Serum Concentrations of 3, 3'-Diiodothyronine, 3', 5'-Diiodothyronine, and 3, 5-Diiodothyronine in Altered Thyroid States

MITSUSHIGE NISHIKAWA*, MITSUO INADA*, KOICHI NAITO**, HITOSHI ISHI***, KIYOSHI TANAKA***, YASUO MASHIO**** AND HIROO IMURA***

* Second Department of Internal Medicine, Kansai Medical University, Moriguchi, Osaka 570
** Department of Health and Environment, Hyogo Prefecture, Japan
*** Second Division, Department of Internal Medicine, Kyoto University School of Medicine, Kyoto
**** Kin-ikyo Sapporo Hospital, Sapporo

Abstract

To investigate the thyroid hormone metabolism in altered states of thyroid function, serum concentrations of 3, 3'-diiodothyronine (3, 3'-T2), 3', 5'-T2 and 3, 5-T2 as well as T4, T3, rT3, 3, 3'-T2 and 3', 5'-T2 were determined by specific radioimmunoassays in 17 hyperthyroid and 10 hypothyroid patients, before and during the treatment. Serum T4, T3, rT3, 3, 3'-T2 and 3', 5'-T2 concentrations were all higher in the hyperthyroid patients than in age-matched controls and decreased to the normal ranges within 3 to 4 months following treatment with antithyroid drugs. In the hypothyroid patients, these iodothyronine concentrations were lower than in age-matched controls and returned to the normal ranges after 2 to 3 months treatment with T4. In contrast, serum 3, 5-T2 concentrations in hyperthyroid patients (mean±SE: 4.0±0.5ng/dl) were not significantly different from those in controls (3.9±0.4ng/dl), although they tended to decrease in 3 of 6 patients after the antithyroid drug therapy. Serum 3, 5-T2 levels in the hypothyroid patients (3.8±0.6ng/dl) were also within the normal range and showed no significant change following the T4 replacement therapy. However, serum 3, 5-T2 as well as 3, 3'-T2 concentrations rose significantly with a marked rise in serum T3 following T3 administration, 75µg/day for 7 days, in Graves' patients in euthyroid state. These results indicate that serum concentrations of 3, 3'-T2 and 3', 5'-T2 well reflect the thyroid function states, but that serum 3, 5-T2 concentrations change little in altered thyroid function states, although it is monodeiodinated from T3 in vivo.

Since radioimmunoassays (RIAs) for 3,3'-diiodothyronine (3,3'-T2), 3',5'-T2 and 3,5-T2 were developed, it is now generally accepted that serum concentrations of 3,3'-T2 and 3',5'-T2 are high in hyperthyroid patients and low in hypothyroid patients (Wu et al., 1976; Burman et al., 1977; Burger & Sokoloff 1977; Gavin et al., 1978; Burman et al., 1978; Chopra et al., 1978; Faber et al., 1979). As to serum 3,5-T2 concentration in altered thyroid states, however, earlier findings are still controversial (Meinhold & Shurnbrand, 1978; Maciel et al., 1979; Pangaro et al., 1980; Kirkegaard et al., 1981).

The present study was designed to
investigate serum concentrations of 3,3'-T2, 3',5'-T2 and 3,5-T2 in patients with hyperand hypothyroidism and their changes during the treatment with either antithyroid drug or thyroxine. In addition, in patients with Graves' disease, who were in a euthyroid state, serum 3,3'-T2 and 3,5-T2 levels were determined before and after T3 administration for T3 suppression test.

**Materials and Methods**

Serum concentrations of T4, T3 and rT3 were determined by commercial RIA kits provided by Dainabot Radioisotope, Chiba, Japan. Serum concentrations of 3, 3'-T2 and 3', 5'-T2 were determined by RIAs developed in our laboratory, the details of which have been reported elsewhere (Nishikawa et al., 1981).

RIA for 3, 5-T2 was performed also as described previously (Nishikawa et al., 1981), although some modifications were employed: 0.15 ml of serum samples were extracted with 0.3 ml of 99.5% ethanol and 0.3 ml of the ethanol extracts were evaporated to dryness, before the determination of 3, 5-T2 levels. Since the mean recovery during the ethanol extraction procedure was 93% and the volume reduction of the sample was 67%, the measured values were corrected by dividing by 0.62 to obtain serum 3, 5-T2 levels. Serum 3, 5-T2 levels in 19 normal subjects ranged from 2.3 ng/dl to 8.3 ng/dl, with a mean (±SE) of 3.9±0.4 ng/dl.

