

**INTRODUCTION**

A growth promoting principle of pituitary gland was discovered in 1921. In the early 1944, bovine growth hormone (GH) was isolated. In the early 1960's, human growth hormone (hGH) was isolated and used in GH-deficient children. In 1979, the cDNA encoding hCG was Cloned and in 1985, it was approved for clinical use.

GH, chorionic somatomammotropin (CS, placental lactogen) and Prolactin (PRL) belongs to a family of hormones evolved from a common precursor. The GH family of proteins contain approximately 200 amino acids with 2-3 disulfide/bonds. The hGH gene-family consists of the 191-amino acid hGH, a GH variant hGH-V, hCS and hPrl. hGH is predominantly non-glycosylated, expressed in placenta and found in the serum during pregnancy. Like GH it promotes fetal growth. Another variant of hGH, termed 20 KDa has been found in pituitary and blood. It lacks amino acid 32-46 of hGH. HCS has minimal growth promoting action and it is expressed in placenta.

In healthy adults, GH exerts several metabolic effects, including those on protein, fat and carbohydrate. Among the metabolic effects, two contradictory actions have been described. They are acute and early insulin-like activity and the late or chronic anti-insulin effects. This chronic effect is also described as GH's diabetogenic activity. Acute insulin-like activities include hypoglycemia, increased glucose and amino acid transport and metabolism, increased protein synthesis, increased glycogenesis and increased lipogenesis. These insulin like activities are seen primarily in vitro or under special circumstances such as following hypophysectomy. GH's anti-insulin activities include hyperglycemia, hyperinsulinemia; increased lipolysis, decreased glucose transport,

increased serum level of non-esterified fatty acids, decreased glucose metabolism and insulin resistance. The anti-insulin activity has been found after relatively long periods of GH treatment, that is, after chronic exposure both in cultured cells and in-vivo are thought to represent a major physiological effect of GH.

To explain these related but opposite activities, as well as other multiple GH activities, three hypothesis has been presented: (1) existence of multiple GH receptors, (2) presence of multiple active centers in GH molecule and (3) the presence of small, active GH fragments that result in multiple activities.

In addition to insulin-like and anti-insulin like activities of GH, other in-vivo assays in for GH activity include an influence on rat tibia size, metabolic and growth effect in hypophysectomized animals, activities on in-vitro cell system expressing GHR.

Many of the functional effects of GH actually results from the action of insulin like growth factor-1 (IGF-1), which is produced in liver, bone and other tissues in response to GH. In 1985, Green put fourth the dual-effect theory of GH action. In this theory, it is postulated that GH acts directly on cells to promote differentiation, while IGF-1 promotes cell multiplication. Conditional disruption of IGF-1 gene in liver of mice significantly reduces IGF-1 levels, but there rates of growth were not effected. Thus serum IGF-1 has no correlation with growth rate, implying that the paracrine and/or autocrine actions of IGF-1 are important.

Somatotropic cells of the anterior pituitary are the major site of GH synthesis and secretion. Production is regulated by the opposing actions of two hypothalamic uropeptides; growth hormone-releasing hormone (GHRH), which stimulates synthesis and secretion of

GH and somatostatin (ST), which inhibits secretion of GH. Natural ligand of growth hormone secretagogue receptor, "ghrelin" was identified in 1999 as a result of a "reverse pharmacology process". Another weak endogenous GH secretagogue (GHs) is met-enkephalin. Other synthetic peptide and non-peptide analogues are GHRP-6, GHRP-2 and hexarelin. The characteristics of GHs is that they have weak effects on GH stimulation from the pituitary in vitro while they are efficacious when administered in vivo. Ghrelin belongs to brain-gut peptide family. It is secreted predominantly from stomach but the highest concentration of the receptor is in hypothalamus and pituitary.

GH exerts its effects through GH receptor (GHR). GHRs have been found on the cell surface of many tissues throughout the body, including liver, muscle, adipose tissue and kidney's, embryo and fetal tissue. GHR is a member of the class-1 hematopoietic cytokine family. It has a large extracellular domain, a small transmembrane domain and an intracellular domain. The soluble portion of the GHR extracellular domain is termed as the growth hormone-binding protein (GHBP). The function of GHBP is unknown, but it might increase the activity of GH by sequestering the molecule from the GHR. The molecular mechanisms by which GH transmits its signals via its receptor has been found in cultured cells or hypophysectomized rats. They belong to JAK-STAT pathway (Janus kinase, signal transducers and activators of transcription) and mitogen activated protein kinase (MAPK) pathways. In addition to these GH also stimulates IRS-1 and IRS-2 of insulin signaling pathways thus promoting example of biologic cross talk.

The IGFs belong to a family of polypeptides that evolved from a common ancestral precursor into IGF-1, IGF-2 and proinsulin. All three members probably evolved before the emergence of pituitary gland, although GH control of IGF-1 appeared near the time that IGF-1 and insulin diverged. Unlike insulin both the growth factors circulate bound to high affinity binding proteins, have more prolonged plasma half-life, different target cell action. As they are ubiquitously present they are major determinants of balanced organ and tissue growth.

The IGFs are a family of six proteins that have differential affinity for IGF-1 and IGF-2. They control the half life and ability to bind receptors, transporting the IGFs into and out of vasculature, controlling tissue localization and distribution, access to receptors and thereby biological response of cells. Amongst all proteins IGF-1 is clinically and biologically most significant.

