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# Pituitary gland and growth hormone

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**Summary**

The pituitary gland (PG) is said to be a "master" endocrine gland and through its tropic hormones influences other endocrine glands to secrete hormones that have a variety of effects on body systems. Growth hormone (GH) is a pituitary gland hormone that has direct and indirect effects produced by somatotrophs in early fetal life. It is essential for normal postnatal growth and has diverse effects across multiple physiological systems. The somatotrophic axis is made predominantly of GH, insulin-like growth factor 1 (IGF-1) and other factors regulating growth. This review summarises the relevant anatomical relationships of the PG, the basic aspect of GH physiology which includes mechanism of action (MOA), regulation and secretion and a direct and indirect action of GH through IGF-1, an important mediator of most of the peripheral action of GH.

**Keywords:** pituitary gland, anterior pituitary gland, growth hormone, insulin-like growth factor 1, insulin-like growth factor binding protein

## Pituitary gland

***Anatomy***: The pituitary gland (PG) is located below the base of the brain encased in a tough fibrous capsule, the sella turcica within the sphenoid bone.[1-3] It is bounded above by the optic chiasm, below by the sphenoid sinus and laterally by the cavernous sinus with the following structures traversing it: the internal carotid artery, cranial nerves II, III, IV, 1st and 2nd divisions of V, and VI.[1-3] The stalk, the floor of the 3rd ventricle and the diaphragm of the sella form the roof. The anterior and posterior relations are sphenoid sinus and sphenoid clivus respectively.[1-3] It is connected to the median eminence of the hypothalamus by the pituitary stalk,[3,4] and is a "partner" to the hypothalamus on the body side of the "mind-body" interface.[3] Although it lies outside the blood–brain barrier, it maintains a close connection with the brain.[4-6]

In humans, it consists of:[1,3,5]

1. The anterior region or adenohypophysis which accounts for 2/3 of the pituitary gland and arises from the ectodermal tissue derived from the Rathke's pouch, a depression in the roof of the developing mouth.
2. The posterior region or neurohypophysis which develops as a direct extension of neural mesodermal tissue.

As a result of the difference in their embryological origin, they are structurally and functionally different.[1,3,5]

### *Anterior pituitary gland (APG)*

It is the glandular lobe of the PG, regulating several physiological processes including stress, growth, reproduction and lactation.[5,7] Its regulatory functions are achieved by the secretion of peptide hormones that act on target organs which would include the adrenal gland, thyroid gland, gonads, bone and liver.[3,4] It is itself regulated by the hypothalamic hormone and negative feedback from these target organs.[1,3,5]

Histologically the anterior pituitary cells are arranged in cords or acinar like structures surrounded by an extensive network of capillary sinusoids.[4] It has both secretory and nonsecretory cells (null cells which make up less than 5% of the anterior pituitary cells).[1] Each of the secretory cells synthesises, stores and secretes one of the families of hormones in response to hormones secreted by the hypothalamus.[1,3,5]

The major hormones are:[1,3-5]

- Follicle stimulating hormone (FSH): (gonadotrophs) – a glycoprotein that targets the gonads sex organs and effect the growth of the reproductive system.
- Luteinising hormone (LH): (gonadotrophs) – a glycoprotein that targets the gonads to effect sex hormone production.
- Prolactin (PLN): (lactotrophs) – a polypeptide whose target is mammary glands and ovaries, it influences the secretion of oestrogens/progesterone and lactation.
- Thyroid stimulating hormone (TSH): (thyrotrophs) – a glycoprotein that targets the thyroid gland and effect the secretion of thyroid hormones.
- Adrenocorticotrophic hormone (ACTH): (corticotrophs) – a polypeptide whose target is the adrenal gland.
- Growth hormone: (somatotrophs, most common cell type, makes up 50% of cells of normal APG):[1]– a polypeptide that targets bone and other tissues to promote growth through carbohydrate, protein and lipid metabolism.

