High muscle lipoprotein lipase activity in thyrotoxic patients

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Abstract. Serum lipoprotein metabolism was studied in 7 women before and after treatment for thyrotoxicosis. Of the lipoprotein lipids, the triglyceride concentration in the low density lipoproteins (LDL) \(P < 0.01\) and the cholesterol concentration in both LDL \(P < 0.01\) and the high density lipoproteins (HDL) \(P < 0.05\) increased significantly during treatment. These changes were accompanied by increases in apolipoprotein B \(P < 0.01\) and A-I \(P < 0.05\) concentrations in serum. Muscle lipoprotein lipase activity (LPLA) was increased in the thyrotoxic state by 46\% \(P < 0.05\) compared with the value after the patients had been rendered euthyroid, but adipose tissue LPLA was only 8\% higher \(\text{ns}\) in the former state. The capacity for removal of exogenous fat, as determined by the fractional elimination rate \(K_2\) at an iv fat tolerance test, was 23\% higher in the thyrotoxic than in the euthyroid state \(\text{ns}\).

It is suggested that the increase in muscle LPLA in the thyrotoxic state may be due to enhanced sensitivity to catecholamines. This may contribute to the increased capacity for plasma triglyceride turnover in thyrotoxicosis.

Thyroid hormones have a substantial impact on plasma lipoprotein metabolism (Valdemarsson 1983). This is manifested as an elevated level of low density lipoprotein (LDL) cholesterol in hypothyroidism (Valdemarsson 1983; Lithell et al. 1981a; Muls et al. 1984) and as a low level of LDL cholesterol in hyperthyroidism (Valdemarsson 1983; Boberg et al. 1984; Muls et al. 1982). The concentration of high density lipoprotein (HDL) cholesterol may be normal (Lithell et al. 1981a) or increased (Muls et al. 1984) in the hypothyroid state but is generally decreased (Valdemarsson 1983; Boberg et al. 1984) during thyrotoxic conditions. Very low density lipoprotein (VLDL) concentrations in plasma are generally not as much affected as those of LDL and HDL (Valdemarsson 1983). However, plasma triglyceride clearance is decreased in hypo- and increased in hyperthyroidism (Nikkilä & Kekki 1972; Tulloch et al. 1973). Lipoprotein lipase activity (LPLA) is important in determining the rate of turnover of the serum triglycerides (Robinson 1970) and it is therefore of interest to study how thyroid dysfunction affects the activity of this enzyme.

We have previously reported observations of low levels of LPLA in skeletal muscle and adipose tissue in hypothyroidism which were restored to normal during substitution therapy (Lithell et al. 1981a). In hyperthyroidism, most studies on LPLA have been restricted to assays in plasma after heparin injection (PHP-LPLA) (Nikkilä & Kekki 1972; Kirkeby 1968; Valdemarsson 1983). Although such an approach may give an overall view of the efficiency of triglyceride removal in the body, it will not reveal possible differences in reaction to thyroid hormones between different organs. We have therefore determined LPLA separately in skeletal muscle and adipose tissue before and after treatment for hyperthyroidism.

Material

Seven women (age 32–48 years; mean 41 years) with Graves' disease, referred to the Thyroid Outpatient Clinic at the Department of Internal Medicine, gave their informed consent to participation in the study. The diagnosis of Graves' disease was based on clinical signs, elevated serum triiodothyronine \(T_3\) and thyroidine \(T_4\)
levels, an absent thyroid stimulating hormone (TSH) response to a thyroid releasing hormone (TRH) test, increased diffuse thyroid uptake of 99mTcO4, fine needle biopsies and thyroid autoantibody findings. All patients were treated with standardized carbimazole (Neo-Mercazole®) regimen with the addition of 0.1 mg of L-thyroxine (Levaxin®) when they had become euthyroid, and this combined treatment was continued for periods of up to 2 years.

Methods

Experimental procedure

Several variables of lipoprotein metabolism were studied in patients, with initial determinations and tests while the patients were thyrotoxic, and subsequent ones following at least 9 months of euthyroidism (12–19 months, mean 14 months, after commencement of treatment). At that time 4 patients were still taking the combined treatment as described above, while 3 patients had been taken off therapy.

After an overnight fast adipose and muscle tissue biopsies were taken for determination of LPLA. Blood was drawn for measurement of the fasting values of lipoproteins and apolipoproteins (apo) and the fasting serum insulin concentration. An iv fat tolerance test (IVFTT) was performed according to the method of Carlson & Rössner (1972).

