Lecture 4

Endocrine Regulation of Growth

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Lecture Objectives

• List the general characteristics of human growth at different stages of development
• Describe the rate of growth at different stages of growth and development
• List the hormones necessary for normal growth and describe their function
• Describe the relative importance of different hormones at different stages of growth
• Describe the metabolic and growth promoting actions of growth hormone.
• Understand the regulation of growth hormone secretion with focus on the roles of hypothalamic factors, glucose, and insulin-like growth factor-I (IGF-I)
Lecture Objectives

- Describe the role of the hypothalamus, growth hormone releasing hormone and somatostatin in the control of growth hormone secretion.
- List the physiological factors which stimulates and inhibits growth hormone secretion.
- Describe the role of growth hormone in regulating growth at different stages of development.
- Describe the pathophysiology of growth hormone hypersecretion or deficiency at different stages of development.
Rate of Human Growth from birth to age 20 years
Relative growth in brain, total body height (a measure of long-bone and vertebral growth), and reproductive organs. Note that brain growth is nearly complete by the age 5, whereas maximal height (maximal bone lengthening) and reproductive-organ size are not reached until the late teens.
Rate of growth in boys and girls from birth to age 20 years
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 during puberty appears earlier in girls.
- Linear growth in females is less than in males due to early closure of epiphyseal plates.
Hormones that contribute to human growth

Postnatal Growth depends on the following Hormones:

• Growth hormone
• Insulin and Insulin like growth factors
• Thyroid hormones
• Androgens and estrogens
• Glucocorticoids
• Other factors: genetic factors, and adequate nutrition
Fetal Growth

• independent of GH
  • Fetal growth is promoted largely by certain hormones from the placenta
  • Size at newborn at birth being determined principally by genetic and environmental factors as well
Relative importance of hormones in human growth at various ages
Growth Hormone (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
Effects of growth hormones

- GH
  - Na⁺ retention
  - Decreased insulin sensitivity
  - Lipolysis
  - IGF-I
    - Insulin-like activity
    - Antilipolytic activity
    - Protein synthesis
    - Epiphysial growth
  - Protein synthesis
  - Epiphysial growth
Actions of Growth Hormone

Kidney
Pancreas
Intestine
Islets
Parathyroid glands
Skin
Connective tissue

Bone, heart, lung
- ↑ Protein synthesis
- ↑ RNA synthesis
- ↑ DNA synthesis
- ↑ Cell size and number
- ↑ Organ size
- ↑ Organ function

Cell size and number

Liver
- ↑ RNA synthesis
- ↑ Protein synthesis
- ↑ Gluconeogenesis
- ↑ Somatomedin

Muscle
- ↓ Glucose uptake
- ↑ Amino acid uptake
- ↑ Protein synthesis
- ↑ Lean body mass

Adipose tissue
- ↓ Glucose uptake
- ↑ Lipolysis
- ↓ Adiposity

Chondrocytes
- ↑ Amino acid uptake
- ↑ Protein synthesis
- ↑ RNA synthesis
- ↑ DNA synthesis
- ↑ Collagen
- ↑ Chondroitin sulfate
- ↑ Cell size and number
- ↑ Linear growth

IGFs
GH- Diabetogenic Effects

- Muscle-- ↓Glucose uptake
- Fat-- ↑Lipolysis
- Liver-- ↑Gluconeogenesis; ↑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 which has a half-life 15–20 minutes).
- This greatly prolongs the growth-promoting effects of the bursts of growth hormone secretion.
- Inhibits GH secretion
- IGF-II: may have a role in fetal development
- IGFs also decrease in catabolic states, especially protein-calorie malnutrition.
Regulation of Growth Hormone Secretion

[Diagram showing the regulation of growth hormone secretion]

- Sleep stress
- Glucose FFA
- Hypothalamus
  - Somatostatin
  - GHRH
- Pituitary
  - GH
- Liver
  - Other tissues
  - Somatomedin
- Somatomedin
  - Stimulate
  - Inhibit
Feedback Control of growth hormone secretion

