Effect of insulin-like growth factor I on the thyroid axis in patients with Laron-type dwarfism and healthy subjects

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We have evaluated the effect of exogenous administration of IGF-I on the thyroid axis in four separate studies: (1) iv bolus injection; (2) single sc injection; (3) seven days’ sc treatment, and (4) four months’ treatment. Thirteen patients with Laron-type dwarfism (LTD) participated in the investigations. In studies 1 and 2, 10 healthy subjects were also included. Before and during long-term treatment (study 4) six LTD patients underwent a TRH test. IGF-I was administered in a dose of 75 µg·kg⁻¹ iv or 120–150 µg·kg⁻¹ sc. Single injections of IGF-I caused significant decreases of serum TSH in LTD patients (iv: 1.7 ± 0.2 to 1.1 ± 0.1 mU/l; sc: from 2.1 ± 0.4 to 1.1 ± 0.2; p < 0.0005). In controls the decrease was for iv from 1.2 ± 0.2 to 0.8 ± 0.2 mU/l (p < 0.02) and for sc from 2.0 ± 0.5 to 0.8 ± 0.2 mU/l (p < 0.05). Long-term administration of IGF-I induces a transitory decrease of both serum TSH and rT₄, followed by a spontaneous rise to pretreatment or even higher values. No changes in T₃ were observed. TSH stimulation by TRH was significantly augmented after four months of IGF-I treatment (p < 0.005). The effects of IGF-I can be explained by an early stimulation of somatostatin release causing a decrease in TSH and followed by the development of compensatory mechanisms. All changes were within the normal ranges, not causing abnormal thyroid function. As the clinical use of recombinant IGF-I extends for longer periods than those described, it is recommended that thyroid function is followed.

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Recent reports have documented that exogenously administered growth hormone (GH) affects thyroid function in both normal individuals (1) and GH deficient adults (2), as well as in children with either GH deficiency (3) or hypothyroidism (4). All the reports describe suppression of the thyroid function during GH administration, but the expression of the results varied. Thus, some reported a lowering of serum T₄ and an increase of serum T₃ (2–4), decrease in ¹³¹I thyroidal uptake (5), or decrease in serum TSH (6). The availability of recombinant IGF-I, the effecter hormone of hGH and its introduction into clinical use made it possible to test whether the GH effect on the thyroid function is a direct one or is mediated by IGF-I.

We report the effect on thyroid function of a single intravenous or subcutaneous injection of IGF-I and short and long-treatment of IGF-I in Laron-type dwarfism (LTD) patients.

Subjects and methods

The effect of rIGF-I on the thyroid function was investigated during four separate studies. Study 1 comprised 10 patients with LTD (5M, 5F) aged 8 to 35 years and a control group of 8 healthy subjects (5M, 3F) aged 8 to 39 years. Thyroid function was studied before and after an iv bolus of rIGF-I (75 µg·kg⁻¹). The study was performed after an overnight fast and blood samples for TSH determinations were drawn at 0, 2, 5, 15, 30, 60, 90 and 120 min.

Study 2 comprised 8 LTD patients (3M, 5F) aged 9 to 35 years and 3 control subjects (2M, 1F) aged 9 to 12.5 years. All received after an overnight fast a sc injection of rIGF-I (150 µg·kg⁻¹) and blood samples for TSH were drawn at 0, 15, 30, 60, 120, 180 and 240 min.

Study 3 consisted of 10 LTD patients (4M, 6F) aged 3.6 to 38 years who underwent 7 days’ treatment by daily sc injections of rIGF-I (120–150 µg·kg⁻¹·day⁻¹). The injection was given after an overnight fast 15–20 min before breakfast. Blood samples for TSH and rT₄ were taken on days 0, 2, 4 and 8, and 7 days after the last injection (day 15). Serum T₃ was determined on days 0 and 8.

In study 4, 8 LTD patients (3M, 5F) aged 5 to 40 years, were investigated during a long-term treatment protocol with daily sc injections of rIGF-I (120–150 µg·kg⁻¹·day⁻¹). The dose was adjusted to reach serum levels of IGF-I within the upper physiological range for age. The drug was administered after an overnight fast, 15 min before breakfast. Blood samples for TSH, rT₄ and T₃ were obtained after an overnight fast, before the initiation of treatment once a week for the first month of
therapy and monthly thereafter for four months. In six out of the eight patients presented, we also studied the TSH response to a TRH stimulation test (100 μg·m⁻²·iv) before the IGF-I treatment and after four months of consecutive therapy.

