A Study of the Relationship between Thermogenesis and Thyroid Hormones*

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ABSTRACT. To investigate the relationship between serum T3 levels and thermogenesis in euthyroid subjects, the conversion of T4 to T3 was partially blocked over a period of 3 weeks by weekly ingestion of 2 g iopanoic acid. Serum T3 decreased by 56 ± 6 ng/100 ml without affecting the metabolic rate or total heat loss. Because an increase in serum T4 levels was observed (3.70 ± 0.2 µg/100 ml), the experiment was repeated in T4-substituted subjects. Serum T3 decreased even more in these subjects, (by 85 ± 12 ng/100 ml), and the increase of serum T4 was also larger (4.6 ± 0.7 µg/100 ml). Again, the metabolic rate did not change. Experiments performed on hypothyroid patients and T3-substituted subjects demonstrated that iopanoic acid alone was without effect on the metabolic rate. Furthermore, the effect of a low energy, high protein diet (1672 kilojoules or 400 Cal) on the metabolic rate was confirmed.

These results show that the decrease in magnitude of serum T3 seen with iopanoic acid is not sufficient by itself to reduce the metabolic rate.

Materials and Methods

Measurements

The MR was measured using an open circuit indirect calorimeter, the principle of which consists of measuring the oxygen consumption and carbon dioxide production of a subject whose head is enclosed in a transparent ventilated hood. The air flow through the hood was accurately measured using a pneumotachograph (Fenyves and Gut, Basel, Switzerland), and the oxygen and carbon dioxide concentrations in the air flowing into and out of the hood were measured using a paramagnetic oxygen analyzer (Servomex, Crowborough, England) and an infrared carbon dioxide analyzer (Uras 2T, Hartmann and Braun, Frankfurt, West Germany). The oxygen consumption and carbon dioxide production of the subject were calculated from these values, and the MR was calculated from the calorific equivalent of a liter of oxygen, derived from the respiratory quotient (12).

Direct calorimetry. A gradient layer direct calorimeter was used to measure each subject's total heat lost. The principle, description, and accuracy of the calorimeter have been fully described in a previous publication (13). Briefly, it consists of a small chamber with a volume of 1.56 m³, the walls of which are maintained at a constant temperature, within 0.005 C of the set temperature, by circulating water through channels in them. A gradient layer, consisting of two copper-printed circuits, one on either side of a 2.4-mm thick epoxy resin sheet, forms the interior walls of the calorimeter. As the electrical resistance of
Thermogenesis and Thermometric Measurements in Seven Euthyroid Subjects Measured Once a Week for 5 Weeks

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yr)</th>
<th>Wt (kg, mean ± SD)</th>
<th>MR (KJ/m²·h)</th>
<th>Total HL (KJ/m²·h)</th>
<th>Dry HL (KJ/m²·h)</th>
<th>Evaporative HL (KJ/m²·h)</th>
<th>Temperature (C)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>CV (%)</td>
<td>Mean ± SD</td>
<td>CV (%)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>M</td>
<td>25</td>
<td>64.6 ± 0.3</td>
<td>156 ± 7.8</td>
<td>5.0</td>
<td>165 ± 9.2</td>
<td>5.6</td>
<td>122 ± 9.0</td>
</tr>
<tr>
<td>M</td>
<td>26</td>
<td>71.0 ± 0.4</td>
<td>196 ± 11.4</td>
<td>5.8</td>
<td>197 ± 32.1</td>
<td>16.3</td>
<td>118 ± 20.0</td>
</tr>
<tr>
<td>M</td>
<td>33</td>
<td>56.8 ± 0.2</td>
<td>160 ± 7.8</td>
<td>4.9</td>
<td>163 ± 7.6</td>
<td>4.7</td>
<td>120 ± 7.1</td>
</tr>
<tr>
<td>M</td>
<td>25</td>
<td>62.0 ± 0.1</td>
<td>171 ± 2.2</td>
<td>1.3</td>
<td>186 ± 13.7</td>
<td>7.4</td>
<td>140 ± 12.7</td>
</tr>
<tr>
<td>M</td>
<td>22</td>
<td>68.1 ± 0.4</td>
<td>176 ± 5.1</td>
<td>2.9</td>
<td>187 ± 12.3</td>
<td>6.6</td>
<td>142 ± 10.0</td>
</tr>
<tr>
<td>M</td>
<td>26</td>
<td>72.4 ± 0.2</td>
<td>171 ± 9.7</td>
<td>5.7</td>
<td>205 ± 28.7</td>
<td>14.0</td>
<td>143 ± 4.8</td>
</tr>
<tr>
<td>M</td>
<td>24</td>
<td>67.3 ± 0.1</td>
<td>172 ± 5.0</td>
<td>2.9</td>
<td>196 ± 22.7</td>
<td>11.6</td>
<td>129 ± 6.5</td>
</tr>
</tbody>
</table>