It has three components:[1,5]

- Pars distalis – comprises the most of APG and is at distal-most part of the anterior lobe producing most of the hormones.
- Pars tuberalis – it is a sheath that extends up from pars distalis and wraps around the stalk.
- Pars intermedia – sits between the posterior pituitary gland (PPG) and pars distalis and is often very small in humans.

### *Posterior pituitary gland*

It comprises the posterior lobe of the PG and is part of the endocrine system. It is not a true gland,[7] but a collection of neuronal projections (axons) extending from hypothalamus supraoptic and paraventricular nuclei terminating behind the APG.[1,5] Hormones of this lobe are synthesised by the hypothalamus;[1,3,5] the axons then release the peptide hormones into hypophysial circulation transported in association with a specific carrier protein (neurophysin), these are then stored in neuro secretory vesicles (Herring bodies) before being secreted by the posterior gland into the systemic bloodstream in response to an appropriate stimuli.[1,5] The posterior gland acts as a storage organ,[7,8] therefore damage to the stalk or pituitary alone does not prevent the synthesis and release of the hormones.

It is composed of two parts:[4,5]

- Pars nervosa – which constitutes most of the posterior lobe and is the site of storage of the gland hormones.
- The infundibulum – which bridges the hypothalamic and hypophyseal systems.

Hormones known as posterior pituitary hormones include:[1,3,5]

1. Anti-diuretic hormone (ADH) – most of which is synthesised and released by the supraoptic nucleus in the hypothalamus. It acts on the collecting ducts of the kidney to facilitate water reabsorption by the kidney into the blood.
2. Oxytocin – most of which is synthesised and released by the paraventricular nucleus in the hypothalamus. It stimulates myometrial contractions during labour and milk ejection.

### *Blood supply*

Blood supply to the medial eminence comes from the superior hypophysial artery (SHA), a branch of the internal carotid. The blood supply to the adenohypophysis and neurohypophysis is from SHA and inferior hypophysial artery (IHA) respectively. These arteries anastomose with each other forming a vascular plexus (capillary network) that surrounds the gland. The capillary plexus of SHA supplies the nerve endings of neurosecretory cells of the hypothalamus as well as the adenohypophysis.[3,5] This capillary plexus gives rise to the tributaries of portal vessels which will drain in the long portal veins. The hypothalamus hormones are secreted in the long portal veins which traverse the stalk and are transported to the anterior pituitary to supply the anterior lobe with portal blood.[3] The portal veins then break up to form the second capillary bed into which the adenohypophysis hormones are secreted. There may be small arterial blood supply to the gland from the trabecula artery; however, the major supply is through the portal venous system, which is important with regards to its function.[1,3]

***Venous drainage:*** from the gland to cavernous sinus and the internal jugular veins.[2]

In contrast, the PPG has a distinct arterial blood supply from the inferior hypophysial branches of the internal carotid artery.[2]

### *Regulation of secretion: feedback control of the hypothalamus and APG*

Hormone secretion in the APG is regulated by hormones secreted by the hypothalamus.[1,3] The hypothalamic neurons release substances to small blood vessels that travel directly to the APG (hypothalamo-hypophyseal portal vessels).[2,3,5] The APG in turn releases tropic hormones into the systemic circulation that will have an effect on the target organ. The target organ will then release a hormone that will have an effect on other tissues.[3,5] If the last hormone in a chain of control (e.g. thyroid hormone) exerts a negative feedback on the hypophysis-pituitary system, it is called long-loop negative feedback.[6] If an anterior pituitary hormone (e.g. TSH) exerts a negative feedback on the hypothalamus, it is called short loop negative feedback.[6,9]

## Growth hormone (Somatotropin)

### *Structure*

Genes encoding for GH are located on chromosome 17 locus q22-24 as part of a cluster of five genes.[5,6,9] It is a single chain polypeptide of 191 amino acids with a molecular size of +/- 22 kDa.[1,9] It is a bundle of four antiparallel helices that are necessary for functional interaction with the GH receptor and an additional three mini helices that are important for binding to its receptor. It also contains two highly conserved intramolecular disulphide bonds ($S\text{-}H_2$) that are important for biological activity.[6,9]

