

## Plasma GH, TSH and PRL Responses to Recombinant Human Insulin-Like Growth Factor-I (IGF-I) in Normal and Acromegalic Subjects

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THE administration of large amounts of recombinant human insulin-like growth factor-I (IGF-I) (rhIGF-I) stimulate plasma GH secretion through hypoglycemia in normal subjects [1]. The effects of rhIGF-I on GH secretion were therefore studied by the glucose clamp methods [2] or nutritional intake [3], but the doses of rhIGF-I which cause hypoglycemia are considered to be pharmacological. In this study, we have examined plasma GH, TSH, PRL, IGF-I and insulin responses to physiological doses of IGF-I, which has no effect on plasma glucose levels, in 6 normal subjects (normal somatotrophs) and 10 patients with active acromegaly (tumorous somatotrophs). This is the first report which examined plasma GH responses to rhIGF-I in patients with acromegaly.

### Materials and Methods

Six healthy adult males (21–24 yr) and 10 patients with active acromegaly (8 males and 2 females, 25–67 yrs old) were studied. Recombinant human IGF-I (50  $\mu$ g, iv) was administered to these subjects. As a control physiological saline was administered intravenously. Blood samples were obtained 30 and 0 min before the IGF-I injection and 15, 30, 45, 60, 90, 120 and 150 min after the injection, and plasma samples were kept frozen at  $-20^{\circ}\text{C}$  until assay. Plasma GH, TSH, PRL, IGF-I, glucose and insulin were measured with

commercial IRMA kits (Daiichi, GH & PRL), RIA kit (Ciba-Corning, IGF-I), Immunofluorometric assay kits (Pharmacia, TSH,  $T_4$ ,  $T_3$ ), EIA kit (Tohso, Insulin) and glucose dehydrogenase method, respectively. The minimal detectable level of plasma GH was 0.006  $\mu$ g/L.

### Results

The bolus injection of 50  $\mu$ g of IGF-I did not affect plasma glucose levels in normal subjects nor in acromegalic patients. The plasma IGF-I value was significantly higher in acromegaly ( $853.8 \pm 100.8$ ) than in normal subjects ( $302.9 \pm 15.8$   $\mu$ g/L,  $P < 0.01$ ). After IGF-I administration, both groups showed similar % increases (Fig. 1), but the maximal increment was significantly greater in acromegaly than in normal subjects ( $132.0 \pm 27.1$  vs.  $42.2 \pm 3.8$   $\mu$ g/L,  $P < 0.01$ ). In normal subjects, plasma GH showed a gradual decrease and reached significant difference at 150 min compared to the control study. In contrast, acromegalic patients showed a clear and significant GH decrease from 90 to 150 min after the injection compared to the control study. Although plasma GH was higher in acromegaly ( $32.0 \pm 5.1$ ) than in normal subjects ( $1.154 \pm 0.444$   $\mu$ g/L), there was no difference between the two in the maximal decrease (% of basal) (acromegaly vs. normal subjects,  $70.8 \pm 6.8$  vs.  $59.8 \pm 25.1$ ) (Fig. 2). The basal plasma insulin level in acromegaly ( $9.7 \pm 2.8$ ) was significantly higher than that in normal subjects ( $3.6 \pm 1.0$   $\mu$ U/ml,  $P < 0.01$ ) and it was significantly suppressed by IGF-I from 15 min to 120 min in acromegalic patients, while normal subjects showed a slight but insignificant decreases (Fig. 3). No significant change was ob-

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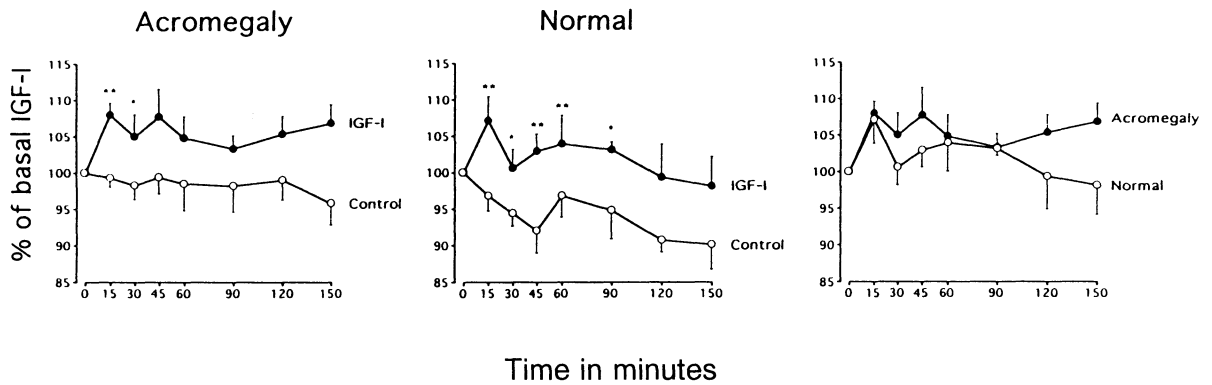


Fig. 1. Plasma IGF-I levels after the administration of rhIGF-I in patients with acromegaly and normal subjects.

