TSH unresponsiveness, a case report

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Abstract. A patient with congenital primary hypothyroidism is presented. His thyroid gland had a normal uptake of radioiodine which was independent of endogenous or exogenous TSH, sympathetic B-receptor blockade or prostaglandin inhibition. Infusion of dibutylcyclic AMP increased the uptake of radioiodine and stimulated release of protein bound ¹³¹I. He had no goitre even when he did not receive thyroxine, but thyroid histology showed evidence of active epithelium in the presence of adequate substitution with thyroxine. We assume that some unknown factor other than TSH stimulates part of the glandular function in this patient, without leading to adequate formation and release of thyroid hormone.

Stanbury et al. (1968) described the first case of hypothyroidism due to thyrotrophin (TSH) unresponsiveness. Since then 3 additional cases have been reported (Codaccioni et al. 1980; Job et al. 1969; Medeiros-Neto et al. 1979). The patients have congenital hypothyroidism, physical stigmata of cretinism, low serum levels of thyroid hormones and high serum levels of TSH, and they have a normal-sized thyroid gland with quantitatively normal uptake of radioiodine, unresponsive to the administration of exogenous TSH.

This report describes a patient with congenital primary hypothyroidism. His thyroid uptake of radioactive iodine was normal and did not change in response to endogenous or exogenous TSH. Infusion of dibutyl-cyclic AMP (dbc-AMP) stimulated the radioiodine uptake and was furthermore followed by increased release of protein bound radioactive iodine. We suggest that this patient was hypothyroid due to a TSH receptor defect, either at the level of the TSH binding site or at the post-receptor level.

Methods

Hormone analysis
All analyses were performed at the Hormone Laboratory, Aker Hospital.

Thyrotrophin releasing hormone (TRH) test and gonadotrophin releasing hormone test
These tests were performed according to Torjesen et al. (1973) and Haug et al. (1974). 0.4 mg TRH (Roche) and 0.1 mg GnRH were injected iv as a bolus. Serum levels of pituitary hormones were measured after 30 and 60 min and compared to the basal levels.

Perchlorate test
Fifty μCi ¹³¹I was given orally and the radioactivity in the thyroid gland was measured after 1 h. 0.4 g KClO₄ was then given orally and the radioactivity was measured every 10 min for 40 min.

Diiodothyrosine (DIT) test
Five μCi [¹²⁵I]DIT was given iv. Urine was sampled during the first and second 2 h periods thereafter, and the radioactivity in urine was compared to the given dose.

Radioactive iodine uptake
Fifty μCi ¹³¹I or ¹²⁵I was given orally and the accumulated radioactivity in the thyroid gland was measured after 1, 24 and 48 h. Thyroid radioactivity was expressed as per cent of given dose (Solberg & Norman 1969).
Dibuturyl-cyclic AMP (dbc-AMP) stimulation

Fifty μCi 131I was given orally and thyroid radioactivity was measured after 1, 2, 3 and 6 h. After 1 week the thyroid radioactivity was again measured before an additional tracer dose of 131I was given. Four hundred mg dibuturyl adenosine 3,5-cyclic phosphoric acid (dbcAMP, Sigma Chemicals Co.) was dissolved in 250 ml 5% glucose and then given as an iv infusion at a rate of 0.1 mg/min/kg body weight for 50 min. The increase in thyroid radioactivity was again measured 1, 2, 3 and 6 h after intake of the tracer. Serum samples for the determination of proteinbound 131I (PB131I) were collected before and 6 h after starting the dbc-AMP infusion (Haug et al. 1972).

Drugs

In some experiments thyroid uptake of radioactive iodine was measured under the influence of drugs which were given from one day before and during the uptake studies: indomethacine (Indocid ‘MSD’) 25 mg × 3, propranolol (Inderal I.C.I.) 80 mg × 3 and teophyllamine (Teophyllamine ‘NAF’) 0.6 g dissolved in 500 ml 5% glucose, infused at a rate of 50 mg/h.

Case Report and Results

The male patient studied was born in 1916 as the youngest of 6 siblings. There was no consanguinity between his parents. Two sisters and one brother were euthyroid while two brothers had been treated for hypothyroidism from early childhood. All attempts by us to investigate them were in vain.

Our patient was found to be hypothyroid at the age of 16 months and treatment with desiccated thyroid was started, but probably carried out irregularly during childhood and also later. He was slightly mentally retarded but could read and write. In adult life he had 2 only sporadic jobs. He never married but claimed to be sexually active. He only occasionally had medical attention. According to old files his basal metabolic rate was 70% of normal in 1939, 80% in 1945 and 97% in 1950. At this latter occasion his plasma cholesterol concentration was somewhat elevated (7.5 mmol/l).

