

Endocrine Control of Growth

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This lecture covers endocrine control of growth. The primary hormone that mediates growth is, unsurprisingly known as growth hormone¹.

¹ sometimes referred to as somatotrop(h)in, hGH, or when generated recombinantly rhGH

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Learning Objectives

For this lecture, the learning objectives are:

- List the hormones important for growth at key times in a person's life.
- Describe the functions of human growth hormone on growth (bones and soft tissues), and on metabolism, and the regulation of its secretion. Explain what 'rhGH' means.
- State the "dual effector hypothesis" for GH actions, and the relative roles of GH and IGF-1 in growth control.
- Describe the interactions among all the key growth-regulating hormones at key times of a person's life: in utero, neonatally, childhood, puberty, adulthood, and senescence.
- Describe the daily regulation of GH levels and the physiological relevance of these cycles.

There are several hormones that are involved in normal growth. The most important is growth hormone, but insulin, thyroid hormones, cortisol, Vitamin D and sex hormones are also very important. These are covered in separate lectures. Generally proper growth (length and mass increase) requires proper nutrition² and a good psychosocial environment.

² both macro- and micronutrients

HUMANS UNDERGO TWO MAJOR GROWTH PHASES. During the first two years there is a dramatic increase in bone, muscle and other organ size. The second major growth phase, which occurs during puberty is at 12-20 years old. Sex hormones³ cause this growth spurt by increasing the levels of both GH⁴ and IGF-1⁵. The hormones required at each stage are shown in Table 1. Vitamin D and the thyroid hormones will be discussed in future lectures.

³ estrogen and testosterone

⁴ Growth hormone, or when generated recombinantly known as rhGH.

⁵ Insulin-like growth factor-1.

| Stage | Age | Hormonal Requirements |
|------------|----------------------------|---|
| Prenatal | (9 months) | Insulin |
| Infantile | 0-1 | Insulin |
| Juvenile | 1-12 years | GH, Insulin, T ₃ , Vitamin D |
| Adolescent | 10-14 (F) and 12-16 (M) | GH, insulin, T ₃ , Vitamin D and Sex Steroids |
| Adult | Puberty - 100 | Normally limited growth |

Table 1: Hormones required at different stages of growth.

Regulation of Growth Hormone and IGF-1 Levels

The main regulator of growth are GH and IGF-1. IGF-1 is regulated by GH, similar to the way that ACTH can promote the release of cortisol. The primary difference is that *both* GH and IGF-1 have important peripheral functions⁶. These hormones are under control of the hypothalamus and pituitary.

⁶ This is known as the *dual-effector hypothesis*, which means that you require both GH and IGF-1 to be functional to see the effects of growth hormone

Hypothalamic and Pituitary Control of Growth Hormone

Growth hormone is released from the somatotroph cells in the anterior pituitary. These cells secrete growth hormone into the circulation upon PKA activation. The two primary regulators of GH secretion are the two hypothalamic hormones GHRH⁷ and somatostatin⁸ which can both be secreted into the hypophyseal portal system from the hypothalamus. The GPCR receptors of these hormones are Gs and Gi linked receptors respectively, so either promote or inhibit the activation of PKA. This process is summarized in Figure 1.

⁷ growth hormone releasing hormone.

⁸ Sometimes called growth hormone inhibiting hormone or GHIH.

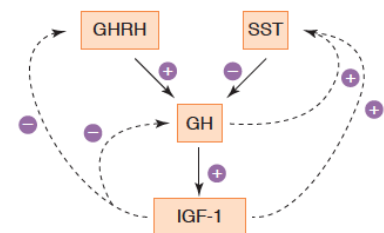


Figure 1: Regulation of GH and IGF-1 levels.

GROWTH HORMONE IS HIGHEST DURING YOUTH WHILE PEOPLE ARE ACTIVELY GROWING. As a person ages, the amount of growth

hormone decreases. This is primarily due to decreases in GHRH secretion from the hypothalamus and not due to an insensitivity of cells to GHRH, GH or IGF-1. Growth hormone also undergoes a normal diurnal rhythm. GH levels are highest shortly after going to sleep and lower during the day. Because of this, most growth occurs during sleeping when nutrients can be used for that purpose and are not needed for normal activities.