## PHYSIOLOGY OF HYPOTHALAMO-PITUITARY-SOMATOTROPH AXIS

GH is secreted by somatotroph in the anterior pituitary gland. The secretion is pulsatile with discrete pulses every 3-4 hrs and virtually undetectable GH concentrations in between. The maximum GH peak occurs during stage IV of non-rapid eye movement sleep. Its secretion varies considerably with age with a sexually dimorphic pattern. During pubertal years under the effect of sex steroid the GH pulse amplitude may be so high that it may be comparable to GH excess states. The average daily output is greater in female. The amplitude of GH peak is determined by GHRH which stimulates both synthesis and release of GH. Somatostatin determines trough level of GH by inhibition of GHRH release from hypothalamus and GH release from the pituitary. Withdrawal of somatostatin tone determines the timing of GH pulse. The neural pathways regulating GH release are predominantly adrenergic and cholinergic. They also form the physiological basis of different pharmacological provocation tests.

The disorders of growth hormone can be categorized into growth hormone excess, growth hormone resistance and growth hormone deficiency.

## GROWTH HORMONE EXCESS

Growth hormone excess leads to disease of spectacular growth and metabolic disarray known as acromegaly. If untreated, it results in gross acral enlargement and disfigurement, musculo-skeletal disability, cardiac failure, respiratory dysfunction, diabetes and accelerated cardiovascular and cancer related mortality. If the disease occurs before fusion of epiphyses, gigantism results. In majority of cases it occurs because of somatotroph adenomas. Rarely excessive GHRH release from bronchial carcinoid, hypothalamic ganglioneuroma and choristoma or source of extrapituitary growth hormone secretion. The diagnosis depends on typical clinical features and mass effect of tumor leading to other pituitary hormone deficiency and visual field effect. Elevated age and sex matched IGF-1 is used as a screening test and definitive diagnosis of active disease is established by non-suppressible growth hormone level ( $> 1$  ng/ml) after giving 75 gms of oral glucose load. Magnetic resonance imaging of the hypothalamo-pituitary area is required to know size of tumor and extensions. Surgery is the main stay of therapy. Radiotherapy, long acting octreotide and GH receptor antagonist (Pegvisomant) are used only in selected cases. The treatment goes are

clinical and biochemical cure, alleviation of compressive symptoms and preservation/re-establishment of normal pituitary functions.

### GH INSENSITIVITY SYNDROME

These are disorders of GH inaction despite adequate or more than adequate GH level. The peripheral tissues are incapable of responding normally to GH thereby leading to primary IGF-1 deficiency. Primary GH insensitivity (GHI) includes defect in: (1) GHR termed as Laron's dwarfism, (2) post receptor defects, (3) defects in the synthesis and actions of IGF-1, (4) bio inactive GH molecule.

The clinical phenotype associated with GHI includes severe postnatal growth failure, small face, frontal bossing, high pitched voice, premature aging, delayed bone age and other features common to severe GHD. Blue sclera and limited extensibility at elbow have also been variably described. Other craniofacial and brain abnormalities recently described are small paranasal sinuses, mastoids, failure of bone marrow maturation in base of skull, thin diploe of calvaria, suture separation, diffuse brain parenchymal loss, lacunar infarcts and cerebellar atrophy.

The patients with IGF-1 synthetic defects had, in addition to postnatal growth failure, intrauterine growth failure, mental retardation, sensory neural deafness and insulin resistance. Some children with idiopathic short stature may have underlying GHI<sup>367</sup>. The diagnosis of GH insensitivity as suggested by extreme short stature decreased IGF-1, IGF-2 and IGF-3 and elevated concentrations of GH.

GH resistance may also occur secondary to systemic illness, malnutrition, glucocorticoids, antibodies to exogenous GH.

### CHILDHOOD GH DEFICIENCY

Amongst the causes of short stature GH deficiency (GHD) is most difficult to diagnose. Untreated GHD cases proportionate short stature in children. GHD can be congenital or acquired and may be isolated or coexist with other pituitary hormone deficiencies (pan-hypopituitarism). Congenital GHD may be due to transcription factor defects (Pit-1, PROP-1), GHRH or GH gene defects, idiopathic. Acquired GHD may be due to birth trauma, Rathke's pouch cyst, cranial irradiation and chemotherapy. The manifestations in neonatal period are hypoglycemia, prolonged jaundice, micropenis in male child. In early infancy and childhood it causes short stature with relative adiposity. Diagnosis depends upon

slow growth rate velocity (< 4 cm/year), height < 3 SD, in appropriate GH response to insulin hypoglycemia or other provocative tests. In children, clonidine test at a dose 4 ug/kg with peak GH response < 10 ng/ml with other features can clinch the diagnosis. MRI of hypothalamo-pituitary area is helpful in finding out structural abnormalities.

Adult growth hormone deficiency usually occurs in a setting of pituitary adenoma, traumatic brain injury, other inflammatory and infiltrative disorders of pituitary, cranial irradiation, cancer chemotherapy. It presents with poor quality of life, sleep, cognitive functions.

Childhood growth hormone deficiency is treated by human recombinant growth hormone at a dose of 12 IU/m<sup>2</sup>/wk. The treatment is monitored by growth rate velocity, bone age, serum IGF-1. The dose is applied in the anterior abdominal wall subcutaneously in the evening time to match the normal physiology. The dose for adult growth hormone deficiency is 400 mg/kg/day. The treatment is monitored by age and sex matched IGF-1. The side effects of growth hormone therapy are hypothyroidism, carpal tunnel syndrome, benign intracranial hypertension, slipped capital femoral epiphysis, pain and irritation at the local site.

Childhood growth hormone deficiency if identified early and treated properly is rewarding. Syndromes of growth hormone insensitivity are treated by IGF-1 which is now commercially available.

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