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Research Article

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Endogenous Growth Hormone (GH)–releasing Hormone Is Required for GH Responses to Pharmacological Stimuli

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Abstract

The roles of hypothalamic growth hormone–releasing hormone (GHRH) and of somatostatin (SRIF) in pharmacologically stimulated growth hormone (GH) secretion in humans are unclear. GH responses could result either from GHRH release or from acute decline in SRIF secretion. To assess directly the role of endogenous GHRH in human GH secretion, we have used a competitive GHRH antagonist, (N-Ac-Tyr^1,D-Arg^2)GHRH(1-29)NH$_2$ (GHRH-Ant), which we have previously shown is able to block the GH response to GHRH. We first tested whether an acute decline in SRIF, independent of GHRH action, would release GH. Pretreatment with GHRH-Ant abolished the GH response to exogenous GHRH (0.33 μg/kg i.v.) but did not modify the GH rise after termination of an SRIF infusion. We then investigated the role of endogenous GHRH in the GH responses to pharmacologic stimuli of GH release. The GH responses to arginine (30 g i.v. over 30 min), L-dopa (0.5 g orally), insulin hypoglycemia (0.1 U/kg i.v.), clonidine (0.25 mg orally), or pyridostigmine (60 mg orally) were measured in healthy young men after pretreatment with either saline or GHRH-Ant 400 μg/kg i.v. In every case, GH release was significantly suppressed by GHRH-Ant. We conclude that endogenous GHRH is required for the GH response to each of these pharmacologic stimuli. Acute release of hypothalamic GHRH may be a common mechanism by which these compounds mediate GH secretion. (*J. Clin. Invest.* 1996. 97: 934–940.) Key words: clonidine • pyridostigmine • arginine • hypoglycemia • dopamine

Introduction

Growth hormone (GH)[1] secretion in all species, including humans, is regulated by a variety of external and internal cues. Several neural pathways, including adrenergic, cholinergic, and dopaminergic neurons, coalesce in the hypothalamus to activate or suppress the activity of GH-releasing hormone (GHRH) or somatostatin (SRIF)-producing neurons (1–3). The interplay between these two neurohormones is thought to produce the periodic secretory pattern of GH. The assessment of the integrity of the neuroendocrine control of GH secretion in physiological and clinical experiments is based, in part, upon GH responses after pharmacologic stimulation of the somatotropic axis. Clonidine, pyridostigmine, arginine, L-dopa, and insulin hypoglycemia all elicit acute GH release in normal individuals, and inadequate responses to these agents have been used to define GH insufficiency (1–3). The physiological mechanisms by which these secretagogues modulate GH secretion, however, have not been defined in humans.

These agents do not act directly on the pituitary to release GH; rather, they promote or inhibit the secretion of hypothalamic GHRH and/or SRIF (1–3). GH release could be mediated by the acute release of GHRH, by the intermittent decline in SRIF secretion, or by both mechanisms. Direct pituitary-portal blood sampling in rats (4) and in sheep (5–7) has shown that acute GHRH release is central for the production of spontaneous GH pulses. However, humans continue to have pulsatile GH discharges during continuous infusion of GHRH (8), and acute rebound GH release can also be elicited by the acute termination of an SRIF infusion in humans (9) as well as in rats (10). Since most of the rebound GH secretion in the rat can be eliminated by GHRH antiserum (10, 11), at least in this species, the GH secretion associated with SRIF withdrawal might depend upon acute GHRH release. Direct approaches used in animal studies (pituitary-portal sampling or selective immunoneutralization of GHRH or SRIF) are impractical in humans, and so the neuroendocrine involvement of endogenous hypothalamic GHRH and SRIF remains unknown in humans. Indirect experimental methods in humans have suggested that some of the centrally active secretagogues promote GH release through the activation of GHRH neurons, whereas other GH releasers act by suppressing SRIF release (1–3).

