Plasma somatostatin is elevated in primary hypothyroidism compared with hyperthyroidism

Ståle Skare, Kristian F. Hanssen and Nils Norman

Medical Department B and the Hormone Laboratory, Aker Hospital, Oslo 5

Abstract. Increased pancreatic somatostatin (somatotrophin release inhibiting factor (SRIF)) has been found in hypothyroid rats. Therefore, we wanted to investigate plasma SRIF in patients with hypo- and hyperthyroidism.

Two groups of patients, 7 cases with autoimmune hypothyroidism, 31–75 years old, and 7 cases with Graves' disease, 19–43 years old, were compared with regard to plasma SRIF before, during and after an arginine infusion (0.5 g/kg/20 min). None of the patients suffered from diabetes mellitus or obesity. Plasma SRIF was higher in the hypothyroid patients (mean basal value 21.5 ± 3.9, peak value 28.7 ± 5.1 pmol/l) compared with the hyperthyroid group (mean basal value 11.6 ± 3.3, peak value 16.2 ± 4.0 pmol/l). The hypothyroid group also had significantly higher serum insulin values during arginine stimulation. No difference was found in plasma glucagon, serum growth hormone (GH) or blood glucose.

In conclusion, plasma SRIF is elevated in primary hypothyroidism compared with hyperthyroidism. The reason for this finding is uncertain, but a reduced SRIF clearance is a possible explanation. The association of our findings with the reduced glucose tolerance in hyperthyroidism is discussed.

Next to the upper gastro-intestinal tract and pancreas, the thyroid gland is the largest SRIF producing organ (Kronheim et al. 1976), where SRIF is located in the C-cells together with calcitonin (Höffelt et al. 1975).

Nevertheless, the contribution of SRIF from the thyroid gland to the peripheral venous blood concentration is thought to be negligible compared to that of the major producing organs, the gastro-intestinal tract and pancreas (Utsumi et al. 1979). Elevated pancreatic SRIF is found in hypothyroidism (Berelowitz et al. 1980).

SRIF infusion is known to inhibit triiodothyronine (T3) and thyroxine (T4) release (Loos et al. 1976; Ahrén et al. 1978). On the other hand, the role of the thyroid hormones on thyroid SRIF content and release is unknown.

Our study was undertaken to compare plasma SRIF in well defined groups of hypo- and hyperthyroid patients during an arginine infusion, supposed mainly to release pancreatic SRIF (Wasada et al. 1980).

Accordingly, possible differences in plasma SRIF between the two groups can be evaluated in comparison with the variations in plasma concentrations of the other islet cell hormones.

Materials and Methods

Seven women with Graves' disease, age 19–43, mean age 34 years, and 7 patients (6 women and 1 man) with Hashimoto's thyroiditis or primary myxoedema, 31–75, mean 53 years old, were investigated (Fig. 1, Table 1). None of the patients suffered from diabetes mellitus, reduced renal function or obesity, although the mean weight among the hypothyroid women was 6 kg above that of the hyperthyroid group. The main clinical and biochemical data are expressed in Table 1.

The stimulus was an arginine infusion (0.5 g/kg/20 min) employed in a test after an over-night fast and half an hour of recumbency. Cannulas were inserted into both antecubital veins, one used for infusion, the other for blood sampling.

Blood samples were taken before, during and after
the arginine infusion, and analysed for plasma SRIF and glucagon, serum insulin and growth hormone (GH) employing specific RIA's, and blood glucose using a glucose dehydrogenase method (Skare et al. 1984; von Schenck & Nilsson 1981; Folling & Norman 1972; Rutlin et al. 1977). The SRIF RIA was chiefly measuring SRIF-14. The reference values for plasma SRIF, plasma glucagon, serum insulin and serum GH are 9-34 pmol/l, <70 pmol/l, <10 mU/l and <5 µg/l, respectively. Serum T3, T4 and TSH were estimated with specific RIA's (Aakvaag et al. 1978; Haug et al. 1977; Torjesen et al. 1973) and antibodies against the follicular cell microsomes were demonstrated with an indirect immunofluorescence technique (Holborow et al. 1959) (Fig. 1, Table 1). All patients gave their informed consent, and none of them experienced untoward effects.

