Negative Feedback Regulation of Pulsatile Growth Hormone Secretion by Insulin-like Growth Factor I

Involvement of Hypothalamic Somatostatin

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Abstract

To investigate the mechanisms of the negative feedback inhibition of growth hormone (GH) secretion by IGF-I, we studied parameters of GH pulsatility in six normal, fed men before and during a 48-h infusion of recombinant human IGF-I (rhIGF-I) (10–15 μg/kg per h). Plasma levels of IGF-I increased from the baseline value of 163.5±9.3 μg/liter (mean±SE) to a new steady state of 452.0±20.9 μg/liter during the infusion. Plasma GH concentrations were measured every 10 min for 24 h during both saline and rhIGF-I infusions using a sensitive chemiluminescent assay. Overall, GH concentrations were suppressed during the rhIGF-I infusion by 85±3%, mainly by attenuating spontaneous GH pulse amplitude (77±4% suppression). The apparent GH pulse frequency was attenuated from 7.8±0.9 to 4.7±0.6 pulses/24 h (P = 0.006). Administration of rhIGF suppressed GH responses to exogenous GH-releasing hormone by 82±3%, and thyroid-stimulating hormone responses to thyrotropin-releasing hormone were also suppressed by 44±9%. This constellation of hormonal effects is most compatible with the rhIGF-I–induced stimulation of hypothalamic somatostatin secretion. (*J. Clin. Invest.* 1994. 94:138–145.) Key words: somatotropin • somatotropin-releasing hormone • somatostatin • insulin-like growth factor I • pituitary

Introduction

Growth hormone (GH)[1] secretion from the pituitary gland is stimulated by periodic discharges of hypothalamic GH-releasing hormone (GHRH) and is tonically inhibited by hypothalamic somatostatin (SRIF) (1, 2). As is common in several other hormonal systems, the end product of the GH effect, IGF-I, inhibits GH secretion in a negative feedback regulatory manner. The mechanism(s) of this negative feedback is complex. Studies in rats using intracerebroventricular injections of IGF-I have shown diminished amplitude of GH pulses in peripheral blood (3, 4). Intracerebroventricular administration of recombinant human IGF-I (rhIGF-I) in the GH-deficient dwarf rat increased somatostatin mRNA and decreased GHRH mRNA, but this effect was not observed with systemic infusions (5). Additionally, IGF-I has been reported to decrease GH secretion from cultured rat pituitary cells and to increase SRIF secretion from cultured rat hypothalamic cells (6, 7). Thus, both circulating IGF-I and locally produced (autocrine/paracrine) hypothalamic IGF-I are likely to participate in the negative feedback inhibition of GH synthesis and secretion.

Most of the information regarding these effects derives from in vivo animal models, predominantly the rat (4–7) and the sheep (8), as well as from in vitro studies involving animal pituitaries (7) or human GH-producing tumors (9). Direct studies of hypothalamic GHRH and SRIF secretion in humans are understandably impractical. Thus, the mechanisms involved in the suppression of GH secretion by IGF-I in normal humans are largely unknown.

The best evidence for the existence of this phenomenon in humans comes from the studies in patients with congenital GH insensitivity syndrome (Laron's type dwarfism). In these individuals the inability of peripheral tissues to generate IGF-I results in very low circulating levels of IGF-I and grossly elevated plasma GH concentrations. Administration of rhIGF-I to these patients suppresses GH into the normal range (10). Additional evidence is provided by the observation that a decline in circulating and, presumably, tissue IGF-I (11) associated with fasting or malnutrition is also accompanied by augmented GH secretion (12–14), which is promptly suppressed by rhIGF-I infusion (15). These earlier studies were able to document the existence of the negative IGF-I feedback but they did not address the potential mechanisms involved.

Since the occurrence of GH pulses likely reflects the periodic exposure of the pituitary somatotrophs to hypothalamic GHRH while the amplitude of GH pulses and, possibly, the interpulse GH concentrations are determined by the prevailing SRIF concentrations (1, 2, 16), ascertainment of the parameters of GH pulsatility provides important, albeit indirect, information about hypothalamic GHRH and SRIF secretion. This paradigm has been used successfully in animal and human studies to investigate the nature of the neuroendocrine mechanisms involved in the alterations of GH secretion during puberty (17), the menstrual cycle (18), aging (19), and in such pathologic conditions as calorie deprivation (12–14), obesity (20), diabetes (21), growth delay (22), and acromegaly (23, 24).