IGF-I (FK-780 Lot 115707 K) was synthesized by recombinant DNA technology by the Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan (7); it has an identical amino-acid sequence with that of natural IGF-I (8, 9). The purity of the preparation was 97.2% as determined by reverse-phase high pressure liquid chromatography. Plasma TSH was determined by an immunoradiometric assay (Ares Serono, Rome, Italy) and serum fT₄ and T₃ by standard RIA.

The studies were approved by the Hospital’s Ethics Committee and the Ministry of Health, and informed consent was obtained from each subject or their parents.

Statistical calculations were performed using Student’s unpaired or paired t-test. The values are expressed as mean ± SEM.

Results

All subjects studied, LTD patients as well as controls, were clinically euthyroid before the IGF-I administration and basal plasma levels of TSH, fT₄, and T₃ were within the normal range.

In Fig. 1 it is seen that the iv injection of IGF-I caused a significant reduction of serum TSH (p = 0.009) in all LTD patients of almost 35% of the basal values (from 1.72 ± 0.19 to 1.15 ± 0.09 mU/l). These nadir occurred in most instances 60 to 90 min after the injection. The control group also showed a significant reduction in serum TSH (from 1.18 ± 0.22 to 0.82 ± 0.17 mU/l; p < 0.02). However, the time of the nadir was more variable.

Study 2—The sc injection of IGF-I also significantly reduced the plasma TSH levels from 2.15 ± 0.41 to 1.12 ± 0.24 mU/l; p < 0.005) in the LTD patients as well as in the control subjects (from 2.03 ± 0.56 to 0.86 ± 0.18 mU/l; p < 0.05). The nadir was later than after the iv bolus, i.e. 180 to 240 min after the drug injection (Fig. 2).

Study 3—Fig. 3 summarizes the mean ± SEM values of serum TSH, fT₄, and T₃, before, during and after seven days of sc administration of IGF-I. It is seen that the TSH values decreased during the first two days (p < 0.005) and a progressive increase towards normal values was already seen on day 4 of IGF-I administration. Some of the values reached the upper values of normal, the day after the last injection and one week after interruption of therapy. Serum fT₄ declined significantly (p < 0.005) throughout the whole period of treatment and rose again during the week of no IGF-I administration. Serum T₃ measured before treatment and after the 7th IGF-I injection showed no change. It is of note that all the described changes were within the limit of normal values and in none of the patients were hypothyroid levels registered.

Study 4—Table 1 summarizes the individual values of TSH, fT₄, and T₃ obtained during prolonged sc IGF-I therapy. It is seen that a statistically significant decrease of TSH (p < 0.008) and fT₄ (p < 0.0009) was registered after three weeks of therapy, with a recovery to pretreatment value after the fourth week. These levels remained unchanged throughout the four months of IGF-I treatment, when a slight increment of the basal levels of TSH and a significant (p < 0.02) increase in serum fT₄ was observed; the values in both cases, however, remained within the normal range. T₃ did not show any significant change during the whole period of treatment.
Fig. 3. Effect of 7 day sc injection of rIGF-I (150 μg·kg⁻¹·day⁻¹) on thyroid function in 10 LTD patients. □ TSH; □ fT₄; ■ T₃. *p<0.05 **p<0.0005.

Table 1. TSH, fT₄ and T₃ levels in eight Laron-type dwarfism (LTD) patients during daily sc injections of IGF-I (120–175 μg/kg).

<table>
<thead>
<tr>
<th>Weeks</th>
<th>TSH (mU/l) N.R. = &lt;6 mean ± SEM</th>
<th>fT₄ (pmol/l) N.R. = 8.5–23.0 mean ± SEM</th>
<th>T₃ (nmol/l) N.R. = 1.2–3.1 mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.1 ± 0.3</td>
<td>13.8 ± 0.4</td>
<td>2.2 ± 0.1</td>
</tr>
<tr>
<td>1</td>
<td>2.1 ± 0.4</td>
<td>13.6 ± 0.9</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>2</td>
<td>1.7 ± 0.3</td>
<td>12.4 ± 0.7</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>3</td>
<td>1.5 ± 0.1</td>
<td>11.4 ± 0.4**</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>Months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.8 ± 0.2*</td>
<td>12.7 ± 0.9</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>2</td>
<td>2.1 ± 0.3</td>
<td>13.2 ± 0.6</td>
<td>2.2 ± 0.1</td>
</tr>
<tr>
<td>3</td>
<td>2.1 ± 0.3</td>
<td>13.8 ± 1.2</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>4</td>
<td>2.4 ± 0.2</td>
<td>16.4 ± 0.9***</td>
<td>2.4 ± 0.1</td>
</tr>
</tbody>
</table>

*p=0.008; **p=0.0009; ***p=0.02.

