Observations on the Stimulation of Growth Hormone Secretion in Patients With Growth Hormone Deficiency

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We examined increases in levels of endogenous growth hormone (GH) secretion through exercise, GH-releasing hormone (GHRH), and GH-releasing peptide (GHRP), in patients with demonstrable GH deficiency (GHD) due to either hypothalamic (HT) or pituitary (HP) disease. Eight of 11 HT and four of five HP patients could produce GH levels greater than 5 mU/L, and six of 16 patients could produce GH levels greater than 9 mU/L in this way. Hypoglycemia-stimulated GH and insulin-like growth factor-1 (IGF-1) levels did not predict response. Of 11 HT patients, three failed to respond to any stimulus; one with IGHD, whose peak GH after hypoglycemia was 4.9 mU/L, had normal responses to both GHRH and to exercise. Three who failed to respond to GHRH responded to exercise. Only three patients were tested with GHRH plus GHRP, but in one the GH levels after GHRH, GHRP, and the combination were 5.5, 1.8, and 16.3 mU/L, respectively. In HP patients, the most potent stimulus to GH secretion was the combination of GHRH plus GHRP; GHRP alone had no effect. GHRH alone induced significant GH secretion in four of five patients, indicating the potential for treatment with such peptides.
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RECENT DATA have shown that patients with growth hormone deficiency (GHD) will benefit from treatment with growth hormone (GH). Many patients with hypothalamic and/or pituitary disease are GH-deficient and the question arises as to whether they should receive GH therapy. Even if this treatment is considered desirable, financial constraints may restrict the long-term use of GH. Thus, alternative methods of achieving the same beneficial effects as have been claimed for GH treatment need to be investigated. Both GH-releasing hormone (GHRH) and GH-releasing peptide (GHRP) are potent stimuli to GH secretion in normal subjects.[1-3] Each binds to specific receptors in the pituitary, and their actions are synergistic both in vitro[4,5] and in normal men.[6,7] Exercise has also been used as a stimulus to GH secretion, particularly in children.[8,9] We have therefore examined the possibility of increasing the level of endogenous GH secretion using these stimuli, in patients who have demonstrable GHD due to either hypothalamic or pituitary disease.

SUBJECTS

Patients with GHD were identified from the results of earlier insulin stress tests (IST); if this had not been done within the previous 12 months, then the GHD was confirmed by a further IST. A peak GH level of less than 9 mU/L was considered to be an inadequate response. Patients who were deficient in sex hormones were receiving replacement treatment. Women were studied in the early follicular phase of their cycle. Patients and controls were within the age range 18 to 50 years. Body mass index was in the range of 21 to 28 kg/m^2. Males and females were included.

GHD was considered to be secondary to hypothalamic disease in the following circumstances: when imaging demonstrated a hypothalamic lesion with no pituitary lesion, when GHD resulted from cranial but not pituitary irradiation, and when the GHD was associated with spontaneous diabetes insipidus. The GHD was attributed to primary pituitary insufficiency when imaging showed a pituitary lesion with no hypothalamic lesion and when there was associated pituitary hormone deficiency; patients who had received irradiation were excluded. Control subjects were age-, sex-, and weight-matched. Subjects who exercised excessively were excluded.

STUDY PROTOCOL

An IST using 0.1 U/kg actrapid was performed where necessary to confirm the diagnosis of GHD, the criterion being a peak GH level less than 9 mU/L with glucose less than 2.1 mmol/L. Patients with additional hormone deficiencies continued their replacement treatment during this and all other tests. Subjects underwent acute stimulatory tests in randomized order, with at least 1 week between each test. Tests used were as follows: GHRH 1 μg/kg, placebo 0.9% saline, GHRP 1 μg/kg, GHRH 1 μg/kg plus GHRP 1 μg/kg, and standarized exercise on an ergometric bicycle. Serum samples were stored at −40°C and assayed together using an IRMA. The study had the approval of the local joint ethical committee.