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1. *Abbreviations used in this paper:* AUC, area under curve; CRC, Clinical Research Center; CV, coefficients of variation; GH, growth hormone; GHRH, GH-releasing hormone; i.v., intravenous; M±SE, mean±standard error; rhIGF-I, recombinant human IGF-I; SRIF, somatotropin release-inhibiting factor (somatostatin); TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

In this study, we investigated pulsatile GH secretory parameters in normally fed men before and during the infusion of rhIGF-I. We show that rhIGF-I infusion suppresses overall GH secretion, mainly by attenuating spontaneous GH pulse amplitude. rhIGF-I also blunts GH response to exogenous GHRH and the response of thyroid-stimulating hormone (TSH) to exogenous thyrotropin-releasing hormone (TRH). This constellation of hormonal effects is most compatible with the rhIGF-I–induced stimulation of hypothalamic SRIF secretion.

Methods

Subjects and study design

The protocol was approved by the Institutional Review Board and the Clinical Research Center (CRC) Review committee at the University of Michigan and conducted in the University of Michigan CRC. Six healthy men, age 18–29, who did not take any medications and who were of normal height and weight (mean body mass index of 22.9 kg/m^2), were studied after providing written informed consent. All had unremarkable clinical histories and physical examinations. Measurements of renal, hepatic, and hematologic function in all subjects were normal. The subjects were admitted to the CRC the evening before the actual studies and had an intravenous cannula placed anterograde in each forearm. They were allowed three daily meals throughout the study. The daily total caloric intake was ~ 2,500 kcal, consisting of 15% protein, 25% fat, and 60% carbohydrates, with ~ 30% of calories given at breakfast (0700 h), ~ 30% at lunch (1200 h), and ~ 40% given at dinner (1900 h). They were not allowed to snack between meals and were allowed to sleep only during specified night hours. Lights were on at 0630 h and off at 2300 h.

On day 1, an infusion of normal saline was started at 0800 h at 20 ml/h and continued until 1200 h the next day. Sampling for GH was done every 10 min from 0700 h on day 1 until 0800 h on day 2. At 0800 h day 2, a 50-μg intravenous bolus of TRH (Thypinone; Abbot Laboratories, North Chicago, IL) was administered, and blood was sampled every 20 min for the next hour for TSH. This dose of TRH was chosen based on its submaximal ability to stimulate TSH secretion (25). At 1000 h an intravenous (i.v.) bolus of GHRH-44 (Bachem California, Torrance, CA) 0.33 μg/kg was administered, and blood for GH was sampled every 10 min for the next 2 h. This dose of GHRH was chosen because of its ability to promote a submaximal rise in plasma GH (26, 27) and to elicit GH responses comparable in magnitude with the endogenous nocturnal GH pulses (28). After completion of the GHRH test, at 1200 h (day 2), an infusion of rhIGF-I was started at either 15 (first two subjects) or 10 μg/kg per h (remaining four subjects). The original infusion rate was chosen in consultation with the supplier (Genentech Inc., South San Francisco, CA) based on the existing safety data specifically to avoid the possibility of hypoglycemia. The change in rhIGF-I dose was necessitated by the development of asymptomatic sinus tachycardia after ~ 24 h of infusion in the first two subjects. However, one of the subjects receiving the 10 μg/kg per h dose also developed sinus tachycardia. Frequent GH sampling (every 10 min) was done from 0700 on day 3 (i.e., 19 h after rhIGF-I infusion was begun) to 1200 on day 4. Similar to the baseline study, TRH 50 μg i.v. was given at 0800 h on day 4, and GHRH 0.33 μg/kg i.v. bolus was given at 1000 h on day 4, during rhIGF-I infusion. Plasma IGF-I was measured at 4-h intervals during saline infusion (0800, 1200, 1600, 2000, 2400, 0400, 0800, and 1200 h), at half-hour to 1-h intervals for 4 h after the beginning of rhIGF-I infusion, at 4-h intervals thereafter until the end of rhIGF-I infusion, and at half-hour to 1-h intervals for 4 h after termination of rhIGF-I infusion. Plasma glucose was measured randomly on several occasions during saline and rhIGF-I infusions and at 30-min intervals for 1 h before and 2 h after the evening meal (1800–2100 h). During both saline and rhIGF-I infusions, plasma total thyroxine (T_4) was measured before TRH administration. Because of rare reports of cardiac arrhythmia with i.v. bolus rhIGF-I injection, patients were on continuous electrocardiogram monitoring by telemetry. They were allowed to be ambulatory within the constraints placed by the frequent blood draws.

Materials

GHRH was purchased from Bachem California and prepared by the University of Michigan Investigational Drug Pharmacy to a concentration of 50 μg/ml. rhIGF-I at a concentration of 5 mg/ml was a generous gift of Genentech Inc. and was diluted in 0.9% saline for infusion.