Mean 26 66.0 172 4.1 186 9.4 131 7.8 55 27.7 36.68 0.44 33.80 0.67

SEM 1.4 2.0 4.9 0.6 6.1 1.7 4.1 1.7 5.4 6.5 0.03 0.06 0.10 0.09

HL, Heat losses; CV, coefficient of variation ([SD/mean] × 100)

Clinical studies

In all experiments the subjects were studied in the morning, between 0800–1100 h, and after a 10 h overnight fast. Each subject was allowed to rest for 30 min in a room in thermal equilibrium with the calorimeter (28°C) before entering the direct-indirect calorimeter.

Experimental groups

Informed consent was obtained from all subjects and patients. The subjects consumed their habitual diets during the course of the experiment, and their body weights were measured before each measurement of thermogenesis.

Group 1. Seven male subjects receiving no treatment at all were studied one morning a week for 5 weeks.

Group 2. To determine whether iopanoic acid had any thermogenic effect, three untreated hypothyroid patients were measured before and 6 days after taking a single dose of 2 g iopanoic acid (orally).

Group 3. Six subjects, two hypothyroid and four euthyroid, were tested while on T₃ substitution. The hypothyroid patients received 75 μg T₃/day orally, (Cytomel, Smith Kline & French, Philadelphia, PA), and the euthyroid subjects received 100 μg T₃/day for 6 weeks preceding the experiment and during 3 weeks of iopanoic acid treatment (2 g, once a week). T₃ was given in a single morning dose. When blood was taken, it was done just before the new dose.

Group 4. Six euthyroid subjects were studied 8 days before and each week for 3 weeks during iopanoic acid treatment. Two grams of iopanoic acid were administered once a week for 3 weeks.

Group 5. Four subjects, three euthyroid and one hypothyroid,
were treated with 200 µg L-T₄/day (orally; Eltroxine, Glaxo, Greenford, Middlesex, UK). The euthyroid subjects received T₄ for 6 weeks before and during the 3 weeks of iopanoic acid treatment (2 g, once a week).

**Group 6.** Four subjects, of whom one was of normal weight and three were overweight [10%, 37%, 214%, and 152% above their ideal body weights (18)] consumed a low energy [1672 kilojoules or 400 Cal], high protein (63% energy) diet for 2 weeks. Measurements of thermogenesis were made before and at the end of the 2-week dietary regimen.

**Results**

**Individual variability (Table 1)**

Individual variability of thermogenesis was studied at weekly intervals for 5 weeks in seven euthyroid subjects (group 1). The individual variability (coefficient of variation) in the MR was 4.1 ± 0.6% (mean ± SEM), and that of the total heat losses was 9.4 ± 1.7%. When the two parameters were compared, the total heat losses were found to be significantly greater than the MR ($P < 0.025$). The much greater variability of evaporative compared to dry heat losses was due to changes in individual perspiration from one test to another. Both internal and mean skin temperatures remained very stable. Serum T₄ and T₃ were also constant over the 5-week period (6.2 ± 0.3 µg/100 ml and 148 ± 12 ng/100 ml, respectively; $n = 35$).

**The thermic effect of iopanoic acid**

In three untreated hypothyroid patients (Table 2, group 2), iopanoic acid had no positive thermic effect when measured 6 days after ingestion. To test the thermic effect of the drug exactly as in the experiments described below, six T₃-substituted subjects (Table 3, group 3) received three doses of iopanoic acid at weekly intervals. Thermogenesis did not change compared to the two measurements before iopanoic acid, and it can therefore be considered to be nonthermogenic.

