Modulation of Postinhibitory Rebound Rise in Plasma GH by Hypothalamic Hormones in Patients with Acromegaly

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Abstract

To evaluate the GH regulating mechanism in acromegalic patients, postinhibitory rebound rise in GH secretion induced by somatostatin was studied in these cases and normal subjects, and was compared with the rebound GH rise induced by dopamine. After somatostatin infusion (500 μg/75 min) both 5 normal and 9 acromegalic subjects showed prompt GH decreases during the infusion (% decrease: 69.1±10.4 vs 74.4±5.1) and showed rebound rises after its termination. However, the rebound rises occurred more promptly and markedly in normal controls than in acromegalic patients, i.e. the rebound peak appeared at 45 min in normal controls and at 75 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 7 patients with acromegaly. Although the maximum inhibition (65.6±6.4% vs 74.4±5.1%) and the inhibitory area (4338.0 ± 481.5%•min vs 3682.5 ± 295.5%•min) during the DA or somatostatin infusion were not different, the rebound at 15 min was significantly greater after DA than after somatostatin (p < 0.02). When TRH was injected at the termination of somatostatin infusion, the rebound increase was significantly enhanced and the rebound peak appeared 45 min earlier than after a single somatostatin administration. Similarly, hp GRF (1-44)-NH₂ enhanced the postinhibitory rebound rises in 4 patients studied. These results indicate that the mechanism participating in the postinhibitory rebound rise is different between normal controls and acromegalic patients, and the rebound rises induced by somatostatin and DA might occur through the different mechanisms. Also, it is evident that the rebound phenomenon in acromegaly is possibly modified by endogenous hypothalamic releasing factors.

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It is widely accepted that plasma levels of human pituitary hormones are apt to show rebound increases followed by returns to the control levels after the administration of inhibitory agents (Hall et al., 1973; Besser et al., 1974a; Leblank et al., 1976; Judd et al., 1978; Leebaw et al., 1978; Kaptein et al., 1980). This rebound phenomenon might occur as a result of maintaining homeostatic hormone secretion. As a postinhibitory rebound rise in GH secretion is also observed in acromegaly (Besser et al., 1974b; Hanew et al., 1980), home-
ostasis of GH secretion might exist even in such a pathologic state. However, the etiology of acromegaly is not clear (Cryer and Daughaday 1977), and the role of endogenous GH-RH (GH-releasing hormone) and GIH (GH-inhibiting hormone; somatostatin) on GH regulation in these patients is not elucidated. To evaluate the GH regulating mechanism in acromegalic patients, postinhibitory rebound rises in GH secretion induced by GIH were studied in these cases and normal subjects, and were compared with another inhibitory agent, dopamine. Furthermore, known hypothalamic GH releasing factors, i.e. TRH and hp GRF (1–44) (human pancreas GH-releasing factor 1–44 NH₂) (Guillemin et al., 1982), in acromegaly were employed whether or not the rebound phenomenon is modified by these agents.

Materials and Methods

Nine patients with active acromegaly, 5 males and 4 females, aged 23 to 59 years were studied. The patients had been on no previous treatments or medications. Every patient had an elevated GH level (>6 ng/ml), enlarged sella turcica, acromegalic features and perspiration. These cases received several tests at 0800 h to 0900 h after an overnight fast with the interval of 3 to 7 days. GIH (500 µg iv for 75 min) (Protein Research Foundation, Osaka) and dopamine (DA) (5 µg/kg/min iv for 90 min) (Kyowa-Hakko, Tokyo) were administered to 9 and 7 patients, respectively, and blood samples were collected at −30, 0 min before and at 15 min intervals over 150 min after GIH and over 180 min after DA infusion tests. In the combination tests with GIH plus TRH (Tanabe, Osaka) or GIH plus hpGRF (1–44) (synthetic human pancreas GH-releasing factor 1–44 NH₂, Peninsula Lab., CA) 500 µg TRH or 100 µg hpGRF (1–44) were injected as a bolus at the termination of the GIH infusion. For comparison, single tests with TRH (500 µg) and hpGRF (1–44) (100 µg) was performed, and blood samples were collected at 15 min intervals over 75 min for each test. Synthetic hpGRF (1–44) was dissolved in physiological saline, and aliquots were sterilized by passage through a 0.22 µm Millipore filter. As controls, five normal volunteers (age 21–27 yrs) received the GIH test. Fluctuations in plasma GH levels in the basal state were examined in 9 acromegalic and 5 normal subjects, where blood samples were obtained for 3 hrs during the slow infusion of physiological saline. Informed consent was obtained from every normal or acromegalic subjects. Plasma GH was measured in duplicate according to the previous methods (Hanew et al., 1980). As basal GH values varied according to the individual, the percent changes from the basal GH were used for comparison of the several tests. Statistical analysis was carried out by Student’s paired t-test, and the variance of the mean was expressed as S.E.M.

