THYROIDAL IODOPROTEINS IN PENDRED’S SYNDROME

K. B. DESAI, M. N. MEHTA, M. C. PATEL, L. RAMANNA and R. D. GANATRA

Radiation Medicine Centre, Bio-Medical Group, Bhabha Atomic Research Centre, Tata Memorial Hospital, Parel, Bombay-12, India

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Pendred’s syndrome is characterized by familial goitre, nerve deafness and a partial release of radio-iodine from the thyroid on perchlorate administration. This last was thought to be due to impaired activity of peroxidase enzymes or to some abnormality of receptor proteins where iodination occurs. Burrow, Spaulding, Alexander & Bower (1973) reported that peroxidase activity in such patients is normal but studies on thyroidal iodoproteins have shown variable results (Medeiros-Neto, Nicolau, Kieffer & Ulhoa-Cintra, 1968; Milutinovic et al. 1969).

A 22-year-old deaf-mute woman (N.G.) with a goitre which had progressively increased in size from infancy was euthyroid in all respects: basal metabolic rate, 10·0%; serum cholesterol concn, 174·3 mg/100 ml; tri-iodothyronine (T₃) red blood cell uptake, 14·6%; stable protein-bound iodine levels, 5·7 μg/100 ml. Radioactive iodine uptake by the thyroid was 65·7% at 2 h, 73·2% at 24 h and 73·5% at 48 h. Administration of 1·0 g perchlorate 2 h after an oral dose of ¹³¹I released 22·0% of accumulated radioactivity within 2·5 h. A 48 h thyroid scan showed an enlarged gland with multiple unlabelled areas. The patient’s brother and 2-year-old daughter were deaf, dumb and goitrous from childhood; her sister was normal.

Eight days before operation, 500 μCi Na¹²⁵I were administered orally. Butanol-extractable iodine was normal 24 h afterwards; T₃ and thyroxine (T₄) were detectable in serum by chromatography using butanol:acetic acid:water (I) and butanol:ethanol:ammonia (II) systems. No abnormality was seen in chromatograms of serum and urine. The microscopic appearance of a surgical specimen was that of a non-toxic nodular goitre. Results obtained from tissue taken from an area showing maximum concentration of label and from an unlabelled area were identical.

The tissue was homogenized in sucrose–Tris–magnesium buffer (pH 7·4), and separated into subcellular fractions. A tryptic digest of the supernatant fraction (105 000 g) was examined by paper chromatography using systems I and II (see above). Soluble proteins in the supernatant fraction were studied by column chromatography on Sephadex G-200, salting out procedures, starch gel electrophoresis and immunological reactions. For methods see Desai, Mehta, Patel, Sharma, Ramanna & Ganatra (1974). Sedimentation co-efficients of soluble proteins were determined by the method of Schachman (1957).

The proportion of ¹²⁵I in nuclear, mitochondrial and microsomal fractions was 0·8%, 1·0% and 1·4%, respectively and the remainder was in the supernatant
soluble fraction (i.e. the distribution of radioactivity was normal). Chromatograms of the tryptic hydrolysate of the supernatant soluble fraction showed that 64·4% of the radioactivity was as monoiodotyrosine (MIT), 10·4 % as di-iodotyrosine (DIT), 3·7 % as $T_3 + T_4$ and 2·4 % as $I^-$. Thus the MIT:DIT and iodotyrosine:iodothyronine ratios were raised. Column chromatography of the supernatant proteins on Sephadex G-200 revealed three peaks corresponding to thyroglobulin, albumin and a small unknown peak; 95% of the total radioactivity and 55·65% of the total protein coincided with the thyroglobulin peak. During salting out procedures, almost 85% of the radioactivity was precipitated before the phosphate buffer concentration reached 2·0 mol/l. Starch gel electrophoresis showed one rather long band corresponding to thyroglobulin and one to albumin. Almost all radioactivity was concentrated in the region of the thyroglobulin band. On the Ouchterlony double diffusion plate, the supernatant fraction gave a strong precipitation reaction with rabbit anti-human thyroglobulin serum and rabbit anti-human serum albumin serum. When these reactions were carried out in the test-tube, 85–90% of the radioactivity was precipitated with antithyroglobulin antibodies, but no significant counts were obtained as precipitates with anti-albumin serum although precipitates were visible. These results suggested that the soluble iodoproteins were more or less normal and were similar to those reported by Milutinovic et al. (1969) and Burrow et al. (1973). However, unlike the findings of Medeiros-Neto et al. (1968) the proportion of $^{125}$I associated with particulate proteins was not increased.

Analytical ultracentrifugation of soluble fraction obtained from various areas in the gland revealed three species of proteins (Plate). The fastest sedimenting protein had a sedimentation co-efficient of $15·2-16·8$ S (30·2%), the intermediate was 8·2–11·0 S (15·5%) and the slowest was 3·8–4·2 S (53·4%). This shows that although the thyroglobulin in Pendred's syndrome is identical with normal thyroglobulin in immunological and solubility characteristics, it has a slower sedimentation rate indicating some abnormality in the molecule. Such an abnormality could explain several intrathyroidal defects in Pendred's syndrome such as a partial organification defect (Fraser, Morgans & Trotter, 1960; Milutinovic et al. 1969), a high MIT:DIT ratio, impairment in the capacity of coupling of iodotyrosines to form iodothyronines (Hollander, Prout, Reinhoff, Ruben & Asper, 1964; Milutinovic et al. 1969). Moreover, patients reported to have goitres associated with an abnormal thyroglobulin showed one or more of the above mentioned intrathyroidal defects (Stanbury, Riccabona & Jansen, 1963; Kusakabe, 1972).

REFERENCES


Ultra centrifugal patterns of soluble proteins of the goitre specimens. Direction of migration is from right to left. Two pictures on the top are from a portion of the gland concentrating radioactive iodine while the two pictures on the bottom are from areas showing less concentration of radioactive iodine on the scan.