Assays

Growth hormone. Plasma GH concentrations were measured in duplicate by a chemiluminescent assay (Nichols Institute, San Juan Capistrano, CA). All samples from each particular subject were analyzed in the same assay. The sensitivity of the assay was conservatively estimated to be 0.01 μg/liter. This point on the standard curve was > 10 standard deviations away from the buffer control, and there was not one instance of the overlap between the replicates of these two points. The mean intra- and interassay coefficients of variation (CV) were both below 5%. rhIGF-I at a concentration of 1,000 μg/liter did not interfere with the measurement of GH by the chemiluminescent assay (data not shown).

IGF-I. Total plasma IGF-I was measured by RIA (29) using rhIGF-I (Mallinckrodt Specialty Chemicals, St. Louis, MO) as a standard and a polyclonal antibody generously donated by the National Hormone and Pituitary Distribution Program of the National Institute of Diabetes and Digestive and Kidney Diseases. Before the RIA, plasma samples were extracted with acid ethanol (29). Assay sensitivity was < 1 μg/liter, and intraassay CV was < 10%. All samples were assayed in triplicate, in a single assay.

TSH. Plasma TSH was measured in duplicate by a chemiluminescent assay (Ciba Corning, Medfield, MA). Assay sensitivity was 0.03 mU/liter, and both intraassay and interassay CVs were below 7%. All samples from a particular study were run in the same assay.

Hematology, serum chemistry, and T_4 measurements were all performed in the Pathology Laboratories of the University of Michigan Medical Center using standard techniques.

Data analysis

Pulsatile GH secretion parameters were analyzed by the computer program Cluster using a power fit, a *t*-statistic of 2, and a cluster size of 2 × 2 (30). Only computer-identified pulses that were greater in amplitude (nadir to peak) than 0.03 μg/liter were considered as true pulses. This cutoff was established on the basis of Cluster analysis of 49 pseudoduplicates of a pooled plasma sample with a GH concentration of 0.03 μg/liter. In this series, Cluster analysis identified four pulses with a mean amplitude (nadir to peak) of 0.0225 μg/liter. Thus, we regarded all Cluster-identified pulses with the amplitude below 0.03 μg/liter as indistinguishable from assay noise. Interpulse GH levels were defined as those segments identified by Cluster as nonpulsatile. Integrated total GH concentration (micrograms × minutes per liter) were calculated as the area under the GH versus time curve (AUC) using the trapezoidal rule. Integrated pulsatile GH concentration (micrograms × minutes per liter) was defined as the AUC during time segments identified as pulses by Cluster and greater in amplitude than 0.03 μg/liter. Integrated nonpulsatile GH (micrograms × minutes per liter) was measured as integrated total minus the integrated pulsatile GH concentrations. The GH responses to GHRH and TSH responses to TRH were defined in terms of incremental rise (a difference between time zero concentration and maximal concentration after the test compound) as well as in terms of AUC.

Two-tailed paired Student's *t* tests were used for statistical comparisons between groups. All results are presented as mean±standard error (M±SE), and $P < 0.05$ was considered significant. Data which were not normally distributed were logarithmically transformed before analy-

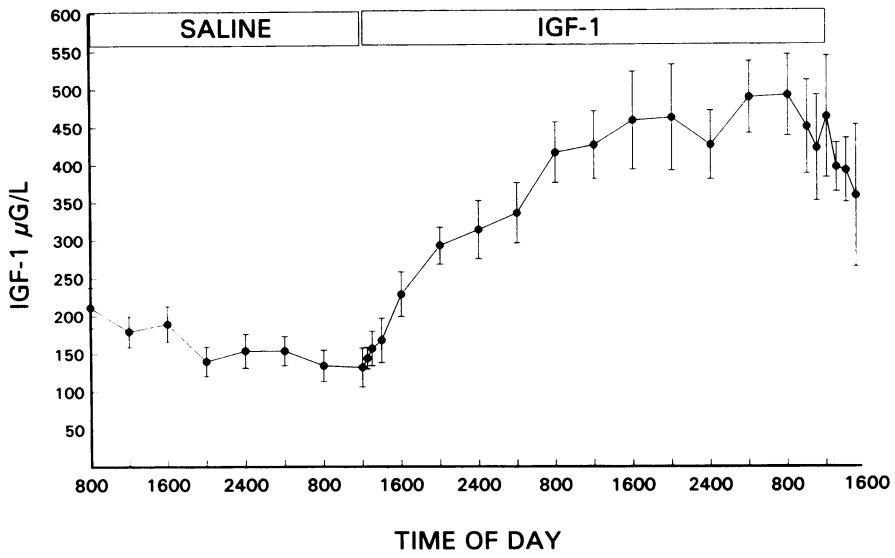

Figure 1. Plasma levels of total IGF-I before and during i.v. infusion of rhIGF-I (10 or 15 μg/kg per h).

sis. In case of multiple comparisons, the overall per study error rate was limited by restricting the per comparison P value to < 0.01 (15).