Results

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

Following GIH infusion, five normal subjects showed a prompt decrease in plasma GH. The minimal value during the infusion (Mean±SEM: 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 GIH infusions plasma GH levels showed a rebound increase exceeding the basal levels. In acromegalic patients, plasma GH levels also decreased promptly from 36.1±10.3 ng/ml to 13.7±5.7 ng/ml (the difference did not reach statistical significance over the wide range of basal and nadir GH values) and showed a rebound increase after the termination of the infusion. Although, the maximal percent decreases caused by GIH were not different between controls and acromegalics (69.1±10.4% vs 74.4±5.1%; P=NS), 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 45 min later in acromegalics. In contrast, fluctuations in plasma GH in basal state were minimal both in 5 controls and in 9 acromegalics.
Fig. 1. Plasma GH responses to somatostatin (GIH) infusion in normal controls (○-○, N=5) and acromegalic patients (▲-▲, N=9). Broken line indicates the fluctuations in plasma GH in basal state in each group. Values given are Mean±SEM.

Plasma GH responses to dopamine infusion in 7 acromegalic patients

Plasma GH fell distinctly from 32.6±11.2 ng/ml to 12.0±4.6 ng/ml after DA infusion, and the peak value in the rebound was 87.8±25.0 ng/ml. As the GH values were so variable, these results were shown as a percent of basal GH. After the cessation of the DA infusion, a rapid and marked rebound was observed (Fig. 2). Although the maximal inhibition (65.6±6.4% vs 74.4±5.1%) and the inhibitory areas (areas surrounded by baseline and response curves: 4338.0±481.5%·min vs 3682.5±295.5%·min) during the infusion were not different between DA and GIH (p=NS), the postinhibitory rebound was greater after DA infusion than after GIH infusion (p<0.02 at 15 min).

Plasma GH responses to TRH, GIH, and GIH plus TRH in 9 patients with acromegaly

In this series, all patients were responsive to TRH. When TRH was administered
at the termination of GIH infusion (at 75 min) all except one showed a much greater increase in the rebound phenomenon. These results are summarized in Fig. 3. In spite of the similar GH inhibition during the GIH infusions, the postinhibitory rebound was clearly enhanced by TRH compared to single GIH administration (p<0.02 at 90, 105 min, p<0.05 at 120 min).

Plasma GH responses to hpGRF (1–44), GIH, and GIH plus hpGRF(1–44) in 4 patients with acromegaly

Four patients received a single injection of 100 µg hpGRF (1–44), and showed prompt increases having the peak value at 15 min after the injection. Like TRH, hpGRF (1–44) clearly enhanced the postinhibitory GH rises induced by GIH (vs GIH alone: p<0.01 at 90 min, p<0.05 at 105 min). However, this combination test of GIH plus hpGRF (1–44) could not exceed the single hpGRF (1–44) test in terms of mean GH response (Fig. 4).

Discussion

In this study, we demonstrated that the postinhibitory rebound increases in plasma GH are different between acromegalic patients and normal subjects, and between the agents employed. Also, it was evident that the postinhibitory GH increases induced by GIH were modified by the additional stimulation of hypothalamic hormones.

