The Mechanism of Postinhibitory Rebound Increases in Plasma GH in Acromegalic Patients

HANEW, K., SASAKI, A., SATO, S., KASAI, M., SHIMIZU, Y., MURAKAMI, O. and YOSHINAGA, K. The Mechanism of Postinhibitory Rebound Increases in Plasma GH in Acromegalic Patients. Tohoku J. exp. Med., 1984, 142 (1), 59-65 —— The mechanism of postinhibitory rebound increase in GH secretion was studied in 5 normal and 7 acromegalic subjects. Both normal and acromegalic subjects showed prompt GH decreases during the infusion of somatostatin (500 μg/75 min) (% decrease: 69.1 ± 10.4 vs. 73.9 ± 6.5) and rebound rises after its termination. The rebound rises occurred more promptly and markedly in normal controls than in acromegalic subjects, i.e. the rebound peak appeared at 15 min in normal controls and at 45 min in acromegalic patients after the cessation of somatostatin infusion. Dopamine (DA) infusion (5 μg/kg/min for 90 min) also induced similar inhibition and postinhibitory rebound rises in GH secretion in 6 patients with acromegaly. Although the maximum inhibitions (67.1 ± 7.3% vs. 73.7 ± 7.1%) and the inhibitory areas (4354.5 ± 171.0%•min vs. 3796.5 ± 322.5%•min) during the DA and somatostatin infusions were not different, the rebound at 15 min was significantly greater after DA than after somatostatin (p < 0.05). All seven patients with acromegaly were TRH responsive in their plasma GH (% of basal: 93.5 to 944.3). When TRH was injected at the termination of somatostatin infusion, the rebound increase was significantly enhanced and the rebound peak appeared 30 min earlier than after single somatostatin administration. These results indicate that the mechanisms participating in the postinhibitory rebound rise are different in normal controls and acromegalic patients, and that the magnitude of the rebound differs with agents employed. Also, it is evident that the rebound phenomenon in acromegaly is possibly modified by exogenous hypothalamic releasing factors.

It is widely accepted that human pituitary hormones are apt to show rebound increases after the administration of inhibitory agents (Hall et al. 1973; Besser et al. 1974a; Leblanc et al. 1976; Judd et al. 1978; Leebaw et al. 1978; Kaptein et al. 1980). Although the exact mechanism is not studied well, the rebound could

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be due to (1) increased hypothalamic releasing factors; (2) decreased hypothalamic inhibiting factors; or (3) an overshoot from the stored pituitary pool (Martin 1976; Judd et al. 1978; Hanew and Rennels 1982).

Such a rebound phenomenon is also seen in acromegalic patients after somatostatin (GH inhibiting hormone; GIH) infusion (Besser et al. 1974b; Hanew et al. 1985). In this study, we administered GIH, dopamine (DA), and TRH to seven acromegalic patients, and discussed about the possible mechanisms of the rebound phenomenon of plasma GH.

SUBJECTS AND METHODS

Seven patients with active acromegaly, 5 males and 2 females, aged 23 to 59 years were studied by TRH test, DA test, somatostatin (GIH) test, and GIH plus TRH test. No patients were taking any previous treatments or medications. As a control, five normal male volunteers (age 21–27 years) received only the GIH test after getting informed consent.

TRH and GIH tests were performed according to the methods previously reported (Hanew et al. 1980). In the combination test of GIH plus TRH 500 µg TRH was injected as a bolus at the termination (75 min) of the GIH infusion. The blood samples were collected at 15 min intervals over 75 min for TRH test, over 180 min for DA test, and over 150 min for GIH alone or for GIH plus TRH tests. GH was measured according to the previous methods (Hanew et al. 1980).

As basal GH values were variable in each individual, the percent changes from the basal GH were used for the comparison of several tests. Statistical analysis was carried out by Student’s paired t test.

RESULTS

Plasma GH responses to GIH infusion in normal controls and acromegalic patients

Following GIH infusion normal subjects showed a prompt decrease in plasma GH. The minimal value during the infusion (0.34 ± 0.04 ng/ml) was significantly
lower than the basal value (1.76±0.57 ng/ml; p<0.05) (Fig. 1). After the termination of GHH infusion the plasma GH level showed a rebound increase exceeding the basal level. In acromegalics, the plasma GH level also decreased promptly from 36.9±13.6 ng/ml to 14.4±7.4 ng/ml (not significant) and showed a rebound increase after the termination of the infusion. Although, the maximal percent decreases caused by GHH were not different in controls and acromegalics (69.1±10.4% vs. 73.9±6.5%; p = not significant), the rebound occurred more quickly in controls than in acromegalics (Fig. 1). Namely, after the cessation of the infusion GH levels returned to the basal levels within 15 min in controls and 30 min later in acromegalics.

Physiological fluctuations of plasma GH were minimal either in controls or in acromegalics (data not shown).

