PITUITARY-THYROID FUNCTION IN THYROTOXIC PATIENTS IN RELATION TO LONG-ACTING THYROID STIMULATOR (LATS) LEVELS

By

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ABSTRACT

Serial changes in TSH, LATS, and thyroxine levels in the sera were studied following administration of an antithyroid drug or a thyroid hormone to thyrotoxic patients who became euthyroid after treatment. These changes were simultaneously determined by means of human TSH radioimmunoassay, McKenzie's bioassay, and the method of Murphy, respectively. Administration of 1-methyl-2-mercaptoimidazole (MMI) led to a decrease in thyroxine concentration and to a 6–10 times increase of the initial values in serum TSH concentration. Following administration of thyroxine at the end of the MMI treatment, the elevated serum TSH was rapidly decreased with an increase in thyroxine concentration. LATS activity, however, showed no significant changes throughout these experiments in which the reciprocal changes between TSH and thyroxine concentrations were observed.

It has long been known that the formation and secretion of thyroid hormone in the normal subject is primarily dependent on TSH, while TSH secretion from the pituitary gland is in turn regulated by the concentration of circulating thyroid hormone. In 1957, Adams & Purves (1957) found another thyroid activator, which has been called long-acting thyroid stimulator (LATS), in the sera of thyrotoxic patients. Several investigators have reported that LATS and TSH have different physicochemical properties.
In our previous study we (Sakagami et al. 1964) indicated that the administration of thyroid hormone suppresses TSH secretion in patients with primary hypothyroidism, but does not suppress LATS activity in thyrotoxic patients. However, few data have been published in which TSH and LATS have been simultaneously assessed in the same thyrotoxic patients, because of low sensitivity and lack of specificity in bioassay. However, recent development in radioimmunoassay has made it possible to determine small quantities of TSH in the serum (Odell et al. 1965; Utiger 1965).

The present study is an extension of previous work, and a further attempt has been made to demonstrate that TSH secretion normally responds, while LATS does not respond to changes in the concentration of circulating thyroid hormone in thyrotoxic patients.

MATERIALS AND METHODS

Three thyrotoxic patients who became euthyroid after treatment were used for this experiment. Results of thyroid function tests are outlined in Table 1. Blood was withdrawn from the patients, before, during, and after oral administration of 30 mg MMI per day 12, 28 and 42 days and also after subcutaneous injection of 2 mg of L-thyroxine at the end of MMI treatment. The serum was then separated for the determination of TSH, LATS and thyroxine respectively.

TSH concentration was determined by human TSH radioimmunoassay using purified

<table>
<thead>
<tr>
<th>Tests</th>
<th>Case T. Y.</th>
<th>Case I. I.</th>
<th>Case M. W.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMR (−10 − +15)⇑ %/o</td>
<td>+30</td>
<td>+54</td>
<td>+86</td>
</tr>
<tr>
<td>Serum PBI (8.0 − 8.0)⇑ µg/dl</td>
<td>16.1</td>
<td>12.5</td>
<td>16.2</td>
</tr>
<tr>
<td>121I-T3 resin sponge uptake (26 − 39)⇑ %/o</td>
<td>43</td>
<td>26</td>
<td>65</td>
</tr>
<tr>
<td>Serum thyroxine value (3.9 − 14.3)⇑ µg/dl</td>
<td>46</td>
<td>2.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Thyroidal 24 h 131I uptake (10 − 40)⇑ %/o</td>
<td>78.7</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>LATS activity, %/o*</td>
<td>474</td>
<td>610</td>
<td>365</td>
</tr>
</tbody>
</table>

Table 1.
Results of thyroid function tests in 3 thyrotoxic patients.

* A, before treatment; B, after treatment.
** less control.
⇑ normal range.
human TSH and anti-human TSH serum, kindly given to us by the National Pituitary Agency, Endocrinology Study Section and the National Institute of Arthritis and Metabolic Diseases, Maryland, USA. Human Thyrotrophin Research Standard A (HTSH R-STD-A) was also kindly supplied to us by the National Institute for Medical Research, London, England, for use as standard. Labelled TSH bound to anti-TSH serum was separated from those not bound, by the double antibody technique (Morgan et al. 1964) with minor modifications, in our laboratory. The anti-TSH serum was used at a dilution of 1:20 000 (0.1 ml) absorbed with 20 IU human chorionic gonadotrophin (HCG), which was added to the incubation mixture. The labelled TSH was used at a dilution of 0.05 ng (0.1 ml) in each assay tube. Anti-rabbit gamma globulin serum was obtained in our laboratory by immunizing a goat with rabbit serum gamma globulin which was separated by sodium sulphate fractionation (Heidelberger et al. 1939).

