INTRODUCTION

Acromegaly is a condition of dysregulated growth hormone (GH) secretion characterized by excessive GH levels. Generally, acromegaly is the result of autonomous GH secretion, most often from a benign pituitary somatotropinoma, although rarely from GH-secreting pituitary carcinoma, ectopic pituitary tumors, or extrapituitary GH-producing tumors. Less frequently, acromegaly may be the result of excess GH-releasing hormone (GHRH) secretion from GHRH-producing tumors such as carcinoid or pancreatic islet cell tumors (1,2). Annual incidence estimates for acromegaly range from three to four cases per million persons, with a prevalence of 60–70 cases per million (2). Onset is insidious, typically resulting in a 10- to 15-yr delay after onset of GH hypersecretion before diagnosis is made. Acromegaly is associated with disfigurement, disability, and a two- to threefold increased mortality rate due to deaths from cardiac, respiratory, metabolic, or malignant complications (2). Early diagnosis and effective therapy are crucial to improve quality of life and normalize life expectancy.

This chapter explores the role of the somatomedins in evaluation of acromegaly. Stimulation of insulin-like growth factor (IGF) production is one of the principal actions of GH. Thus, the common lesion in acromegaly is increased GH, but the clinical and biochemical sequelae characteristic of the condition are largely the result of excessive GH-dependent production of IGF-I. Indeed, IGF-I concentrations are markedly elevated in acromegaly and reduced in states of GH deficiency. In contrast, IGF-II levels are unchanged in acromegaly and modestly reduced in GH deficiency (3). These observations suggest that IGF-I is the primary mediator of the sequelae of GH action in acromegaly. Moreover, IGF-I exhibits greater GH dependency, is more potent in growth promotion than IGF-II, and participates in the negative feedback of GH synthesis and
secretion. Conversely, IGF-II has more insulin-like activity compared to IGF-I (4) and does not appear to be a useful marker for diagnosis or monitoring of acromegaly.

**Review of GHRH–GH–IGF-I Axis**

**Physiology of GH Secretion**

GH is required for normal linear growth, for maintaining normal carbohydrate and lipid metabolism, and for normal body composition. The GH gene consists of a cluster of five highly conserved genes spanning approx 66 kb on the long arm of chromosome 17 (5). The most 5’ of these genes is designated hGH-N, which is expressed exclusively in somatotrophs of the anterior pituitary, and encodes a 22-kDa protein consisting of 191 amino acids (6, 7). Absolute concentration of GH secreted is age dependent. Circulating levels are elevated at puberty, decline after adolescent growth, remain stable until mid-adulthood, and then progressively decline with age. Moreover, levels are also gender dependent with higher integrated concentrations in premenopausal women than in men (8). GH levels in the normal individual are modulated by a variety of physiological and pharmacological stimuli necessitating coordinated, multifaceted regulation. The main regulatory loop for the integrated control of GH secretion is composed of GH, IGF-I, GHRH, and somatostatin.

GHRH mediates enhanced GH secretion and gene transcription. In contrast to GHRH, somatostatin attenuates GH secretion and has little effect on GH synthesis. GHRH circulates as 37-, 40-, or 44-amino-acid peptides that derive from a single gene encoding a preprohormone for GHRH-44 (9). Somatostatin molecules are produced from a prohormone and are of varying amino acid length (10). Both peptides are produced in the hypothalamus and are transported via axons to the hypophyseal portal system. Five somatostatin receptors have been characterized to date (11). Variable tissue-specific receptor subtype expression likely determines the distinct biologic effects of somatostatin (12,13).

GH secretion from the anterior pituitary is pulsatile. Normally intermittent secretory bursts occur on a background interpulse level of secretion that falls below the limit of detection of standard assays. More than 95% of total GH is secreted in the pulses, while tonic interpulse secretion accounts for the remainder (14, 15). The pattern of GH secretion may determine tissue responses and is dependent upon a number of factors including nutritional status, sex steroids, sleep, stress, body composition, and physical activity (16,17). Moreover, there is a distinct diurnal rhythm to GH secretion, with the majority of GH secreted near the onset of deep sleep when secretory peaks occur with greater amplitude and increased frequency (18,19).

Pulsatile secretion of GH is elicited by the opposing actions of GHRH and somatostatin, which are likewise secreted in asynchronous periodic pulses from the hypothalamus. Human and animal studies suggest that hypothalamic GHRH secretion is primarily responsible for generating GH pulses (20–22), whereas interpulse GH secretion is dependent upon tonic somatostatin inhibition (21,22). Interestingly, pulsatility continues despite persistently elevated GHRH, as seen in patients with GHRH-producing tumors or receiving GHRH continuous infusion (6,23). These observations suggest that intermittent somatostatin decrements may also contribute to pulse generation. Chronic GHRH stimulation in normal individuals results in somatotroph desensitization and subsequent down-regulation of GH release.

In acromegaly, somatotrophs fail to desensitize to administered GHRH (24,25). Indeed, GHRH receptor gene expression is up-regulated specifically in GH-secreting adenomas.