He was first admitted to our service in 1969 for erysipelas. He weighed 108 kg and was 162 cm tall. His thyroid gland was normal on palpation. He appeared mentally slow. Upon admission he had been off thyroxine for almost 10 years and his serum proteinbound iodine (PBI) was 158 nmol/l (normal 300–600 nmol/l). A T3 binding test revealed normal thyroid hormone binding capacity in serum (40.7% vs 38% in control serum). On thyroid scintigrams his thyroid gland had normal size and location. Twenty-four h uptake of 131I was 28.2% of dose with no further increase after 48 h. Skull X-ray showed enlarged sella turcica.

No evidence was obtained for any associated endocrine dysfunction. He had normal serum concentration of Ca and PO4. The work-up includes a metryrapon-test which revealed a normal pituitary ACTH-response adequately suppressed by 1 mg of dexamethasone orally. The serum level of testosterone was in the lower normal range and a GnRH-test was normal (LH increased from 0.8 μg/l to 2.5 μg/l and FSH from 0.8 μg/l to 1.2 μg/l).

After 1969 he was seen in the department from time to time. In 1974 serum PBI was 110 nmol/l. In 1977, when he again had been neglecting his thyroxine medication, serum levels of T3 and T4 were 0.5 nmol/l and 4.0 nmol/l, respectively (reference values in Table 1). At that time serum TSH was markedly elevated to 4.5 μg/l and increased further to 8.9 μg/l after a TRH injection.

In 1979 the patient acquired chronic lymphatic leucæmia which was treated with cyclophosphamide and prednisone. He was splenectomized in 1980 but died from this disease in May 1981.

Special thyroid function studies

Perchlorate test. One hour after an oral dose of 50 μCi 131I 6.7% of the radioactivity administered was found in the thyroid gland. No reduction in glandular radioactivity was detectable within 40 min after oral administration of 0.4 KCIO4, thus excluding the possibility of an iodine binding defect.

DIT test. Only 2.8% of the radioactivity was excreted in the urine during 4 h after iv administration of 5 μCi [128I]DIT, which excludes a dehalogenase defect.

Urinary excretion of iodine. To exclude nutritional iodine deficiency the daily renal excretion of iodine was measured several times, and ranged from 600 to 1200 nmol/24 h, which are normal values in Oslo (Frey et al. 1974).

Uptake of radioactive iodine. Over a period of 12 years we have measured his thyroid uptake of radioactive iodine several times and at different degrees of hypothyroidism. The iodine uptake was always within normal limits. The absolute glandular uptake of stable iodine, calculated from the
increase in thyroid radioactivity and the concomitant specific activity of urinary iodine, was normal, 600 nmol/24 h.

Our patient was regularly re-admitted throughout these years as he failed to take his thyroxine. On these occasions his serum level of TSH was always elevated. When thyroxine medication was started, serum TSH was normally suppressed (Table 1). Thyroid uptake of $^{131}$I on the other hand seemed not to be influenced by the level of endogenous TSH (Table 2). Exogenous TSH (Actyron 'Ferring') also had no effect on the uptake of $^{131}$I even after prolonged stimulation (5 IU daily for 7 days, Fig. 1). The unresponsiveness to TSH was further demonstrated by lack of increase in serum PB$^{131}$I levels after TSH stimulation (Fig. 1, Haug et al. 1974).

In search for factors other than TSH that might stimulate thyroid accumulation of iodine, the uptake of radioactive iodine was measured during oral treatment with either propranolol or indomethacin and during infusion with theophyllamine. None of these experimental regimens had any influence on uptake of radioactive iodine (Table 3).

dbc-AMP stimulation. In order to further characterize the molecular mechanism of the TSH unresponsiveness, he was on two occasions given continuous infusions of dbc-AMP (0.1 mg/min/kg body weight for 50 min). This dose had only small effect on heart rate and blood pressure. A 6 h radioactive uptake test was performed one week

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**Table 1.**

Effects of thyroxine substitution on serum levels of TSH, T4 and T3.

<table>
<thead>
<tr>
<th></th>
<th>Nov. 02.78</th>
<th>Nov. 13.78</th>
<th>Nov. 20.78</th>
<th>Dec. 20.78</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (μg/l)</td>
<td>3.4</td>
<td>2.7</td>
<td>3.1</td>
<td>1.7</td>
<td>0.2–1.2</td>
</tr>
<tr>
<td>T4 (nmol/l)</td>
<td>25</td>
<td>44</td>
<td>59</td>
<td>79</td>
<td>64–135</td>
</tr>
<tr>
<td>T3 (nmol/l)</td>
<td>0.8</td>
<td>1.0</td>
<td>1.3</td>
<td>1.3</td>
<td>1.4–2.8</td>
</tr>
</tbody>
</table>

1 On admission to hospital October 29th 1978 the patient had been off thyroxine therapy for several weeks. Treatment with 0.1 mg thyroxine orally once a day was started and continued during the investigative period.

