14 Human Growth Hormone

Le N. Dao, Barbara Lippe, and Michael Laird

INTRODUCTION

Human growth hormone (hGH) is a protein hormone essential for normal growth and development in humans. hGH affects many aspects of human metabolism, including lipolysis, the stimulation of protein synthesis, and the inhibition of glucose metabolism. Human growth hormone was first isolated and identified in the late 1950s from extracts of pituitary glands obtained from cadavers and from patients undergoing hypophysectomy. The first clinical use of these pituitary-extracted hGHs for stimulation of growth in hypopituitary children occurred in 1957 and 1958 (Raben 1958). From 1958 to 1985 the primary material used for clinical studies was pituitary-derived growth hormone (pit-hGH). Human growth hormone was first cloned in 1979 (Goeddel et al. 1979; Martial et al. 1979). The first use in humans of recombinant human growth hormone (rhGH) was reported in the literature in 1982 (Hintz et al. 1982). The introduction of rhGH coincided with reports of a number of cases of Creutzfeldt-Jakob disease, a fatal degenerative neurological disorder, in patients receiving pituitary-derived hGH. Concern over possible contamination of the pituitary-derived hGH preparations by the prion responsible for Creutzfeldt-Jakob disease led to the removal of pit-hGH products from the market in the US in 1985 followed by the FDA approval of rhGH later in the year. The initial rhGH preparations were produced in bacteria (*E. coli*) but, unlike endogenous hGH, contained an N-terminal methionine group (met-rhGH). Natural sequence recombinant hGH products have subsequently been produced in bacteria, yeast, and mammalian cells.

L.N. Dao (✉)
Clinical Pharmacology, Genentech Inc., 1 DNA Way, MS463a, South San Francisco, CA 94080, USA
e-mail: le1@gene.com

B. Lippe, M.D.
Endocrine Care, Genentech Inc, South San Francisco, CA, USA

M. Laird, Ph.D.
Department of Bioprocess Development, Division of Medical Affairs, Genentech Inc, South San Francisco, CA, USA

HGH STRUCTURE AND ISOHORMONES

The major, circulating form of hGH is a non-glycosylated, 22 kDa protein composed of 191 amino acid residues linked by disulfide bridges in two peptide loops (Fig. 14.1). The three dimensional structure of hGH includes four antiparallel alpha-helical regions (Fig. 14.2) and three mini-helices. Helix 4 and Helix 1 have been determined to contain the primary sites for binding to the growth hormone receptor. In addition, two of the three mini-helices located within the connecting link between Helix 1 and 2 have been shown to play an important role in the binding of growth hormone to its receptor (Root et al. 2002; Wells et al. 1993). Endogenous growth hormone contains a variety of other isoforms including a 20 kDa monomer, disulfide-linked dimers, oligomers, proteolytic fragments, and other modified forms (Boguszewski 2003; Lewis et al. 2000). The 20 kDa monomer, dimers, oligomers, and other modified forms occur as a result of different gene products, different splicing of hGH mRNA, and posttranslational modifications. These isoforms are generally expressed at lower amounts compared to the 22 kDa protein (Baumann 2009).

There are two hGH genes in humans, the "normal" hGH-N gene and the "variant" hGH-V gene. The hGH-N gene is expressed in the pituitary gland. The hGH-V gene is expressed in the placenta and is responsible for the production of several variant forms of hGH found in pregnant women. Non-glycosylated and glycosylated isoforms of hGH-V have been identified (Ray et al. 1989; Baumann 1991).

PHARMACOLOGY

■ Growth Hormone Secretion and Regulation

Growth hormone is secreted in a pulsatile manner from somatotrophs in the anterior pituitary. Multiple feedback loops are present in normal regulation of hGH

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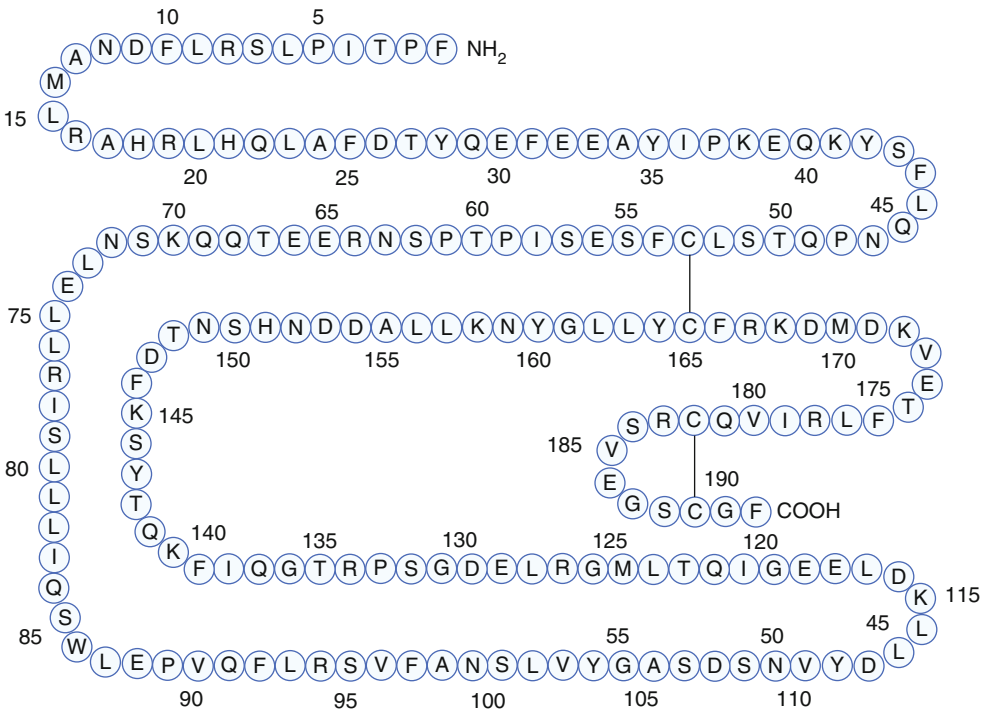

Figure 14.1 ■ Primary structure of recombinant human growth hormone.

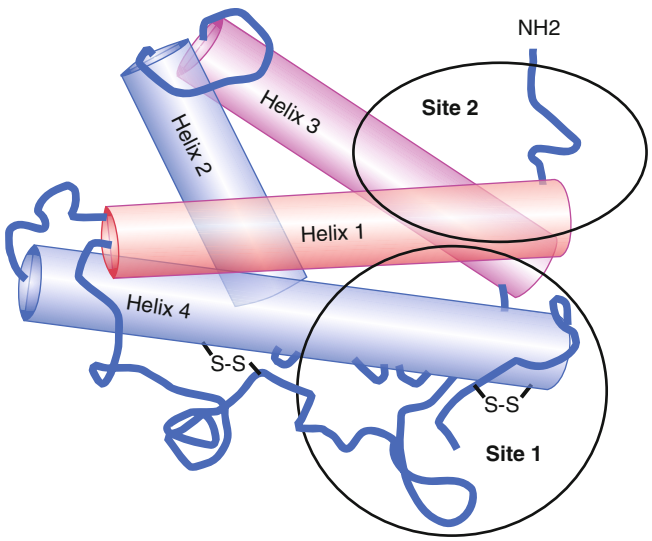

Figure 14.2 ■ Schematic 3-D structure of hGH showing four antiparallel α-helices and receptor binding sites 1 and 2. Approximate positions of the two disulfide bridges (*S-S*) are also indicated (Modified from Wells et al. (1993)).

secretion (Casanueva 1992; Giustina and Veldhuis 1998) (Fig. 14.3). Growth hormone release from the pituitary is regulated by a "short loop" of two-coupled hypothalamic peptides – a stimulatory peptide, growth hormone releasing hormone (GHRH), and an inhibitory peptide, somatostatin (also known as somatotropin release-inhibitory factor (SRIF)). GHRH and somatostatin are, in turn, regulated by neuronal input to the hypothalamus and the GH secretagogue, ghrelin (Kojima et al. 2001). There is possibly also an "ultrashort loop" in which hGH release is feedback regulated by growth hormone receptors present on the somatotrophs of the pituitary themselves. Growth hormone secretion is also regulated by a "long loop" of indirect peripheral signals including negative feedback via insulin-like growth factor (IGF-1) and positive feedback via ghrelin. Growth hormone-induced peripheral IGF-1 inhibits somatotroph release of hGH and stimulates somatostatin release.