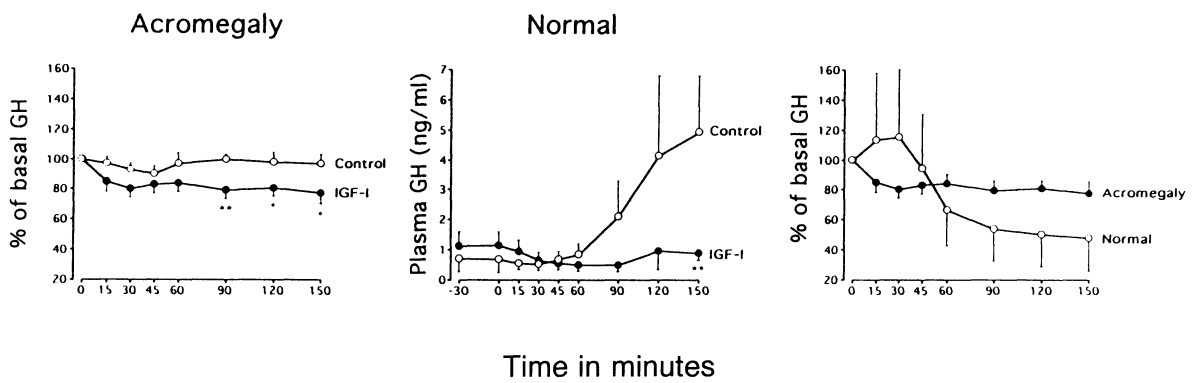


Fig. 2. Plasma GH responses to rhIGF-I in patients with acromegaly and normal subjects.

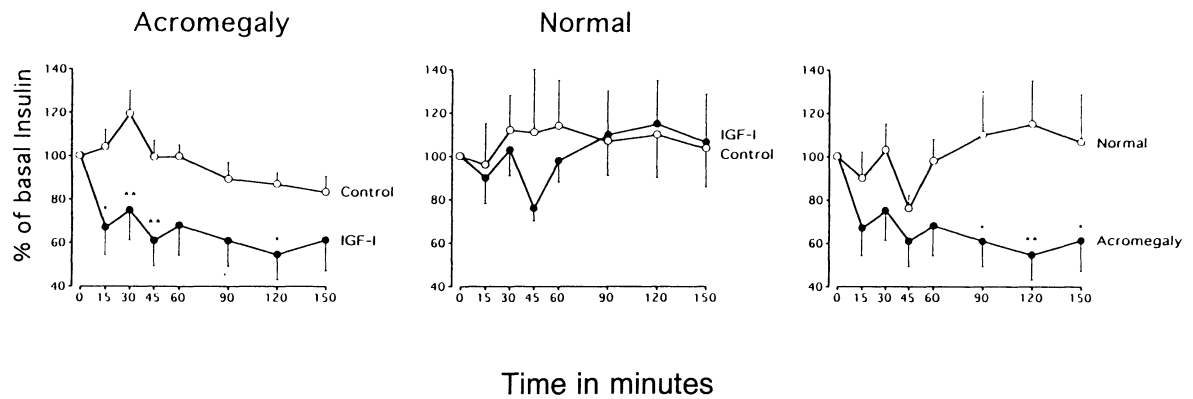


Fig. 3. Plasma insulin responses to rhIGF-I in patients with acromegaly and normal subjects.

served in plasma TSH and PRL levels in either groups.

### Discussion

In this study, a slight increase in plasma IGF-I significantly inhibited plasma GH secretion in normal subjects and acromegalic patients. It is therefore concluded that IGF-I is the physiologically important regulator of GH secretion not only in normal subjects but also in acromegalic patients.

It has been reported that plasma insulin in man is suppressed by much larger amounts of rhIGF-I

[2]. Following the administration of small amounts of IGF-I, plasma insulin level was significantly decreased in acromegalic patients but not in normal subjects. The sensitivity of pancreatic beta-cells to IGF-I therefore seems to be greater in acromegaly than in normal subjects.

Although, Bermann *et al.* [3] have observed a significant TSH decrease after rhIGF-I infusion, neither acromegalic patients nor normal subjects showed a sign of such a decrease in our study.

Regarding the difference between the two groups in plasma IGF-I values following IGF-I, it is not clear whether the differences of basal plasma IGF-I, IGF-BP3 levels or other factors are concerned.

### References

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