We recently used a competitive GHRH antagonist, (N-Ac-Tyr^1,D-Arg^2)GHRH(1-29)NH$_2$ (GHRH-Ant) to assess directly the role of GHRH in human physiology. A single intravenous bolus of GHRH-Ant, 400 μg/kg, suppressed by 95 and 80% the GH response to GHRH, 0.33 μg/kg, given 1 and 6 h later, respectively, and the same dose of GHRH-Ant given at 2200 h suppressed nocturnal GH pulsatility by 75% (12). We have subsequently used GHRH-Ant first to investigate whether GHRH plays a role in the GH response to SRIF withdrawal in humans and then to determine if GH secretion during pharmacologic stimulation is GHRH dependent.

Methods

The study was approved by the University of Michigan Institutional Review Board and the General Clinical Research Center (GCRC)

1. *Abbreviations used in this paper:* AUC, area under the curve; GH, growth hormone; GHRH, GH-releasing hormone; GHRH-Ant, GHRH antagonist; SRIF, somatostatin.

Review Committee, and all subjects signed an informed consent document before their participation. Healthy men (ages 20–35 yr) of normal height (1.70–1.95 m) and body mass index (20–27 kg/m^2) were studied. All had unremarkable medical histories, physical examinations, screening biochemical indices, and complete blood counts, and none were taking prescription medications. The subjects were admitted to the GCRC at 0730 h after an overnight fast, and intravenous catheters were placed in forearm veins for blood sampling and for the administration of the study medications. During the studies, the subjects remained at rest in a bed (insulin) or in a chair (all other studies). Napping was not permitted. Each subject was studied twice, once while receiving GHRH-Ant, 400 µg/kg, and once while receiving normal saline, both of which were administered intravenously over 6 to 8 min. The order of study was randomized, and there were at least 5 d between studies. Our previous experiments have demonstrated that the effect of a GHRH-Ant 400 µg/kg bolus on GH release was gone by 24 h (12).

In the first experiment, we determined whether the GH response associated with the termination of an SRIF infusion was GHRH dependent. This protocol was based on a paradigm proposed by Hindmarsh et al. (9). SRIF-14 (Sigma Chemical Co., St. Louis, MO) was diluted in normal saline and infused intravenously by syringe (model 2001; Medfusion Inc., Duluth, GA) at the rate of 166 µg/h from 0900 to 1200 h and from 1300 to 1600 h. GHRH-Ant or a saline bolus was given at 1500 h. Blood was sampled every 10 min for GH from 0800 to 1800 h. In five subjects, blood was collected for the measurement of plasma SRIF at 1250, 1400, 1500, 1600, 1610, and 1630 h and then every 30 min through 1800 h.

In the second set of experiments, we studied the effects of GHRH-Ant on the GH responses to pharmacologic GH stimuli. After the administration of GHRH-Ant, 400 µg/kg, or saline at 1000 h, the subjects were given (*a*) GHRH (Bachem California, Torrance, CA), 0.33 µg/kg i.v. (*n* = 5) at 1100 h; (*b*) L-dopa (DuPont Pharmaceutical Co., Wilmington, DE), 500 mg orally at 1030 h (*n* = 9); (*c*) arginine (Kabi Pharmacia, Piscataway, NJ), 30 g i.v. over 30 min beginning at 1030 h (*n* = 9); (*d*) clonidine (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT), 0.25 mg orally at 1040 h (*n* = 6); (*e*) pyridostigmine (ICN Pharmaceuticals, Costa Mesa, CA), 60 mg orally at 1000 h (*n* = 6); or (*e*) human recombinant regular insulin (Eli Lilly and Co., Indianapolis, IN), 0.1 U/kg i.v. at 1015 h (*n* = 6). The timing of administration of GH secretagogues was derived from the literature on the time course of GH responses (2, 3), so that the peak of the GH response would occur ∼ 60–90 min after the administration of GHRH-Ant. In each experiment, blood was sampled every 20 min from 0900 until 1400 h. The control data were from a similar group of young men (*n* = 9) who were receiving a saline infusion during an identical time period (13).

