The Spectrum of GH Responses to GHRH and Somatostatin in Patients with Acromegaly

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HANEw, K., SATo, S., GOH, M., SASasaki, A., SHIMizu, Y., SUGAWARA, A., OHTSUKA, T. and YOSHINAGA, K. The Spectrum of GH Responses to GHRH and Somatostatin in Patients with Acromegaly. Tohoku J. exp. Med., 1988, 155 (3), 233-239 —— Plasma GH responses to GHRH and somatostatin were examined in 43 patients with active acromegaly. Thirty-two of these patients showed GH increases 50% above the basal values in response to at least 1 of 3 stimuli (TRH, LHRH, arginine) (categorized as group I). The remaining 11 patients showed no response to any of the stimuli (categorized as group II). Following somatostatin infusion, group I (n = 31) showed significantly greater GH suppression than group II (n = 11) from 30 to 90 min (p < 0.05-0.01). In addition, plasma GH responses to GHRH at 15 and 30 min was also greater in group I (n = 12) than in group II (n = 5) (p < 0.05 & 0.01). There was a positive correlation between the log value of the peak GH after GHRH and the maximal % decrement after somatostatin (r = 0.64, p < 0.02). However there were no differences in the responses of normal thyrotrophs (TSH) to TRH between the two groups. These results indicate that there are two types of acromegaly, i.e., one is more responsive and another is less responsive to either non-specific (TRH & LHRH) or specific GH stimulations (GHRH & somatostatin). ——— acromegaly; GH; GHRH; somatostatin; autonomy

We have previously reported that there are two types of acromegaly, one is less responsive and another is more responsive in their plasma GH to exogenous stimuli (Hanew et al. 1980). In this study, we have administered TRH, LHRH and arginine to larger number of acromegalic patients, and divided these patients into the two types mentioned above. Then, responses of the pituitary adenomas to the physiological GH regulators, i.e., somatostatin and GHRH, and responses of the normal pituitary thyrotrophs to TRH were compared in the two types of acromegaly.
MATERIALS AND METHODS

Fourty-three patients with active acromegaly, 20 men and 23 women, aged 21 to 73 years, were studied. Every patient had an elevated plasma GH level (> 6 ng/ml; range, 9.3-373.0 ng/ml), enlarged sella turcica, acromegalic appearance, and other clinical manifestations of GH excess. Fourty of 43 patients were untreated, and the other two received incomplete transsphenoidal adenomectomy and the remaining one received pituitary irradiation previously. Pituitary-adrenal and -thyroid functions were normal in all patients. Informed consent was obtained from every patient. All tests were started between 08:00-09:00 hr after an overnight fast. TRH (500 μg, iv; Tanabe, Osaka), LHRH (100 μg, iv; Daiichi, Tokyo), arginine (0.5 g/kg, iv for 30 min; Morishita, Osaka) and somatostatin (500 μg, iv for 75 min; Protein Research Foundation, Osaka) were administered to these acromegalic patients according to the methods previously reported (Hanew et al. 1980). One hundred μg of GHRH (1-44) NH₂ (Sumitomo, Osaka) was injected intravenously and blood samples were obtained 30 and 0 min before and 15, 30, 45, 60, 90 and 120 min after the injection. Plasma samples obtained were kept frozen at −20°C until assayed. Plasma GH, PRL and TSH were measured using commercial RIA kits (GH: Dainabot, Tokyo; PRL: Sorin, Gif-sur Yvette, France; TSH: Daiichi, Tokyo), and their minimal detectable concentrations were 0.2 ng/ml, 1 ng/ml, and 0.15 μU/ml, respectively (Sasaki et al. 1983; Hanew et al. 1987). Wilcoxon’s non-parametric analysis was used for statistical analysis, and the variance of the mean was expressed as s.e.

RESULTS

Plasma GH responses to TRH, LHRH, and arginine in 43 patients with acromegaly

All 43 patients with acromegaly were administered TRH, LHRH and arginine. Thirty-two of these patients (Nos. 1-32) showed an increase in GH in
excess of 50% of the basal value in response to at least 1 of the 3 stimuli (categorized as group I). The remaining 11 patients (Nos. 33-43), however, showed no response to any of the stimuli (categorized as group II; Fig. 1). In group I, 31 patients (97%) showed responses to TRH, 15 (47%) showed responses to LHRH, and 25 (78%) to arginine. Fourteen patients showed GH responses to the all 3 agents.