Growth hormone secretion changes during human development, with the highest production rates observed during gestation and puberty (Giustina and Veldhuis 1998; Brook and Hindmarsh 1992). Growth hormone production declines approximately 10–15 % each decade from age 20 to 70. Endogenous hGH secretion also varies with sex, age, nutritional status, obesity, physical activity, and in a variety of disease states. Endogenous hGH is secreted in periodic bursts over a 24-h period with great variability in burst frequency, amplitude, and duration. There is little detectable hGH released from the pituitary between bursts. The highest endogenous hGH serum concentrations of 10–30 ng/mL usually occur at night when the secretory bursts are largest and most frequent.

■ Growth Hormone Biologic Actions

hGH has well-defined growth-promoting and metabolic actions. hGH stimulates the growth of cartilage

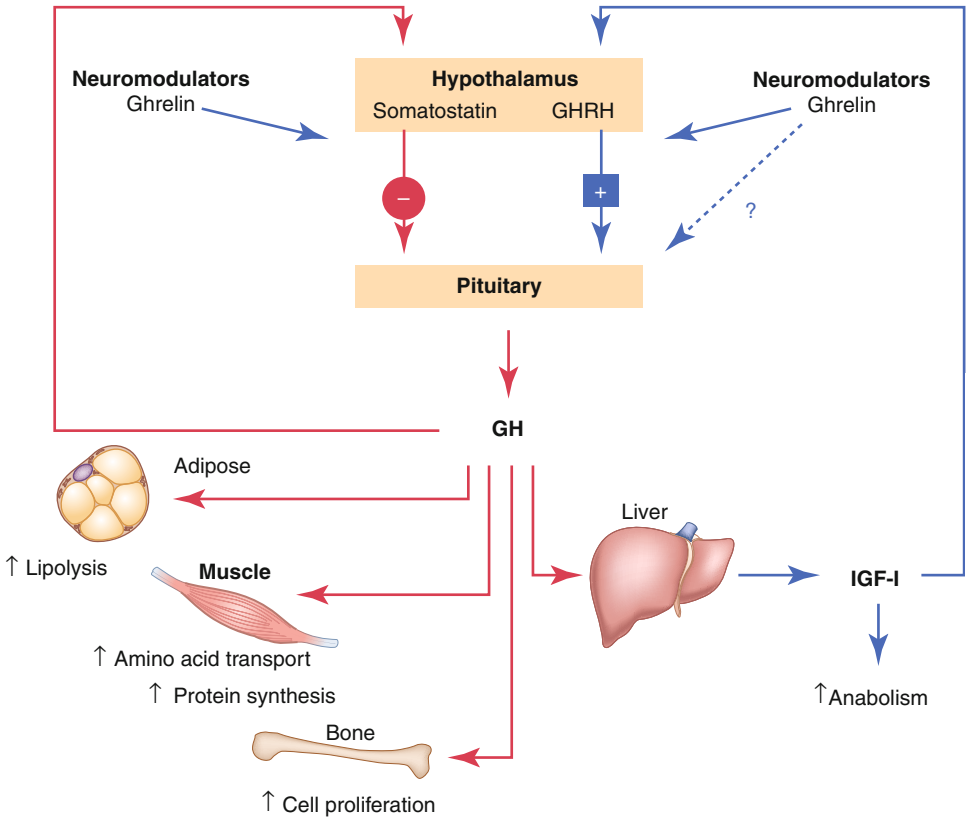

Figure 14.3 ■ Schematic representation of hGH regulation and biologic actions in man. "Short loop" regulation of hGH secretion occurs between the hypothalamus and pituitary. GHRH stimulates GH release. Somatostatin inhibits GH release. "Long loop" regulation of hGH secretion occurs through peripheral feedback signals, primarily negative feedback from insulin-like growth factor 1 (IGF-1). hGH acts directly on muscle, bone, and adipose tissue. Other anabolic actions are generally mediated through IGF-1.

and bone directly, through hGH receptors in those tissues, and indirectly, via local increases in IGF-1 (Isaksson et al. 2000; Bouillon 1991). Metabolic actions, which may be directly controlled by hGH, include the elevation of circulating glucose levels (diabetogenic effect) and acute increases in circulating concentrations of free fatty acids (lipolytic effect). Other hGH anabolic and metabolic actions believed to be mediated through increases in local or systemic IGF-1 concentrations include the following: increases in net muscle protein synthesis (anabolic effect), skeletal muscle growth, chondroblasts and osteoblasts proliferation, and linear growth; modulation of reproduction in both males and females; maintenance, control, and modulation of lymphocyte functions; increases in glomerular filtration rate and renal plasma flow rate (osmoregulation); influences on the release and metabolism of insulin, glucagon, and thyroid hormones (T3, T4); and possible direct effects on pituitary function and neural tissue development (Casanueva 1992; Strobl and Thomas 1994; Le Roith et al. 1991).

■ hGH Receptor and Binding Proteins

The hGH receptor (GHR) is a member of the hematopoietic cytokine receptor family. It has an extracellular domain consisting of 246 amino acids, a single 24-amino-acid transmembrane domain, and a 350-amino-acid intracellular domain (Fisker 2006). The extracellular domain has at least six potential N-glycosylation sites and is usually extensively glycosylated. GHRs are found in most tissues in humans. However, the greatest concentration of receptors in humans and other mammals occurs in the liver (Mertani et al. 1995).

As much as 40–45 % of monomeric hGH circulating in plasma is bound to one of two binding proteins (GHBP) (Fisker 2006). Binding proteins decrease the clearance of hGH from the circulation (Baumann 1991) and may also serve to dampen the biological effects of hGH by competing with cell receptors for circulating free hGH. The major form of GHBP in humans is a high-affinity ($Ka = 10^{-9}$ to 10^{-8} M), low-capacity form which preferentially binds the 22 kDa form of hGH (Baumann 1991; Herington et al. 1986). Another low-affinity ($Ka = 10^{-5}$ M), high-capacity GHBP is also present which binds the 20 kDa form with equal or slightly greater affinity than the 22 kDa form. In humans, the high-affinity GHBP is identical to the extracellular domain of the hGH receptor and arises by proteolytic cleavage of hGH receptors by a process called ectodomain shedding. Since the high-affinity binding protein is derived from hGH receptors, circulating levels of GHBP generally reflect hGH receptor status in many tissues (Fisker 2006; Hansen 2002).