Plasma GH was measured in duplicate by RIA as previously described (12) using materials generously donated by the National Institute of Diabetes and Digestive and Kidney Diseases (National Institutes of Health, Bethesda, MD). Mean assay sensitivity was 0.3 µg/liter, and the intraassay coefficient of variation was < 9% at GH concentrations between 1.0 and 20 µg/liter. In five subjects undergoing a patterned SRIF infusion (both during saline and GHRH-Ant studies), additional blood samples were collected in prechilled tubes containing aprotinin 1,000 KIU/ml of whole blood, and plasma SRIF was measured by the University of Michigan Diabetes Research and Training Center Chemistry Core using an RIA that has been previously described (14) with intraassay coefficient of variation of 6%. Fasting SRIF in a group of normal volunteers was 174±23 ng/liter (mean±SD). All GH or SRIF samples for an individual subject were run in the same assay. Plasma glucose was measured with a glucose analyzer (version II; Beckman Instruments, Inc., Fullerton, CA).

Since the variance varied directly with the amplitude of the GH response, data were logarithmically transformed before analysis. The GH responses after the administration of GHRH, after SRIF withdrawal, and to the pharmacologic stimuli of GH secretion were calculated as both the maximum incremental increase of GH over the
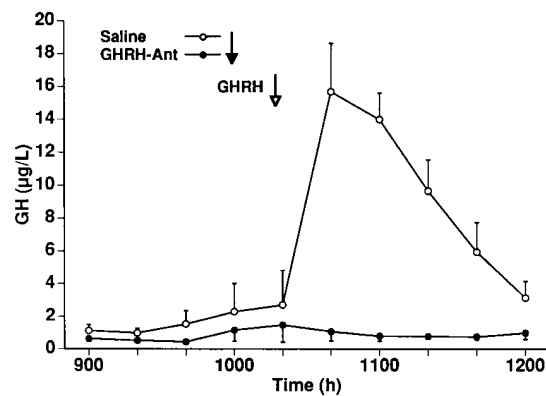

Figure 1. GH response to GHRH, 0.33 µg/kg, after saline or GHRH-Ant bolus. The closed arrow marks the time of saline or GHRH-Ant, 400 µg/kg, administration, and the open arrow indicates the time of GHRH administration. The GH response to GHRH was significantly suppressed by GHRH-Ant. (*n* = 5).

baseline (Δ Max) and as the GH area under the curve (AUC) for 2 h after the GH stimulus. The GH responses during saline and GHRH-Ant were compared by paired *t* tests. During the SRIF withdrawal experiment, individual time points between 1600 and 1800 h were also compared by two-way repeated measures ANOVA. One-way ANOVA followed by Dunnett's multiple comparisons against a single control (15) was used to determine whether the GH responses during GHRH-Ant treatment were different from the expected baseline GH secretion. Data are reported as mean±SE.

Results

During the saline infusion, spontaneous GH AUC was 217±164 µg × min/liter between 1100 and 1300 h. The maximum spontaneous absolute fluctuation of plasma GH during the same time period was 2.3±2.1 µg/liter. The GH response to GHRH, 0.33 µg/kg, is shown in Fig. 1 and Table I. The GH response to this dose of GHRH given 1 h after GHRH-Ant bolus was blocked, and both the AUC for GH and maximum incremental increase in GH were indistinguishable from those obtained during saline treatment alone.

The plasma SRIF and GH concentrations during the SRIF infusion protocol are given in Fig. 2. The baseline SRIF before the second infusion was 168±22 ng/liter, and SRIF rose to a maximum of 1,030±92 ng/liter. Within 10 min of terminating the SRIF infusion, plasma SRIF concentration fell to baseline and remained stable for the remainder of the study. There was a small GH response after the first withdrawal of the SRIF infusion at 1200 h (Δ Max 0.54±0.19 µg/liter). This was accounted for by four and three subjects having minor increases in GH when SRIF was stopped during the saline and GHRH-Ant treatment days, respectively. After the second withdrawal of SRIF at 1600 h, the GH response after saline administration was greater than that at 1200 h (Δ Max 4.0±1.8 µg/liter; *P* < 0.001), but it was also highly variable. Administration of GHRH-Ant did not modify the GH rise to termination of SRIF infusion. There were no differences in the GH responses between the two treatments as measured by the Δ Max (4.0±1.8 vs 3.4±1.4 µg/liter; *P* = 0.17; saline vs GHRH-Ant), AUC (152±98 vs 168±63 µg × min/liter; *P* = 0.3), or between individual time points (*F* = 1.1, *P* = 0.3) during the 2 h after termination of the SRIF infusion (1600 to 1800 h).

