Extrathyroidal synthesis and biologic action of thyroid receptor antibody (TRAb) in Graves' disease


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Abstract. In a patient with Graves' disease who underwent thyroidectomy with subsequent radiiodine therapy thyroid receptor antibody could be detected by radioligand assay. No thyroid tissue could be detected by $^{131}$I-scintiscanning. Thyroglobulin was repeatedly negative. Biologic activity of this patients serum could be demonstrated in the nude mice bio assay. $^{131}$I-incorporation and secretion of human thyroglobulin could be stimulated by injecting thymusdysplastic nude mice with transplants of thyroid tissue from a patient with Graves' disease with the athyroid patients serum. These results demonstrate evidence for extrathyroidal production and biologic activity of TRAb in vivo.

The accepted pathophysiological concept of Graves' disease as an organ specific autoimmune disease is in accordance with reports characterizing the thyroid as the major source of thyroid receptor antibody (TRAb) production. Measurements of TRAb in thyroid veins (Kendall-Taylor et al. 1984), TRAb production of thyroid lymphocytes (McLachlan et al. 1986) and morphometric evidence for local stimulation of thyroid epithelial cells by lymphocytes (Paschke et al. 1986) are evidence to assume the thyroid gland as the major source of TRAb-production in Graves' disease.

In spite of these findings it is known that the accumulation of lymphoid tissue in the thyroid is only one aspect of a generalized lymphoid hypertrophy in Graves' disease. Besides TRAb-production by thyroid lymphocytes, spontaneous TRAb production by lymphocytes from thyroid lymph nodes and bone marrow could be demonstrated (Weetman et al. 1984). Therefore, the repeated detection of TRAb by radioligand assay in a patient who had undergone thyroidectomy and radiiodine ablation of the remnant thyroid tissue for Graves' disease was reason for us to investigate the biologic activity of this patients thyroid receptor antibody.

Patients and Methods

The 32 year old female patient suffered from Graves' disease with nodular goitre class II and endocrine ophthalmopathy since 1983. She underwent thyroidectomy in 2/84 with subsequent hypothyroidism. $^{131}$I-ablation of remnant thyroid tissue due to progressive ophthalmopathy was done in 5/84. Myxoedema of both legs occurred 1 year later (7/85). In spite of 3 courses of steroid therapy and 2 courses of radiation therapy the ophthalmopathy required surgical decompression in 9/84. Whole body scintiscanning and thyroid scintiscanning in 7/85 one year after thyroidectomy and $^{131}$I-ablation could not demonstrate any circumscribed $^{131}$I-accumulation in the cervical region or any circumscribed $^{131}$I-accumulation elsewhere. Ultrasound in 9/86 revealed two maximal 13 x 12 mm large cervical tissue areas most likely representing scar tissue. After $^{131}$I-ablation thyroglobulin rose to 3.0 ng/ml and microsomal antibodies had their maximum with 280 mU/ml in 6/84. Thereafter thyroglobulin and microsomal antibody were repeatedly negative until now.
After thyroidectomy and radioiodine therapy the following thyroid receptor antibody (TRAb) titres could be determined by radioligand assay (RLA): 8/84: 269 mU/ml, 11/84: 194 mU/ml, 7/85: 445 mU/ml, 2/86: 506 mU/ml. To further elucidate the pathophysiologic action of the TRAb detected by radioligand assay we examined the nature of this TRAb in a biologic assay. Thyroid tissue from a patient with Graves’ disease was obtained during surgery and transplanted to 18 thymus dysplastic nude mice. Four weeks after transplantation the animals received 0.5 ml serum ip. Group A was injected with the serum of this patient under maximal suppressive therapy (TRAb 506 mU/ml, TSH < 0.01 and 0.07 µE/ml after TRH). Controls received normal serum (Group B). Three days after injection of sera each animal received 100 µC: 131I-intraperitonially. Twenty-four h later the 131I-uptake of the removed transplants was measured in a gamma counter. Radio-labelled human thyroglobulin, secreted by the transplants was measured in the nude mice sera by gamma counter after precipitation of human 131I-labelled thyroglobulin with a rabbit anti human thyroglobulin antibody and a second precipitating antibody (Henning, Berlin). Nuclear volume was determined by histometry for 100 nuclei per transplant after fixation with boins solution and paraffine embedding.

Results

131I-uptake of transplants in Group A stimulated with the patients serum was 100 400 cpm/mg of transplant tissue compared to 46 995 cpm/mg of transplant tissue in Group B. Human thyroglobulin secreted by the transplants and measured by cpm was 232 cpm in Group A stimulated with the patients serum and 105 cpm in Group B. 131I-uptake of the mouse thyroids did not show any significant differences between the two groups. Background activity of muscle in Group B was 20 cpm and 41 cpm in Group A. Nuclear volume in Group A was 68.8 µm³ (SEM: 14.3) and 88.7 µm³ (SEM: 17.1) in Group B.

Discussion

Thyroid growth-blocking antibodies have been detected in primary myxoedema (Drexhage et al. 1981). Since the radioligand assay (RLA) does only measure binding and not action of thyroid receptor autoantibodies the biologic action of the TRAb measured by RLA had to be determined. Stimulation of 131I-incorporation as well as stimulation of thyroglobulin secretion could demonstrate activation of thyroid function by the thyroid patients thyroid receptor autoantibody. Absence of thyroid tissue in this patient could be demonstrated by 131I-scintiscanning and repeatedly negative TG determinations (once in hypothyroidism with TSH 96 µE/ml).

There are several investigations which identify the thyroid gland as the major source of thyroid receptor autoantibody production in Graves’ disease. Much greater concentrations of thyroid stimulating antibodies could be measured in the thyroid vein than in the peripheral blood (Kendall-Taylor et al. 1984) and spontaneous production of TSH receptor antibody could be demonstrated with thyroid lymphocytes in culture (McLachlan et al. 1986). The thyroid is also the major site of production for microsomal and thyroglobulin antibody (McLachlan et al. 1983). Furthermore, there is morphometric evidence for stimulation of thyroid epithelial cells in the vicinity of lymphocytes (Paschke et al. 1986).

On the other hand, the generalized lymphoid hypertrophy is a well known sign in Graves’ disease. Spontaneous thyroglobulin and microsomal antibody production could be demonstrated by lymphocytes obtained from Graves’ disease patients cervical lymphnodes, thyroid and bone marrow (Weetman et al. 1984). The exact contribution made by each site cold not be determined. In rats immunized against thyroglobulin the bone marrow appears to be the most important site of thyroglobulin antibody synthesis besides spleen and cervical lymphnodes (Weetman et al. 1982). Furthermore in the BB/W rat the immune response to thyroglobulin does not take place in the thyroid but in the draining lymphnodes (Voorbij et al. 1986).

In this context the functionally active thyroid receptor antibody in this athyroid patient as shown by stimulation of 131I-uptake, thyroglobulin secretion and nuclear volume of human thyroid tissue suggests an important contribution of extrathyroidal antibody production sites in Graves’ disease. Although the existence of a small amount of thyroid tissue can not be completely excluded this eventually remaining thyroid tissue is unlikely to account for the relatively high TSH receptor antibody values in this patient. Therefore extrathyroidal production of TSH receptor antibody in this patient must be assumed. The
demonstration of autoantibody production after elimination of the antigen can be interpreted as persistant of an antigen-specific suppressor defect. It must also be discussed with regard to possible implications for therapeutic strategies. Whether there is any pathophysiological connection between the persistant of TRAb and the still active ophthalmopathy in this patient is a matter of controversal discussion.

References


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