Results

Total IGF-I plasma concentrations. During the saline infusion, plasma IGF-I concentrations were stable throughout the day, and the mean plasma IGF-I concentration was 163.5±9.3 μg/liter (Fig. 1). During the rhIGF-I infusion, a steady rise in plasma IGF-I levels was seen within 1–2 h, the levels became significantly higher than the baseline at 4 h, and a stable new steady state was achieved after ~ 16 h of starting the infusion, before the onset of frequent GH sampling. In the first two volunteers who received 15 μg/kg per h of rhIGF-I, mean steady state IGF-I levels were 594.8±15.7 μg/liter. In the remaining four volunteers who received the lower dose (10 μg/kg per h), mean steady state IGF-I levels were 377.9±18.4 μg/liter. Most of the discrete parameters of spontaneous GH secretion, GH responses to GHRH, and TSH responses to TRH (see below) during saline and rhIGF-I infusion in subjects 1 and 2 were within the range of the same parameters in subjects 3–6. Similarly, when the analysis was restricted only to subjects 3–6 who received rhIGF-I at 10 μg/kg per h, the conclusions were identical to the analysis of the entire group of six subjects (data not shown). Since there were no differences in plasma GH and TSH dynamics or in plasma glucose levels between the two groups, all data were summarized for the final analysis. Overall, steady state IGF-I concentrations of 452.0±20.9 μg/liter were achieved during the final 28 h of the infusion, i.e., at the time when both pulsatile GH profiles and dynamic GH and TSH responses were assessed. After termination of the infusion, there was a slow decline in the IGF-I levels, and 4 h later plasma IGF-I levels were 358.5±108.5 μg/liter, i.e., ~ 79% of the infusion value. This agrees well with the calculated half-life of IGF-I of ~ 8–10 h (10).

Plasma glucose concentrations. rhIGF-I is well known to cause hypoglycemia, although this is rare in fed individuals at the doses used by us (10). Random plasma glucose levels did not differ between the saline and rhIGF-I infusions (104.7±2.6 vs 107.2±2.1 mg/dl; $P = 0.72$). The preprandial (dinner time) glucose levels were slightly but significantly higher during rhIGF-I infusion (91.2±3.3 vs 100.5±2.8 mg/dl, $P = 0.043$) but still in the normal range. The postprandial glucose levels (115.8±3.6 vs 125.0±4.9 mg/dl; $P = 0.099$) were similar during both the saline and rhIGF-I infusions.

Pulsatile GH profiles. During the baseline saline infusions, GH profiles were noted to be pulsatile in all patients. The mean 24-h GH concentration was 1.69±0.47 μg/liter. The pulse frequency ranged between 4 and 10 per 24 h (7.8±0.9), and the mean amplitude of all pulses was 4.92±1.01 μg/liter. The mean amplitude of the maximal pulse demonstrated by each patient was 21.50±4.23 μg/liter. The values for 24-h integrated GH levels (AUC) are also shown in Table I, along with the interpulse and nadir GH levels. The actual GH profiles of each of the subjects are shown in Fig. 2. Examples of pulsatile GH

Table I. Parameters of GH Secretion during Saline and IGF-I Infusions

	Saline	IGF-I	P value
Plasma IGF-I (*μg/liter*)	163.5±9.3	452.0±20.9	0.002
Mean 24-h GH (*μg/liter*)	1.69±0.47	0.29±0.12	0.011
24-h AUC (*μg × min/liter*)			
Total	2428.6±678.5	411.4±173.5	0.011
Pulsatile	2368.3±650.9	365.0±168.9	0.009
Nonpulsatile	60.4±29.4	47.0±13.5	0.64
Pulse frequency (*n/24 h*)	7.8±0.9	4.7±0.6	0.006
Pulse amplitude (*μg/liter*)			
Mean	4.92±1.01	1.12±0.39	0.004
Maximal	21.50±4.23	3.54±1.57	0.002
Interpulse GH (*μg/liter*)	0.25±0.16	0.07±0.02	0.068
Nadir GH (*μg/liter*)	0.05±0.02	0.045±0.017	0.44
GH response to GHRH			
Peak increment (*μg/liter*)	14.85±5.22	2.34±0.79	0.002
AUC (*μg × min/liter*)	691.2±248.4	106.6±37.1	0.0005