Table I. Effect of GHRH-Ant on GH Responses to Pharmacologic Stimuli

Stimulation test	Saline	GHRH-Ant	P
Saline (n = 9)			
Δ Max GH (μg/L)	2.3±2.1		
AUC (μg × min/L)	217±164		
GHRH (60 min after GHRH-Ant, n = 5)			
Δ Max GH (μg/L)	14.4±1.9	1.0±0.6	0.002
AUC (μg × min/L)	1,009±158	112±33	0.002
SRIF withdrawal (60 min after GHRH-Ant, n = 10)			
Δ Max GH (μg/L)	4.0±1.8	3.4±1.4	0.17
AUC (μg × min/L)	152±98	168±63	0.3
L-dopa (30 min after GHRH-Ant, n = 10)			
Δ Max GH (μg/L)	10.9±1.6	2.6±0.9	0.007
AUC (μg × min/L)	776±111	242±39	0.008
Arginine (30 min after GHRH-Ant, n = 10)			
Δ Max GH (μg/L)	10.0±3.3	3.3±1.0	0.02
AUC (μg × min/L)	684±200	296±73	0.03
Clonidine (40 min after GHRH-Ant, n = 6)			
Δ Max GH (μg/L)	15.3±3.2	2.6±0.9	0.0004
AUC (μg × min/L)	975±230	206±71	0.0002
Insulin hypoglycemia (15 min after GHRH-Ant, n = 6)			
Δ Max GH (μg/L)	85.1±18.2	6.7±2.8	0.0003
AUC (μg × min/L)	6,474±1,436	454±175	0.0001
Pyridostigmine (0 min after GHRH-Ant, n = 6)			
Δ Max GH (μg/L)	10.0±2.9	1.2±0.4	0.0006
AUC (μg × min/L)	710±217	170±29	0.007
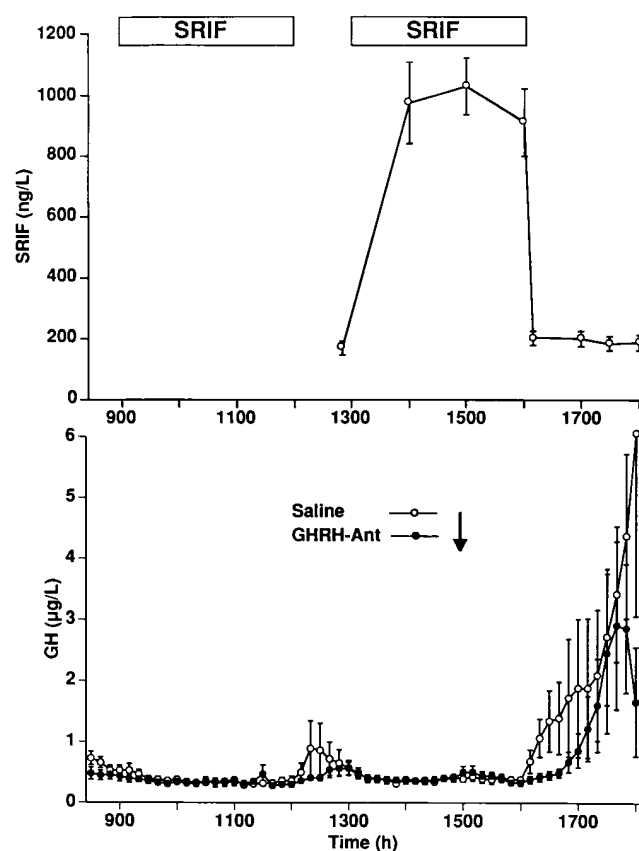
The GH responses to L-dopa, arginine, clonidine, pyridostigmine, and insulin-induced hypoglycemia are given in Figs. 3–7 and in Table I. In each case, the GH response was significantly diminished by GHRH-Ant. There was no difference in timing or nadir (1.72±0.11 vs 2.05±0.11 mmol/liter; $P = 0.1$) of the hypoglycemia or in the time course of glucose recovery after insulin administration between the two arms of the protocol. By Dunnett's test, all of the GH responses to pharmacologic stimulation after GHRH-Ant administration, except for insulin, were indistinguishable from treatment with saline alone ($P < 0.05$ for insulin).

