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Action of Human Growth Hormone (hGH) on Extrathyroidal Conversion of Thyroxine (T_4) to Triiodothyronine (T_3) in Children with Hypopituitarism

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Summary

To study the action of human growth hormone (hGH) on peripheral metabolism of serum thyroxine (T_4), an oral loading dose of levothyroxine (1.2 mg/m^2) was administered to seven children with hypopituitarism before initiation of hGH therapy. Serum concentrations of triiodothyronine (T_3), T_4, reverse triiodothyronine (rT_3), and thyroxine-binding globulin (TBG) capacity were measured sequentially for 6 days. The study was repeated after 4 wk of treatment with hGH. Serum concentrations of T_4 were not affected by hGH therapy. In contrast, mean basal serum concentration of T_3 increased significantly after treatment with hGH. Also, changes in serum concentrations of T_3 and in the ratio of T_3/T_4 after an oral dose of levothyroxine were significantly augmented during hGH therapy. Serum concentrations of rT_3 changed in the opposite direction of T_3 during therapy. After treatment with hGH, the mean basal level of serum rT_3 decreased, and increases in serum concentrations of rT_3 after oral levothyroxine were significantly attenuated. No changes in mean serum concentrations of thyroid stimulating hormone (TSH) and TBG capacity were observed.

These data suggest that administration of hGH to children with hypopituitarism enhances the extrathyroidal conversion of T_4 to T_3 and concomitantly decreases the serum concentration of rT_3.

Speculation

The increase in serum concentration of triiodothyronine after administration of human growth hormone may play a role in the growth-promoting action of growth hormone in children with hypopituitarism.

The use of human growth hormone (hGH) in the treatment of children with hypopituitarism may result in decreased serum levels of thyroxine (T_4) (7) and, in some instances, in clinical hypothyroidism (7, 13). It has been shown that this effect, at least in part, is owing to the suppressive action of hGH on pituitary thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) (7, 9, 12). Data on the effect of hGH on extrathyroidal metabolism of thyroid hormones are contradictory at this time. Root *et al.* (12) observed a significant increase in serum concentration of triiodothyronine (T_3) after a 9-day course of therapy with hGH in children with hypopituitarism. Sato *et al.* (13) subsequently reported a similar increase in serum concentrations of T_3 as well as a marked elevation in the ratio of T_3/T_4 in eight hypopituitary children after one month of treatment with hGH. In contrast, Lippe *et al.* (7) observed overt hypothyroidism and a decrease in serum concentrations of T_3 in six patients with hypopituitarism who were receiving hGH therapy. Inasmuch as therapy with hGH may cause hypothyroidism, the discrepancies in these studies may be related to the status of thyroid function rather than the direct action of hGH on the metabolism of T_4. In the present report, attempts have been made to study the action of hGH on the metabolism of T_4 in a euthyroid state.

MATERIALS AND METHODS

Participating in this study were seven prepubertal children with growth hormone deficiency. Their ages ranged from 5½ to 16 years, and the hypopituitarism was established by conventional methods (4). Other than two patients being treated with levothyroxine (L-T_4), none was receiving any other medication. The clinical data are summarized in Table 1. The hypopituitarism was newly diagnosed in patient 1; he had never received hGH until the time of the study. The other patients had received previous courses of treatment with hGH, but therapy had been discontinued at least 6 months before the study.

hGH (batches of P-3 to P-8) for treatment was generously supplied by The National Pituitary Agency. The following study protocol was approved by our Committee for the Protection of Human Subjects, and informed, written consents were obtained from patients and/or their parents.

Before initiation of hGH therapy, each patient received an oral loading dose of L-T_4 (1.2 mg/m^2) after an overnight fast. This dose has been found to be adequate for weekly replacement therapy in patients with hypothyroidism (16). Serum samples for determination of levels of T_3 and T_4 were obtained at 0, 2, 4, 6, 12, 18, and 24 hr, respectively, and daily (at 9 AM) thereafter for 6 days. Serum samples for measurement of reverse T_3 were obtained at 9 and 24 hr, respectively, and daily thereafter. Serum samples for determination of thyroxine-binding globulin (TBG) and TSH were obtained only at 0 time. Those patients receiving replacement therapy with L-T_4 were not given their daily dose during the 6-day period. All patients received a regular diet during this study. Treatment with hGH, 2 to 3 units IM three times per wk (Table 1), was started on the seventh day, and the identical study was repeated after 4 wk of therapy with hGH. The hGH was administered on a daily basis during the 6 days of the L-T_4 study.

