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Different Mitogen-Mediated Beta-Adrenergic Receptor Modulation in Murine T Lymphocytes Depending on the Thyroid Status

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Key Words

β-Adrenergic receptor · Mitogen-mediated proliferation · T lymphocytes · Thyroid hormones

Abstract

Objective: The aim of this work was to analyze β-adrenergic receptor (βAR) regulation of T-lymphocyte proliferation in mice according to different thyroid hormone statuses. ***Methods:*** T cells from eu-, hypo- (by propylthiouracil treatment) and hyperthyroid (by thyroxine, T4 administration) mice were purified and specific radioligand binding assays were performed. The effects of the β-agonist isoproterenol (ISO) on intracellular levels of cyclic AMP (cAMP) were determined. Mitogen-induced T-cell proliferation was measured by [^{3}H]-thymidine incorporation. Finally, protein kinase C (PKC) activity in cytosol and membrane fractions were determined using radiolabelled enzymatic substrates. ***Results:*** A decrease or a non-significant increase in βAR number was found on T lymphocytes from hypo- and hyperthyroid mice compared to euthyroid controls. ISO stimulation of cAMP levels was lower in hypothyroid and higher in hyperthyroid T lymphocytes compared to controls. T-selective mitogen-induced proliferation was increased in T4-treated animals, but decreased in hypothyroid mice. During the peak of proliferation, downregulation of βAR was observed in all animals. However, a higher or a lower decrease was observed in hyper- and hypothyroid T cells, respectively. In parallel, a higher translocation of PKC activity was observed in hyperthyroid cells, and a lower one was found in hypothyroid lymphocytes with respect to controls. ***Conclusions:*** These results indicate that intracellular signals triggered by mitogen activation, namely PKC, would be related to differential βAR downregulation in T lymphocytes depending on the thyroid hormone status, contributing to the distinct proliferative responses found in hypo- or hyperthyroidism compared to the euthyroid state.

Introduction

In addition to regulatory mechanisms that are provided by immune cells, it is known that complex bidirectional interactions between the immune and the nervous systems influence the function of cellular activities associated with both systems [1, 2]. These interactions are not only necessary for maintenance of homeostasis, but play a role in many pathological situations as well [3]. Sympathetic autonomic nervous system control of lymphocyte

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function is supported by several evidences: (1) the presence of direct sympathetic innervation of lymphoid organs [4, 5]; (2) the direct contact of noradrenaline-containing nerve terminals with lymphocytes [3, 6], and (3) at the molecular level, the presence of β-adrenergic receptors (βARs), from the β_2 subtype, functionally coupled to the cyclic AMP (cAMP)-adenylate cyclase (AC) signaling pathway on lymphocytes [2, 3]. Furthermore, a selective distribution of βAR was described on lymphocyte subpopulations with higher receptor density in B than in T cells [2, 3]. However in CD4+ T cells, only β-AR expression was found in Th_1, but not in Th_2 cell subtypes [7]. Also, efficiency of coupling to the effector system was not related to receptor number as T lymphocytes showed higher coupling than B cells [2]. These effects would probably indicate a differential modulatory function of βAR on distinct lymphoid subsets.

Several lines of evidence suggest that βAR activation, leading to intracellular cAMP increase, regulate growth, proliferation and apoptosis of a variety of cells, including lymphocytes [8]. In fact, noradrenaline, βAR agonists or cAMP-elevating agents inhibit T-cell proliferation induced by mitogens in vitro [9, 10], which is mediated through the increment of intracellular levels of cAMP [2, 3, 10]. Additionally, it was also demonstrated that β-agonists operating via the AC pathway or cell-permeable cAMP analogues inhibit T-cell activation by interfering with the phosphatidylinositol turnover [11].

Absence of functional βAR was demonstrated on different hyperproliferative T- and B-lymphoid cell lines [12]. Also, a mutant variant of the S49 T lymphosarcoma cell line showing absence of functional βARs displayed a higher proliferation rate than the well-known βAR-rich wild-type S49 cell line [13]. In the BW5147 T lymphoma cell line, which shows a reduced number of βAR sites, isoproterenol (ISO) stimulation led to an increase in both cell proliferation and protein kinase C (PKC) activity which was specifically blocked by the β-antagonist propranolol [14].

Conversely, modulation of the βAR number was demonstrated after in vitro or in vivo T- and B-lymphocyte activation. A decreased βAR number was found in concanavalin A (ConA)-stimulated murine T lymphocytes at the peak of proliferation, which was accompanied by a diminished response to specific agonist stimulation and impaired by the previous blockade of proliferative activity by tyrosine kinase or PKC inhibitors [15]. These findings are supported by the demonstration that mitogen-induced activation of T cells results in a PKC-dependent increase in the expression of receptor-associated kinases [16]. Also, after in vivo antigenic challenge, a sharp decrease in the βAR number and in the β_2AR mRNA concentration was described in rat thymus [17].