Plasma GH responses to somatostatin in two groups of acromegaly

After the somatostatin infusion, group I (n = 31) and group II acromegalic patients (n = 11) showed a gradual decrease in GH from 15-75 min after the start of the infusion and a prompt increase in GH after the termination of the infusion (Fig. 2). However, the mean GH decrement in group I was significantly greater than that in group II from 30-90 min (p value: <0.05-0.01). In addition, the post-inhibitory GH rise was greater in group I than in group II (at 150 min, p <0.05; Fig. 2).

Plasma GH responses to GHRH in two groups of acromegaly

Twelve of group I and 5 of group II patients received GHRH injection. Plasma GH responses to GHRH were greater in group I at 15 min (336.8±101.1 vs. 138.8±16.2% p<0.05) and 45 min (292.1±55.3 vs. 134.1±7.1%, p<0.01) compared to group II (Fig. 3). There were no relations between the basal plasma GH levels and the peak GH values on GHRH tests (r=0.32, p=n.s.), while the mean basal GH value in group II was significantly higher than that in group I (144.8±34.8 vs. 65.8±16.8 mg/ml, p<0.05).
Correlations between the maximal GH responses to GHRH and to somatostatin in group I patients

In eleven group I patients, there were positive correlations between the peak
GH values on GHRH test (log value) and the nadir values on somatostatin (% decrement) \( (r=0.64, p<0.02; \text{Fig. 4}) \).

Clinical and laboratory data in two groups of acromegaly

There were no statistical differences in age (46.6±2.6 vs. 39.5±2.8 year), basal plasma GH (55.2±12.1 vs. 79.6±20.4 ng/ml), and basal PRL values (23.8±6.2, \( n=31 \) vs. 16.4±6.0 ng/ml, \( n=10 \)) between group I and group II. Again, as shown in Fig. 5, no differences were observed in basal plasma TSH (1.2±0.1 vs. 0.8±0.2 \( \mu U/ml \)) and peak TSH values (7.8±0.9 vs. 7.1±1.4 \( \mu U/ml \)) on TRH tests between group I and II.

Discussion

In this study, 32 (74%) out of 43 patients with acromegaly showed plasma GH responses at least to one of TRH, LHRH, or arginine tests. The remaining 11 patients (26%) showed no responses to any of these agents. Plasma GH responses to physiological GH regulators, i.e. somatostatin and GHRH, were much greater in the former (group I) than in the latter (group II). In contrast, similar responses of plasma TSH, which is secreted from normal pituitary tissues, were observed in the two groups after TRH injection.

These results indicate that the pituitary adenomas in group II are less responsive to somatostatin and to GHRH compared to group I patients. Relating to this, differing numbers and affinities of somatostatin receptors are indicated in pituitary adenomas of individual acromegalic patients (Ikuyama et al. 1986; Reubi et al. 1987). Although, the exact reason for the difference between the group I and group II is not clear, it is plausible that the receptor and post receptor system in group II somatotrophs are less operative than in group I. The fact that
the postinhibitory GH rise after somatostatin infusion was much smaller in group II than in group I suggests the following possibilities, 1) intracellularly stored GH pool was smaller in these patients due to lesser GH inhibition, 2) negative feedback effects on their hypothalamic GHRH or somatostatin were less prominent, or 3) these somatotrophs were less responsive to endogenous hypothalamic stimulations through such feedback (Hanew et al. 1984). From the data of similar plasma TSH responses to TRH in the two groups, it seems that negative feedback effects of GH on hypothalamic somatostatin secretion are essentially not different in the two groups, since it is well known that somatostatin can regulate TSH secretion in man and rat (Siler et al. 1974; Chihara et al. 1978).

Pieters et al. (1984) have reported the positive correlation between the basal plasma GH level and GHRH induced GH release in acromegalic patients. However, we could not observe such a correlation. The patients who are more responsive to non-specific stimuli (TRH & LHRH) are also more responsive to specific stimuli (somatostatin & GHRH), and vice versa. This may indicate that the abnormal or normal receptor and post-receptor systems have mutual relationships in acromegalic pituitary adenomas, although each receptor site might be different (Shibasaki et al. 1986). Relating to this, the receptor site of GHRH and somatostatin, using the pituitary adenomas in vitro, are reported to be different (Lamberts et al. 1984). We have, however, observed a definite correlation between the responses to GHRH and to somatostatin. This may also indicate the mutual relationships of GHRH and somatostatin receptors on the levels of adenoma cells, possibly in their receptor coding genes. To further elucidate the differences in less and more autonomous types of acromegaly, the receptor (number & affinity) and the post-receptor system (transcription & translation of mRNA) to specific and non-specific hypothalamic hormones should be examined.

In conclusion, there are two types of acromegaly, i.e., one is more responsive and another is less responsive to either non-specific (TRH & LHRH) or specific GH stimulations (GHRH & somatostatin).

References
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