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**Table 2.**

Relationship between serum TSH levels and thyroid uptake of $^{131}$I.

<table>
<thead>
<tr>
<th>Date</th>
<th>TSH$^1$ (μg/l serum)</th>
<th>Thyroid uptake of $^{131}$I % of total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0.2–1.2)</td>
<td>1 h (1.5–15)</td>
</tr>
<tr>
<td>June 19.69</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Feb. 21.71</td>
<td>4.5</td>
<td>5</td>
</tr>
<tr>
<td>Nov. 15.78</td>
<td>2.7</td>
<td>8</td>
</tr>
<tr>
<td>Dec. 20.78</td>
<td>1.7</td>
<td>5</td>
</tr>
</tbody>
</table>

1 Normal values in parenthesis.
2 TSH radioimmunoassay not available. Biochemically the patient was hypothyroid with butanol extractable iodine (BEI) = 0.8 μg/100 ml (2–4 μg/100 ml).
prior to and then simultaneous with the dbc-AMP infusion. Fig. 2 shows that dbc-AMP increased thyroid uptake considerably. dbc-AMP, in contrast to TSH, also caused a significant increase in the release of $^{131}$I from the thyroid gland.

**Antibody studies.** No thyroid antibodies, either cellular or microsomal, were detected in serum, which was also tested for the presence of thyroid stimulating antibodies (Mr. Rees Smith, Royal Victoria Infirmary, Newcastle, England) and long acting thyroid stimulating factor (Dr. C. Rerup, Institute of Pharmacology, University of Lund, Sweden). None of these factors were detected.

**Autopsy studies**

The autopsy showed enlarged lymph nodes with a completely affaced architecture made up of mostly small lymphocytes consistent with chronic lymphocytic leukaemia of B-cell type. Lymphocytic infiltrates were found in the bone marrow, the liver, the adrenal glands and the pituitary gland. No infiltrates were demonstrated in the thyroid gland.

**Table 3.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
<th>Thyroid uptake of $^{131}$I (%) of total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 h (5–15)</td>
</tr>
<tr>
<td>Sept. 21.79</td>
<td>Propranolol</td>
<td>5</td>
</tr>
<tr>
<td>Oct. 01.79</td>
<td>Teophyllamine</td>
<td>9</td>
</tr>
<tr>
<td>Oct. 08.79</td>
<td>Indomethacine</td>
<td>7</td>
</tr>
</tbody>
</table>

1 Normal values in parenthesis.
The thyroid gland was pale pink and had a weight within the normal range (27 g). The light microscopical picture was unusual (Fig. 3). The follicles were mostly small, although occasionally a few medium sized or large follicles were seen. They were lined by cuboid or flattened epithelium and mostly contained no colloid. In many areas the epithelium appeared hyperplastic without formation of distinct follicles. There was an increase in the stroma which formed fibrous septa.

Electron microscopy of thyroid tissue from the autopsy was performed after fixation with glutaraldehyde followed by osmium tetroxide. (Fig. 4). The cytoplasm of the epithelial cells appeared filled with membrane-bound vesicular structures containing amorphous material. They probably represent endoplasmatic reticulum which has been fragmented due to the autolysis. Lysosome-like structures were seen abundantly in some of the epithelial cells. The basal lamina of the epithelial cells appeared to have a normal thickness.

Post-mortem samples of the thyroid gland were examined with an immunohistochemical technique for the presence of TSH receptors. (Dr. A. Attromadal, Rikshospitalet, Oslo). No TSH receptors were detected, but neither were such receptors found in the thyroid gland in control samples obtained at other autopsies.

Discussion

Our patient had primary hypothyroidism with low levels of T₃ and T₄ and elevated levels of immunoreactive TSH. Illig et al. (1975) and Peterson et al. (1978) have described cases with hypothyroidism and increased serum levels of immunoreactive, but biologically inactive TSH. In contrast to our case, thyroid radiiodine uptake was stimulated by bovine TSH when given for 3–7 days. They also had other symptoms of hypothalamo-pituitary disease, while our patient had normal pituitary function even though his sella turcica was enlarged. Such enlargement is a relatively common finding in
primary hypothyroidism of long duration (Tur-Kaspa et al. 1979).

The presence of congenital enzyme defects in the thyroid gland is made unlikely by the results of the different function tests used, although we have only indirect evidence against the possibility of a coupling defect. The absence of a goitre also speaks strongly in favour of this view. A partial enzyme defect, incompletely compensated by a maximal secretion of TSH, is also unlikely in the absence of goitre, and one would then expect the radioiodine uptake to vary with changing levels of TSH, which was not the case in our patient.

