THYROID FUNCTION MODULATES THYMIC ENDOCRINE ACTIVITY

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INTRODUCTION

Several evidences have been accumulated indicating that thyroid function influences the immune system, but the precise mechanism(s) involved remain to be elucidated. Some of the more common thyroid disorders such as Hashimoto's thyroiditis, idiopathic myxedema and Graves' disease are typical organ-specific autoimmune disorders. These conditions have a common basic immunologic disturbance, but differ in the abnormality of thyroid function, which ranges from hypothyroidism to hyperthyroidism. Whether and to what extent the altered thyroid function observed in thyroid autoimmune diseases may affect the immune system in general and/or thyroid immune surveillance is still unclear.

As reviewed in detail elsewhere, in spite of some inconsistencies, the immunological abnormalities observed in animals with experimental hypothyroidism appear to be mediated by impaired thymic function. In keeping with this notion, several recent data obtained in our and other laboratories provided evidence that thyroid function modulates the thymic activity of the thymus.

In the present paper, attention will be focused on the studies showing that thyroid status affects in humans the plasma concentration of the thymic hormone called thymulin. Before reporting these results, we shall briefly review present knowledge on the relationship between the thyroid gland and the thymus.

THYROID FUNCTION AND THYMUS

Both experimental and clinical data suggest that thymic function is not completely autonomous, but appears to be regulated by the neuroendocrine system and, in particular, by thyroid status. There is indirect evidence that the outflow of T cells from the thymus is altered by thyroid dysfunction, as judged from the distribution of T cell subsets and from their functional capacity in peripheral lymphoid organs. In both animals and in man, hyperthyroidism and hypothyroidism are associated with hyper- and hypoplasia of the thymus, respectively.

Thymic function may also be evaluated by measuring plasma concentrations of thymic hormones. It is in fact presently recognized that the thymus produces hormone-like substances, some of which have been chemically characterized, such as thymosin-alpha, thymopoietin and the factor called "Facteur Thymlque Serique" (FTS), more recently called thymulin in its zinc-bound biologically active form (Zn-FTS). No biochemical similarity exists among these different factors, although they are all produced by the epithelial cells of the thymus and circulating plasma levels of such factors reflect the functional state of the thymus. In

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particular, plasma concentrations of these factors decline progressively with advancing age, and this decline parallels the age-dependent involution of the thymus22-24. Since these factors are required to sustain the proliferation and the differentiation of thymocytes to mature T-cells17-19, which are responsible for cell-mediated immunity, the major cause of the age-associated decline in immune capacity might be due to the progressive failure of thymic hormonal production25.

As stated before, previous studies provided evidence that in experimental animals the secretion of thymic factors is modulated by thyroid hormones. In rodents thyroidectomy4,5 and propylthiouracil treatment6 cause reduction of circulating thymulin. Furthermore, the lack of detectable thymulin levels in old mice is reversed by administration of thyroidine (T4), and this reversal is followed by an increased immune efficiency at peripheral level10,26.

In contrast to experimental animal models, until recently no information was available on the relationship between thyroid function and the circulating thymic hormones in humans. To study this problem, we measured thymulin by a rosette inhibition assay in a variety of conditions associated with abnormal thyroid function, as detailed below.

PLASMA THYMULIN LEVELS IN HYPERTHYROID AND HYPOTHYROID PATIENTS

The purpose of this section of the study7 was to measure circulating thymulin concentrations in a series of hypothyroid or hyperthyroid patients before and after correction of the metabolic disturbance by appropriate treatment.

Patients

A total of 64 patients was studied. The hypothyroid group included 28 patients (6 men and 22 women aging 16-76 years) with untreated hypothyroidism due to total thyroidectomy for thyroid carcinoma (n=22), previous radiodine therapy for toxic diffuse goiter (n=3), or idiopathic myxedema (n=3). The hyperthyroid group included 36 patients (16 men and 20 women, aging 26-28 years) with untreated hyperthyroidism due to toxic diffuse goiter (n=18), toxic multinodular goiter (n=12), or toxic adenoma (n=8). Eight hypothyroid (2 men and 6 women) and 9 hyperthyroid (3 men and 6 women) patients were studied after L-T4 or antithyroid drug treatments, respectively. The control group included 88 normal subjects (47 men and 41 women, aging 1 month - 90 years).

In all cases measurements of serum T4 and triiodothyronine (T3) concentrations was done by radioimmunoassay using commercial kits (T4-RIA and T3-RIA, ARIA II, Becton Dickinson S.p.A., Milan, Italy). Anti-thyroglobulin and anti-thyroid microsomal antibodies were determined by passive hemagglutination and immunoradiometric assays27,28.

Thymulin determination

Thymulin activity was measured in plasma samples by the method of Dardenne and Bach29 with minor modifications. Briefly, plasma was filtered through a Centrife Amicon Membrane with a cut-off of 50,000 daltons (Amicon Corp., Lexington, Ma, U.S.A.). Duplicate 50 µl of filtrate or serial dilutions of it made with Hank's solution were mixed with 200 µl of spleen cell suspension from thyroidectomized mice (final suspension 7.5 x 10⁶/ml) and incubated at 37°C for 30 min. After washing, the cells were resuspended in 250 µl of a solution of azathioprine (The Wellcome Foundation Ltd., London, U.K.) at a concentration of 10 µg/ml; this concentration is able to inhibit the formation of rosettes by T lymphocytes but not by non-T spleen cells29. Cell suspensions were then incubated at 37°C for 60 min, after which 250 µl of a sheep red blood cell suspension containing 12.5 x 10⁹/ml added. After a further 5 min incubation at 37°C, cells were centrifuged in the cold at 100 x g for 5 min, resuspended for 5 min by using a rotating mixer, and counted in a hemocytometer chamber. The rosette-forming cells (RFCs) present in 18,000 spleen cells were counted, and values were recorded as RFCs per 1 x 10⁶ cells. The maximal dilution that induced azathioprine sensitivity in 50% of RFCs from thyroidectomized mice was taken as the thymulin titer. This procedure will be indicated thereafter as "conventional method".

To overcome the possible interference of zinc deficiency, occurring either in vivo30 or resulting in vitro from dilution of the plasma filtrate by zinc-free medium, thymulin activity was also measured in duplicate using Hank’s medium containing 200 nM zinc sulfate. This zinc concentration was chosen on the basis of preliminary experiments performed with graded concentrations ranging from 1 pH to 10 pH. This procedure will be indicated in the following paragraph as the "modified assay".