Serum samples were obtained from 17 patients with untreated hyperthyroidism and 10 patients with untreated hypothyroidism. The ages and numbers of 17 hyperthyroid patients studied were: 21-29, 5; 30-39, 7; 40-49, 3; 50-59, 2; and those of 10 hypothyroid patients studied were: 31-39, 3; 40-49, 5; 50-59, 2. Eight of 17 hyperthyroid patients were followed up to observe changes in serum thyroid hormone concentrations during the treatment with either antithyroid drug or thyroxine. In addition, in patients with Graves' disease, who were in a euthyroid state, serum 3,3'-T2 and 3,5-T2 levels were determined before and after T3 administration for T3 suppression test.

**Results**

Serum thyroid hormone concentrations in hyper-and hypothyroid patients (Table 1)

Serum concentrations of T4, T3, rT3, 3,3'-T2, 3',5'-T2, and 3,5-T2 in hyper- and hypothyroid patients are summarized in Table 1. Since there are age-related changes in serum thyroid hormone concentrations (Nishikawa et al., 1981) and the age distributions of hyper- and hypothyroid groups were slightly different, serum hormone concentrations were compared with those in the age-matched controls. The mode of the age distribution of hyperthyroid patients studied was 30–39, and an equal number of the patients were scattered under and over the decade. Therefore, they were compared with normal controls aged 30–39. Similarly, the mode of age distribution of hypothyroid patients was 40–49, with 3 under and 2 over the decade. Therefore, they were compared with 40–49 year-old normal controls.

Serum 3,5-T2 concentrations were compared with 30–49 year-old normal controls. Serum 3,5-T2 concentrations were compared with 30–49 year-old controls because of the relatively small number of the patients studied.

Serum concentrations of T4, T3, rT3, 3,3'-T2 and 3',5'-T2 were significantly higher in hyperthyroid and lower in hypothyroid patients than in the age-matched normal controls (Table 1). However, serum 3,5-T2 concentrations both in hyper- and hypothyroid patients were not significantly different from those in normal controls (Table 1).

Changes in serum thyroid hormone concentrations during antithyroid drug treatment (Figure 1)
Changes in serum T₂ concentrations in hyperthyroid patients treated with methimazole are shown in Figure 1. Serum T₄, T₃, and rT₃ concentrations were decreased to the normal ranges (mean±2SD) within 3–4 months as the clinical signs and symptoms subsided. Serum 3',3'-T₂ concentrations also clearly declined as the patients became euthyroid, clearly reflecting the thyroid function. 3',5'-T₂ concentrations also fell to within the normal range after the treatment in 3 of 8 patients who showed high 3',5'-T₂ values before the treatment. In the remaining 5 patients, serum 3',5'-T₂ levels were within the normal range before the treatment, and remained virtually unchanged during the treatment (Figure 1). Therefore, serum 3',3'-T₂ levels reflect better the altered thyroid state than 3',5'-T₂.

Serum 3,5-T₂ concentrations in hyperthyroid patients remained within the normal range after the antithyroid drug administration, although they tended to decrease to the low normal levels in 3 of 6 patients (Figure 1).

Changes in serum thyroid hormone concentrations in the patients with hypothyroidism during T₄ replacement therapy (Figure 2)

Serum concentrations of T₄, T₃, and rT₃ were increased to the normal ranges as the patients received synthetic T₄ of 50 µg to 125 µg per day for 1 to 2 months. 3',3'-T₂ and 3',5'-T₂ concentrations were also increased within or to the normal ranges by the T₄ replacement therapy (Figure 2). However, serum 3,5-T₂ concentrations did not show any significant changes (Figure 2).

Changes in serum T₃, 3',3'-T₂ and 3,5-T₂ concentrations before and after T₃ administration (Table 2)

Table 2 shows changes in serum T₃, 3',3'-T₂ and 3,5-T₂ concentrations before and after the administration of 75 µg/day (in three divided doses) of T₃ for 7 days to Graves' patients who were euthyroid with or without the maintenance doses of methimazole. Serum T₃ concentrations were markedly elevated by the T₃ administration (p<0.01, paired t-test). Similarly, serum 3',3'-T₂ concentrations showed a significant increase (p<0.01, paired t-test). Serum 3,5-T₂ levels also showed a statistically significant elevation after the treatment (p<0.01, paired t-test).

Contamination of 3,5-T₂ in the T₄ and T₃ tablets

To exclude the possible interference by 3,5-T₂ contaminated in the tablets of T₄.
and T₃, or the cross-reaction of T₃ or T₄ with 3,5-T₂ antiserum used, 3,5-T₂ contents in the tablets were measured after the ethanol extraction. However, 3,5-T₂ was not detected up to the concentrations of 25 μg/dl of T₄ and 500 ng/dl of T₃ in the ethanol extracts.