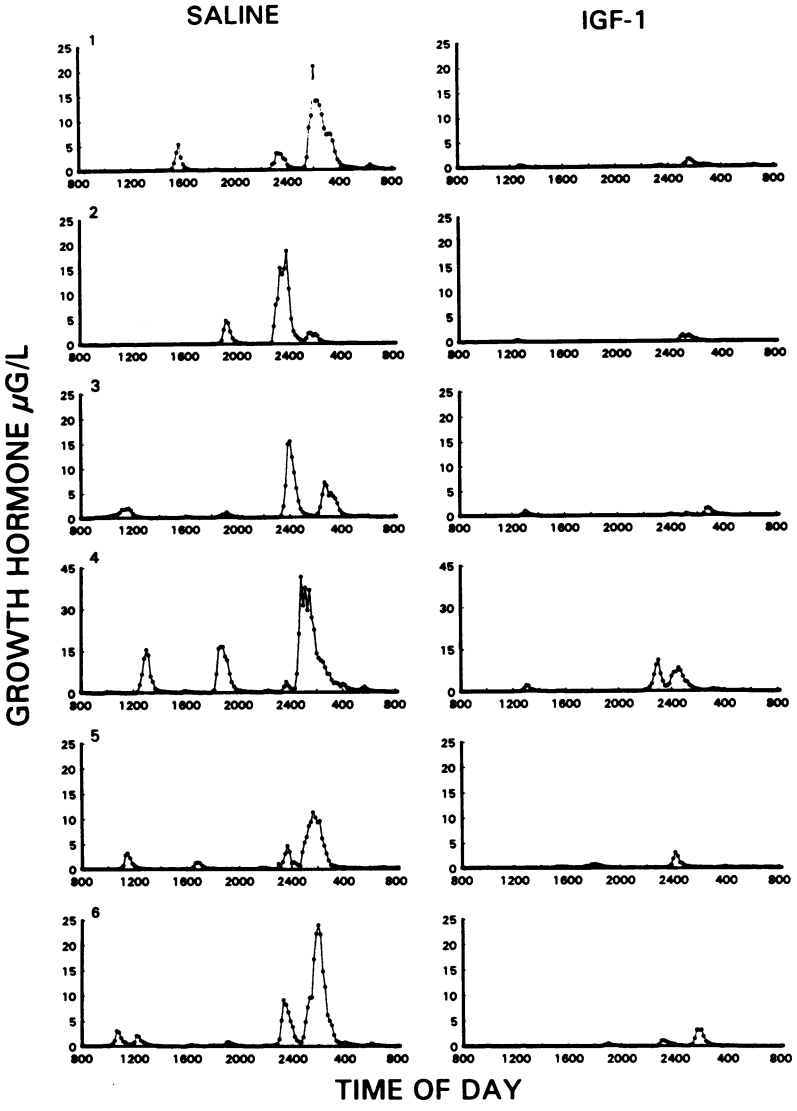

Figure 2. Plasma GH concentration profiles in six men during saline (*left*) and rhIGF-I (*right*) infusion. Subjects 1 and 2 received rhIGF-I at a rate of 15 μg/kg per h, and the rest were infused with rhIGF-I at a rate of 10 μg/kg per h. Plasma for GH was sampled every 10 min for 24 h.

profiles of subject 1, who received rhIGF-I at 15 μg/kg per h, and of subject 3, who received rhIGF-I at 10 μg/kg per h, are shown in Fig. 3 and are specifically enhanced to allow better visualization of small GH pulses and interpulse intervals.

During infusion of rhIGF-I, GH profiles were again noted to be pulsatile. The mean 24-h GH level decreased to 0.29±0.12 μg/liter (P = 0.011), i.e., 85±3% suppression. The pulse frequency ranged between three and seven per 24 h (4.7±0.6, P = 0.006 vs saline infusion). The mean pulse amplitude was also decreased to 1.12±0.39 μg/liter (P = 0.004) during rhIGF-I infusion, which corresponds to a mean suppression of 77±4%. The maximal pulse amplitude decreased to 3.54±1.57 μg/liter (P = 0.002), i.e., 85±4% suppression. The total and pulsatile integrated GH levels were significantly suppressed during rhIGF-I infusion by 85±3 (P = 0.011) and 87±2% (P = 0.009), respectively. The integrated nonpulsatile and nadir GH levels were not significantly different. The mean interpulse GH levels decreased almost fourfold from 0.25±0.16 to 0.07±0.02 μg/liter, and there was a trend for statistical significance (P = 0.068). The overall (M±SE) GH concentration profiles in all six subjects during saline and rhIGF-I infusions are shown in Fig. 4.

GH response to GHRH (Fig. 5). Administration of exogenous GHRH at 0.33 μg/kg during saline infusion produced a GH peak to a maximum of 14.85±5.22 μg/liter. During the infusion of rhIGF-I, the GH response to GHRH was attenuated to 2.34±0.79 μg/liter (P = 0.002). This corresponds to a mean suppression of 81±5%. The comparison of GH AUCs reached similar conclusions (576.0±226.7 vs 88.8±33.9 μg × min/liter; 81±3% suppression; P = 0.0005).