Fig. 4 shows the response of TSH to an iv TRH stimulation in six of the LTD patients studied before and at four months of IGF-I treatment. It is seen that IGF-I treatment does not suppress the TSH response to TRH and that four months' continuous IGF-I administration led to a small but significant (p<0.02) rise in the basal TSH levels (1.6±0.2 vs 2.8±0.3 mU/l) and a higher peak TSH response (8.0±1.0 vs 10.3±1.2 mU/l; p<0.01).

Discussion

LTD is a syndrome of resistance to GH (10, 11) due to a defect in the GH receptor (12–14) leading to an inborn inability to generate IGF-I, the effector hormone of GH. This disease is a model to study other hormone activities after long-term deprivation of circulating IGF-I and thus determine their dependence on normal IGF-I function. The recent availability of biosynthetic IGF-I and its introduction into clinical use also made it possible to study the effect of IGF-I administration on a variety of other hormone functions.

In a survey of 29 LTD patients (11) we observed that long-term IGF-I deprivation did not affect thyroid function. This was confirmed by the study of a further 10 patients (unpublished data) and a group of patients with
isolated GH deficiency due to gene deletion (15) who also suffer from early onset IGF-I deficiency.

In the present investigations comprising 13 LTD patients, the above findings were again confirmed. Thus it can be concluded that normal thyroid function is independent of circulating IGF-I levels. Acute administration of exogenous IGF-I, whether by iv bolus or by single sc injections, decreased serum TSH, both in LTD patients and in healthy controls. This occurred concomitantly with a decrease of GH, insulin and GHRH (8, 16) and can therefore be explained by an IGF-I induced stimulation of somatostatin release. This hypothesis has recently been supported experimentally in rats by showing that acute IGF-I administration depletes the hypothalamic somatostatin stores (Gil-Ad, Koch, Laron—unpublished observations).

Administration of one daily dose of IGF-I for seven days resulted in a transitory decrease of serum TSH but a progressive decline of serum FT4 for the whole period of IGF-I administration which cannot be explained by the measured changes in circulating TSH. It is possible that the intracellular effect of TSH is more prolonged and/or there was increased turnover of FT4 to T3, but determinations of serum T3 performed were unable to prove the latter.

Long-term administration of IGF-I for four months again revealed a transitory decline of circulating TSH during the first month, with a rebound rise to pretreatment or even slightly higher values during the second to the fourth month. Serum FT4 showed a similar pattern, whereas T3 values remained unchanged. The basal serum TSH levels and peak response to an iv TRH injection in LTD patients treated for four months were statistically significantly higher than those of the control subjects. The tendency for a slight increase in TSH and FT4 during prolonged IGF-I administration can be viewed either as a tendency towards the development of resistance to T4 or changes involving TBG similar to those observed for IGFBP's (Kaneti et al., unpublished observation). The difference between the long-term and short-term effects, both occurring within the limits of normal values may also be viewed as a result of counter-regulatory adaptive mechanisms of the body to the administered IGF-I.

The early lowering effect of IGF-I on serum TSH described by us previously (17) and in the present report, resembles the findings of several authors after the administration of exogenous GH. Thus Root et al. (18) described a marked fall in thyroidal $^{131}$I uptake in 8 out of 15 GH-deficient children, an effect reversed by TSH. These authors also observed a fall in serum TSH in hypothyroid patients after hGH administration. Porter et al. (6) also reported a decrease in basal and TRH stimulated TSH in GH-treated GH-deficient adolescents. Lippe et al. (19) observed a decline in serum T4 with no change in serum T3 during GH therapy in GH-deficient children, a finding similar to that found by us during the seven-day IGF-I treatment study.

In our short-term or long-term studies of IGF-I administration, we did not register an increase of serum T3, as reported by Jorgensen (2) during GH treatment of GH-deficient adults and Sato et al. (3) and Rezvani et al. (4) in GH-deficient children. Grunfeld et al. (1) administering high doses of GH to healthy adults registered an enhanced peripheral conversion of T4 to T3.

The lack of evidence for this in our studies may be linked to dosage of IGF-I used and resulting levels of circulating IGF-I. It seems to us that IGF-I and not GH directly influences the hypothalamic-pituitary axis, but further comparative studies would be useful to clarify this issue.

As the clinical use of biosynthetic IGF-I will expand and treatment periods of LTD or other patients will be prolonged, evaluation of thyroid function should be included in the follow-up protocol, to enable the diagnosis of possible changes beyond the normal limits.

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References

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