

Physiological role of somatostatin on growth hormone regulation in humans

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Introduction

This scientific review discusses Human Growth Hormone and how it is regulated.

Conclusions

Growth Hormone (GH) is released by the pituitary gland in a pulse-like fashion. GH is secreted when somatostatin secretion is low. GH also relies on GH Releasing Hormone (GHRH) to allow the release of GH. Somatostatin inhibits the release of GH, but not the synthesis of GH.

Starvation/fasting/low protein/calorie restriction all increase GH levels. Meanwhile, obese individuals have reduced levels of GH with fewer and less powerful bursts of GH, and this effect is partially reversed by weight loss. Somatostatin levels tend to be elevated in obese, as well - inhibiting GHRH.

Amendments

Physiological Role of Somatostatin on Growth Hormone Regulation in Humans

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Growth hormone (GH) secretion in man is pulsatile and this pattern is regulated by both GH-releasing hormone (GHRH) and somatostatin. A large body of experimental evidence in both man and animals supports the model that bursts of GH secretion are mediated by a reduction of tonic hypothalamic somatostatin secretion. Our studies have been performed in normal subjects with frequent blood sampling for GH measurements (from 20-minute to 30-second intervals); the data have been analyzed by computer algorithms to objectively determine pulse characteristics and, in some studies, to estimate both pituitary secretion and clearance rates using deconvolution analysis. The studies include profiles of GH secretion in normal men and women in fed and fasted states; analysis of GH secretion during sleep; and administration of GHRH during different stages of sleep and after sleep deprivation. The variable GH response to exogenous GHRH and the attenuated response after 6 hours of GHRH infusion to GHRH, while not to hypoglycemia, as well as the pulsatile profile of GH secretion in response to continuous GHRH infusions (24 hours to 14 days), all support the thesis that it is hypothalamic somatostatin that determines the timing of bursts of GH secretion. This is further confirmed by the profile of GH secretion in a patient with acrotic GHRH secretion. Recently, we have initiated studies with the novel synthetic GH releasing hexapeptide, HisDTrpAlaTrpDProLysNH₂ (GHRP). Our studies show that it acts synergistically with GHRH. Several lines of evidence suggest that GHRP stimulates GH secretion independently of GHRH receptors and acts at both the hypothalamic and pituitary levels. It may act to functionally antagonize somatostatin.

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1 GROWTH HORMONE (GH) is secreted from the anterior pituitary in a pulsatile fashion and the regulation of this secretion has been under intensive study in animals and humans. In humans, for ethical reasons, it is not possible to block endogenous somatostatin effects by passive immunization. Therefore, to determine the role of endogenous somatostatin it is necessary to address the question using multiple approaches and then develop a model based on logic and circumstantial information, which should be consistent with direct data from animal studies. In essence, it is now clear that the timing of a burst of GH secretion occurs during withdrawal of tonic hypothalamic somatostatin secretion.¹⁻³ However, GH secretion is also dependent on the hypothalamic secretion of GH-releasing hormone (GHRH). GHRH stimulates both transcription of GH messenger RNA and GH release.^{4,5} Hypersecretion of GHRH may induce somatotrope hyperplasia.^{6,7} In contrast, somatostatin through various intracellular mechanisms inhibits GH release, but has no effect on synthesis.^{8,9}

Specific information supporting the role of somatostatin in the timing of pulsatile growth hormone secretion comes from two major areas of study: (1) the wide variability in the GH response to a bolus injection of GHRH both within and among subjects;¹⁰ and (2) the profile of pulsatile GH secretion maintained in patients with GHRH-secreting tumors (who have high sustained levels of GHRH in their peripheral blood) and in normal subjects receiving chronic, continuous intravenous (IV) GHRH infusions.¹¹ In patients who have a GHRH secreting tumor, the pituitary is exposed to constant supramaximal GHRH doses for days, months, or years. The

pulsatile profile of GH secretion can only reasonably be accounted for by varying somatotrope responsiveness to the GHRH. This change in responsiveness is likely mediated by varying somatotrope exposure to endogenous hypothalamic somatostatin.