Discussion

The activity of the hypothalamic GHRH and SRIF neurons is regulated by a multitude of neurotransmitter systems, including adrenergic, cholinergic, and dopaminergic neuronal circuits (1–3). Additionally, metabolic factors such as glucose, amino acids, and free fatty acids also elicit or suppress GH release, apparently by altering acute GHRH or SRIF release (1–3). Ascertainment of the discrete neuroendocrine sites of action of these stimuli is of significant importance. Specifically, administration of neuroactive compounds and manipulation of

Figure 2. (*Upper panel*) Plasma SRIF concentration during patterned SRIF infusion. There were no differences in SRIF concentrations between the two study days. SRIF values represent the mean±SE over all studies. (*Lower panel*) GH concentrations during the patterned SRIF infusion. Saline or GHRH-Ant, 400 μg/kg, was administered at 1500 h (*arrow*). After the termination of the infusion at 1600 h, plasma GH rose in both studies, and there were no differences in the GH responses during saline and GHRH-Ant studies. ($n = 10$).
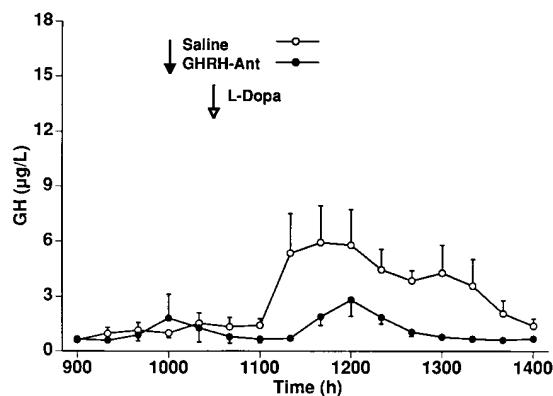
Figure 3. GH response to 0.5 g L-dopa administered orally after saline or GHRH-Ant bolus. The closed arrow indicates administration of saline or GHRH-Ant, 400 μg/kg, at 1000 h, and the open arrow marks the time of L-dopa administration. (*n* = 9).

Figure 5. GH response to 0.25 mg clonidine administered orally after saline or GHRH-Ant bolus. The closed arrow indicates administration of saline or GHRH-Ant, 400 μg/kg, at 1000 h, and the open arrow marks the time of L-dopa administration. (*n* = 6).

these metabolic cues serve as a cornerstone in the diagnosis of GH deficiency in adults and children.

The physiologic mechanisms through which these stimuli release GH have not been established in humans. The present understanding of their effects has been based upon in vitro studies of hypothalamic and pituitary tissues, indirect animal and human studies, and direct measurement of hypothalamic GHRH and SRIF output in animals. A suprapituitary site of action of these stimuli is exemplified by the lack of GH responses in animals that have undergone hypothalamic ablation (16) and in humans with hypothalamic lesions (17), by the inability of these stimuli to release GH from isolated pituitaries (18), and by the modulation of GHRH and/or SRIF release in vitro (19) and in vivo (20, 21) during pharmacologic stimulation.