Hormone concentrations

Serum T3, T4 and TSH levels were assessed by radio-immunoassays in routine diagnostic use at the Department of Clinical Chemistry, University Hospital, Uppsala. T3U was determined by the ‘Phadebas T3U Test’ (Pharmacia, Uppsala, Sweden). FT3I and FT4I were calculated as the products of the T3 or T4 and corresponding T3U values, respectively. The reference range for FT3I is 1.2–2.8 arbitrary units (AU), for FT4I 67–153 AU and for TSH < 8 mU/l.

Lipoprotein and apolipoprotein concentrations

VLDL in serum were isolated in the top fraction after ultracentrifugation at a density of 1.006 in a Beckman LKB-65 ultracentrifuge, using a 40.3 rotor. LDL were precipitated from the bottom fraction after the ultracentrifugation step, using a heparin-manganese chloride precipitation technique, and HDL were isolated in the supernatant after the precipitation. The concentrations of triglycerides and cholesterol were determined in whole serum, VLDL, HDL and the bottom fraction at a density of 1.006. The lipid concentrations in LDL were calculated as the differences between the concentrations in the bottom fraction and those in HDL. A Technicon AutoAnalyzer II was employed for determinations of triglycerides and cholesterol. For measuring the concentrations of apo B and A-I in whole serum an immunoassay was used. The details of the antibody production, purification and standardization and assay techniques as well as details regarding the lipoprotein quantification have been given previously (Vessby et al. 1980).

Analyses of LPLA and the fractional removal rate at an iv fat tolerance test

In specimens of abdominal adipose tissue and in specimens of skeletal muscle, taken from the lateral vastus muscle, LPLA was determined as described earlier (Lithell et al. 1981a), with some modifications (Arner et al. 1981). One nmol of fatty acid release per min was defined as 1 μmol enzyme activity. The fractional removal rate of the IVFTT was calculated (Carlsson & Rössner 1972).

Statistical methods

Mean values and sd were calculated by conventional statistical methods. A two-way analysis of variance was used to test the effect of treatment.

Results

All patients showed increased values of FT3I and FT4I and low or normal levels of TSH prior to antithyroid drug treatment and all were rendered euthyroid during the treatment period (Table 1). The average change in body weight from the pre- to post-therapy measurement was 7.8 kg, with a range of –0.8 to 17 kg. There was no significant change in the serum insulin level (Table 1).

The mean muscle LPLA in the thyrotoxic state was 46% higher than the value following attainment of euthyroidism. LPLA in adipose tissue, on

| Table 1. Variables describing thyroid function (free T3 index (FT3I), free T4 index (FT4I) and serum thyroid stimulating hormone (S-TSH), body weight and fasting-serum insulin concentration. Mean ± sd. Significant changes are indicated by P < 0.05, P < 0.01 and P < 0.001. |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Before treatment | After treatment | P-value         |
| FT3, AU                        | 6.7 ± 2.8       | 1.9 ± 0.4       | P < 0.01        |
| FT4, AU                        | 292 ± 9         | 108 ± 23        | P < 0.01        |
| S-TSH, mU/l                    | 1.8 ± 0.6       | 2.6 ± 0.7       | ns              |
| Body weight, kg                | 61.7 ± 7.4      | 69.5 ± 12.9     | P < 0.05        |
| fS-insulin, mU/l               | 8.7 ± 2.5       | 8.5 ± 3.9       | ns              |

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Table 2.
Lipoprotein lipase activity (LPLA) in muscle and adipose tissue and the K2 value of iv fat tolerance test (IVFTT). Statistics as in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle LPLA, mU/g</td>
<td>57 ± 8</td>
<td>39 ± 15</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Adipose tissue LPLA, mU/g</td>
<td>268 ± 39</td>
<td>248 ± 51</td>
<td>ns</td>
</tr>
<tr>
<td>K2 IVFTT, %/min</td>
<td>8.6 ± 3.8</td>
<td>7.1 ± 4.7</td>
<td>ns</td>
</tr>
</tbody>
</table>

the other hand, was only 8% higher in the thyrotoxic than in the euthyroid state.

The average change of the K2 value of the IVFTT was not significant (Table 2). However, the K2 value decreased in all patients except one, in whom the K2 value increased from 14.7 to 16.6% / min. This patient had the highest K2 values and these were not explained by high LPLA in either muscle or adipose tissue.