The following fundamental data of our double antibody method were obtained by the usual procedure of radioimmunoassay. The minimal detectable dose of HTSH R-STD-A was 0.1 µU (0.5 µU/ml serum); no significant effects were observed when bovine TSH (International Standard of Bovine TSH, NIMR: 0.4–8.0 mIU), HCG (Pregnyl®, Organon: 1–50 IU), human post-menopausal gonadotrophin (Humegon®, Organon: 0.1–4.0 µg), human growth hormone (Raben: 2–50 ng), and human gamma globulin (0.1–10 mg) were added to the incubation mixture; multiple doses of the Bates-Condliffe highly purified HTSH and the acetone-dried powder of pituitary gland and multiple dilutions of hypothyroid sera resulted in curves parallel to that obtained by HTSH R-STD-A; the recovery of HTSH R-STD-A added to the serum was 99.6 ± 9.5% (mean ± sp) and the between-assay reproducibility of serum HTSH assays was ± 3.5% (sp of the variations).

LATS activity was determined by the method of McKenzie (1958) with minor modifications, in our laboratory (Miyai et al. 1969) and the assay response was expressed in percentage of the initial value as reported previously (Miyai et al. 1967).

The thyroxine concentration in serum was measured by the method of Murphy & Jachan (1965), using Tetrasorb-125 kit (Dainabot RI Laboratory, Tokyo, Japan).

RESULTS

The results in summary are shown in Figs. 1–3.

As shown in Fig. 1, in the case of T. Y., the administration of 30 mg of MMI per day resulted in a decrease in the thyroxine concentration and an increase in the TSH concentration from 2.5 µU/ml to 13 µU/ml. LATS activity in the serum showed little change throughout the experiment.

As shown in Figs. 2 and 3, the same experiment was performed on two other cases, i.e. I. I. and M. W. The TSH concentration in these cases increased from 2.0–1.0 µU/ml to 20–5.5 µU/ml respectively, whereas the thyroxine concentration decreased in both cases. In these two cases, at the end of the antithyroid drug treatment, the subcutaneous injection of 2 mg of L-thyroxine produced a prompt fall in serum TSH concentration and an increase in the concentration of circulating thyroid hormone. However, no significant changes were observed in the LATS activity.

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DISCUSSION

It is well known that the thyroid function of most thyrotoxic patients fails to be suppressed by the administration of thyroid hormone, even when they are
in the euthyroid state after treatment (Werner 1956). The mechanism of this has so far been discussed in relation to LATS.

Since LATS activity is generally accepted to be present in the sera of half or more of the thyrotoxic patients, it is interesting to investigate whether or not TSH secretion and LATS activity are regulated by the concentration of circulating thyroid hormone.

Using McKenzie's bioassay, Adams & Kennedy (1965) suggested that TSH activity was detectable in concentrated sera with LATS obtained from a patient who was in a severe hypothyroid state following treatment of thyrotoxicosis. However, it seems to be difficult to determine serial changes of TSH levels in sera containing LATS by the McKenzie's bioassay, since the method is too insensitive to measure the TSH concentration in the serum of euthyroid patients, and cannot differentiate between the effect of TSH and that of LATS, when the serum contains LATS activity. By means of the recent development of the radioimmunoassay for human TSH (Odell et al. 1965; Utiger 1965), it has been demonstrated that TSH concentration in the sera of thyrotoxic patients increases after therapy (Odell et al. 1967). These data suggested that TSH secretion in the thyrotoxic patients who became euthyroid normally responded to the concentration of circulating thyroid hormone. TSH secretion, however, has not been observed in the case of a thyrotoxic patient with LATS in the serum.

The present study clearly indicates, however, that TSH secretion in the thyrotoxic patients, who became euthyroid after treatment, normally responds...
to changes in the concentration of circulating thyroid hormone, even when
LATS activity is present in the serum for a long period. In the same way,
LATS activity showed no response to the changing levels of circulating thyroid
hormone.

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**REFERENCES**

734.
Sakagami A., Fukuchi M., Masui H., Miyai K., Iwatsubo H., Kumahara Y. &

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