Factors that 
Inhibit GH secretion

Factors that 
Promote GH secretion

Hypoglycemia
Exercise
Amino acids,
Ghrelin
e.g., arginine, leucine

Elevated glucose

SS GHRH

Deep sleep

Growth hormone

Liver (and other organs)

Anterior pituitary

Ghrelin

Hypothalamus

IGF-I

GHRH

SST

Pituitary somatotrophs
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.
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)
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.
- May explain increased wrinkling of the skin, diminished rates of function of some of the organs, and diminished muscle mass and strength.
The Actions of Growth Hormone Releasing Hormone (GHRH) and Somatostatin
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.

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Pathophysiology of growth hormone

• Prepubertal Growth Hormone Deficiency

• Congenital
  • mutations in genes for factors that are important in pituitary gland development
  • IGF receptors deficiency or resistance in receptors
  • Failure to generate IGF in the liver

• Acquired:
  • hypothalamic-pituitary tumor, head trauma, radiation therapy
Prepubertal Growth Hormone Deficiency

- GHD is Known as Dwarfism or Pituitary Dwarfism which is characterized by:
  - short stature and delayed skeletal maturation.
  - Tendency to episodes of hypoglycemia.
  - Children with GHD have abnormally short stature with normal body proportions
  - mild obesity, and delayed puberty.
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)

• 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 due GH secreting tumor
- Untreated patients develops panhypopituitarism, due to gland destruction
- Death may occur during early adulthood
Abnormalities of growth hormone hypersecretion

Acromegaly

• It is caused by a postpubertal excessive secretion of growth hormone.

• Increased IGF-I causes most of the changes occurring in acromegaly.

• 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.
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 (coarsening of the facial features, including downward forward growth of the mandible.
  • Carpal tunnel syndrome.
  Increased hat size
  • kyphosis
Clinical Features of Acromegaly

- **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 pituitary
Role of Thyroid Hormone in Growth

- Next to growth hormone, T3 and T4 are most prominent hormones promoting growth during infancy and childhood.
- Necessary for normal rate of growth hormone secretion. In the absence of thyroid hormones, growth hormone secretion is also depressed.

- The thyroid hormones (TH)—thyroxine (T₄) and triiodothyronine (T₃)—are essential for normal growth because they are required for both the synthesis of growth hormone and the growth-promoting effects of that hormone.
- Accordingly, infants and children with hypothyroidism (deficient thyroid function) manifest retarded growth due to slowed bone growth.
- Response to hypoglycemia is frequently blunted in hypothyroidism.
- Patients who are dwarfed because of panhypopituitarism do not mature sexually, they have juvenile features due to thyroid hormone deficiency.
Thyroid Hormone Effects on Growth

- Thyroid hormones have widespread effects on:
  - ossification of cartilage
  - growth of teeth, the contours of the face, and the proportions of the body.
  - Brain development
    - TH is permissive for normal development of the central nervous system during fetal life
    - Inadequate production of maternal and fetal TH due to severe iodine deficiency during pregnancy is one of the most common preventable causes of mental retardation, termed endemic cretinism.
  - Hypothyroid dwarfs (also known as cretins) have infantile features
    - Cretinism characterized by mental retardation, short stature, delayed motor development, and protuberant abdomen
    - In hypothyroid children, bone growth is slowed and epiphysial closure delayed.
    - Early detection of hypothyroidism and early treatment leads to normal mental and physical development
Importance of insulin for Growth

• Adequate amounts of insulin are necessary for normal growth since insulin is an anabolic hormone.
• Its inhibitory effect on protein degradation is particularly important
• regard to growth (general anabolic effect )
• insulin exerts direct, specific growth-promoting effects on cell differentiation and cell division during fetal life in utero (and possibly during childhood).
• Women with diabetes deliver large weight babies due to hyperinsulinemia
• Infants with pancreatic agenesis are very small at birth
• Insulin deficiency in adults and children produce marked catabolic effects associated with wasting of lean body mass
• Insulin is required for normal production of IGF-I.
Sex and Adrenal Steroids

• Normally important for growth spurt during puberty

• Excess sex steroids before puberty accelerate growth but also cause early closure of epiphysial plates and maturation of skeletal tissue

• Unlike growth hormone, however, the sex hormones not only stimulate bone growth, but ultimately stop it by inducing epiphyseal closure.