On the other hand, regulation of immune responses by thyroid hormones has been described [18]. Data obtained either in animals with experimentally induced hyper- or hypothyroidism or in humans with altered thyroid function showed alterations in immune responses. Although with some controversy, in general, the hyperthyroid state appeared to upregulate while hypothyroidism seemed to downregulate several humoral and cellular immune responses [19–21]. Also, thyroid hormones can regulate the βAR number in several tissues [22–25].

Based on these results, the aim of the present work was to analyze the expression of βAR on T lymphocytes from mice with distinct thyroid statuses and their possible involvement in cell proliferation upon selective mitogen stimulation. In this study, despite an up- and downregulation of the βAR number and function in T lymphocytes from hyper- and hypothyroid mice, respectively, an inverse effect was found on mitogen-induced stimulation. However, during the peak of T lymphocyte proliferation, a higher reduction in βAR sites accompanied by a higher translocation of PKC was observed in the hyperthyroid state compared to controls. The inverse situation took place in T cells from hypothyroid mice. The possibility that sympathetic control of lymphocyte activity could be modulated by the thyroid state is also discussed.

Materials and Methods

Mice

Inbred BALB/c (H-2^d) female mice were obtained from the 'Instituto de Tecnología Agropecuaria de la República Argentina'. All animals were used at the age of 60–70 days.

In vivo Thyroid Hormones and Antithyroid Agent Treatments

Thyroxine Hormone (T4) Treatment. BALB/c mice (n = 40) received an intraperitoneal injection of 40 μg thyroxine (T4; Sigma, St. Louis, Mo., USA) dissolved in 0.1 *N* NaOH and diluted 1:10 with phosphate-buffered saline (pH 7.2, Millipore, Billerica, Mass., USA, filtered) 5 times per week for 1 month. Mice injected with the vehicle alone were used as controls.

Propylthiouracil (PTU) Treatment. To promote low circulating levels of thyroid hormones in BALB/c mice (n = 80), PTU was given in the drinking water (0.5 mg/ml) for 18 days as previously described [19]. The daily ingested amount of PTU was approximately 6 mg/100 g body weight (BW)/day.

PTU Combined with T3 Treatment. Half of the animals treated with PTU also received 20 μg T3/100 g BW/day (dissolved in the same vehicle as used for thyroxine) intraperitoneally for the last 6 days of treatment. Control animals received the vehicle of the hormone alone.

Cell Suspensions and Culture Conditions

Lymphoid cell suspensions from BALB/c inbred mice lymph nodes, as well as nylon-wool-purified T cells, were prepared aseptically as described before [26]. Cells were cultured at a concentration of 1×10^6 cells/ml, in RPMI 1640 medium (Gibco) supplemented with 10% heat-inactivated fetal calf serum, 2 m*M* glutamine and antibiotics, alone or in the presence of optimal mitogenic concentrations of concanavalin A (ConA, 2 μg/ml) or phytohemagglutinin (PHA, 25 μg/ml). Both mitogens were from Sigma. All cultures were incubated for 3 days, as microcultures settled at a final volume of 0.2 ml in 96-well flat-bottom microtiter plates or as macrocultures in T-25 culture flasks (Corning, N.Y., USA).

Proliferation Assays

Proliferation was evaluated by 16 h lasting pulses of [^{3}H]-thymidine ([^{3}H]TdR, New England Nuclear, Boston, Mass., USA, 25 Ci/mmol) in both microcultures and 0.2-ml aliquots from the macrocultures as described before [15]. Results from dpm values were expressed as stimulation indexes (SI) calculated as the ratio between dpm values in experimental cultures and dpm from control values obtained with unstimulated cells.

[^{125}I]Cyanopindolol ([^{125}I]CYP) Binding to Intact Cells

Cells (2–3 $\times$ 10^6 cells/tube), from different experimental conditions as indicated in the Results, were incubated with [^{125}I]CYP (New England Nuclear, 2,200 Ci/mmol) solutions, 1–300 p*M* radioligand concentrations in 50 m*M* phosphate buffer, made isotonic with NaCl, 10 m*M* $MgCl_2$ and 10^{-4} *M* phentolamine. After a 30-min incubation at 30°C, samples were filtered through Whatman GF/C filters (Whatman, Brentford, UK) as indicated previously [12, 15], and filters were counted in a Wallac counter. Total binding curves were analyzed using the computer program LIGAND as already described [12, 15]. The non-specific binding parameter fitted by LIGAND from the total binding curves did not differ from those determined experimentally using 1 μ*M* l-propranolol, as demonstrated by data from tubes containing the β-antagonist that were included in all binding assays. It is worth noting that non-specific binding was always $\leq$20% of total binding. B_{max} values expressed as sites/cell were calculated from B_{max} p*M* values determined by LIGAND analysis, according to:

$$B_{max}\,(\text{sites/cell}) = \frac{B_{max}\,(\times 10^{-12}\,M) \times Vi\,(\text{ml}) \times 6.023 \times 10^{23}\,\text{sites/mol}}{1{,}000\,(\text{ml/l}) \times \text{number of cells/assay tube}}$$

where Vi = incubation volume.