TSH response to TRH (Fig. 6). During saline infusion, baseline TSH concentrations were 1.22±0.15 mU/liter, and the mean increment of TSH was 4.68±0.46 mU/liter (baseline to maximum excursion). During rhIGF-I infusion, both baseline TSH concentrations (0.61±0.07 mU/liter) as well as TSH increment to TRH (3.33±0.68 mU/liter) were significantly suppressed (P = 0.04 and 0.03, respectively). The incremental TSH rise was suppressed by 31±11%. Similar data were obtained when integrated TSH responses (AUC) were analyzed (193.3±27.6 vs 108.4±21.3 mU × min/liter, 44±9% suppres-

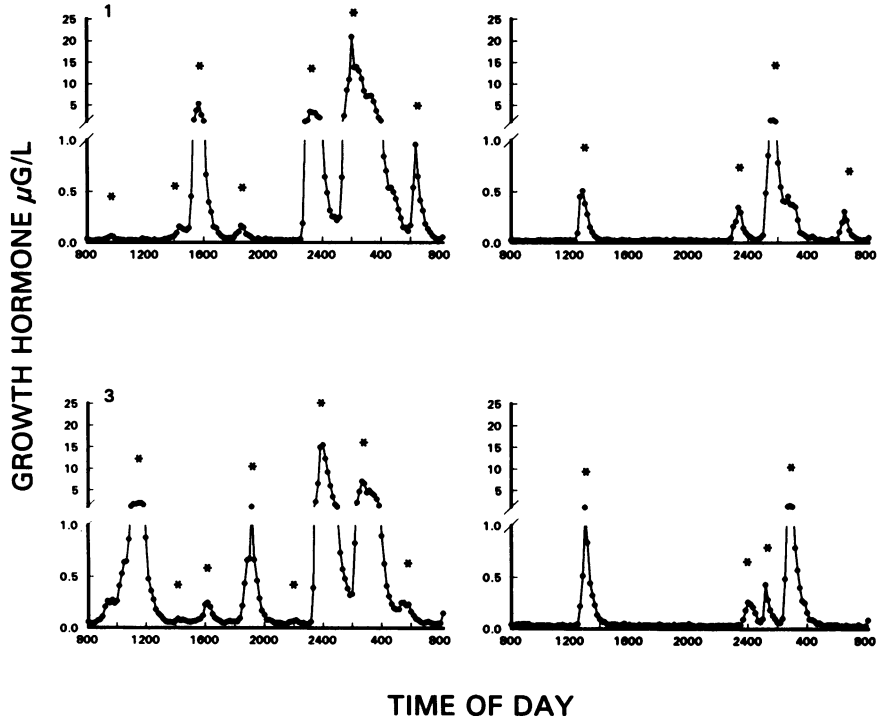

Figure 3. Plasma GH concentration profiles in subjects 1 (*top*) and 3 (*bottom*) during saline and rhIGF-I infusions. The y-scales were broken to allow better visualization of the low GH range. Asterisks mark significant GH pulses.