• Testosterone, but not estrogen, exerts a direct anabolic effect on protein synthesis in many nonreproductive organs and tissues of the body.

• Higher levels of testosterone in males could explain the increased muscle mass of men, compared with women.
Glucocorticoids

- Hypersecretion of glucocorticoids (Cushing Syndrome) cause cessation of growth
- May be due to the effects of these hormones on cartilage formation and bone synthesis
- High levels of these hormones are associated with muscle wasting, osteoporosis and easy busing
- 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.
## Summary of hormonal effects on growth

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<th>Hormone</th>
<th>Principal Actions</th>
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| Growth hormone | Major stimulus of postnatal growth: Induces precursor cells to differentiate and secrete insulin-like growth factor I (IGF-I), which stimulates cell division  
                                | Stimulates secretion of IGF-I by liver  
                                | Stimulates protein synthesis |
| Insulin        | Stimulates fetal growth  
                                | Stimulates postnatal growth by stimulating secretion of IGF-I  
                                | Stimulates protein synthesis |
| Thyroid hormones | Permissive for growth hormone’s secretion and actions  
                                | Permissive for development of the central nervous system |
| Testosterone   | Stimulates growth at puberty, in large part by stimulating the secretion of growth hormone  
                                | Causes eventual epiphyseal closure  
                                | Stimulates protein synthesis in male |
| Estrogen       | Stimulates the secretion of growth hormone at puberty  
                                | Causes eventual epiphyseal closure |
| Cortisol       | Inhibits growth  
                                | Stimulates protein catabolism |
Bone Growth In Length

• Epiphyseal cartilage (close to the epiphysis) of the epiphyseal plate divides to create more cartilage
• The diaphyseal cartilage (close to the diaphysis) of the epiphyseal plate is transformed into bone.
• This increases the length of the shaft.
• Chondrocytes undergo cell division and hypertrophy (elongation)
• Calcification of matrix lead to death of chondrocytes due to lack of nutrients and blood supply
• Dead chondrocytes are cleared by osteoclasts
• Osteoblasts move up away from diaphysis and deposit bone on the disintegrating cartilage layer
Changes During Puberty And Closure Of Epiphyseal Plate

• At puberty, growth in bone length is increased dramatically by the combined activities of growth hormone, thyroid hormone, and the sex hormones.

• As a result osteoblasts begin producing bone faster than the rate of epiphyseal cartilage expansion.

• Thus the bone grows while the epiphyseal plate gets narrower and narrower and ultimately disappears.
Bone Width Growth

• Osteoblasts beneath the periosteum secrete bone matrix on the external surface of the bone. This makes the bone thicker.

• At the same time, osteoclasts on the endosteum break down bone and thus widen the medullary cavity.

• This results in an increase in shaft diameter even though the actual amount of bone in the shaft is relatively unchanged.
Bone Width Growth

• Bones grow in width using a process called appositional growth
• Osteoblasts under the periosteum secrete bone matrix
• Osteoclasts near the medullary cavity dissolve bone, enlarging the cavity.
• The osteoblasts create new bone at a slightly faster rate than the osteoblasts destroy bone.
• This means the bones get wider and slightly thicker as they grow.
Articular cartilage
Bone of epiphysis
Epiphyseal plate
Bone of diaphysis
Marrow cavity

Bone of epiphysis
Resting chondrocytes

Bone of epiphysis

Epiphyseal plate
Diaphysis

Causes thickening of epiphyseal plate

Chondrocytes undergoing cell division
Older chondrocytes enlarging
Calcification of extracellular matrix (entrapped chondrocytes die)
Dead chondrocytes cleared away by osteoclasts
Osteoblasts swarming up from diaphysis and depositing bone over persisting remnants of disintegrating cartilage

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Clinical Case

- 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 include 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.