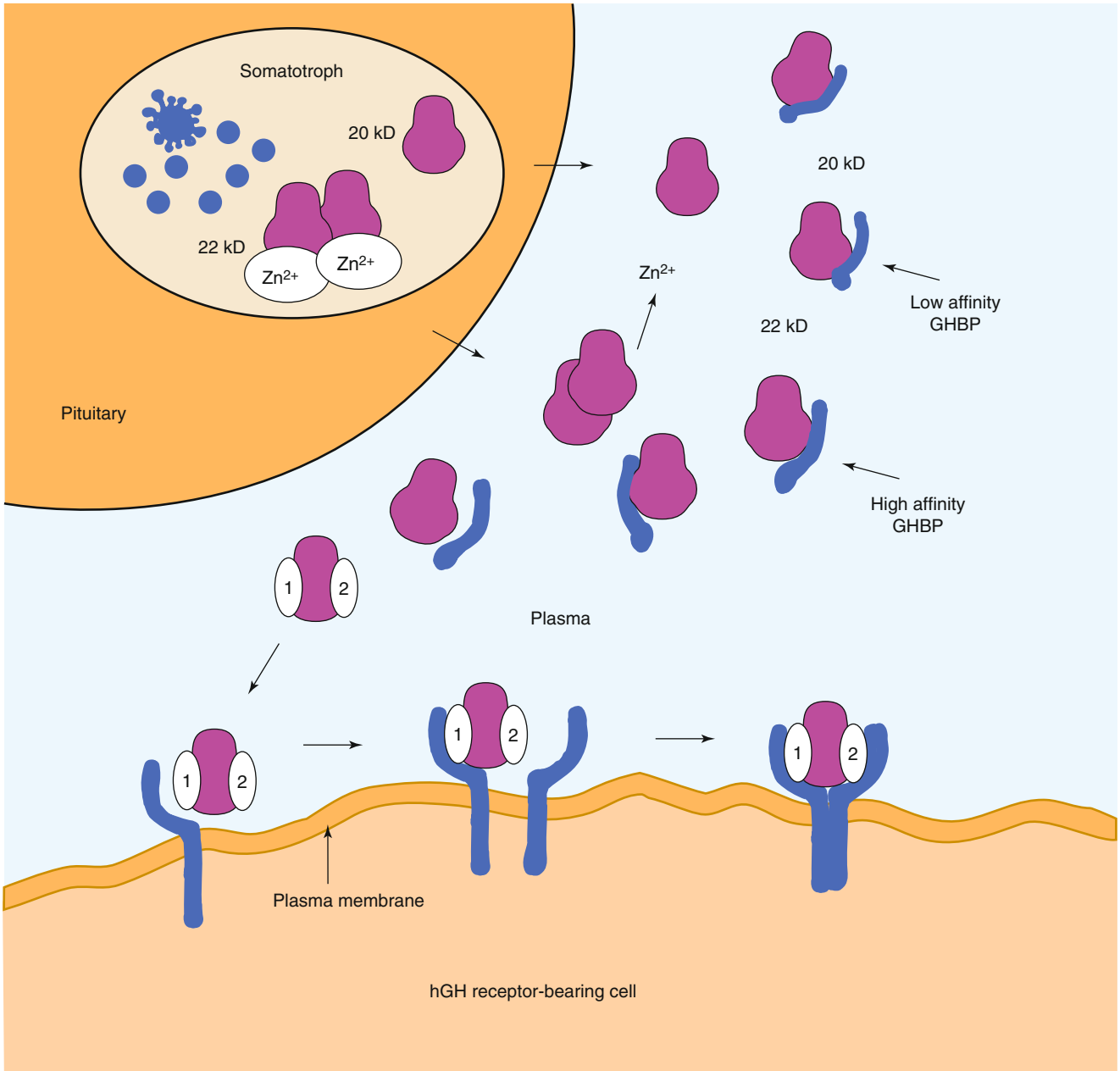

Figure 14.4 ■ Growth hormone secreted isoforms, binding proteins, and receptor interactions. Both 22 and 20 kDa forms are secreted by the pituitary. Pituitary hGH is stored bound to zinc (Zn^{2+}) which is released upon secretion from the pituitary. Secreted hGH is free or bound to either the low- or high-affinity GHBP in plasma. Receptor activation involves dimerization of two receptor molecules with 1 molecule of hGH (Modified from Wells et al. (1993)).

■ Molecular Endocrinology and Signal Transduction

X-ray crystallographic studies and functional studies of the extracellular domain of the hGH receptor suggest that two receptor molecules form a dimer with a single growth hormone molecule by sequentially binding to Site 1 on Helix 4 of hGH and then to Site 2 on Helix 3 (Fig. 14.4) (Wells et al. 1993). Signal transduction may occur by activation/phosphorylation of JAK-2 tyrosine kinase followed by activation/phosphorylation of multiple signaling cascades (Herrington and Carter-Su 2001; Piwien-Pilipuk et al. 2002; Brooks and Waters 2010).

■ Dosing Schedules and Routes

The dosing levels and routes for exogenously administered growth hormone were first established for pit-hGH in growth hormone deficient (GHD) patients (Laursen 2004; Jorgensen 1991). The initial pit-hGH regimen, three times weekly by intramuscular (IM) injection, was based on a number of factors including

patient compliance and limited availability of hGH derived from cadaver pituitaries and the assumption that intramuscular injections would be less immunogenic. Subsequent clinical evaluations found a very strong patient preference for subcutaneous (SC) administration and data supporting no increased immunogenicity. Furthermore, increased growth rates were observed with daily SC injections compared to the three times weekly injection schedules (MacGillivray et al. 1996). The abdomen, deltoid area, and thigh are commonly used subcutaneous injection sites. Current dosing schedules are usually daily SC injections, often self-administered with a variety of injection devices.

■ Pharmacokinetics and Metabolism

The earliest pharmacokinetic studies were conducted with pituitary-derived hGH (pit-hGH). The pharmacokinetic profiles of pit-hGH, met-rhGH, and rhGH have been compared (Hansen 2002; Laursen 2004) and shown to be very similar. The pharmacokinetics of hGH have been studied in normal, healthy children and adults and a variety of patient populations (Hansen 2002; Laursen 2004; Jorgensen 1991).

Exogenously administered pit-hGH, met-rhGH, and rhGH are rapidly cleared following intravenous (IV) injection with terminal half-lives of approximately 15–20 min (Hansen 2002; Laursen 2004). Distribution volumes usually approximate the plasma volume. hGH clearance in normal subjects ranges from 2.2 to 3.0 mL/kg/min. hGH clearance decreases with increasing serum GH concentrations, most likely due to saturation of hGH receptors at concentrations >10–15 μg/L (Hansen 2002). Comparative analyses of total hGH clearance have not shown consistent population differences based on age, sex, or body composition. However, hGH clearance is controlled by a complex interaction between free hGH, GHBP-bound hGH, and GH receptor status (Hansen 2002). Individual subject variations in GHBP or GH receptor levels may result in substantial differences in hGH clearance.

Human growth hormone is slowly, but relatively completely, absorbed after either IM or SC injection. Time to peak concentration ranges from 2 to 4 h following IM bolus administration and 4 to 6 h following SC bolus administration (Laursen 2004; Jorgensen 1991). Subcutaneously administered rhGH is approximately 50–80 % bioavailable (Laursen 2004). The rate of absorption of hGH is slightly faster after injection in the abdomen compared with the thigh (Laursen 2004), but the extent of absorption is comparable. Elimination half-lives following extravascular administration (2–5 h) are usually longer than the IV terminal half-lives indicating absorption rate-limited kinetics.

hGH pharmacokinetics in the presence of growth hormone deficiency, diabetes, obesity, and critical illness or diseases of the thyroid, liver, and kidney have been evaluated. Results suggest disposition is not significantly altered compared with normal subjects except in severe liver or kidney dysfunction (Hansen 2002; Haffner et al. 1994; Owens et al. 1973; Cameron et al. 1972). The reduction in clearance observed in severe liver (30 %) or kidney dysfunction (40–75 %) is consistent with the role of the liver and kidney as major organs of hGH elimination.