Significant species-specific differences in GH neuroregulation (5) make the extrapolation of animal data to human physiology questionable. Data on peripheral GHRH and SRIF concentrations during GH stimulation are conflicting and of unclear significance. Arginine (22, 23) and ornithine (24) have been reported to have no effect on systemic GHRH. In contrast, L-dopa is thought to release hypothalamic GHRH, since
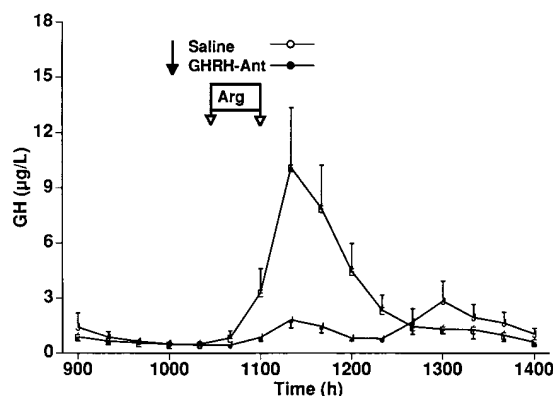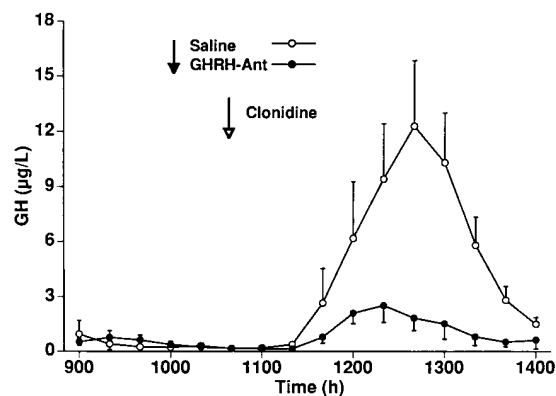
L-dopa administration increased peripheral GHRH in normal subjects (17, 23, 25, 26) but not in children with hypothalamic GHRH deficiency (17). Clonidine has been reported either to increase (27) or to have no effect (23, 26) on systemic GHRH. Similarly, a rise in peripheral GHRH during hypoglycemia was documented by some (22, 28) but not all groups (23, 26, 27). The several thousand–fold dilution of pituitary-portal GHRH and SRIF in the systemic circulation makes these data difficult to interpret, and, moreover, systemic GHRH (28, 29) and SRIF (30) are not necessarily of hypothalamic origin.

Since direct sampling of pituitary-portal GHRH and SRIF is impractical in humans, only indirect indices of hypophysiotropic hormone secretion have been used in clinical investigation. In one approach, the GH response to a secretagogue is compared with the response to the secretagogue plus a maximal dose of GHRH. If the GH stimulus potentiates the effect of GHRH, it has been assumed to do so by suppressing SRIF secretion (1–3). Based upon this logic, dopamine agonists have been regarded as GHRH stimulants (31), α_2 adrenergic agonists as either GHRH stimulants (32) or SRIF suppressors (33), and both arginine (34) and cholinergic agonists (35) as purely SRIF-suppressing compounds. The neuroendocrine
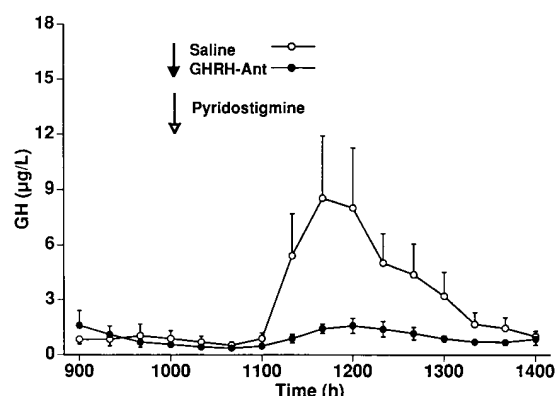

Figure 4. GH response to arginine, 30 g i.v., after saline or GHRH-Ant bolus. The closed arrow indicates administration of saline or GHRH-Ant, 400 μg/kg, at 1000 h, and the open arrows mark the time during which arginine was infused. (*n* = 9).