The results are expressed as mean values ± SEM. For statistical analysis the Wilcoxon test for pair differences and the Wilcoxon rank sum test, suitable for comparison of groups, were employed. P-values < 0.05 were considered significant.

Results

The mean T3, T4 and TSH values ± SEM in the hyper- and hypothyroid groups were 6.9 ± 2.6 and 0.7 ± 0.2 nmol/l, 232 ± 14.3 and 25 ± 5.9 nmol/l, 2.3 ± 0.5 and 91 ± 17 mU/l, respectively. The other results are expressed in Fig. 1.

Comparison of the groups

Plasma SRIF is significantly higher in hypo- than hyperthyroidism at −15 min (P < 0.02), 5 min (P < 0.04), 20 min (P < 0.02) and 25 min (P < 0.03). Serum insulin is significantly higher in hypo- than in hyperthyroidism at 5 min (P < 0.03), 20 min (P < 0.03), 30 min (P < 0.03) and 45 min (P < 0.04). The mean glucagon values are highest in the hypothyroid group, but no significant difference is found. The values for serum GH and blood glucose are superimposable in hypo- and hyperthyroidism.
Main clinical data in 7 hyperthyroid patients with Graves' disease and 7 hypothyroid patients with Hashimoto's disease.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age Years</th>
<th>Sex</th>
<th>Duration of disease</th>
<th>Accompanying disease</th>
<th>Thyroid gland</th>
<th>T$_4$ nmol/l</th>
<th>T$_3$ nmol/l</th>
<th>TSH mIU/l</th>
<th>Microsomal antibody titre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>F</td>
<td>2 months</td>
<td>–</td>
<td>moderately enlarged, diffuse</td>
<td>235</td>
<td>7.0</td>
<td>3.5</td>
<td>1: 1600</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>F</td>
<td>5 months</td>
<td>–</td>
<td>moderately enlarged, diffuse</td>
<td>192</td>
<td>4.7</td>
<td>2.4</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>F</td>
<td>1 month</td>
<td>–</td>
<td>enlarged, diffuse</td>
<td>213</td>
<td>4.9</td>
<td>1.9</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>F</td>
<td>8 months</td>
<td>–</td>
<td>enlarged, diffuse</td>
<td>193</td>
<td>3.4</td>
<td>1.6</td>
<td>1: 6400</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>F</td>
<td>24 months</td>
<td>–</td>
<td>enlarged, diffuse</td>
<td>243</td>
<td>5.0</td>
<td>4.3</td>
<td>1: 6400</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>F</td>
<td>6 months</td>
<td>–</td>
<td>enlarged, diffuse</td>
<td>300</td>
<td>8.3</td>
<td>2.1</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>F</td>
<td>12 months thyrotoxicosis 5 years ago</td>
<td>–</td>
<td>enlarged, diffuse</td>
<td>250</td>
<td>14.9</td>
<td>0.2</td>
<td>–</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>37</td>
<td>F</td>
<td>10 years</td>
<td>–</td>
<td>normal</td>
<td>23</td>
<td>0.9</td>
<td>131</td>
<td>1: 400</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>F</td>
<td>12 months</td>
<td>–</td>
<td>moderately enlarged, firm</td>
<td>15</td>
<td>0.5</td>
<td>89</td>
<td>1:25 600</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>F</td>
<td>5 months</td>
<td>–</td>
<td>moderately enlarged, firm</td>
<td>15</td>
<td>0.4</td>
<td>90</td>
<td>1: 6400</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>F</td>
<td>12 months</td>
<td>–</td>
<td>enlarged, firm</td>
<td>58</td>
<td>1.8</td>
<td>37</td>
<td>1: 1600</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>F</td>
<td>12 months</td>
<td>–</td>
<td>enlarged, firm</td>
<td>30</td>
<td>1.0</td>
<td>169</td>
<td>1:38 400</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>F</td>
<td>2 months</td>
<td>–</td>
<td>enlarged, firm</td>
<td>15</td>
<td>0.2</td>
<td>62</td>
<td>1:25 600</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>M</td>
<td>10 years</td>
<td>–</td>
<td>enlarged, firm</td>
<td>21</td>
<td>0.2</td>
<td>62</td>
<td>1:25 600</td>
</tr>
</tbody>
</table>

Normal ranges in serum: T$_4$: 70–150 nmol/l; T$_3$: 1.2–2.5 nmol/l; TSH: < 11.6 mIU/l.