Both the kidney and the liver have been shown to be important in the clearance of hGH in humans (Hansen 2002). The relative contribution of each organ has not been rigorously quantitated in humans, but the preponderance of studies in laboratory animals and in isolated perfused organ systems suggests a dominant role for the kidney at pharmacologic levels of hGH. Receptor-mediated uptake of hGH by the liver is the major extrarenal clearance mechanism (Harvey 1995).

PROTEIN MANUFACTURE, FORMULATION, AND STABILITY

Commercially available hGH preparations are summarized in Table 14.1. All recombinant growth hormones except Serostim®/Saizen®/Zorbtive® are produced in bacteria (*E. coli*) or yeast (*S. cerevisiae*). Serostim®/Saizen®/Zorbtive® are produced in mammalian cells (C127 mouse cells). Growth hormone produced in the cytoplasm of *E. coli* may contain an N-terminal methionine residue. Natural sequence rhGH is produced either by enzymatic cleavage of the methionine residue during the purification process or by secreting the rhGH into the periplasmic space where the signal peptide is removed by the cell and the native N-terminus of rhGH is revealed. rhGH can be produced in the periplasm in a soluble, properly folded form (Chang et al. 1989) or as refractile/inclusion bodies which require the insoluble rhGH to be extracted, denatured, and refolded (Shin et al. 1998) (cf. Chap. 3). The rhGH is released from the cells by osmotic shock (periplasm) or mechanical lysis (cytoplasm & periplasm), and the protein is recovered and purified. rhGH synthesized in yeast and mammalian cells is transported across the endoplasmic reticulum and secreted directly into the culture medium from which it is recovered and purified (Catzel et al. 2003).

Historically, the potency of hGH products was expressed in International Units per mg (IU/mg). The initial standard, established in 1982 for pit-hGH preparations, was 2 IU/mg. The standard for rhGH products was 2.6 IU/mg until September 1994. The current WHO standard, established in September 1994, is 3.0 IU/mg. Dosages are usually expressed as IU/kg or IU/m^2 in Europe and Japan and as mg/kg in the USA. However, the use of IU dosages is no longer necessary due to the high level of purity and consistent potency of recombinant hGH products.

Source	Brand names	Product	Container	Injection device	Manufacturer
Recombinant protein produced in bacteria *(E. coli)*	Genotropin® Genotonorm	Lyophilized powder Multiple-dose cartridge: 5 and 12 mg Single-dose Miniquick cartridge: 0.2–2 mg	Two-chamber cartridge	Genotropin Pen® Genotropin Miniquick® Genotropin Mixer® GoQuick™ pen	Pfizer
	Norditropin®	Liquid FlexPro® and NordiFlex® cartridges: 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL NordiFlex® pen: 30 mg/3 mL	Cartridge	Norditropin FlexPro® Norditropin NordiFlex® NordiFlex PenMate® NordiPen® with Norditropin® SimpleXx® NordiPenMate® Norditropin NordiPen® Norditropin NordiLet®	Novo Nordisk
	Nutropin®	Lyophilized powder: 10 mg	Vial	Single-use syringe	Genentech, Inc
	Nutropin AQ®	Liquid Vial: 10 mg Cartridges: 5 mg/2 mL, 10 mg/2 mL, 20 mg/2 mL	Vial and cartridge	Single-use syringe Nutropin AQ® pen Nutropin AQ® NuSpin	
	Humatrope® Umatrope	Lyophilized powder Vial: 5 mg/5 mL Cartridge: 6 mg/3 mL, 12 mg/3 mL, 24 mg/3 mL	Vial and cartridge	Single-use syringe HumatroPen™	Eli Lilly & Co.
	Zomacton® Bio-Tropin® SciTropin® Growject®	Lyophilized powder	Vial	Single-use syringe Needle-free device:Zomajet 2 Vision	Ferring
	Tev-Tropin™	Lyophilized powder Vial: 5 mg	Vial	Single-use syringe Needle-free device:Tjet®	Teva Pharmaceuticals
	Omnitrope® Omnitrop	Lyophilized powder Vial: 5.8 mg	Vial	Single use syringe	Sandoz
	Omnitrope® Omnitrop	Liquid Cartridge: 5 mg/1.5 mL 10 mg/1.5 mL	Cartridge	Omnitrope® pen	

Recombinant protein produced in yeast cells (*S. cerevisiae*)	Valtropin®	Lyophilized powder Vial: 5 mg	Vial	Single-use syringe	BioPartners GmbH LG Life Sciences
Recombinant protein produced in mammalian cells (C127 mouse cell line-derived)	Serostim® (AIDS wasting)	Lyophilized powder Vials: 4 mg, 5 mg, 6 mg, 8.8 mg	Vial with click.easy® reconstitution device	Syringe one.click® Needle-free devices: cool. click and cool.click® 2	Serono
	Saizen® (growth inadequacy)	Lyophilized powder Vial: 5 mg, 8.8 mg	Vial with click.easy® reconstitution device	Single-use syringe easypod® one.click® Needle-free devices: cool. click and cool.click® 2	
	Zorbtive® (short bowel syndrome)	Lyophilized powder Vial: 4 mg, 5 mg, 6 mg, 8.8 mg	Vial	Single-use syringe	

Note: This table represents most rhGH products available globally and is not meant to be an exhaustive list of available marketed hGH products

Table 14.1 ■ Recombinant hGH products.

All current rhGH products are available as lyophilized or liquid preparations. Lyophilized formulations usually include 5 or 10 mg of protein in a glycine and mannitol or sucrose-containing phosphate buffer excipient. The materials are usually reconstituted with sterile water for injection for single use or with bacteriostatic water or bacteriostatic saline for multiple injection use. Liquid formulations of rhGH (Nutropin AQ®, Omnitrope ®, Norditropin® SimpleXx®) contain excipients such as mannitol or sodium chloride, histidine or citrate buffer, poloxamer 188 or polysorbate 20, and phenol or benzyl alcohol. Product stability has been very good with shelf lives of approximately 2 years at 2–8 °C. Omnitrope® (US/EU) and Valtropin (EU only), lyophilized rhGH preparations, were approved for marketing as the first "biosimilar" rhGH products in 2006. Two strengths of Omnitrope® (5 and 10 mg cartridges) were approved for marketing in 2008 for use in two pen devices [Omnitrope Pen® 5 and Omnitrope Pen® 10 (US/EU)].

CLINICAL USAGE

Clinical usage of rhGH has been reviewed for pediatric and adult indications (Franklin and Geffner 2011). Investigations of clinical usage of hGH have focused, generally, on two major areas of hGH biologic action: (1) linear growth promotion and (2) modulation of metabolism. Growth-promoting indications in children which have been approved for the market include growth hormone deficiency, idiopathic short stature, growth failure associated with chronic renal insufficiency, growth failure in children born small for gestational age, and short stature in Prader-Willi syndrome, Turner's syndrome, Noonan syndrome, and short stature homeobox-containing gene deficiency on the X chromosome (SHOX). Modulation of metabolism is the primary biologic action in long-term replacement therapy in adults with GH deficiency of either childhood or adult onset or for GH supplementation in AIDS wasting or cachexia and in short bowel syndrome. Contraindications to rhGH use include use in patients with active malignancy, active proliferative or severe nonproliferative retinopathy, acute critical illness, children with Prader-Willi syndrome (PWS) who are severely obese or have severe respiratory impairment, children with closed epiphyses, and hypersensitivity to somatropin or excipients.