Growth Hormone Regulates IGF-1 Secretion

While growth hormone has some effects on growth, several important effects are mediated by another hormone IGF-1⁹, whose expression is regulated by growth hormone. IGF-1 is a protein hormone synthesized and released primarily from the liver and signals through receptor tyrosine kinases. In addition to regulation by growth hormone, IGF-1 can also be regulated by nutrient status, such that if a person is starving, IGF-1 levels are low, even if GH levels are elevated.

⁹ insulin-like growth factor 1

Effects of Growth Hormone

The main role of the GH/IGF-1 axis is to encourage muscle, bone and other organ growth and to divert important nutrients such as proteins, carbohydrates and lipids towards that end. As such, GH/IGF-1 has catabolic actions in storage depots such as adipose tissue, but anabolic actions in growing bones and muscles. In this way GH/IGF-1 function both anabolically (in growing muscle and bone) and catabolically (in storage tissues).

Growth Hormone and IGF-1 Signaling

GH functions through a receptor¹⁰ of the JAK/STAT family. These receptors function primarily by phosphorylating a class of transcription factors known as STATs¹¹ which then produce new mRNAs by binding to specific DNA binding sites on promoters of those genes. IGF-1 on the other hand functions through a receptor tyrosine kinase, similar to insulin. This can result in rapid activation of enzymes that are important for distributing nutrients towards growing tissues.

¹⁰ The Growth Hormone Receptor.

¹¹ Signal Transducer and Activator of Transcription. For GH signaling, the most important is STAT5.

Bone and Soft Tissue Growth

Bones grow via expansion of a region known as the epiphyseal growth plate. A specialized cell type known as osteoblasts form bone at the edge of the plate in concert with chondrocytes, which lay down cartilage in the interior. This is shown in Figure 2.

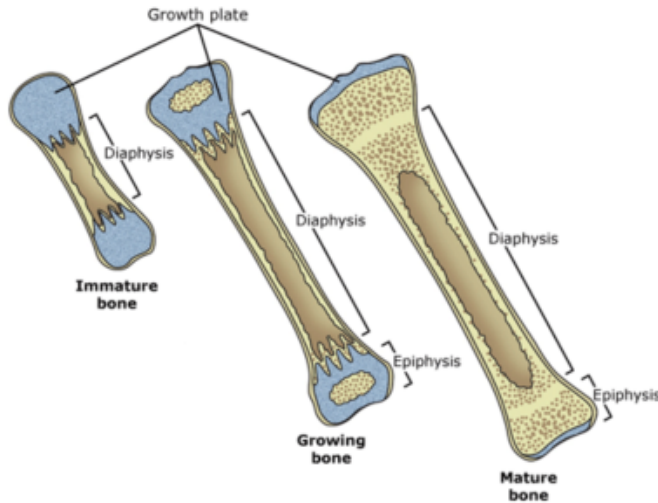


Figure 2: Growth of bone from the growth plate.

MUSCLE GROWTH OCCURS PRIMARILY VIA TWO MECHANISMS, THE INDUCTION OF PROTEIN SYNTHESIS AND THE GENERATION OF NEW MUSCLE CELLS¹² Both of these processes are primarily controlled by IGF-1, which activates a nutrient sensing protein kinase called mTORC1¹³. The signaling pathway by which IGF-1 activates mTORC1 is very similar to the insulin signaling pathway we will discuss in the lecture on the pancreas and insulin action. Once activated mTORC1 mediates both myogenesis and muscle growth.

¹² This is known as myogenesis.

¹³ mechanistic target of rapamycin

Regulation of Metabolism

In addition to promoting protein synthesis in muscle, GH/IGF-1 signaling has several other important peripheral effects. In order to provide substrates for bone and soft tissue growth, GH induces liver gluconeogenesis and promotes lipid breakdown in adipose tissue, to provide substrates for further gluconeogenesis. To allow for glucose to enter the muscle, IGF-1 stimulates glucose uptake in muscle and promotes glycogen and lipid storage in these tissues. The mechanism for this is the same as insulin action, which will be discussed in the lecture on pancreatic function.