Serum concentrations of T_3, T_4, and TSH were measured by double-antibody radioimmunoassay as previously reported (10). To avoid the influence of interassay variability on the results, serum samples collected from each patient before and after initiation of hGH therapy were assayed in one batch. Serum concentrations of reverse triiodothyronine (rT_3) were assayed in one batch by the radioimmunoassay kit for rT_3 manufactured by Serono Laboratories (Braintree, MA). The coefficient of variation within the assay was less than 3%. Serum concentrations of TBG capacity were measured by Bio-Science Laboratories, Van Nuys, CA. Statistical analysis was performed by using two-way analysis of variance (paired *t* test) (3).

Table 1. *Clinical data*

Name	Sex	Chronological age (yr)	Height age (yr)	Diagnosis	Pituitary deficiency[1]	Dose of hGH[2]	L-T_4 (μg/day)
C. J.	M	5 9/12	4	Histiocytosis X	hGH, ADH[3]	2	None
B. N.	M	7	3 6/12	Idiopathic	hGH	2	None
K. L.	F	9	4 6/12	Idiopathic	hGH	2	None
L. N.	F	11	6 6/12	Idiopathic	hGH	2	None
J. M.	M	11 6/12	6	Idiopathic	hGH	2	None
E. P.	M	12 6/12	6 6/12	Idiopathic	hGH, TSH	3	150
D. G.	F	16 6/12	9	Histiocytosis X	hGH, TSH, ADH	3	150

[1]Because gonadotropin deficiency could not be documented in prepubertal children, some of the patients in this study may prove to have gonadotropin deficiency in the future.

[2]Units administered IM three times per wk.

[3]ADH, antidiuretic hormone.

RESULTS

Values for serum concentrations of T_4 after the administration of a single dose of L-T_4 are shown in Figure 1. Peak concentration of serum T_4 was achieved after 4 hr and decreased gradually therafter. By the sixth day, values approached the baseline. Treatment with growth hormone did not cause any significant change. Although the mean basal concentration of serum T_4 at 0 time decreased after hGH therapy (7.4 ± 2.2 μg/dl before hGH *versus* 6.3 ± 1.3 μg/dl after hGH therapy), the difference was not statistically significant. It is of interest that the basal concentrations of T_4 in both patients who received replacement therapy with L-T_4 also decreased after the course of therapy with hGH.

Serum concentrations of T_3 after ingestion of L-T_4 are shown in Figure 2. The mean serum concentration of T_3 peaked at 4 hr after ingestion of L-T_4 and declined to a nadir at 12 hr. A second rise in mean serum concentration of T_3 was observed at the 48-hr period. The nadir was significantly lower than 48-hr peak ($P = 0.03$), but it was not statistically different from the 4-hr peak ($P = 0.09$). Mean serum concentration of T_3 declined after the 48-hr period and approached the baseline values by the sixth day of the study. Treatment with growth hormone caused significant increases in serum levels of T_3 at the 0 time ($P < 0.01$), 24 hr ($P < 0.04$), second day ($P < 0.01$), third day ($P < 0.05$), fourth day ($P < 0.01$), fifth day ($P < 0.01$), and sixth day ($P < 0.02$). Basal concentrations of serum T_3 increased after hGH therapy in both patients who were receiving replacement therapy with L-T_4 (mean of 119 ng/dl before hGH treatment *versus* 174 ng/dl after hGH therapy). The biphasic behavior of the curve was not altered by hGH therapy. Again, the nadir was significantly lower than the 48-hr peak ($P < 0.006$), but it was not statistically different from the 4-hr peak ($P = 0.07$).

Inasmuch as serum concentrations of T_3 are closely related to those of T_4, analysis of ratios of T_3/T_4 is depicted in Figure 3. An inverse relationship was noted between the ratio of T_3/T_4 and changes in serum concentrations of T_4. Sudden increases in serum values of T_4 resulted in sharp decreases in the ratio of T_3/T_4. As the serum concentrations of T_4 returned to normal, the ratio rose and approached baseline values. Treatment with growth hormone resulted in significant increases in ratios of T_3/T_4 at the 0 min ($P < 0.007$), 24 hr ($P < 0.009$), second day ($P < 0.005$), third day ($P < 0.05$), fourth day ($P < 0.03$), fifth day ($P < 0.05$), and sixth day ($P < 0.02$).