### *Regulation of GH secretion*

GH is synthesised and secreted by the somatotrophs of the APG,[6,10] in a pulsatile and in a circadian rhythm,[9,11,12] in response to GHRH. In humans, the diurnal pattern is fully developed after puberty, with maximum release in the 2nd part of the night. GH secretion is gender, age and puberty status dependent.[9,10]

The pulsatile secretion of GH is regulated predominantly by growth hormone releasing hormone (GHRH) and growth hormone inhibiting hormone (GHIH).[10,11]

### *GH stimulation*

1. **GHRH:** indications are that this hormone is responsible for the pulsatile nature of secretion.[11]
2. **Ghrelin**: is secreted by the stomach and hypothalamus and conveys nutritional regulation of the GH-IGF-1 axis.[6] It amplifies the hypothalamic GHRH and synergises with its pituitary GH secretion stimulating effects.[6,10,11]

3. **Other GH releasing neuromodulators that may augment GH discharge via GHRH**: alpha 2 adrenergic, gabaergic agonists,[10] dopamine, galanin (or inhibit the secretion of SRIH, secondarily increasing the sensitivity of somatotrophs to GHRH: dopaminergic, serotonergic and muscarinic agonist, beta adrenergic antagonist and amino acids such as arginine.[6,11]
4. **Some factors stimulating secretion of GH:** testosterone and estrogen,[10] hypoglycaemia,[10,11] deep sleep, insulin, glucagon, fasting, vigorous exercise.[11]

### *GH inhibition*

1. **Somatostatin (GHIH):** Normal pulsatile GH production and release by the APG is inhibited by GHIH.[5] Inhibition by GHIH regulates the magnitude of the troughs and the amplitudes of peaks.[13]
2. **High circulating levels of GH and IGF-1**: GH can regulate its own secretion.[9,13]
3. **Other GH inhibiting neuromodulators that may depress GHRH or increase GHIH secretion**: beta adrenergic agonists.[11]
4. **Some factors inhibiting GH secretion**: hyperglycaemia, glucocorticoid.[11]

### *Mechanism of action of GH*

GH uses a cell surface receptor that is associated with Janus kinase 2 (JAK2) and a tyrosine kinase second messenger system which has two specific receptor binding sites. One molecule of GH binds to its two receptors sequentially and links the two GHR molecules through these two distinct receptor binding sites.[6,10,14] This conformational change in turn induces cross phosphorylation of tyrosine residues in the kinase domain of each JAK2 molecule followed by tyrosine phosphorylation of the GHR.[6,10] Phosphorylated residues of JAK2 and GHR form and serve as docking sites for different S-$H_2$ domains containing signalling molecules, including signal transducers and activators of transcription (STATS).[5,10] Stimulation through the JAK2-STAT signalling pathway leads to production of IGF-1, a major mediator of GH effects.[10,16] It also exerts some of its effects by binding to receptors on target cells, where it activates the mitogen activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway and through this pathway it directly stimulates division and multiplication of chondrocytes of the cartilage.[6,16] Many of the signalling events and phosphorylation cascades culminate in GH-regulated changes in the expression of genes in target cells, likely to mediate its long term physiological actions.[14,15]

***Physiological effects of GH:*** The major biological effect of GH is to promote growth in all internal organs.[1,6] Its effects on the tissues of the body can generally be described as anabolic.[8,15]

***Indirect effects:*** Most of the effects of GH hormone are mediated by IGF-1.[10,14,17] It is a 70 amino acid peptide with three $SH_2$ bridges, 99% bound to a transport protein. Although it is synthesised by multiple mesenchymal and epithelial cell types, e.g. bone where it may have an important and crucial local paracrine and autocrine effect, liver is the major producer accounting for more than 75% of circulating IGF-1.[10,15] The production and release into the bloodstream of IGF-1 by the liver is mediated by GH stimulation via its cell surface receptor; it functions as a classic endocrine hormone as it has a stimulating effect on a variety of tissues. It exerts its biological activity in both autocrine/paracrine and endocrine fashion[11,12,18] but exhibits no diurnal variation.[9,10]