Integration of GH with Other Endocrine Factors

Several other hormones work with, or against GH to regulate growth. As stated above, nutrient status is extremely important for growth hormone signaling but insulin and thyroid hormones also enhance GH signaling. These are summarized in Table 2

IN ADDITION TO THE DIRECT EFFECTS OF T₃ ON BONE GROWTH,

| Hormone | Effects |
|----------------------------|---|
| Insulin | Fetal Growth IGF-1 Secretion Protein Synthesis |
| Thyroid Hormone | GH Production CNS Development |
| Testosterone & Estrogen | GH Secretion at puberty Eventual epiphysial closure protein synthesis (T) |
| Cortisol | Inhibits growth hormone release Protein catabolism |

Table 2: Other hormones involved in growth.

thyroid hormone¹⁴ is absolutely required for growth hormone synthesis in the pituitary. This occurs via direct activation of GH transcription in the pituitary somatotropes in response to T₃. Without this input, one of the major consequences of hypothyroidism is reduced GH levels and stunted growth.

¹⁴ This was covered by Dr. Parthasarathi in his lectures on the thyroid gland

IN CONTRAST TO THE GROWTH-PROMOTING EFFECTS OF THE SEX HORMONES, thyroid hormones and insulin, cortisol antagonizes many of the effects of GH/IGF-1 signaling. In times of stress, when cortisol is elevated nutrients are required for essential functions and growth is interrupted. This relationship is complex though, as cortisol blocks the release of GHRH in the hypothalamus but also promotes GH synthesis. This is so that after the stress (and cortisol levels) are resolved, sufficient GH is available to quickly resume normal function.

Pathologies Associated with Growth Hormone Signaling

Since growth hormone decreases dramatically with age, the effects of GH on bone growth and muscle development also decrease. This, while part of the normal aging process is one of the reasons that the elderly are at higher risk for sarcopenia¹⁵ and fractures. In addition to these normal aging effects there are two diseases that are associated with altered GH signaling.

¹⁵ degenerative muscle loss

Acromegaly

A pituitary tumor of the somatotroph cells results in constitutive release of GH into the blood stream, a condition known as acromegaly. These patients have excessive bone and muscle growth, characterized by increased height, protruding jaw and increased muscle mass.

From a dental perspective, the increased jaw growth results in characteristic over-spacing of teeth. These patients also tend to be lean¹⁶ and are insulin resistant¹⁷. Acromegalics are often treated with somatostatin, or via surgical removal of the pituitary tumor.

Dwarfism

The other end of the spectrum is dwarfism. While most cases of dwarfism are due to the activation of FGFR₃^{18,19}. A smaller proportion of dwarfism is due to growth hormone deficiency. This could be due to mutations in GHRH, GH, IGF-1 or their receptors. These patients are smaller, and have muscle weakness, but also have enhanced risk of hypoglycemia²⁰. This can be caused by several things, including immune destruction of pituitary somatotropes, congenital mutations in the growth hormone or its receptor or in response to chemotherapy or radiation exposure.

AS DESCRIBED ABOVE, THYROID HORMONE IS AN IMPORTANT POSITIVE REGULATOR OF GH SIGNALING. As such, hypothyroidism also resembles growth hormone deficiency as growth hormone signaling is impaired. These conditions are often treated with recombinant growth hormone if detected early enough.

IN THE NEXT LECTURE we will discuss the role of the pancreas in the regulation of nutrient homeostasis and discuss hormonal control of feeding.

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References

Rita Shiang, Leslie M. Thompson, Ya Zhen Zhu, Deanna M. Church, Thomas J. Fielder, Maureen Bocian, Sara T. Winokur, and John J. Wasmuth. Mutations in the transmembrane domain of FGFR₃ cause the most common genetic form of dwarfism, achondroplasia.

¹⁶ due to the constitutive activation of lipolysis

¹⁷ potentially due to the disruptive effects of increased fatty acid flux into muscle tissue

¹⁸ This is a negative regulator of growth hormone signaling in bone that we have not discussed. This condition is known as achondroplasia.

¹⁹ Rita Shiang, Leslie M. Thompson, Ya Zhen Zhu, Deanna M. Church, Thomas J. Fielder, Maureen Bocian, Sara T. Winokur, and John J. Wasmuth. Mutations in the transmembrane domain of FGFR₃ cause the most common genetic form of dwarfism, achondroplasia. *Cell*, 78(2):335–342, 1994. ISSN 00928674. DOI: 10.1016/0092-8674(94)90302-6

²⁰ due to impaired fasting induced GH secretion, discussed in the next lecture.

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