Available data thus indicate thyrotrophin unresponsiveness. Both endogenous and exogenous TSH was found unable to increase the normal thyroid uptake of radioactive iodine, while the gland responded to dbc-AMP stimulation.

A trait with TSH unresponsiveness was first described by Stanbury et al. (1968), and since then 3 additional cases have been reported (Job et al. 1969; Medeiros-Neto et al. 1979; Codaccioni et al. 1980). The clinical features are much the same as in our patient: hypothyroidism appearing early in life, normal sized thyroid gland with normal uptake of radioactive iodine. Consanguinity seems to be common, but was not present in this case.

TSH unresponsiveness might involve defect binding of TSH to the thyroid cells, defect coupling between the binding site and the catalytic unit of adenylate cyclase entity, or a defect in the catalytic unit. We were unable to demonstrate the presence or absence of TSH receptors in our patient, possibly because samples from the thyroid gland are not allowed to be removed until 8 h after death.

**Fig. 3.**
Light micrograph of thyroid specimen removed at autopsy. Fibrous septa separate areas of epithelium with only a few distinct follicles containing colloid. × 200.
Electron micrograph of thyroid specimen removed at autopsy. Parts of two or three epithelial cells are seen with indistinct plasma membrane probably due to the autolysis. The cytoplasm contains numerous vesicular structures (V) representing a fragmented endoplasmatic reticulum. IC, intercellular space between epithelial cells. L, lysosome-like structures. M, mitochondria. N, nucleus of epithelial cell. Unlabelled arrow, basal membrane. X 11500.
Codaccioni et al. (1980) found that the binding capacity as well as the adenylate cyclase activity were normal in thyroid biopsies obtained from their patient with TSH unresponsiveness, findings compatible with the existence of a defect coupling between TSH receptors and the adenylate cyclase system. Farfel et al. (1980) have described a trait with pseudohypoparathyroidism in which the defect can be localized to the N-component in the membrane of parathyroid cells, interfering with the receptor-adenylate cyclase coupling. Such patients often have additional endocrine abnormalities involving peptide hormones, e.g. hypothyroidism with increased serum levels of TSH. Our patient had normal serum levels of Ca and PO$_4$, and no other endocrine dysfunction was found. Still, the lack of effect of TSH in our patient might be explained as a defect N-component in his thyroid cells.

Normal thyroid uptake of radioiodine in patients with TSH unresponsiveness is not easily explained. The consensus is that TSH mediates all its effects via cyclic AMP, but according to Burke et al. (1971), TSH stimulated $^{131}$I trapping is mediated by another intracellular messenger. Their hypothesis offers an explanation for the normal radioiodine uptake in such patients. However, the present study and that of Codaccioni et al. (1980) have demonstrated that dbc-AMP infusion effectively stimulates uptake of radioactive iodine. We have also documented that this function is not influenced by changing serum levels of TSH. It is therefore unlikely that TSH is responsible for the normal uptake of radioiodine in our patient.

What other factors might then be responsible? Thyroid stimulating antibodies were not demonstrated in patient serum. Prostaglandins activate the adenylate cyclase system in the thyroid cell via another receptor than TSH (Kotani et al. 1975) but still with the same consequences as after TSH stimulation (Zor et al. 1969). It is therefore not likely that prostaglandins were responsible for the normal uptake of radioactive iodine. Furthermore, administration of indomethacin was without effect. Beta$_2$-receptors probably stimulate thyroid cells via adenylate cyclase (Melander et al. 1973), but propranolol administration was without effect in our case, as was administration of the phosphodiesterase inhibitor theophylline in ordinary clinical doses.

The histologic picture appears to be a mixture of hyperplastic thyroid epithelium, inactivity and atrophy with fibrosis consistent with previous observations (Stanbury et al. 1968; Codaccioni et al. 1980). A distention of the endoplasmatic reticulum as demonstrated by Codaccioni et al. (1980) is in accordance with our finding. A similar distension has also been observed in congenital goitre with a defect in the thyroglobulin synthesis (Michel-Bechet et al. 1969). We could not, however, confirm the observation of a thickened basal membrane of the follicles (Codaccioni et al. 1980).

The striking feature was the appearance of a stimulated gland. Our patient had received thyroxine (0.1 mg/day) for more than 100 days when he died. His TSH was suppressed to normal levels. Also, he had not developed a goitre even during years when he had been without treatment. We must therefore assume that some other factor than TSH have stimulated part of the function of the thyroid cell, but we have no explanation as to the nature of this factor.

Acknowledgments

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References


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