GH secretion in humans can be studied by measuring blood samples obtained at frequent intervals over a 24-hour or greater period.¹¹ These data may then be analyzed using a statistically based computer algorithm, such as Cluster¹² or Ultra,¹³ which objectively identifies hormone pulses and calculates their quantitative characteristics. In one of the earlier studies we performed,¹⁴ samples were drawn at 20-minute intervals from young women, young men, older women, and older men. When these data were submitted to stepwise regression analysis serum estradiol, but not testosterone, correlated with the 24-hour integrated GH concentration. When the effects of estradiol were removed from the analysis neither age nor sex influenced the integrated GH concentration. These data, together with others, suggest that gonadal steroids, particularly estradiol are important in the regulation of GH secretion. In other studies of sampling at 5-minute intervals over 24 hours, we found that in young men and women the number of pulses per 24 hours were 6.7 and 11, respectively (Cluster analysis). The total integrated GH concentration was 2.6 in men and versus 4.1 $\mu\text{g}\cdot\text{min}/\text{mL}$ in women and the total nonpulsatile integrated GH concentration was 0.65 and 1.2 $\mu\text{g}\cdot\text{min}/\text{mL}$ in men and women, respectively.¹⁵

For a number of years it has been known that prolonged starvation (as occurs in protein-calorie malnutrition) may be associated with increased GH concentrations. We studied young men and women before, on the first day, on the second day, and on the fifth day of a fast with blood samples drawn at 20- or 5-minute intervals.¹⁶⁻¹⁸ The 5-minute data series were studied with deconvolution analysis,¹⁹ which allows quantitation of the number of secretory bursts, the amplitude, temporal location, and duration of the secretory bursts, the mass of hormone per secretory burst, and the one component (mono-exponential) disappearance rate constant. In this way, the secretion impulse is determined by removing the effects

2 1. Growth Hormone (GH) is released by the pituitary gland in a pulse-like fashion. GH is secreted when somatostatin secretion is low. GH also relies on GH Releasing Hormone (GHRH) to allow the release of GH. Somatostatin inhibits the release of GH, but not the synthesis of GH.

2. Sex steroids, especially estrogen, play a role in regulating GH, as well. Women pulse more GH than men.

3 3. Starvation/fasting/low protein/calorie restriction all increase GH levels. Meanwhile, obese individuals have reduced levels of GH with fewer and less powerful bursts of GH, and this effect is partially reversed by weight loss. Somatostatin levels tend to be elevated in obese, as well - inhibiting GHRH.

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of ongoing metabolic clearance from the concentration-time series. Using this analysis we demonstrated that the increase in GH concentrations during fasting results from increased endogenous secretion mediated by enhanced pulse frequency and amplitude with no significant change in GH clearance.^{17,18} In contrast, GH secretion in obesity is usually inhibited or lower than normal. In a similar study of obese adults compared with normal subjects, a triple defect was uncovered: (1) a shorter endogenous growth hormone half-life of 12 ± 1.6 versus 19 ± 1.5 minutes; (2) fewer apparent GH secretory bursts (3.2 ± 0.5 v 9.1 ± 1.0 per day); and (3) less GH secreted per secretory burst (2.1 ± 0.4 v 9.0 ± 2.4 ng/ml of distribution volume).²⁰ The GH response to GHRH is blunted in obese subjects and is partially reversed by significant weight loss following bariatric surgery.²¹ These findings suggest that somatostatin secretion is diminished during fasting and is increased in obesity. This hypothesis is supported by the observation that in the fed state, deconvolution-resolved GH secretory bursts occur in volleys with intervening periods of secretory quiescence while in the fasted state, bursts of GH are secreted with the same frequency as occurs within volleys in the fed state, without the long periods of absent secretion. Thus an underlying rhythm of GHRH release may be uncovered by fasting which presumably occurs via a decrease in somatostatin secretion.^{18,22}

GH secretion has been considered to be regulated by sleep. We have examined this question by measuring circulating GH concentrations every 30 seconds for 8 hours in six normal men with simultaneous electroencephalographic monitoring of sleep. GH secretion was correlated with sleep. The highest GH levels were associated with sleep stages 3 and 4.²³