■ Growth Hormone Deficiency (GHD)

The major indication for therapeutic use of hGH is the long-term replacement treatment for children with classic growth hormone deficiency in whom growth failure is due to a lack of adequate endogenous hGH secretion. Children with GHD fall into a variety of etiologic categories including genetic defects in the hypothalamic pituitary axis, developmental anomalies of the brain with or without identifiable syndromes, acquired events such as CNS lesions (craniopharyngioma most commonly) or from the treatment of CNS tumors (medulloblastoma, gliobastoma, etc.), trauma, or other events requiring CNS irradiation. When diagnosed in otherwise healthy children, it is called idiopathic. In patients suspected of having GHD, the diagnosis is usually defined based on an inadequate response to two hGH provocation tests implying a functional deficiency in the production or secretion of hGH from the pituitary gland. In patients with documented organic causes, especially if panhypopituitarism is present, two stimulation tests may not be required. Usual doses range from 0.24 to 0.30 mg/kg/week administered as daily SC injections in prepubertal children. Doses up to 0.7 mg/kg/week have been approved for GHD adolescent subjects to improve final height based on a clinical trial (Mauras et al. 2000) showing hGH treatment results in increased growth velocity and enhancement in final adult height. For most GHD children the growth response is greatest in the first year of treatment and correlates positively with hGH dose, degree of short stature, and frequency of injections and negatively with chronological age at onset of treatment. hGH therapy in children is usually continued until growth has been completed, as evidenced by epiphyseal fusion. rhGH treatment of idiopathic GH-deficient children has a positive overall safety profile documented in long-term clinical registries (Bell et al. 2010; Darendeliler et al. 2007). However, in those with organic causes, the safety profile may be dependent on the underlying medical condition and its prior treatment. In childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm (Sklar 2002), and this information is communicated under warnings and precautions in the product labels.

■ Idiopathic Short Stature (ISS)

Idiopathic short stature (ISS) comprises a heterogeneous group of growth failure states for which the proximate cause remains unknown. Postulated defects include impaired spontaneous hGH secretion, hGH resistance due to low levels of hGH receptors, or other defects in either secreted hGH, hGH receptors or post-receptor events, or other genetic defects yet to be elucidated. Nevertheless, studies have documented that many patients in the "idiopathic" group respond to exogenous growth hormone treatment with acceleration of growth and improvement in final height. As a consequence of several long-term multicenter trials to final height, rhGH was approved for the treatment of

ISS in the United States (Hintz et al. 1999; Leschek et al. 2004). The risk benefit assessment of improved growth in what is generally considered to be a population of "healthy" children continues to be debated, and while short-term safety has been documented (Bell et al. 2010), long-term safety is still a question that is being addressed by a multi-country study in Europe looking at adult patients treated with rhGH as children. Based on preliminary data and published reports (Carel et al. 2012; Savendahl et al. 2012), the FDA and the EMA preliminary assessments are that there should be no change in prescribing information with emphasis on adherence to approved dosages. Final assessments are expected to be available in 2013.

■ Turner Syndrome (TS)

Turner syndrome is a disease of females caused by partial or total loss of one sex chromosome and is characterized by decreased intrauterine and postnatal growth, short final adult height, incomplete development of the ovaries and secondary sexual characteristics, and other physical abnormalities. Although serum levels of hGH and IGF-1 are not consistently low in this population, hGH treatment (0.375 mg/kg/week), alone or in combination with oxandrolone, significantly improves growth rate and final adult height in this patient group, and its use in Turner syndrome is now an accepted indication (Rosenfeld et al. 1998; Kappelgaard and Laursen 2011).

■ Prader-Willi Syndrome (PWS)

Prader-Willi syndrome is a genetic disease usually caused by the functional deletion of a gene on the paternal allele of chromosome 15. Clinical manifestations in childhood include lack of satiety, obesity, hypotonia, short stature, hypogonadism, and behavior abnormalities. PWS children have especially high rates of morbidity due to obesity-related illnesses. Growth hormone treatment (0.24–0.48 mg/kg/week) has been shown to improve height and, perhaps more importantly, improve body composition, physical strength, and agility in PWS children (Allen and Carrel 2004). However, growth hormone treatment is contraindicated in the face of severe obesity or severe respiratory impairment since sudden deaths in this group of patients, when treated with growth hormone, have been reported.

■ Small for Gestational Age (SGA)

Growth hormone is approved for use in long-term treatment of growth failure in children born small for gestational age who fail to manifest catch-up growth. Children born at birth weights and birth lengths more than two standard deviations below the mean are considered small for gestational age. Children who fail to catch up by age two to three are at risk for growing into adults with substantial height deficits (Rappaport 2004). Growth hormone treatment at doses of 0.24–0.48 mg/kg/week can induce catch-up growth, with the potential to normalize height at an earlier age and the potential to improve adult height.

■ Chronic Renal Insufficiency (CRI)/Chronic Kidney Disease (CKD)

Children with renal insufficiency, which is termed chronic kidney disease (CKD) grow slowly, possibly related to defects in metabolism, nutrition, metabolic bone disease, and/or defects in the IGF-1/hGH axis. Basal serum hGH concentrations may be normal or high, and IGF-1 responses to hGH stimulation is usually normal. However, there are reported abnormalities in the IGF-binding protein levels in CKD patients suggesting possible problems with GH/IGF-1 action. Growth hormone therapy (0.35 mg/kg/week) in children with chronic renal insufficiency results in significant increases in height velocity (Greenbaum et al. 2004). Increases are best during the first year of treatment for younger children with stable renal disease. Responses are less for children on dialysis. Growth hormone has not been approved for children posttransplant.

■ Noonan Syndrome

First called male Turner syndrome due to similar phenotypic characteristics, Noonan syndrome, an autosomal dominant disorder, was later recognized as a separate condition. It occurs in both males and females. Its key features are short stature (although some patients will achieve normal adult height), congenital heart disease, most commonly pulmonic stenosis or hypertrophic cardiomyopathy, a short and often webbed neck, ptosis, and chest/sternum deformities. While the GH/IGF axis is intact in Noonan syndrome, and the mechanisms through which the mutations cause short stature are unknown, clinical trials with rhGH demonstrated significant increases in growth rate and modest increases in final height (Osio et al. 2005), resulting in FDA approval of this indication in 2007. Pediatric patients with short stature associated with Noonan syndrome are given up to a rhGH dose of 0.066 mg/kg/day. Safety concerns in treatment with rhGH have been raised with respect to progression of cardiomyopathy although data to date do not support this clinical concern.

■ Short Stature Homeobox-Containing Gene (SHOX)

The SHOX gene is located on the pseudoautosomal region of the X chromosome and the homologous distal region on the Y chromosome. Healthy males and females express two active copies of the SHOX gene, one from each of the sex chromosomes. Females with

TS missing an X chromosome or part of an X chromosome have one copy of the SHOX gene. A significant percentage of the growth failure in TS females is secondary to this gene loss. The variably expressed SHOX gene in long bones tends to be in the mesomelic segments. Mutations resulting in haploinsufficiency of SHOX are also responsible for the short stature in some patients with a pseudoautosomal dominant condition of mesomelic dyschondrosteosis called Leri-Weill syndrome. In addition, sporadic mutations are also responsible for short stature in a small percentage of patients who would otherwise be characterized as idiopathic short stature (Rao et al. 1997). A multicenter study of a heterogeneous group of patients with SHOX haploinsufficiency demonstrated a clinically significant effect of rhGH on growth in children with SHOX mutations compared to the untreated control group. In addition, the efficacy of rhGH treatment was similar to that seen in a comparable group of girls with TS, leading to approval of the SHOX indication (Blum et al. 2007). The FDA-approved rhGH dose for SHOX deficiency is 0.35 mg/kg/week. To date no specific safety signals attributable to rhGH treatment have emerged in these children.

