Growth hormone, insulin, and thyroid hormone are needed for normal growth
- Hypothyroidism following delivery causes irreversible abnormalities in nervous system maturation, which in turn lead to mental retardation (cretinism).
- Acquired hypothyroidism later in childhood will slow growth and reduce bone advancement but will not cause mental retardation.
- Replacement of hormone deficiencies creates a period of catch-up growth, but it is soon replaced with a normal growth rate.
- There is no major role for gonadal sex steroids on prepubertal growth or for glucocorticoids, but glucocorticoid excess will slow growth.
- Hypersecretion of growth hormone prior to puberty (pituitary adenoma) results in giantism.
- It also delays pubertal changes like growth spurt
- Hypersecretion of GH in adults leads to acromegaly

Growth Changes at Puberty

- At puberty, if T4 is normal, ↑ androgens drive ↑ growth hormone, which drives ↑ IGF-I.
- IGF-I is the major stimulus for cell division of the cartilage-synthesizing cells located in the epiphyseal plates of long bones.
- In males, the increased androgen arises from the testes (testosterone)
- In females, from the adrenals
- Near the end of puberty, androgens promote the mineralization (fusion or closure) of the epiphyseal plates of long bones.
- Estrogen can also cause plate closure, even in men.
- In females, the growth spurt begins early in puberty and is near completion by menarche.
- In males, the growth spurt develops near the end of puberty.

Thyroid hormones and growth

- Necessary for a completely normal rate of growth hormone secretion
- Basal growth hormone levels are normal in hypothyroidism, but the response to hypoglycemia is frequently blunted.
- Have widespread effects on the ossification of cartilage, the growth of teeth, the contours of the face.
- Patients who are dwarfed because of panhypopituitarism , do not mature sexually, they have juvenile features due to thyroid hormone deficiency

Adrenocortical hormones

- Exert a permissive action on growth.
- High levels of glucocorticoids are potent inhibitors of growth because of their direct action on cells
- Treatment of children with pharmacologic doses of steroids slows or stops growth for as long as the treatment is continued.

Short suture

- Pituitary Dwarfism dependent of specific defects in the growth hormone axis.
- cretinism It is characteristic of childhood hypothyroidism
- Precocious puberty.
- Turner syndrome A syndrome of gonadal dysgenesis seen in patients who have an XO chromosomal pattern instead of an XX or XY pattern
- Various bone and metabolic diseases also cause stunted growth
- constitutional delayed growth, there is no known cause .
- Psychosocial dwarfism Chronic abuse and neglect can also cause dwarfism in children, independent of malnutrition. This condition is known as
- Achondroplasia, the most common form of dwarfism in humans, is characterized by short limbs with a normal trunk. It is an autosomal dominant condition caused by a mutation in the gene that codes for fibroblast growth factor

Clinical Case B

- A middle-aged male patient consults his family physician because he has noticed that his hat and wedding ring are tight and his shoe size has increased one size during the past couple of years. He complains of joint aches and pains. He also states that he has noticed his voice getting deeper and his facial features being thicker and coarser when compared to his pictures of 10 years ago. Laboratory values
- show increased growth hormone and IGF-I levels and increased fasting plasma glucose. An intravenous infusion of glucose fails to decrease growth hormone levels. Brain MRI reveals a tumor localized to the pituitary. The patient is diagnosed with acromegaly resulting from a growth hormone–producing tumor.
- ***Acromegaly*** occurs as a result of growth hormone production in middle-aged adults. The symptoms of acromegaly develop slowly over many years, resulting in a frequent delay in diagnosis after the estimated onset of symptoms.
- The clinical manifestations result from soft tissue growth in response to growth hormone stimulation. This is evident in thickening of facial features, hands, and feet but is also associated with ***organomegaly*** (enlargement of internal organs). Because of growth hormone's anti-insulin actions in adipose tissue, patients present with increased fasting plasma glucose levels or ***impaired glucose tolerance***. Diagnosis is made by measurement of growth hormone release during the 2-hour period following a 75-g oral glucose load (similar to that used for the ***glucose tolerance test***), as well as by measurement of peripheral IGF-I levels. Treatment consists of administration of long-acting somatostatin analogs such as ***octreotide*** and surgical removal of the tumor in cases that do not respond to medical treatment. There are also ***GH receptor antagonists*** currently available that can be used to treat the symptoms of GH excess.