To examine whether sleep modulates the pituitary response to GHRH, a collaborative study was undertaken among the research groups of Dr Georges Copinschi of the Free University in Brussels, Dr Eve Van Cauter at the same institution and the University of Chicago, and our own group.²⁴ Eight normal non-obese men aged 25 to 30 years participated in each of seven studies. In four studies the subjects slept from 11:00 PM to 7:00 AM. In the first study, no GHRH was administered. In the second, GHRH was administered 60 seconds into the first episode of slow wave sleep. In the third, GHRH was administered 60 seconds into the third REM period. In the fourth, GHRH was administered at 8:45 AM, when the subject was awake. In the last three studies, the subjects were kept awake at night and allowed to sleep from 4:00 AM to 12:00 PM. In the first study, no GHRH was administered. In the second, GHRH was administered at the usual time of the first episode of slow wave sleep (between 11:00 and 12:00 PM). In the last study, GHRH was administered 60 seconds into the first episode of slow wave sleep (after 4:00 AM). A 0.3 µg/kg dose of GHRH was administered and studies were separated by at least 1 week with the order being randomized. Blood was sampled at 5 to 15-minute intervals from 8:00 PM to 12:00 AM. The Ultra algorithm was used to characterize pulsatile secretion. The GH secretory rates were also mathematically derived from plasma levels by deconvolution assuming a one compartment model for distribution and metabolism with a half-life of 15 to 19 minutes and a distribution volume of 7% of body weight. These studies demonstrated that each time the subject fell asleep

during the first slow wave sleep a GH pulse occurred (in 39 of 39 studies). When sleep was delayed until 4:00 AM, GH pulses occurred in 12 of 16 subjects at the time of the usual slow wave sleep (between 11:00 and 12:00 PM). These pulses for the most part were smaller than those observed during each subject's first slow wave sleep. In each subject studied, the amount of GH secreted in response to GHRH in the awake period correlated strongly with that secreted during slow wave sleep with an *r* value of .942 (*P* < .001). When GHRH was administered in awake subjects either at 8:45 AM or between 11:00 and 12:00 PM (during the delayed sleep studies) the GH response was similar. The GH response to GHRH during slow wave sleep was the same during the normal time of sleep onset or with delayed sleep onset. However, the response was greater than that observed when the subject was administered GHRH awake. During REM sleep the response was smaller although this did not reach statistical significance. The frequent occurrence of a GH pulse at the time that slow wave sleep should have occurred, on the nights when sleep was delayed, suggests that there is a circadian rhythm for GH. That GH secretion is facilitated and the response to GHRH is augmented during slow wave sleep suggests that endogenous hypothalamic somatostatin secretion is low at that time. In contrast, during REM sleep GH secretion is lower and the response to GHRH tends to be smaller suggesting that hypothalamic somatostatin secretion is higher than during slow wave sleep.

GH-releasing peptide (GHRP) is a synthetic hexapeptide developed using conformational energy, peptide synthesis, and biological activity approaches by Bowers et al.²⁵ It releases GH *in vivo* in multiple species and appears to stimulate GH release by acting both at the hypothalamic and pituitary levels. GHRP does not interact with the GHRH receptor and probably does not interact with the somatostatin receptor.²⁵⁻²⁷ In studies performed in collaboration with Dr C.Y. Bowers, the effect of GHRP administration in normal men was studied.²⁸ There was a dose related increase in GH secretion with doses ranging from 0.1 µg/kg to 1 µg/kg body weight. The GH response to the 1 µg/kg GHRP was greater than that observed after the same dose of GHRH. When a subthreshold dose of GHRP, 0.1 µg/kg, was administered simultaneously with GHRH a synergistic effect was observed. When higher doses of GHRP were used, the effects were additive but not synergistic. Considering the results of *in vitro* and *in vivo* studies, it is likely that GHRP may act to functionally antagonize somatostatin secretion.

Information has been presented to support the hypothesis that episodic GH secretion is timed by withdrawal of tonic somatostatin secretion. GHRH is necessary for GH secretion as it is vital for GH messenger RNA transcription and synthesis. Fasting increases the number of secretory bursts while obesity is associated with a decreased number of secretory bursts as well as other changes in GH secretion. It is proposed that fasting is associated with low hypothalamic somatostatin secretion and obesity with high somatostatin secretion. Studies with GHRH-secreting tumors and exogenous GHRH support the concept of somatostatin as the "Zeitgeber" for secretion of GH pulses. The sleep studies suggest that there may well be a circadian rhythm for GH in humans and that variations of somatostatin secretion may account for differ-

4. Sleep releases GH, with the greatest releases during stages 3 and 4 (deep sleep).

5

5. Somatostatin is produced by the hypothalamus (as well as the pancreas and other tissues and cells)

ences in sensitivity to GHRH during different phases of sleep. Thus, slow wave sleep may be associated with low hypothalamic somatostatin secretion while REM sleep is associated with high somatostatin secretion. Finally, GHRP may act as

a functional somatostatin antagonist and may be useful in elucidating the role of somatostatin in normal and pathological GH secretion in humans.

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