Figure 6. GH response to 60 mg pyridostigmine administered orally after saline or GHRH-Ant bolus. The closed arrow indicates administration of saline or GHRH-Ant, 400 μg/kg, at 1000 h, and the open arrow marks the time of pyridostigmine administration. (*n* = 6).
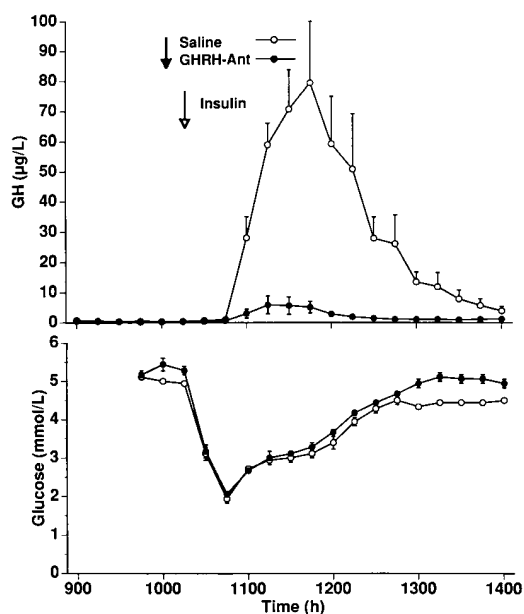
Figure 7. (*Upper panel*) GH response to hypoglycemia after saline or GHRH-Ant bolus. (*Lower panel*) Plasma glucose concentrations after administration of insulin, 0.1 U/kg. The closed arrow marks the time of administration of saline or GHRH-Ant, 400 μg/kg, and the open arrow indicates the time of the intravenous insulin bolus. There were no differences between the saline and GHRH-Ant treatment groups with regard to either the degree of or the recovery from hypoglycemia. ($n = 6$).

mechanism of GH secretion after insulin hypoglycemia has been attributed to SRIF withdrawal (36) and/or a "third" mechanism (37, 38).

More recently, direct sampling of pituitary-portal blood in unanesthetized sheep has provided direct data on the hypothalamic regulation of GH secretion and challenged the conclusions obtained from indirect studies. Although cholinesterase inhibitors release GH synergistically with GHRH in sheep (20) and in humans (35), thus suggesting SRIF suppression as the mechanism of action, direct measurements of pituitary-portal GHRH and SRIF after neostigmine administration found an increase in GHRH but no change in SRIF concentration (20). Similarly, clonidine was found to augment GHRH-stimulated GH secretion and to release GHRH without decreasing hypothalamic SRIF secretion (21). Such data underscore possible pitfalls in indirect studies on the neuroendocrine regulation of GH secretion.

To assess the role of GHRH in pharmacologically stimulated GH secretion in humans more directly, we have used a specific competitive antagonist of GHRH, which we previously used to demonstrate the GHRH dependency of the nocturnal GH pulsatility in humans (12). The virtually complete suppression of the GH response to a "physiologic" dose of GHRH in this and in our previous report (12) demonstrates the biological activity of the GHRH-Ant dose used for these studies. Since the GH response to pharmacologic testing could also be due to an acute fall in pituitary-portal SRIF, we first sought to determine whether the GH response after SRIF withdrawal is GHRH dependent. In vitro (39) and in vivo animal (10) data have shown that rebound GH secretion occurs after acute withdrawal of SRIF, and similar results were found in humans (9). Immunohistochemical studies have shown connections between hypothalamic SRIF and GHRH neurons (40, 41), suggesting that SRIF disinhibition of GHRH might be a stimulus for GHRH release. The elimination of the GH response to SRIF withdrawal in rats by GHRH antiserum (10, 11) and a small rebound rise in pituitary-portal GHRH in sheep treated with a single injection of a SRIF analogue (42) support this hypothesis.

During the SRIF infusion, plasma SRIF concentration rose to five times the baseline concentration and then fell to baseline within 10 min after termination of the infusion, consistent with the short plasma half-life of SRIF (30). Similar to the data from Hindmarsh et al. (9), the GH response to the second SRIF withdrawal was of greater magnitude than that after the first withdrawal. These responses were modest in magnitude and quite variable, and they resulted in a GH peak 1–2 h after the SRIF infusion was stopped. The modest size of this response after saline and the inability of GHRH-Ant to block the GH rise after SRIF withdrawal are consistent with a model in which SRIF withdrawal in humans, independent of acute GHRH effect, is, at best, a weak stimulus for GH secretion (43).