The effect of thyroid hormone changes on thermogenesis

Iopanoic acid decreased serum T₃ levels by 56 ± 6 ng/100 ml (mean ± SEM), and, as expected, rT₃ increased (Fig. 1, group 4). However, serum T₄ levels increased slightly up to 9.8 ± 0.9 µg/100 ml, compared to 7.3 ± 0.5 µg/100 ml before treatment ($P < 0.05$), and stabilized after 10 days. The serum free T₄ fraction was 0.021 ± 0.001% (mean ± SEM) and 0.024 ± 0.002% after 3 weeks of treatment ($P = NS$). The serum free T₃ concentration was 1.6 ± 0.2 ng/100 ml before treatment and increased to 2.6 ± 0.30 ng/100 ml after 3 weeks of treatment ($P = NS$). For serum free T₃, the respective values were 0.189 ± 0.014% before treatment and 0.217 ± 0.021% after 3 weeks of treatment ($P = NS$ or 0.29 ± 0.02 vs. 0.20 ± 0.02 ng/100 ml ($P < 0.001$). These serum thyroid hormone changes did not influence any of the metabolic parameters measured.

To exclude the possibility that in these euthyroid subjects the decreased serum T₃ level induced TSH secretion resulting in a compensatory increase of serum T₄, four subjects (group 5) were studied during T₄ substitution (200 µg/dl). Serum thyroid hormone changes are given in Fig. 2. The complete dependence on exogenous T₄ did not abolish the increase in serum T₄, which was, in fact, even more pronounced than that in the euthyroid subjects. The free hormone changes were as follows. The free T₄ concentration was 0.022 ± 0.002% or 2.04 ± 0.26 ng T₄/100 ml 7 days before treatment and 0.023 ± 0.002% or 3.38 ± 0.41 ng/100 ml after 3 weeks of treatment ($P = NS$). For free T₃ the respective values were 0.189 ± 0.014% or 0.358 ± 0.049 ng/100 ml before treatment and 0.217 ± 0.021 or 0.258 ± 0.053 ng/100 ml after 3 weeks of treatment ($P = 0.05$). In the third week of treatment with iopanoic acid, a TRH test was also performed in three of the euthyroid subjects; the maximal TSH response was less than 1.5 mU/ml, indicating that thyroidal secretion was blocked. Once again, no changes were observed in the metabolic parameters, as can be seen from the detailed individual results presented in Table 4.

The results of the low energy diet experiment are

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>MR (Kj/m²·h)</th>
<th>Heat losses (Kj/m²·h)</th>
<th>T₄ (µg/100 ml)</th>
<th>T₃ (ng/100 ml)</th>
<th>MR (Kj/m²·h)</th>
<th>Heat losses (Kj/m²·h)</th>
<th>T₄ (µg/100 ml)</th>
<th>T₃ (ng/100 ml)</th>
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<tr>
<td>¹° Hypothyroidism</td>
<td>F</td>
<td>68</td>
<td>115</td>
<td></td>
<td>1.7</td>
<td>57</td>
<td>115</td>
<td>2.0</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>¹° Hypothyroidism</td>
<td>F</td>
<td>26</td>
<td>122</td>
<td>135</td>
<td>1.3</td>
<td>56</td>
<td>125</td>
<td>1.3</td>
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<tr>
<td>²° Hypothyroidism</td>
<td>F</td>
<td>30</td>
<td>126</td>
<td>149</td>
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<td>66</td>
<td>115</td>
<td>1.6</td>
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<td></td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td></td>
<td></td>
<td>113</td>
<td>142</td>
<td>1.5</td>
<td>60</td>
<td>118</td>
<td>1.6</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td><strong>SEM</strong></td>
<td>3.2</td>
<td>7</td>
<td>0.1</td>
<td>3</td>
<td>3.3</td>
<td>0.2</td>
<td>3</td>
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</table>
Table 3. Change in MR, total heat losses, and body temperature measurements in T₃-substituted subjects who received three doses of 2 g iopanoic acid at weekly intervals for 3 weeks