Although the exact mechanisms have not been studied well, the rebounds could 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). In regard to the rebound phenomenon in normal and acromegalic subjects, a decrease in endogenous GIH secretion would not seem to be the cause, since the rebound occurred promptly just after the infusion. The GIH dosage used in this study (16.7×10^6 pg/min over 75 min) was far larger than the plasma levels of GIH in normal and acromegalic subjects (30–40 pg/ml) previously reported (Peeters et al., 1981; Wass et al., 1981). Therefore, it is expected that the GIH levels at the beginning of the rebound rises would be higher than those of the basal state even taking into consideration the short half life of GIH (Brazeau et al., 1974; Sheppard et al., 1979; Bethge et al., 1981). In rat, the episodic GH secretion, i.e. formation of peak and trough, is not modified by the administration of GIH antiserum or by the destruction of GIH neurons (Ferland et al., 1976; Urman and Critchlaw 1983; Willoughby et al., 1983). These results indicate a minor role, if any, of GIH in the rebound or the episodic elevation of plasma GH. Therefore, the difference in the rebound increase between acromegalic patients and normal controls can be explained by the difference in the regulation of GH release by the hypothalamic GH-RH and by the somatotrophs having different secretory properties, or by the different disappearance rate of GIH action exogenously administered. Concerning this, a reverse relationship was observed in patients with prolactin-secreting pituitary adenoma which shows more quicked and more marked rebound increases in their plasma prolactin than normal subjects after the cessation of DA infusion (unpublished data). This might indicate the differences in the hormone secretory properties and of hormone regulatory mechanism in GH-
prolactin-secreting adenomas.

In this study, every acromegalic patients examined was TRH and hpGRF (1-44) responsive, and the rebound GH rise induced by GIH was significantly enhanced by these hypothalamic hormones. This finding seems to indicate that endogenous GH-releasing factors (including GH-RH and TRH) can participate in the phenomenon when their secretions are increased in vivo. The magnitude of GH responses to a single administration of TRH and hpGRF (1-44), however, varied from case to case, and were not comparable with the combination test of GIH plus TRH or GIH plus hpGRF (data not shown). These results indicate the different sensitivities of somatotrophs to TRH and hpGRF in the basal and suppressed state. The fact that the episodic GH secretion in rats disappears after the administration of GH-RF antiserum or the destruction of the GH-RH nucleus indicates a possible role of endogenous GH-RH on the postinhibitory rebound phenomenon (Wehrenberg et al., 1982; Eikelbloom and Tannenbaum 1983). The determination of the GH-RH concentration in pituitary portal vessels would provide a valid conclusion.

Although we could not find a significant correlation between the GH decrease due to GIH and the postinhibitory increase (r = -0.43, p = NS), the overshoot from the stored hormone pool (during the inhibition) might account for the phenomenon, because the postinhibitory GH rise is seen even in the absence of a hypothalamic contribution (i.e. in vitro system) (Stachura 1976; Good yer et al., 1977; Adams et al., 1981; Lawton et al., 1981; Cowan et al., 1983). The overshoot seen in the in vitro system may mainly reflect the intracellular GH secretory property of somatotrophs.

Following the termination of DA infusion in acromegaly, DA caused a more rapid and marked rebound increase in GH than GIH, though DA caused a similar decrease in GH to that in GIH in terms of maximal suppression and inhibitory area. The half disappearance time of DA is not clear, but is expected to be very short as that of norepinephrine is reported to be within 3 min (Benedict et al., 1978; Fitzgerald et al., 1979). Although the exact difference between the effect of DA and GIH in degradation rate is not clear, the disappearance of the DA action might be quicker than that of the GIH action at the somatotroph level. In addition, it must be taken into consideration that DA has dual actions on GH release in man: a releasing effect via the hypothalamus, as it is seen in normal subjects, and a direct inhibitory effect on the pituitary gland (Tallo and Malarkey 1981; Marcovitz et al., 1982). Therefore, it is possible that dopamine stimulates the GH releasing factor 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). If this is true, the stimulated GH-RF may enhance the rebound phenomenon.

In conclusion, the hypothalamic regulation and the secretory properties of somatotrophs might be different between acromegalic and normal subjects. Additionally, the action of DA in acromegaly is different from that of GIH. Also, the rebound phenomenon in acromegaly is possibly modified by exogenous or endogenous hypothalamic releasing factors. The intracellular GH secretory property and the hypothalamic GH-RF would be more important than GIH in the homeostatic GH secretion in acromegaly.

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