The triglyceride and cholesterol concentrations in VLDL were not significantly altered during treatment, but those in LDL increased significantly. HDL cholesterol increased from 1.25 to 1.45 mmol/l (Table 3). Apo B and A-I increased significantly by averages of 48 and 12%, respectively, whereas the average increase in apo A-II by 12% was not statistically significant (Table 3)

Discussion

During hyperthyroidism lipolytic acitivity in post-heparin plasma has been reported to be decreased (Arons et al. 1972), low normal (Tulloch et al. 1973) or increased (Nikkilä & Kekki 1972). In a recent study PHP-LPLA, measured by a specific method, was found to decrease by about 10% in thyrotoxic patients during treatment (Valdemarsson et al. 1983). In the present study the percentage decrease of LPLA in adipose tissue was much less than that of LPLA in muscle tissue. In overt hypothyroidism the values for adipose and muscle tissue LPLA have been found to be 17 and 40% below the average value reached after substitution therapy (Lithell et al. 1981b). These results indicate that thyroid dysfunction has a greater effect on LPLA in muscle than in adipose tissue.

Table 3.
Triglyceride (Tg) and cholesterol (Chol) concentrations in very low (VLDL), low (LDL) and high (HDL) density lipoproteins (mean ± SD) are indicated before and after treatment for thyrotoxicosis, as well as Tg and Chol concentrations in serum, apolipoprotein (apo) B, apo A-I and apo A-II (arbitrary units, AU) concentrations. Statistics as in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
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<tbody>
<tr>
<td>VLDL-Tg, mmol/l</td>
<td>0.54 ± 0.25</td>
<td>0.72 ± 0.52</td>
<td>ns</td>
</tr>
<tr>
<td>VLDL-Chol, mmol/l</td>
<td>0.22 ± 0.12</td>
<td>0.28 ± 0.24</td>
<td>ns</td>
</tr>
<tr>
<td>LDL-Tg, mmol/l</td>
<td>0.31 ± 0.13</td>
<td>0.49 ± 0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-Chol, mmol/l</td>
<td>2.77 ± 0.72</td>
<td>4.06 ± 0.86</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-Tg, mmol/l</td>
<td>0.21 ± 0.06</td>
<td>0.27 ± 0.06</td>
<td>ns</td>
</tr>
<tr>
<td>HDL-Chol, mmol/l</td>
<td>1.25 ± 0.18</td>
<td>1.45 ± 0.17</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum-Tg, mmol/l</td>
<td>1.08 ± 0.36</td>
<td>1.50 ± 0.61</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum-Chol, mmol/l</td>
<td>4.29 ± 0.74</td>
<td>5.98 ± 1.10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Apo B, AU</td>
<td>94 ± 11</td>
<td>139 ± 38</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Apo A-I, AU</td>
<td>102 ± 14</td>
<td>114 ± 16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Apo A-II, AU</td>
<td>98 ± 16</td>
<td>110 ± 16</td>
<td>ns</td>
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About half of the hydrolysis of circulating triglycerides takes place in muscle tissue and only 20% in sc adipose tissue after an overnight fast (Rössner 1974). This is consistent with the finding that muscle LPLA is better correlated to the removal capacity of circulating triglycerides (K\textsubscript{2} value) than adipose tissue LPLA (Lithell et al. 1978). Therefore, our finding of increased muscle LPLA in hyperthyroidism may explain the increased K\textsubscript{2} value at IVFTT found in most patients with this condition (Tulloch et al. 1973 and present study).

Hyperthyroidism is more common in women who have a higher proportion of their total body mass as adipose tissue and have higher adipose tissue LPLA than men (Taskinen & Nikkilä 1979). It is therefore conceivable that PHP-LPLA reflects adipose tissue LPLA to a greater extent than muscle LPLA in a thyrotoxic population. As the increase in adipose tissue LPLA was less pronounced than that in muscle LPLA, this may explain the relatively small increase in PHP-LPLA noted earlier. In thyrotoxic patients PHP-LPLA does not seem to constitute a good estimate of the extent to which muscle LPLA is affected, which may explain the discrepancy between post-heparin lipolytic activity and fractional catabolic rate observed in previous studies (Tulloch et al. 1973).

Muscle tremor is a common feature of the thyrotoxic state. It is generally explained by increased sensitivity to adrenergic hormones which is induced by thyroid hormones (Anonymous 1977) and is effectively treated by beta blockade (Schanks et al. 1969). There are several indications that catecholamines also take part in the regulation of muscle LPLA (Lithell et al. 1981b; Górski & Stankiewicz-Choroszucha 1982). The skeletal muscle LPLA in the thyrotoxic state was at a level usually seen in well-trained men (Kiens et al., in press). The increased LPLA in skeletal muscle may represent a response to enhanced sensitivity to catecholamines in muscles tissue in the thyrotoxic state. The increased production rate of VLDL (Nikkilä & Kekki 1972) would balance this, resulting in normal or only slightly decreased serum triglyceride values.

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