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yr)</th>
<th>BW (kg; mean ± sd)</th>
<th>Day -8</th>
<th>Day -1</th>
<th>Day 6</th>
<th>Day 13</th>
<th>Day 20</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MR</td>
<td>HL</td>
<td>MR</td>
<td>HL</td>
<td>MR</td>
</tr>
<tr>
<td>M</td>
<td>41</td>
<td>70.6 1.2 164 166</td>
<td>36.46 33.26 163 164</td>
<td>36.35 33.42 163 193 36.59 33.43 169 189 36.33 33.39 169 182 36.41 33.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>26</td>
<td>60.2 0.7 203 25</td>
<td>36.80 33.27 197 200 36.75 33.41 188 209 37.12 33.42 206 222 36.99 33.63 199 220 36.64 33.65</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>M</td>
<td>26</td>
<td>67.0 1.9 176 200</td>
<td>36.71 33.09 187 190 36.31 33.63 188 191 36.34 33.73 179 207 36.84 34.48 182 178 36.80 33.94</td>
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</tr>
<tr>
<td>M</td>
<td>26</td>
<td>72.1 0.6 134 145</td>
<td>36.80 33.48 159 160 35.4 33.10 159 168 36.88 33.52 150 160 36.34 33.73</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>22</td>
<td>57.3 0.8 166 178</td>
<td>37.04 33.11 163 189 37.2 33.20 162 154 37.2 32.9 149 146 135 138 37.24 33.32</td>
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<thead>
<tr>
<th>Sex</th>
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<tr>
<td>F</td>
<td>23</td>
<td>57.3 0.8 164 178</td>
<td>37.04 33.11 163 189 37.2 33.20 162 154 37.2 32.9 149 146 135 138 37.24 33.32</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**HL, Heat losses; MST, mean skin temperature. Both HL and MST values are expressed as kilojoules per m²-h.**

**Fig. 1.** Changes in thermogenesis and serum thyroid hormones under iopanoic acid (2 g/week) treatment in otherwise untreated euthyroid subjects (mean ± SEM; n = 6).

Presented in Table 5. The MR decreased in all subjects, and after 2 weeks it had fallen significantly by 20 ± 2 Kj/m²-h (P < 0.005), which represents a 12% fall in the MR. Similarly, serum T3 levels fell by 50 ± 10 ng/dl (Table 5; P < 0.005). However, no change in serum T4 levels was apparent.

**Fig. 2.** Changes in serum thyroid hormones under iopanoic acid (2 g/week) treatment in four T₄-substituted subjects (200 μg/day). The symbols for the thyroid hormones are the same as in Fig. 1.

**Discussion**

To investigate the relationship between serum thyroid hormone levels and MR it was first necessary to study
The variability of an individual's MR, total heat losses, and body temperature under control conditions over the same period of time as the experimental period. Internal temperature and mean skin temperature remained very constant from week to week when the subject was exposed to the same environmental conditions (28°C and 30% relative humidity). The MR, calculated from the respiratory exchange data, also had a low coefficient of variation when compared with the total heat losses. Total heat losses were found to be greater than the MR, demonstrating a negative heat balance which is common in fasting individuals of normal weight (19).

On the low energy diet, a fall in body weight, MR, and serum T₃ was observed which is in agreement with the results of Bray (6). However, to investigate whether decreased serum T₃ levels play a role in the decrease in the MR it was necessary to dissociate thyroid hormone changes from starvation. This was accomplished by using iopanoic acid, which caused a significant decrease in serum T₃ levels in subjects consuming their normal diets. These decreases in serum T₃ levels are very likely due to a decreased conversion of T₄ to T₃, which is supported by in vitro data (11). This is further supported by the unchanged serum T₃ levels in the T₃-substituted subjects treated with iopanoic acid.

However, serum total and free T₃ concentrations increased during iopanoic acid treatment. This is probably due to a decreased MCR, as it also occurs in T₃-substituted subjects. In contrast to this, there is no evidence for a decreased MCR of T₄ during starvation (20).

Iopanoic acid itself did not have any thermogenic properties (Table 2). Nevertheless, the decreased serum T₃ level induced by it did not cause a decrease in thermogenesis. The unchanged thermogenesis could be explained by the increase in total and free serum T₄ concentrations, which might compensate for a decrease in T₃. However, one would have to postulate that a decreased clearance of T₄ by itself would potentiate the action of T₃, as in group 5 where T₄ intake was kept constant. There are no data to prove or disprove this hypothesis, which would imply a direct action of T₄.

Undoubtedly, severely decreased serum thyroid hor-
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Mones will decrease the MR. However, in fed subjects the changes induced with iopanoic acid do not seem to be sufficient by themselves to reduce the MR. These changes are, however, very similar to those observed during starvation, where it is well established that there is a fall in the MR (group 6).

We therefore suggest that in starvation the thyroid hormone changes are of minor significance in the reduction of the MR.

Acknowledgments

We would like to thank Prof. E. Jequier, Department of Physiology, University of Lausanne, Prof. M. B. Vallotton, Division of Endocrinology, and A. F. Muller, Department of Medicine, University of Geneva, for their continued interest in this work.

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