■ Growth Hormone Deficient Adults

Early limitations in hGH supply severely limited treatment of adults with GHD. With the increased supply of recombinant rhGH products, replacement therapy for adults was evaluated and, ultimately, approved as a clinical indication. Growth hormone has been approved for two growth hormone deficient adult populations: (a) adults with childhood-onset GHD and (b) adults with adult-onset GHD usually due to pituitary tumors, CNS irradiation, or head trauma. Growth hormone treatment (starting dose of 0.006–0.025 5 mg/kg/week in patients under 35 years old and 0.0125 mg/kg/week in patients over 35 years old or a starting dose of 0.2–0.4 mg/day and progressing based on IGF and clinical symptoms) reduces body fat, increases lean body mass, and increases exercise capacity. Increases in bone density have been observed in some bone types although treatment duration greater than 1 year may be necessary to see significant effects. hGH treatment consistently elevates both serum IGF-1 and insulin levels. Women have also been shown to require higher doses to normalize IGF-1 levels than men, especially women taking oral estrogens.

■ Clinical Malnutrition and Wasting Syndromes

Growth hormone is approved for treatment of short bowel syndrome (SBS) in adults, a congenital or acquired condition in which less than ~200 cm of small intestine is present. Short bowel syndrome patients have severe fluid and nutrient malabsorption and are often dependent upon intravenous parenteral nutrition (IPN). Administration of growth hormone, 0.1 mg/kg/day to a maximum of 8 mg for 4 weeks, alone or in combination with glutamine, reduces the volume and frequency of required IPN (Keating and Wellington 2004). Growth hormone is indicated for use in adult patients who are also receiving specialized nutritional support. Usage for periods >4 weeks, or in children, has not been investigated. Usage of growth hormone for SBS remains controversial due to potential risks associated with IGF-1-related fibrosis and cancer (Theiss et al. 2004).

Growth hormone is also approved for use in wasting associated with AIDS. Growth hormone treatment (~0.1 mg/kg daily, max. 6 mg/day), when used with controlled diets, increases body weight and nitrogen retention. rhGH treatment is also under investigation for HIV-associated lipodystrophy, a syndrome of fat redistribution and metabolic complications resulting from the highly active antiretroviral therapy commonly used in HIV infection (Burgess and Wanke 2005).

■ Other Conditions Under Investigation

Growth hormone levels and IGF decline with age, prompting the initiation of multiple clinical trials for use in adults over age 60 (Di Somma et al. 2011). However, clear long-term efficacy in muscle strength or improvements in activities of daily life have not been sufficiently demonstrated to gain regulatory approval for this indication. The use of hGH therapy to ameliorate the negative nitrogen balance seen in patients following surgery, injury, or infections has been investigated in a number of studies (Takala et al. 1999; Jeevanandam et al. 1995; Ponting et al. 1988; Voerman et al. 1995). However, due to the increased mortality found in a study of severe critical illness (Takala et al. 1999) and the subsequent contraindication for use in acute critical illness, very few registration trials examining the use of hGH for these conditions have been initiated. Studies of hGH effects in burns have shown significant effectiveness in acceleration of healing in skin graft donor sites and improvements in growth in burned children (Herndon and Tompkins 2004). Growth hormone has been shown to significantly reduce multiple disease symptoms and improve well-being and growth in children and adults with Crohn's disease, a chronic inflammatory disorder of the bowel (Theiss et al. 2004; Slonim et al. 2000; Denson et al. 2010). Growth hormone has also shown benefit in cardiovascular recovery and function in congestive heart failure (Colao et al. 2004). Recent studies indicate that growth hormone treatment improves growth, pulmonary function, and clinical status in children with cystic fibrosis (Stalvey et al. 2012).

■ Safety Concerns

hGH has been widely used for many years and has been proven to have a positive safety profile for most pediatric indications (Growth Hormone Research Society 2001). However, sudden death in some patients with PWS and severe obesity associated with rhGH treatment resulted in a contraindication to its use in severely obese or respiratory compromised PWS children (Eiholzer 2005). Adverse events have been reported in a small number of children and include benign intracranial hypertension, glucose intolerance, and the rare development of anti-hGH antibodies. In most cases, the formation of anti-hGH antibodies following rhGH treatment has not been positively correlated with a loss in efficacy.

Growth hormone therapy is also not associated with increased risk of primary malignancies or tumor recurrence (Growth Hormone Research Society 2001; Sklar et al. 2002). However, an increase in secondary malignancies in childhood cancer survivors, especially those treated with CNS irradiation, has been described (Sklar 2002).

Growth hormone inhibits 11βhydroxysteroid dehydrogenase type 1 (11βHSD-1) activity in adipose/hepatic tissue and may impact the metabolism of cortisol and cortisone (Gelding et al. 1998). Treatment with rhGH could potentially unmask undiagnosed central (secondary hypoadrenalism) or increase the requirement for maintenance or stress doses of replacement corticosteroid in those already diagnosed with adrenal insufficiency.

Growth hormone has caused significant, dose-limiting fluid retention in adult populations resulting in increased body weight, swollen joints and arthralgias, and carpal tunnel syndrome (Carroll and van den Berghe 2001). Symptoms were usually transient and resolved upon reduction of hGH dosage or upon discontinuation of the hGH treatment. Growth hormone administration has been associated with increased mortality in clinical trials in critically ill, intensive-care patients with acute catabolism (Takala et al. 1999) and is, therefore, contraindicated for use in critically ill patients.

Growth hormone's anabolic and lipolytic effects have made it attractive as a performance enhancement drug among athletes. Illicit hGH usage has been anecdotally reported for the last 20 years. Detection of rhGH abuse proximate to the time of testing is now possible due to the development of assays which rely on detecting changed ratios of exogenous rhGH (22 kDa only) and endogenous hGH (22 kDa, 20 kDa and other forms). Screening for proximate rhGH abuse, based on the new ratio assays, was included in the 2006 Olympic Games for the first time (McHugh et al. 2005).

CONCLUDING REMARKS

The abundant supply of rhGH, made possible by recombinant DNA technology, has allowed enormous advances to be made in understanding the basic structure, function, and physiology of hGH over the past 20 years. As a result of those advances, recombinant hGH has been developed into a safe and efficacious therapy for a variety of growth and metabolic disorders in children and adults. Continuing basic research in GH and IGF-1 biology, genomics, and GH-related diseases and continuing clinical investigation into additional uses in pediatric growth disorders or disorders of metabolism may yield as yet new indications for treatment.

SELF-ASSESSMENT QUESTIONS

■ Questions

1. One molecule of hGH is required to sequentially bind to two receptor molecules for receptor activation. What consequences might the requirement for sequential dimerization have on observed dose–response relationships?
2. Growth hormone is known or presumed to act directly upon which tissues?
3. You are investigating the use of hGH as an adjunct therapy for malnutrition/wasting in a clinical population which also has severe liver disease. What effects would you expect the liver disease to have on the observed plasma levels of hGH after dosing and on possible efficacy (improvement in nitrogen retention, prevention of hypoglycemia, etc.)?