Changes in serum concentration of rT_3 after ingestion of L-T_4 are shown in Figure 4. Treatment with hGH caused a significant decrease in serum concentrations of rT_3 at 0 time ($P < 0.01$), first day ($P < 0.001$), third day ($P < 0.01$), fourth day ($P < 0.03$), fifth day ($P < 0.001$), and sixth day ($P < 0.04$).

Values for serum concentrations of TBG capacity measured at 0 time periods are given in Table 2. Treatment with hGH had no effect on the mean concentration of serum TBG capacity.

The concentrations of radioimmunoassayable TSH in different batches of hGH used in the study were between 0.5 and 2.0 mIU/unit of hGH.

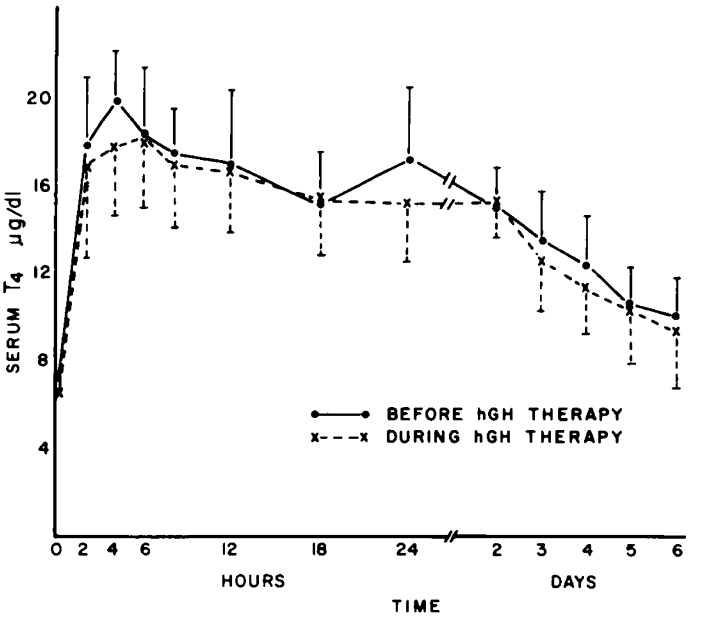

Fig. 1. Mean (± S.D.) serum concentrations of L-T_4 after the oral dose of T_4 in seven patients with hypopituitarism before and one month after treatment with hGH.

Mean basal concentration of serum TSH measured at 0 time before initiation of hGH therapy (3.9 ± 2.5 μIU/ml) was not significantly different from that during hGH treatment (3.5 ± 1.7 μIU/ml).

DISCUSSION

These data indicate that replacement therapy with hGH in children with hypopituitarism causes a substantial increase in serum concentration of T_3. The increase could not be all due to increased production or release of T_3 by the thyroid gland because even those patients on replacement therapy were found to have higher concentrations of T_3 in their sera after hGH therapy.

This finding confirms our previous observation (12) and agrees with reports of Sato *et al.* (13) who also found an increase in serum concentrations of T_3 in eight hypopituitary patients during replacement therapy with hGH. Lippe *et al.* (7), however, observed a decline in serum levels of T_3 in six hypopituitary patients who developed overt symptomatic hypothyroidism during treatment with hGH. This discrepancy may be attributable to preselection of patients who had become hypothyroid after hGH therapy by Lippe *et al.* (7), whereas in the present study, patients were not preselected for their thyroid status. Although our data still remain indirect, we believe that the increase in serum concentrations of T_3 after hGH therapy is best explained by an increase in extrathyroidal conversion of T_4 to T_3. We have, nevertheless, considered