***IGF-1 MOA:*** It exerts its effect via IGF receptor which is widely distributed and is expressed in many tissues in the body.[1,10,15] IGF-1 receptor is heterotetrametric glycoprotein composed of two alpha subunits containing the IGF binding domain and two beta subunits which contain the transmembrane domain followed by a tyrosine kinase domain.[14,15] It uses the tyrosine kinase second messenger system which, following a number of reactions, will in turn activate the MAPK/ERK pathway, leading to stimulation of cell growth.[10,16]

***IGF binding proteins:*** A family of six high affinity transport proteins.[9,10,14] They control the ability of IGF-1 to bind to the receptor. Less than 1% of the total IGF-1 in plasma is in an unbound state and it is this form that is capable of activating the receptor.[10,14] The complexed IGF-1 and the acid labile subunit (ALS) represent the storage form of the hormone and prolong its half-life for several hours.[8,15,18] IGFBP-3 is the most abundant in plasma with the highest affinity for IGF-1.[14]

### *Effects on tissue growth*

#### *Skeletal (bone)*

***Direct:*** GH acts directly at the epiphyseal plate to stimulate linear growth.[3,8] It stimulates and enhances the differentiation and proliferation of chondoblasts in the germinal layer and subsequent mineralisation of the epiphyseal growth plate of children and adolescents resulting in growth of long bones.[3,6]

***Indirect:*** via IGF -1, GH stimulates proliferation and differentiation of chondrocytes; these will then secrete IGF-1 which will in turn stimulate clonal expansion and maturation of chondrocytes, resulting in increases in dimension and volume.[3,8,14]

By increasing amino acid availability, increase in DNA synthesis, increase in collagen chondroitin sulphate synthesis will lead to increase in cell size and number, increase in organ size and function and linear growth.[14]

### *Extra skeletal hyperplasia and hypertrophy*

***Liver:*** Apart from effects on hepatic gluconeogenesis and glycogenolysis, it directly stimulates IGF-1 production and the subsequent increase in RNA, protein synthesis and IGFBP production.[14,18]

***Muscle:*** Through IGF-1, it stimulates both the differentiation and proliferation of myoblasts, amino acid uptake and protein synthesis by the muscle; the net result is an increase in lean body mass.[1,10]

***Effects of GH on metabolism:*** These are dictated by the nutritional status of the individual.[9,10,17] In the state of abundance where insulin is increased in the liver and IGF-1 production is stimulated, GH promotes protein anabolism whereas in a state of decreased nutrient intake, during exercise and during sleep the direct effects of GH are more predominant and they are characterised by stimulation of lipolysis.[9,15] IGF-1 is one of the most potent stimulators of cell growth, affecting almost all cells of the body.[1,10]

Both direct and indirect effects may be at play.[6,10,15]

**$Ca^{2}$+/$Na^{+}$/$K^{+}$ and phosphate metabolism:** GH promotes retention of these substances that are required for the growth of the body.[5]

***Protein metabolism:*** In general GH (and IGF-1) stimulates protein anabolism in many tissues which includes increased uptake of amino acids, stimulation of nucleic acid and protein synthesis, decrease in oxidation of proteins and induction of positive balance.[10,15,17]

***Lipid metabolism:*** GH enhances the utilisation of fat by stimulating lipolysis through inhibition of lipoprotein lipase and oxidation in adipocytes, and decreased glucose uptake. Neutral fats and triglycerides are broken down to release free fatty acids (FFA). They are utilised for energy supply to the tissues.[14,19]

***Carbohydrates metabolism:*** It suppresses the ability of the insulin to stimulate uptake of glucose in the peripheral tissues (liver, muscle, adipose tissue) (antagonise insulin action) and enhances glucose synthesis through increase in gluconeogenesis predominantly and glycogenolysis by the liver,[1,15] thus assisting in the maintenance of blood glucose within the normal range.[4,19]

Lipid and carbohydrate metabolism effect by the GH requires the permissive effect of cortisol.[8,19]

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