■ Answers

1. Sequential dimerization will potentially result in a "bell-shaped" dose–response curve, i.e., response is stimulated at low concentrations and inhibited at high concentrations. The inhibition of responses at high concentrations is due to blocking of dimerization caused by the excess hGH saturating all the available receptors. Inhibition of in vitro hGH binding is observed at high hGH (mM) concentrations. Reductions in biological responses (total IGF-1 increase and weight gain) have also been seen with increasing hGH doses in animal studies. However, inhibitory effects of high concentrations of hGH are not seen in treatment of human patients since hGH dose levels are maintained within normal physiological ranges and never approach inhibitory levels.
2. Growth hormone is known to act directly on both bone and cartilage and possibly also on muscle and adipose tissue. Growth hormone effects on other tissues appear to be mediated through the IGF-1 axis or other effectors.
3. Severe liver disease may reduce the clearance of the exogenously administered hGH, and observed

plasma levels may be higher and persist longer compared to patients without liver disease. However, the increased drug exposure may not result in increased anabolic effects. The desired anabolic effects require the production/release of IGF-1 from the liver. Both IGF-1 production and the number of hGH receptors may be reduced due to the liver disease. To understand the results (or lack of results) from the treatment, it is important to monitor effect parameters (i.e., IGF-1 and possibly IGF-1 binding protein levels, liver function enzymes) in addition to hGH levels.

REFERENCES

Allen DB, Carrel AL (2004) Growth hormone therapy for Prader-Willi Syndrome: a critical appraisal. J Pediatr Endocrinol Metab 17:1297–1306

Baumann G (1991) Growth hormone heterogeneity: genes, isohormones, variants and binding proteins. Endocr Rev 12:424–449

Baumann GP (2009) Growth hormone isoforms. Growth Horm IGF Res 19:333–340

Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B (2010) Long-term safety of recombinant human growth hormone in children. J Clin Endocrinol Metab 95:167–177

Blum WF, Crowe BJ, Quigley CA, Jung H, Cao D, Ross JL, Braun L, Rappold G, Shox Study Group (2007) Growth hormone is effective in treatment of short stature associated with short stature homeobox-containing gene deficiency: two-year results of a randomized, controlled, multicenter trial. J Clin Endocrinol Metab 92:219–228

Boguszewski CL (2003) Molecular heterogeneity of human GH: from basic research to clinical implications. J Endocrinol Invest 26:274–288

Bouillon R (1991) Growth hormone and bone. Horm Res 36(Suppl 1):49–55

Brook CGD, Hindmarsh PC (1992) The somatotropic axis in puberty. Endocrinol Metab Clin North Am 21:767–782

Brooks AJ, Waters MJ (2010) The growth hormone receptor: mechanism of activation and clinical implications. Nat Rev Endocrinol 6(9):515–525

Burgess E, Wanke C (2005) Use of recombinant human growth hormone in HIV-associated lipodystrophy. Curr Opin Infect Dis 18:17–24

Cameron DP, Burger HG, Catt KJ et al (1972) Metabolic clearance of human growth hormone in patients with hepatic and renal failure, and in the isolated perfused pig liver. Metabolism 21:895–904

Carel J-C, Ecosse E, Landier F, Meguellati-Hakkas D, Kaguelidou F, Rey G, Coste J (2012) Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. J Clin Endocrinol Metab 97:416–425. doi:10.1210/jc.2011-1995

Carroll PV, van den Berghe G (2001) Safety aspects of pharmacological GH therapy in adults. Growth Horm IGF Res 11:166–172

Casanueva F (1992) Physiology of growth hormone secretion and action. Endocrinol Metab Clin North Am 21:483–517

Catzel D, Lalevski H, Marquis CP, Gray PP, Van Dyk D, Mahler SM (2003) Purification of recombinant human growth hormone from CHO cell culture supernatant by Gradiflow preparative electrophoresis technology. Protein Expr Purif 32(1):126–234

Chang JY, Pai RC, Bennett WF, Bochner BR (1989) Periplasmic secretion of human growth hormone by Escherichia coli. Biochem Soc Trans 17(2):335–337

Colao A, Vitale G, Pivonello R et al (2004) The heart: an end-organ of GH action. Eur J Endocrinol 151:S93–S101

Darendeliler F, Karagiannis G, Wilton P (2007) Headache, idiopathic intracranial hypertension and slipped capital femoral epiphysis during growth hormone treatment: a safety update from KIGS. Horm Res 68(Suppl 5):41–47

Denson LA, Kim MO, Bezold R et al (2010) A randomized controlled trial of growth hormone in active pediatric Crohn disease. J Pediatr Gastroenterol Nutr 51:130–139

Di Somma C, Brunelli V, Savanelli MC et al (2011) Somatopause: state of the art. Minerva Endocrinol 36:243–255

Eiholzer U (2005) Deaths in children with Prader-Willi syndrome: a contribution to the debate about the safety of growth hormone treatment in children with PWS. Horm Res 63(1):33–39

Fisker S (2006) Physiology and pathophysiology of growth hormone binding protein: methodological and clinical aspects. Growth Horm IGF Res 16:1–28

Franklin SL, Geffner ME (2011) Growth hormone: the expansion of available products and indications. Endocrinol Metab Clin North Am 38:587–611

Gelding SV, Taylor NF, Wood PJ, Noonan K, Weaver JU, Wood DF, Monson JP (1998) The effect of growth hormone replacement therapy on cortisol-cortisone interconversion in hypopituitary adults: evidence for growth hormone modulation of extrarenal 11 beta-hydroxysteroid dehydrogenase activity. Clin Endocrinol (Oxf) 48(2):153–162

Giustina A, Veldhuis JD (1998) Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and in the human. Endocr Rev 19(6):717–797

Goeddel DV, Heyreker HL, Hozumi T et al (1979) Direct expression in Escherichia coli of a DNA sequence coding for human growth hormone. Nature 281:544–548

Greenbaum LA, Del Rio M, Bamgbola F et al (2004) Rationale for growth hormone therapy in children with chronic kidney disease. Adv Chronic Kidney Dis 11(4):377–386

Consensus:. Critical evaluation of the safety of recombinant human growth hormone administration: statement from the Growth Hormone Research Society (2001) J Clin Endocrinol Metab 86(5):1868–1870

Haffner D, Schaefer F, Girard J et al (1994) Metabolic clearance of recombinant human growth hormone in health and chronic renal failure. J Clin Invest 93:1163–1171

Hansen TK (2002) Pharmacokinetics and acute lipolytic actions of growth hormone: impact of age, body composition, binding proteins and other hormones. Growth Horm IGF Res 12:342–358

Harvey S (1995) Growth hormone metabolism. In: Harvey S, Scanes CG, Daughaday WH (eds) Growth hormone. CRC Press, Inc, Boca Raton, pp 285–301

Herington AC, Ymer S, Stevenson J (1986) Identification and characterization of specific binding proteins for growth hormone in normal human sera. J Clin Invest 77: 1817–1823

Herndon DN, Tompkins RG (2004) Support of the metabolic response to burn injury. Lancet 363:1895–1902

Herrington J, Carter-Su C (2001) Signaling pathways activated by the growth hormone receptor. Trends Endocrinol Metab 12(6):252–257

Hintz RL, Rosenfeld RG, Wilson DM et al (1982) Biosynthetic methionyl human growth hormone is biologically active in adult man. Lancet 1:1276–1279