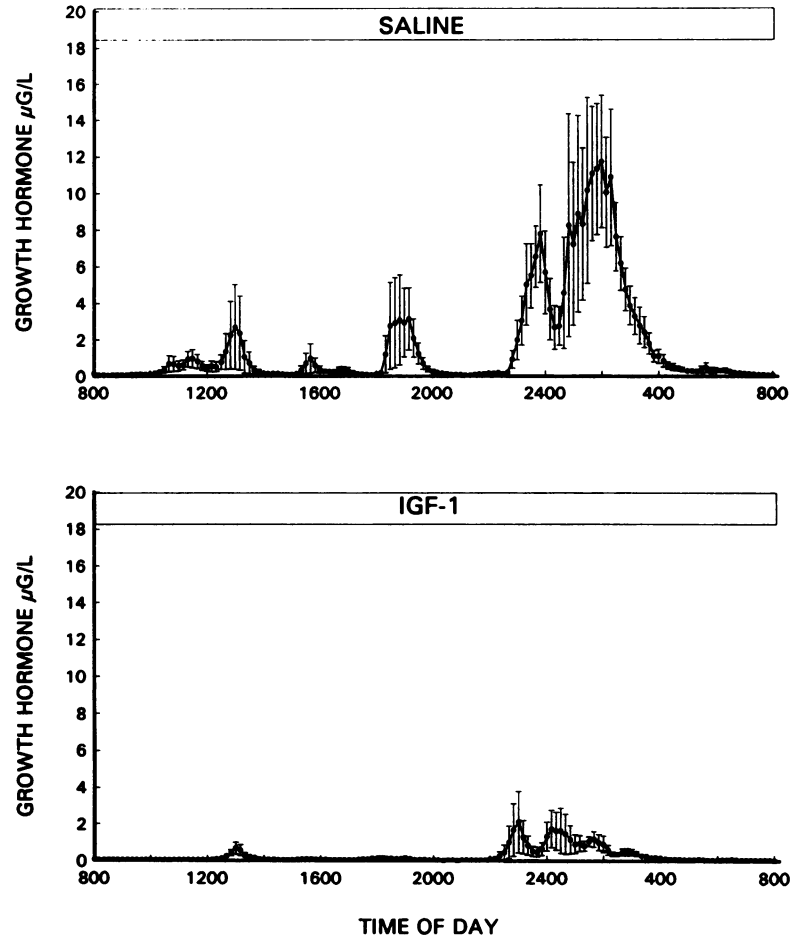

Figure 4. A composite picture of plasma GH concentration profiles (M±SE) in all six subjects during saline (*top*) and rhIGF-I (*bottom*) infusions.

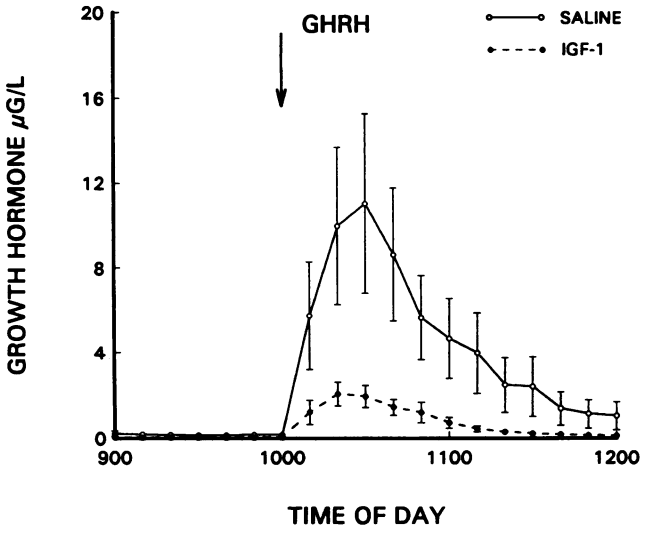

Figure 5. Plasma GH responses to GHRH (0.33 μg/kg i.v.) during saline and rhIGF-I infusions (M±SE).

sion, $P = 0.01$). The mean serum T_4 level during saline (7.1±0.4 μg/dl) was not significantly different from the level during rhIGF-I infusion (7.5±0.6 μg/dl, $P > 0.05$).

Discussion

In this study, administration of rhIGF-I increased plasma peptide levels approximately threefold, and this was followed by an ~ 85% suppression of total GH concentrations. Thus, even in a fed state, rhIGF-I exerts a powerful negative feedback on GH secretion. This was accounted for almost entirely by the attenuation of the pulsatile GH secretion component (~ 87% suppression). Three potential mechanisms (alone or in combination) can be involved in this effect: (*a*) direct pituitary inhibition of GH secretion (6, 7), (*b*) suppression of GHRH secretion (31), or (*c*) stimulation of SRIF release (6).

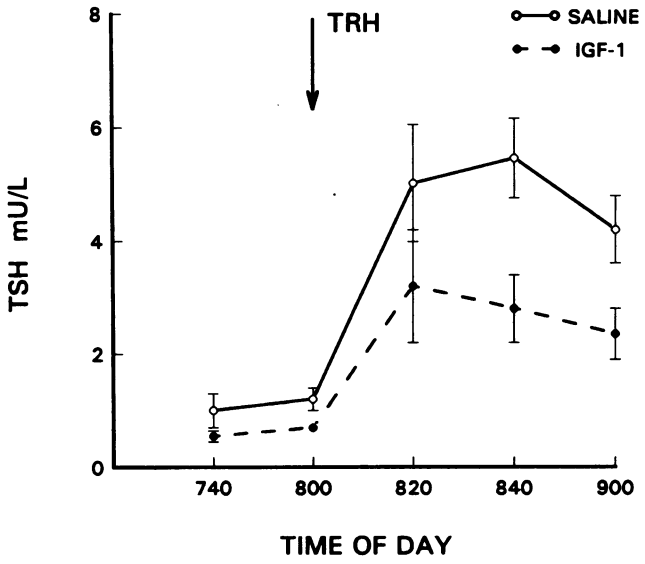

Figure 6. Plasma TSH responses to TRH (50 μg i.v.) during saline and rhIGF-I infusions (M±SE).