**Plasma GH responses to dopamine infusion in six acromegalic patients**

Plasma GH fell distinctly from 29.6±12.7 ng/ml to 10.3±5.0 ng/ml after DA infusion, and the peak value in the rebound was 77.7±27.0 ng/ml (Table 1). As the GH values were so variable, these results were shown as a percent of basal GH. After the cessation of the DA infusion, rapid and marked rebound was observed (Fig. 2). Although the maximal inhibitions (67.1±7.3% vs. 73.7±7.1%) and the inhibitory areas (areas surrounded by the baseline and response curves) (14354.5±471.0%•min vs. 3796.5±322.5%•min) during the infusion were not different between DA and GHH, the postinhibitory rebound was greater at 15 min in DA infusion than in GHH infusion (p<0.05; Fig. 3).

**Table 1. Plasma GH responses to DA, GHH, TRH, and GHH plus TRH in 7 acromegalic patients**

<table>
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<tr>
<th>Patient</th>
<th>DA Basal*</th>
<th>GHH Basal</th>
<th>GHH+TRH Basal</th>
<th>TRH Basal</th>
<th>DA Nadir†</th>
<th>GHH Nadir§</th>
<th>GHH+TRH Nadir§</th>
<th>TRH Nadir§</th>
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* Basal GH value (ng/ml).
† GH values within 90 min following DA infusion.
‡ Peak GH values after the termination of DA or GHH.
§ GH values within 75 min following GHH infusion.
Plasma GH responses to TRH, GIH, and GIH plus TRH in 7 patients with acromegaly

In this series, all patients were responsive to TRH (Table 1). When TRH was administered at the termination of GIH infusion (at 75 min) all except one
(Case 6) showed much greater increases in the rebound phenomenon (Table 1). These results are summarized in Fig. 4. In spite of similar GH inhibitions during the GIH infusion, the postinhibitory rebound was clearly enhanced by TRH as compared to single GIH administration ($p < 0.02$ at 90 min, $p < 0.05$ at 105 and 120 min).

**DISCUSSION**

In this study, we demonstrated that the postinhibitory rebound increases in GH are different in acromegalic patients and normal subjects, and with drugs employed. Also, it was evident that the postinhibitory GH increases induced by GIH were modified by the additional stimulation by TRH. To the rebound phenomenon in acromegaly, the decreases in endogenous GH secretion might not contribute, since the rebound occurred promptly just after the infusion. The GIH used in this study ($16.7 \times 10^6$ pg/min over 75 min) was far larger than plasma levels of GIH in normal and acromegalic subjects (30-40 pg/ml) previously reported (Wass et al. 1980; Peeters et al. 1981). Therefore, it is expected that the GIH levels at the beginning of the rebound rise would not be lower than those of steady state even when taking into consideration the short half life of GIH (Brazeau et al. 1974; Sheppard et al. 1979; Bethge et al. 1981).

Since exogenous TRH modified the rebound rise, it is probable that increased endogenous GH-releasing factors (including TRH) participate in the phenomenon.

Although we could not find a significant correlation between GH decrease by

![Fig. 4. Plasma GH responses to TRH, GIH, and GIH plus TRH in seven acromegalic patients. $p$-Value (GIH vs. GIH + TRH): *$<0.05$, †$<0.02$.](image-url)
GIH and the postinhibitory increase \( (r = -0.25, \text{ not significant}) \), the overshoot from stored hormone pool (during the inhibition) might account for the phenomenon, because the postinhibitory GH rise was seen even in the absence of hypothalamic contribution (i.e. in the in vitro system) (Stachura 1976; Goodyer et al. 1977; Adams et al. 1981; Lawton et al. 1981; Hanew and Rennels 1982). Theoretically, this overshoot is explained by the inactivation (or degradation) of GIH which bound to somatotrophs, or by the dissociation of GIH from these cells.

The reason why dopamine caused more rapid and marked rebound increases in GH than GIH is not clear. However, one may postulate that the degrees of the inactivation or of the dissociation of these agents are different from each other on the somatotroph levels. In addition, it has been reported that dopamine has dual actions on GH release in man; a releasing effect via the hypothalamus and a direct inhibitory effect on the pituitary gland (Tallo and Malarkey 1981; Marcovitz et al. 1982). Therefore, it is plausible that dopamine stimulates the GH releasing factors from peptidergic GH-RF neurons at the level of the median eminence which lies outside of the blood brain barrier (Martin 1973; Leebaw et al. 1978; Bansal et al. 1981). From these considerations, the difference in the rebound increase between acromegalic patients and normal controls can be explained by a difference in the regulations of GH release by the hypothalamus and somatotrophs having different degrees of binding and dissociation of GIH.

In conclusion, the postinhibitory rebound increases in GH are different in acromegalic and normal subjects and are different between GIH and dopamine in acromegalic patients. The rebound phenomenon in acromegaly is possibly modified by exogenous or endogenous hypothalamic releasing factors.

Acknowledgments
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References