Discussion

The presented model of investigation was chosen because it might amplify possible differences in plasma SRIF.

The group of hypothyroid patients had significantly higher plasma SRIF values than those suffering from hyperthyroidism. In hypothyroidism, plasma SRIF was higher before, during and after the arginine infusion, indicating a higher basal secretion of SRIF from the gastro-intestinal tract and pancreas, rather than elevated release following stimulation. Our SRIF values in normal individuals were measured against another batch of standard, giving somewhat higher results (Skare et al. 1984), and accordingly we could not statistically compare our controls with the hypo- or hyperthyroid groups. However, correcting for the different standards, the normal individuals have mean plasma SRIF concentrations falling between the hypo- and hyperthyroid patients.

Our findings are in agreement with those of Berelowitz et al. (1980), showing increased pancreatic SRIF in hypothyroid rats.

Our method measures chiefly SRIF-14 and does not reveal possible differences in SRIF-28, known to have different potencies on the release of insulin, glucagon and GH (Mandarino et al. 1981).

The elevated lipid concentrations found in hypothyroidism could interfere in assay systems, but not in the present SRIF RIA (Skare et al. 1984).

The slightly elevated plasma SRIF in hypothyroidism could further reduce the release of thyroid hormones (Loos et al. 1976; Ahrén et al. 1978). Gavin et al. (1983) have shown that SRIF inhibits the hepatic T$_4$-5'-deiodinase. However, the elevated plasma SRIF in hypothyroidism is
probably without significance in reducing $T_4$ to $T_3$ conversion, because the serum $T_3$ is an unreliable indicator of hypothyroidism (Ingbar & Woebner 1981). Because the abdominal portal vein is a major contributor to the SRIF measured in peripheral venous blood, SRIF must be related to the other islet cell hormones.

The mean plasma glucagon was higher in hypothyroidism, but in contrast to Seino et al. (1973), we did not find significant differences between the patient groups.

Serum insulin during arginine stimulation was higher in hypo- than in hyperthyroidism. This is in agreement with the results of Seino et al. (1973) (Fig. 1). Thyroid hormones affect glucose and insulin metabolism in several ways (Andersen et al. 1977). Glucose intolerance is frequently detected in hyperthyroidism and reduced insulin release to glucose is sometimes found. In hypothyroidism the insulin clearance is reduced (Ingbar & Woebner 1981). Even though the mean weight was higher in the hypothyroid group, none of the patients were obese. Relative insulin resistance cannot be ruled out as a contributing factor for the elevated insulin in this group. The combination of elevated SRIF together with elevated insulin does not fit with the experimental models, where SRIF reduces insulin and insulin reduces SRIF, at least in diabetic animals (Schusdziarra 1980; Schusdziarra et al. 1978). Thus, the usual feedback regulations between the islet cell hormones cannot explain our findings in hypo- and hyperthyroidism.

An increased release of insulin, SRIF and possible glucagon from the islets of Langerhans, caused by hypothyroidism could explain our results. The finding that SRIF as well as insulin are increased in hypothyroidism and reduced in hyperthyroidism, is compatible with a common mechanism governing the levels of these hormones in thyroid disorders. The altered metabolic clearance rate, also affecting SRIF, would fit our results. This has not been investigated, but reduced clearance rates of substances and hormones are frequently found in hypothyroidism (Ingbar & Woebner 1981).

In conclusion, plasma SRIF is higher in primary hypothyroidism than in hyperthyroidism. We favour the view that reduced SRIF clearance in hypothyroidism possibly combined with increased release from the pancreas is the most likely explanation for this finding. The reduced plasma SRIF in hyperthyroidism might contribute to the glucose intolerance through accelerated gastro-intestinal absorption rate, while the reduced insulin response must seek other explanations (Schusdziarra 1980).

Acknowledgments

The expert technical assistance of the laboratory staff, especially Miss Vera Kriz, is gratefully acknowledged.

This work was financially supported by the Hormone Laboratory, Aker Hospital.

References


Received on April 24th, 1985.