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Growth Hormone:
A Current Perspective

M.O. THORNER, M.L. HARTMAN, C.M. SILVA, B.D. GAYLINN,
J.A. ALOI, S.E. KIRK, S.S. PEZZOLI, AND M.L. VANCE

It is well recognized that growth hormone (GH) acts at multiple peripheral tissues, including, among other tissues, the liver, adipocytes, muscle, and the growth plate. There is good evidence in animals that GH deficiency is associated with combined immune deficiency, which suggests a potential physiological role for GH in the regulation of immune function. However, in humans there is no definitive evidence to indicate such a role for GH in immune modulation. Perhaps this will be the focus of a future meeting. In this volume, we focus our attention on the somatotrophic axis and the reproductive process. This is a new area, and it is our hope that the chapters herein will clarify those issues that have been resolved and focus the attention of researchers on those areas where there are gaps in our knowledge.

GH Secretion

Growth hormone is secreted from the anterior pituitary under the dual control of the hypothalamic peptides somatostatin (SRIH) and growth hormone releasing hormone (GHRH). GH is secreted in a pulsatile fashion; prominent changes in the pattern of GH secretion occur at different stages of the life cycle (reviewed in 1). One unresolved question that is central to future strategies for GH replacement therapy is whether the pulsatile pattern of GH is important for some or all of the actions of GH in humans.

GH is detectable at the end of the first trimester and reaches a peak of 100–150 µg/L at about 20 weeks of gestation. GH levels decline to about 30 µg/L in cord serum and continue to decline for about 3 months. GH secretion increases to maximal levels during puberty and progressively
declines with increasing age. Beyond age 60 GH secretion is similar to that observed in GH-deficient children. This diminished GH secretion associated with aging may reflect an alteration in the release of GHRH and/or SRIH, enhanced sensitivity to insulin-like growth factor I (IGF-I) feedback, or decreased somatotroph mass. This hyposomatotropism of aging may contribute to the frailty of aging, which includes decreased muscle and bone mass and increased adiposity. Gonadal steroids have a profound effect on GH secretion, such that premenopausal women have greater GH secretion than age-matched men.

During the day, GH secretion is suppressed by food ingestion and stimulated by exercise. At night, GH secretion is maximal during slow wave sleep. Nutrient deprivation and type I diabetes mellitus are associated with increased GH concentrations, while GH secretion is suppressed in obese subjects. GH-deficient subjects have higher percent body fat and lower lean body mass (LBM) than normal subjects. These changes in body composition are reversed by GH administration (reviewed in 2).

GH Receptor

We have developed a homologous assay to study human GH receptor (GH-R) signal transduction using the IM-9 human B cell lymphocyte cell line that has receptors for GH, insulin, IGF-I, IGF-II, and glucocorticoids. The GH-R is a member of the cytokine family of receptors, and activation of the GH receptor leads to tyrosine phosphorylation of at least three proteins in the human IM-9 lymphocyte cell line: a 134-kd protein that represents the GH-R itself (3) and a 120-kd protein and 93-kd protein whose natures have yet to be elucidated. Recently, in a 3T3 mouse fibroblast cell line, the 120-kd protein has been shown to be the tyrosine kinase JAK2 (4). The IM-9 cell line has been useful in demonstrating that receptor dimerization is necessary for GH-R signal transduction and that mutant GH molecules with defective site 2 not only are incapable of activating the receptor, but also act as receptor antagonists (Fig. 1.1). In this volume we will read about molecular modeling and peptide engineering studies and the expectations for major advances that will come from these approaches as they relate to the GH-R.

GH Secretagogues

The possibilities for future therapeutic manipulation of the somatotrophic axis are encouraging. There are two major classes of compounds that could serve as GH secretagogues with therapeutic potential. The first is GHRH and its analogs; the second is GH releasing peptide (GHRP) and its analogs, including a recently developed nonpeptidal GHRP mimetic.