Discussion

Previous studies (Wu et al., 1976; Burman et al., 1977; Burger et al., 1977; Gavin et al., 1978; Burman et al., 1978; Chopra et al., 1978; Faber et al., 1979) have demonstrated that serum T₄, T₃, rT₃, 3,3'-T₂ and 3',5'-T₂ concentration are elevated
Table 2. Serum concentrations of thyroid hormones before and after the administration of T3, 75 μg/day for 7 days in 7 patients with Graves’ disease in the euthyroid state.

<table>
<thead>
<tr>
<th></th>
<th>T3</th>
<th>3, 3'-T2</th>
<th>3, 5-T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before T3</td>
<td>145±9.8</td>
<td>4.2±0.4</td>
<td>3.0±0.2</td>
</tr>
<tr>
<td>After T3</td>
<td>504±47a</td>
<td>5.9±0.2a</td>
<td>5.0±0.4a</td>
</tr>
</tbody>
</table>

Values given are the mean±SE (ng/dl).

The differences in serum thyroid hormone concentrations are shown by the paired t-test: a, p<0.01.

in hyperthyroidism, while they are diminished in hypothyroidism. The present study confirmed these previous observations and further demonstrated that serum 3,3'-T2 and 3',5'-T2 concentrations changed parallel with T4, T3 and rT3 concentrations to the normal ranges in hyperthyroid patients during the methimazole treatment and in hypothyroid patients during the T4 replacement therapy. These data show that serum 3,3' -T2 and 3',5'-T2 concentrations reflect well the altered thyroid function, similar to T4, T3 and rT3 levels in serum.

Serum 3,5-T2 levels in normal subjects measured after ethanol extraction were 3.9±0.4 ng/dl in our present experiments, although we previously reported higher values (10.3±0.2 ng/dl) determined by a direct RIA (Nishikawa et al., 1981). This difference could be explained by the interference of serum in a direct RIA system. Similar values were reported by Maciel et al. (7.3±1.5 ng/dl; 1979), Pangaro et al. (4.3±0.2 ng/dl; 1980) and Kirkegaard et al. (5.5±2.7 ng/dl; 1981). Nevertheless, there is still controversy regarding serum 3,5-T2 levels in altered thyroid states. Maciel et al. (1979) reported that serum 3,5-T2 concentrations in hyper- or hypothyroid patients were not significantly different from normal controls. On the other hand, Pangaro et al. (1980) reported that serum 3,5-T2 concentrations were high in hyperthyroidism and low in hypothyroidism. More recently, Kirkegaard et al. (1981) reported elevated serum 3,5-T2 concentrations in hyperthyroid patients, although they failed to show a significant difference in 3,5-T2 levels between hypothyroid patients and normal controls.

In the present study, serum 3,5-T2 concentrations in hyper- or hypothyroid patients were not significantly different from those in normal controls. Although serum 3,5-T2 levels tended to decrease after the treatment in 3 of 6 patients with hyperthyroidism, the remaining 3 patients showed no significant changes. Moreover, serum 3,5-T2 levels remained unchanged in 3 hypothyroid patients who were given T4. These findings are consistent with the results of Maciel et al. (1979), and show that the estimation of serum 3,5-T2 levels is of little value in evaluating thyroid function.

Pangaro et al. (1980) demonstrated a significant rise in serum 3,5-T2 levels after T3 administration in obese patients during fasting and also found a significant positive correlation between serum T3 and 3,5-T2 levels, suggesting the monodeiodination of T3 to 3,5-T2. In the present study, however, serum 3,5-T2 levels were elevated with a marked increase in serum T3 in euthyroid patients after the T3 administration, whereas they were not significantly changed in hypothyroid patients treated with T4, despite an increase in serum T3 to the normal range. These results suggest that 3,5-T2 production from T3 might be less pronounced and the changes might become evident only when serum T3 levels were markedly elevated by T3 administration. Unchanged 3,5-T2 levels in hyperthyroid patients might be explained by a preferential 3,3'-T2 production from T3 and by the enhanced metabolism of 3,5-T2. It can be assumed that the 3,5-T2 turnover rate might be slowed down in hypothyroid patients, thus maintaining the 3,5-T2 levels normal in these patients. It is possible that serum 3,5-T2 levels remain in the normal range in altered thyroid states as its production and degradation are changed in the same way. The kinetic data for 3,5-T2 on the production and metabolism
in altered thyroid function states are needed to elucidate further the T₃ metabolism.

References