One could argue that GHRH-Ant did not block the GH response to SRIF withdrawal because of the waning potency of the single bolus of GHRH-Ant. This is unlikely for several reasons. First, the magnitude of GH release to SRIF withdrawal was significantly ($P < 0.01$) smaller than the GH rise to GHRH, 0.33 μg/kg, implying that the amount of GHRH conceivably released by SRIF withdrawal was also likely to be small and therefore readily inhibited by GHRH-Ant. In addition, the same dose of GHRH-Ant inhibited the GH response to GHRH given 6 h later by 80% (12). Thus, if the termination of the SRIF infusion had mediated the GH rise exclusively through activation of GHRH release, GHRH-Ant would have significantly diminished the GH response.

Although there was a rapid fall in SRIF in the systemic circulation, it is not clear how well our model mimics the normal changes in pituitary-portal SRIF concentration that might occur during either spontaneous pulsatile or pharmacologically stimulated GH secretion. We are not aware of direct data on portal SRIF concentrations in humans, and there have been few direct studies in animals. In rats, the changes in pituitary-portal SRIF during a time of presumed spontaneous GH pulse were modest (4). In sheep, changes in portal SRIF concentration during pulsatile GH have been more variable (5–7), although less than the fivefold changes that we observed in our study, and variations in SRIF have not correlated with either spontaneous (5–7) or pharmacologically induced (20, 21) GH secretion. Thus, our model, in which the pituitary is transiently exposed to very high SRIF concentrations followed by a sudden fall in SRIF, may not be fully equivalent to the naturally occurring fluctuations in the pituitary-portal SRIF concentrations. However, our data clearly differ from the results obtained in rats, where the GH rise after SRIF withdrawal was blocked by anti-GHRH serum (10, 11). This underscores the species specificity of GH regulation. More direct human investigations will rely upon the development of a safe and reliable inhibitor of endogenous hypothalamic SRIF secretion or effect.

In contrast to its lack of effect on the GH response to SRIF withdrawal, GHRH-Ant significantly suppressed the GH responses to each of the pharmacologic agents. The most direct

interpretation of these data is that acute GHRH release is the mediator of GH secretion after administration of these drugs. This model is consistent with the recent data by Magnan et al. in which neostigmine (20) and clonidine (21) promoted GH secretion by acutely simulating GHRH release without obvious suppression of SRIF. One could also envision a paradigm in which acute inhibition of SRIF by one or more of the pharmacologic GH secretagogues elicits GH release only if the pituitary is simultaneously exposed to tonic GHRH. In this model, GHRH-Ant would block the acute responses by eliminating the GHRH effect. Data from direct pituitary-portal sampling (20, 21), and our data in humans exposed to patterned SRIF infusion, argue against this possibility. Alternatively, at least some of the centrally active secretagogues might stimulate hypothalamic release of a still unidentified GH releasing factor that might be able to exert its full effect only in the presence of activated GHRH receptors. An indirect support for this hypothesis comes from the comparison of our data on insulin hypoglycemia with the results of Vance et al. (44). In their studies, a continuous infusion of GHRH inhibited the GH response to a bolus of GHRH but did not block the GH response to insulin hypoglycemia. Our data clearly demonstrate that GHRH is needed for the GH response to hypoglycemia, and the difference between the outcomes of the two seemingly similar experimental paradigms merits further investigation and may point to the existence of a "third factor" in the regulation of GH secretion. A GH-releasing peptide-like molecule is one potential candidate for that role (45). In any case, our data prove that endogenous GHRH plays a major role in the generation of pharmacologically induced GH release, since elimination of its effect by GHRH-Ant attenuated GH responses by 70–90%.

In conclusion, our data demonstrate that the acute GH release after termination of an SRIF infusion appears to be independent of acute GHRH effect. In contrast, stimulation of GH secretion in humans by dopaminergic, cholinergic, and α_2-adrenergic pathways, by arginine, and by acute hypoglycemia all require endogenous GHRH. This information is important for the proper interpretation of physiologic studies of human GH secretion in normal and pathologic states.

Acknowledgments

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