Hintz RL, Attie KM, Baptista J, Roche A (1999) Effect of growth hormone treatment on adult height of children with idiopathic short stature. N Engl J Med 340:502–507

Isaksson OG, Ohlsson C, Bengtsson B et al (2000) GH and bone-experimental and clinical studies. Endocr J 47(Suppl):S9–S16

Jeevanandam M, Ali MR, Holaday NJ et al (1995) Adjuvant recombinant human hormone normalizes plasma amino acids in parenterally fed trauma patients. J Parenter Enteral Nutr 19:137–144

Jorgensen JOL (1991) Human growth hormone replacement therapy: pharmacological and clinical aspects. Endocr Rev 12:189–207

Kappelgaard AM, Laursen T (2011) The benefits of growth hormone therapy in patients with Turner syndrome, Noonan syndrome, and children born small for gestational age. Growth Horm IGF Res 21(6):305–313

Keating GM, Wellington K (2004) Somatropin (zorbtive™) in short bowel syndrome. Drugs 64(12):1375–1381

Kojima M, Hosoda H, Matsuo H et al (2001) Ghrelin: discovery of the natural endogenous ligand for the growth hormone secretagogue receptor. Trends Endocrinol Metab 12(3):118–126

Laursen T (2004) Clinical pharmacological aspects of growth hormone administration. Growth Horm IGF Res 14:16–44

Le Roith D, Adamo M, Werner H, Roberts CT Jr (1991) Insulin-like growth factors and their receptors as growth regulators in normal physiology and pathologic states. Trends Endocrinol Metab 2:134–139

Leschek EW, Ross SR, Yanovski JA, Troendle JF, Quigley CA, Chipman JJ, Crowe BJ et al (2004) Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, double blind, placebo-controlled trial. J Clin Endocrinol Metab 89:3140–3148

Lewis UJ, Sinhda YN, Lewis GP (2000) Structure and properties of members of the hGH family: a review. Endocr J 47:S1–S8

MacGillivray MH, Baptista J, Johanson A (1996) Outcome of a four-year randomized study of daily versus three times weekly somatropin treatment in prepubertal naïve growth hormone deficient children. J Clin Endocrinol Metab 81:1806–1809

Martial JA, Hallewell RA, Baxter JD (1979) Human growth hormone: complementary DNA cloning and expression in bacteria. Science 205:602–607

Mauras N, Attie KM, Reiter EO et al (2000) High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. J Clin Endocrinol Metab 85:3653–3660

McHugh CM, Park RT, Sonksen PH et al (2005) Challenges in detecting the abuse of growth hormone in sport. Clin Chem 51(9):1587–1593

Mertani HC, Delehaye-Zervas MC, Martini JF et al (1995) Localization of growth hormone receptor messenger RNA in human tissues. Endocrine 3:135–142

Osio D, Dahlgren J, Wikland KA, Westphal O (2005) Improved final height with long-term growth hormone treatment in Noonan syndrome. Acta Paediatr 94(9):1232–1237

Owens D, Srivastava MC, Tompkins CV et al (1973) Studies on the metabolic clearance rate, apparent distribution space and plasma half-disappearance time of unlabelled human growth hormone in normal subjects and in patients with liver disease, renal disease, thyroid disease and diabetes mellitus. Eur J Clin Invest 3: 284–294

Piwien-Pilipuk G, Huo JS, Schwartz J (2002) Growth hormone signal transduction. J Pediatr Endocrinol Metab 15:771–786

Ponting GA, Halliday D, Teale JD et al (1988) Postoperative positive nitrogen balance with intravenous hyponutrition and growth hormone. Lancet 1:438–440

Raben MS (1958) Treatment of a pituitary dwarf with human growth hormone. J Clin Endocrinol Metab 18: 901–903

Rao E, Weiss B, Fukami M et al (1997) Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. Nat Genet 16:54–63

Rappaport R (2004) Growth and growth hormone in children born small for gestational age. Growth Horm IGF Res 14:S3–S6

Ray J, Jones BK, Liebhaber SA, Cooke NE (1989) Glycosylated human growth hormone variant. Endocrinology 125(1):566–568

Root AW, Root MJ et al (2002) Clinical pharmacology of human growth hormone and its secretagogues. Curr Drug Targets Immune Endocr Metabol Disord 2: 27–52

Rosenfeld RG, Attie KM, Frane J et al (1998) Growth hormone therapy of Turner's syndrome: beneficial effect on adult height. J Pediatr 132:319–324

Savendahl L, Maes M, Albersson K, Borgstrom B, Carel J-C, Henrad S, Speybroeck N, Thomas M, Xandwijken G, Hokken-Koelega A (2012) Long-term mortality and causes of death in isolated GHD, ISS and SGA patients treated with recombinant growth hormone during childhood in Belgium, the Netherlands, and Sweden: preliminary report of a 3 countries participating in the EU SAGhE study. J Clin Endocrinol Metab 97:E213–E217. doi:10.1210/jc.2011-2882

Shin NK, Kim DY, Shin CS, Hong MS, Lee J, Shin HC (1998) High-level production of human growth hormone in Escherichia coli by a simple recombinant process. J Biotechnol 62(2):143–151

Sklar CA, Mertens AC, Mitby P et al (2002) Risk of disease recurrence and second neoplasms in survivors of children cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 87(7):3136–3141

Slonim AE, Bulone L, Damore MB et al (2000) A preliminary study of growth hormone therapy for Crohn's disease. N Engl J Med 342:1633–1637

Stalvey MS, Anbar RD, Konstan MVV, Jacobs JR, Bakker B, Lippe B, Geller DE (2012) A multi-center controlled trial of growth hormone treatment in children with cystic fibrosis. Pediatr Pulmonol 47:252–263. doi:10.1002/ppul.21546

Strobl JS, Thomas MJ (1994) Human growth hormone. Pharm Rev 46:1–34

Takala J, Ruokonen E, Webster NR et al (1999) Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 341(11):785–792

Theiss AL, Fruchtman S, Lund PK (2004) Growth factors in inflammatory bowel disease. The actions and interactions of growth hormone and insulin-like growth factor-I. Inflamm Bowel Dis 10(6): 871–880

Voerman BJ, van Schijndel RJM S, Goreneveld ABJ et al (1995) Effects of human growth hormone in critically ill non-septic patients: results from a prospective, randomized, placebo-controlled trial. Crit Care Med 23: 665–673

Wells JA, Cunningham BC, Fuh G et al (1993) The molecular basis for growth hormone-receptor interactions. Recent Prog Horm Res 48:253–275

FURTHER READING

Boguszewski CL (2003) Molecular heterogeneity of human GH: from basic research to clinical implications. J Endocrinol Invest 26:274–288

Brooks AJ, Waters MJ (2010) The growth hormone receptor: mechanism of activation and clinical implications. Nat Rev Endocrinol 6(9):515–525

Fisker S (2006) Physiology and pathophysiology of growth hormone binding protein: methodological and clinical aspects. Growth Horm IGF Res 16:1–28

Giustina A, Veldhuis JD (1998) Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and in the human. Endocr Rev 19(6):717–797

Harvey S, Scanes CG, Daughaday WH (eds) (1995) Growth hormone. CRC Press, Inc, Boca Raton

Harris M, Hofman PL, Cutfield WS (2004) Growth hormone treatment in children. Pediatr Drugs 6(2):93–106

Laursen T (2004) Clinical pharmacological aspects of growth hormone administration. Growth Horm IGF Res 14: 16–44

Simpson H, Savine R, Sonksen P et al (2002) Growth hormone replacement therapy for adults: into the new millennium. Growth Horm IGF Res 12:1–33