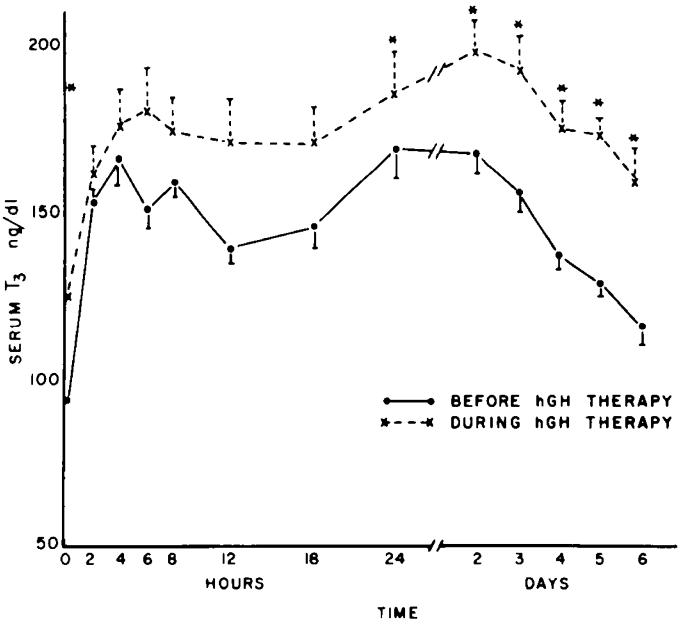

Fig. 2. Mean (± S.D.) serum concentrations of T_3 after the oral dose of L-T_4 in seven patients with hypopituitarism before and one month after therapy with hGH. *Asterisks*, statistically significant increases in serum concentrations of T_3 after therapy with hGH.

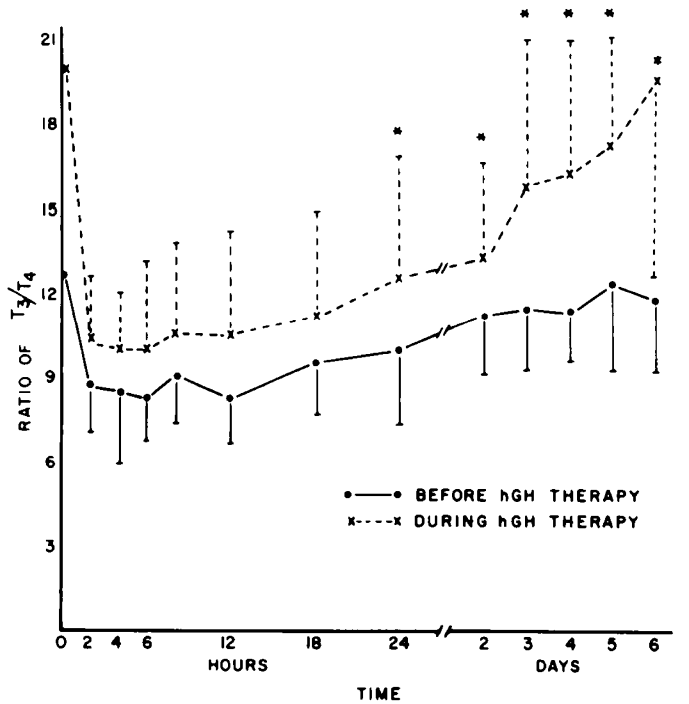

Fig. 3. Mean (± S.D.) ratio of T_3/T_4 after the oral administration of L-T_4 in seven patients with hypopituitarism before and one month after therapy with hGH. *Asterisks*, statistically significant increases in the ratios after therapy with hGH.

other possible factors which could have induced the increase in serum concentration of T_3.

(1) TSH contamination of hGH preparations used in the study may be a possible factor. Recent studies have suggested that the thyroid gland produces T_3 preferentially when it is stimulated by TSH (14). Although the amount of TSH present in the hGH preparations was found to be very small, it may be of physiologic significance and could possibly be sufficient to increase serum concentration of T_3 (15). This is an unlikely explanation for changes observed in the present study because the mean basal concentration of serum TSH was the same before and after therapy with hGH.

(2) Suppression of TSH secretion by hGH may induce hypothyroidism in patients with hypopituitarism (7, 11). Inada *et al.* (6) have demonstrated an increase in extrathyroidal conversion of T_4 to T_3 in the early stages of hypothyroidism. This may explain the increase in serum levels of T_3 in the study by Sato *et al.* (13) because a significant decrease in serum concentration of T_4 occurred in their patients after hGH therapy. In the present study, basal serum levels of T_4 decreased in five of the patients after one month of hGH therapy. Although the change in mean basal serum concentration of T_4 was not statistically significant, one might argue that even small changes in serum levels of T_4 could be sufficient to enhance the conversion of T_4 to T_3. The data from the oral loading dose of T_4, however, make this possibility remote because serum concentration of T_3 and the ratio of T_3/T_4 were significantly increased after hGH therapy whereas the serum levels of T_4 were kept in a euthyroid to hyperthyroid range.