RESULTS

Subjects recruited were as follows: eight control subjects, with a mean age of 31.4 years (range, 24 to 38); five hypopituitary (HP) patients, with a mean age of 39.6 years (range, 24 to 49); and 11 hypothalamic (HT) GHD patients, with a mean age of 30.8 years (range, 20 to 49). IGF-1 levels were as follows: controls, 23.5 ± 1.6 (SD) nmol/L; HT patients, 14.5 ± 1.9 nmol/L; and HP patients 13.8 ± 3.9 nmol/L. By IST, peak growth hormone responses were as follows: HT, 2.8 ± 0.6 mU/L; and HP, 2.0 ± 0.5 mU/L. IST were not performed in the group of normal subjects. Placebo studies were performed in a total of eight patients, taken from each group; no GH response was seen in any of this group. With GHRH, the peak GH response in HT patients was 7.2 ± 3.2 mU/L. Four of these subjects achieved levels greater than 5 mU/L and one a level greater than 9 mU/L. The mean peak GH level in HP patients was 7.7 ± 2.3 mU/L; four of five patients achieved levels greater than 5 mU/L and three of five levels greater than 9 mU/L. In control subjects, the mean peak GH level was 31.6 ± 4.7 mU/L. HP patients did not respond to GHRP, with the mean peak GH level being 1.4 ± 0.7 mU/L. GHRP was administered to only three HT patients and only one responded, but achieved a peak GH level of 46.4 mU/L.

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GHRH plus GHRP when given in combination led to stimulated GH secretion in excess of that seen with GHRH alone. In the three HT patients tested, the mean peak GH level was 23.6 ± 11.7 mU/L, and all three achieved levels greater than 5 mU/L (range, 8.0 to 59.0 mU/L). Exercise induced peak GH secretion in control subjects of 24.7 ± 7.7 mU/L (n = 6) and in HT patients a mean level of 6.5 ± 2.1 mU/L, of whom five achieved levels greater than 5 mU/L.

DISCUSSION

The major finding from this study is that many patients with undoubted GHD can be stimulated by one or more of these stimulants to secrete GH, such that eight of 11 HT and four of five HP patients could produce GH levels greater than 5 mU/L and six of 16 patients could produce GH levels greater than 9 mU/L. Neither hypoglycemia-stimulated GH nor IGF-1 levels predicted which patients had the potential to respond to these other agents. In the HT group of 11 patients, three failed to respond to any stimulus; one patient with IGHD, whose peak GH level after hypoglycemia was 4.9 mU/L, had entirely normal responses to both GHRH and to exercise. Three patients who failed to respond to GHRH responded to exercise. Only three patients have as yet been tested with GHRH plus GHRP, but this combination induced the highest levels; for example, in one patient, the GH levels after GHRH, GHRP, and the combination were 5.5, 1.8, and 16.3 mU/L, respectively. In HP patients, the most potent stimulus to GH secretion was the combination of GHRH plus GHRP, although GHRP alone had no effect. GHRH alone induced significant GH secretion in four of five patients, indicating the potential for treatment with this agent. IST was a poor stimulus to GH secretion. Although the patients have been classified into pituitary or hypothalamic groups, this cannot be done with absolute certainty. However, it would appear that the use of GHRH or GHRP tests to discriminate between pituitary or hypothalamic GHD may not be reliable.

Although these data have been obtained from acute tests, they indicate that the use of stimulatory procedures may be able to induce biologically significant levels of GH in GHD patients, even though the peak GH levels are lower than would be expected in normal individuals. Many previous studies have shown that children and adults with IGHD, usually of hypothalamic origin, respond to GHRH[10] and GHRH has been evaluated as a therapeutic option in these patients.[11] The mechanism of GHRP action on GH is still not fully understood, but GH-releasing peptides are being developed that will be active by mouth and with longer duration of action. These peptides have been shown to be active in patients with IGHD. However, our studies show that there is also the possibility of stimulating endogenous GH secretion in patients with a variety of hypothalamic or pituitary conditions. Detailed studies are needed to investigate the use of combined stimuli, the timing of the stimulus, and the optimum frequency of repetitive stimuli.

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