Both animal (1, 2, 16) and human (32) data have shown that periodic GH pulses are largely dependent on phasic GHRH release. Thus, a decrease in the apparent GH pulse frequency during rhIGF-I infusion may be conceivably attributed to attenuated GHRH secretion. A direct suppressive effect of rhIGF-I on hypothalamic GHRH synthesis and secretion has been documented in vitro using rat hypothalamic slices (31) and in vivo using intracerebroventricular rhIGF-I infusion in rats (5), although a systemic administration of rhIGF-I was incapable of altering hypothalamic GHRH mRNA content (5). However, the 40% decline in GH pulse frequency observed in this study is not sufficient by itself to explain the 80% attenuation of the total GH secretion. Since any pulse detection program requires a certain minimal elevation of hormone concentration above the baseline as a prerequisite for definition of a pulse, it is likely that the apparent decline in GH pulse frequency during rhIGF-I infusion was due to the suppressive effect of rhIGF-I upon spontaneous GH pulse amplitude and GH responsiveness to GHRH. Taking into account the ~ 80% suppressive effect of rhIGF-I on pulse amplitude, any GH pulse with the intended amplitude of below 0.15 μg/liter would be expressed as a GH rise of < 0.03 μg/liter, i.e., indistinguishable from assay noise. Indeed, during the baseline study, an average of 1.5±0.5 GH pulses per subject had amplitudes below the 0.15 μg/liter cutoff range. Correcting for these pulses, only 6.3±1.1 pulses/24 h would have remained "visible" during rhIGF-I infusion, and the difference in pulse frequency between the basal and the IGF-I stages of the protocol would vanish ($P = 0.15$). Thus, elimination of the stimulatory influence of GHRH is an unlikely mechanism of IGF-I negative feedback. Instead, one would have to postulate the involvement of a suppressive mechanism, such as a direct pituitary effect of IGF-I or a stimulation of hypothalamic SRIF secretion.

The conclusive differentiation between these two mechanisms would require estimation of the hypothalamic SRIF output in the pituitary-portal vessels. This approach is, of course, impossible in humans. Therefore, we used the measurement of basal and TRH-stimulated TSH secretion as an independent marker of hypothalamic SRIF secretion. IGF-I does not influence TSH secretion from the pituitary in vitro (6), but TSH is readily suppressed by SRIF (33–35). The observed suppression of both basal and TRH-induced TSH levels suggests that hypothalamic SRIF secretion was indeed augmented by rhIGF-I infusion. Our data cannot exclude the possibility that, at least in part, the suppressive effect of rhIGF-I upon GH secretion is expressed directly at the level of pituitary somatotrophs. This mechanism was documented clearly in vitro using normal rat pituitary cells (6, 7) and human somatotropinomas (9). On the other hand, an increase in hypothalamic SRIF secretion capable of suppressing TSH secretion by 44% may by itself be sufficient to completely account for the 80% suppression of GH secretion. Indeed, in the study by Williams et al. (36), SRIF infusion, at a rate of 50 μg/h that increased plasma SRIF 20-fold (still presumably in the physioslogic range), suppressed TSH response to TRH by 43±5 and GH response to GHRH by 78±5%, respectively. These values are remarkably similar to the relative degrees of inhibition of both hormones in our study during rhIGF-I infusion. Thus, the existence of an additional pituitary mechanism of IGF-I action needs not be invoked. Since tonic

secretion of SRIF is believed to maintain low interpulse GH concentrations (1, 2), a decline in this parameter would be expected if rhIGF-I indeed stimulated SRIF secretion from the hypothalamus. While we were unable to document such an effect statistically, a strong trend was actually present. Additional studies using a larger number of subjects will be needed to clarify this point.

GH by itself is also a powerful negative feedback regulator of its own secretion (37–39). It appears to exert its effect both by stimulating SRIF synthesis and secretion and by suppressing GHRH synthesis and secretion (40). In the present study, GH secretion was suppressed during rhIGF-I infusion, and this by itself would be expected to result in high GHRH and low SRIF milieu. Since our data suggest strongly that rhIGF-I causes stimulation of SRIF secretion, the potential effect of lowered GH must have been minimal at best and grossly outweighed by the influence of high circulating IGF-I.

In conclusion, we are presenting the first detailed account of the effects of systemically administered rhIGF-I upon parameters of GH pulsatility in normal, nutritionally uncompromised men. Our data indicate that a threefold increase in circulating IGF-I concentrations powerfully suppresses total GH output, mainly at the expense of attenuated GH pulse amplitude. This is accompanied by a proportionate decline in pituitary sensitivity to GHRH and by significant suppression of basal and TRH-stimulated TSH secretion. This constellation of findings suggests that the main target of the IGF-I negative feedback in humans may be expressed at the level of hypothalamic SRIF neurons. This is supported further by the trend of the interpulse GH levels to decline during rhIGF-I infusion. While some decline in GH pulse frequency might suggest rhIGF-I–induced attenuation of GHRH secretion, it more likely reflects high SRIF milieu with the resultant blockade of the pituitary somatotroph responses to an unchanged GHRH pulsatility.

Acknowledgments

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