(3) Decrease in disposal rate of serum T_3 after hGH therapy may explain the elevation of serum T_3 in this study. Recent preliminary data have suggested that hGH may increase the serum half-life of T_3 (2). The data on the serum concentration of rT_3, however, are not in favor of such a mechanism. If the increase in serum concentration of T_3 resulted only from prolongation of the

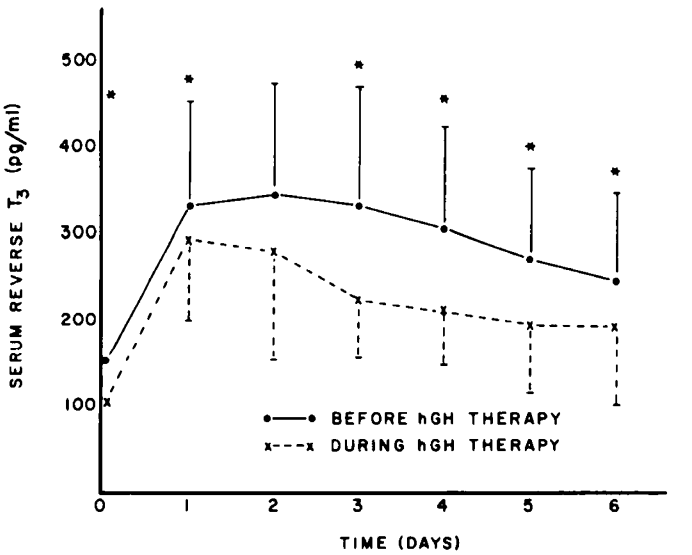

Fig. 4. Mean (± S.D.) serum concentrations of rT_3 after the oral dose of L-T_4 in seven patients with hypopituitarism before and one month after treatment with hGH. *Asterisks*, statistically significant decreases in serum concentrations of rT_3 after therapy with hGH.

Table 2. *Serum concentrations of T_4-binding globulin capacity (μg/dl)[1] in seven children with hypopituitarism*

Patient	Before hGH	During hGH
1	22.0	18.4
2	19.0	23.0
3	19.0	17.0
4	20.0	16.0
5	26.3	22.0
6		19.0
7	16.0	25.0
Mean ± S.D.	20.3 ± 3.4	20.0 ± 3.3

[1]Normal range, 10 to 26 μg/dl as T_4.

half-life of T_3, one would expect an increase in the disposal rate of T_4 through conversion to rT_3. The reciprocal decrease in serum concentration of rT_3 during hGH therapy suggests that elevation of serum levels of T_3 observed in this study may be due to an increase in conversion of T_4 to T_3.

(4) Because the half-life of serum T_4 is prolonged (8), it is conceivable that some of the increase in serum T_3 observed in this study is related to the lingering amount of T_4 from the previous dose of oral L-T_4 used 4 wk earlier. This does not seem plausible because the mean basal concentration of serum T_4 after the 4-wk period was not different from that obtained at the beginning of the study before administration of oral L-T_4.

(5) An increase in serum concentration of TBG after hGH therapy could also explain the elevation in serum levels of T_3 in this study. Serum concentrations of TBG capacity, however, remained unchanged during hGH therapy. Moreover, serum levels of T_4 did not change after therapy. If there was an increase in serum concentration of TBG, an increase in serum levels of T_4 would have also been expected.

The mechanism by which hGH enhances extrathyroidal conversion of T_4 to T_3 remains speculative. Nutritional factors have been shown to exert a substantial effect on the conversion of T_4 to T_3 (18). Starvation, specifically carbohydrate deprivation, results in a decrease in serum concentration of T_3 and a reciprocal increase in serum levels of rT_3 (17). Inasmuch as hGH is a potent anabolic agent, it is conceivable that its absence causes a chronic state of nutritional depletion at the cellular level and a decrease in production rate of T_3. Administration of hGH repletes the cells and reverts the production rate of T_3 to normal. The reciprocal decrease in serum concentration of rT_3 after hGH therapy observed in this study favors this hypothesis.

The physiologic significance of changes observed in this study remains unclear at this time. It is of interest, however, that Hennemann *et al.* (5), in their early studies, were able to show an increase of 20 to 25% in the basal metabolic rate in three hypopituitary patients after hGH therapy. This could be explained by an increase in serum concentration of T_3 induced by administration of hGH.

With the changes seen in the present study, one might anticipate increased serum concentration of T_3 in patients with acromegaly. Corrigan *et al.* (1), however, found no change in serum concentrations of T_3 in 21 patients with active acromegaly. The validity of such extrapolation is open to question because acromegaly represents a generalized debilitating condition, and serum concentrations of growth hormone in these patients are far from normal.

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