cAMP Production in Intact Cells

Cells (1×10^7 cells/ml) in RPMI 1640 were incubated with 3 isobutyl-l-methylxanthine (1 m*M*) at 37°C for 20 min and were then left alone (basal value) or were incubated 3 min with 10 μ*M* ISO. At the end of the incubation time, 2 ml of chilled ethanol were added. The cells were then homogenized and centrifuged at 3,500 *g* at 4°C for 15 min. The supernatants were collected and pellets were re-homogenized in 1 ml of ethanol:water (2:1) and centrifuged. Supernatants were joined and evaporated at 55°C under N_2 stream. The cyclic nucleotide present in the residue was dissolved in 0.5 ml of assay buffer (50 m*M* Tris-HCl, pH = 7.4, 8 m*M* theophylline, 6 m*M* 2-mercaptoethanol and 1 m*M* EDTA) and stored at –20°C until the assay was carried out. Aliquots of 50 μl were taken for nucleotide determination using a previously described procedure [15].

Table 1. Serum levels of thyroid hormones in mice after hormone or anti-thyroid drug treatment

Treatment	T3, ng/dl	T4, μg/dl
None	78.5 ± 7.2	3.7 ± 0.4
T4	834.8 ± 20.4*	69.2 ± 6.0*
PTU	45.3 ± 4.1*	1.7 ± 0.2*
PTU+T3	106.6 ± 20.1*	1.2 ± 0.3*

* $p < 0.01$ vs. control. BALB/c mice were treated with thyroxine (T4), PTU or T3 during PTU treatment (PTU+T3) or with vehicle alone (none, control animals) as indicated in the Materials and Methods. Serum levels of T3 and T4 were determined by radioimmunoassays using commercial kits. Results are the mean ± SEM of n = 40 for each group.

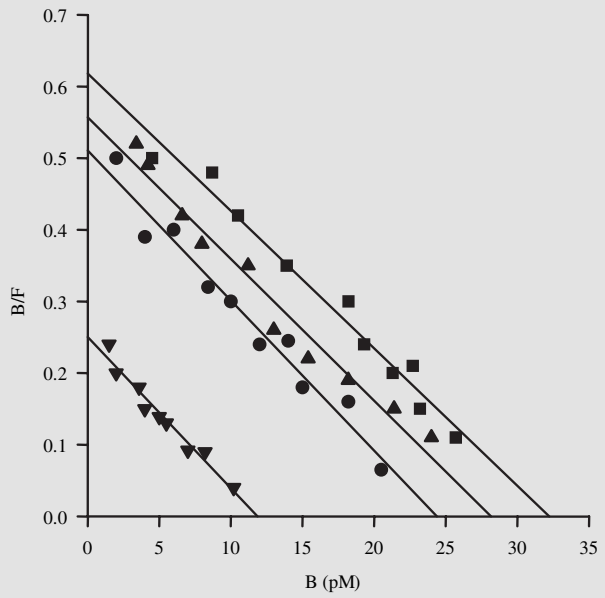
Protein Kinase C (PKC) Determination

Lymph node cells from mice with different thyroid hormone statuses were incubated for 72 h in the presence of ConA (2 μg/ml) and were immediately frozen at a concentration of 1×10^7 cells/sample in liquid N_2. PKC was purified from subcellular fractions as previously described [27]. PKC activity was assayed by measuring the incorporation of ^{32}P from [γ-^{32}P]-ATP into histone H_1 [27]. Incubations were conducted in a final volume of 85 μl at 30°C for 30 min. In the final concentrations, the assay mixture contained 25 m*M* ATP (0.4 mCi), 10 m*M* Mg acetate, 5 m*M* β-mercaptoethanol, 50 mg of histone H_1, 20 m*M* HEPES, pH = 7.5, and, unless otherwise indicated, 0.2 m*M* $CaCl_2$ and 10 mg/ml of phosphatidylserine vesicles. The incorporation of [^{32}P]-phosphate into histone was linear for at least 30 min. The reaction was stopped by the addition of 2 ml of ice-cold 5% trichloroacetic acid with 10 m*M* H_3PO_4. The radioactivity retained on GF/C glass fiber filters after filtration was determined by counting the filters in 2 ml of scintillation fluid. PKC activity was determined after subtracting the ^{32}P incorporation in the absence of Ca^{2+} and phospholipids. Data were expressed as picomoles of phosphate incorporated into the substrate per min and per 10^7 cells (pmol/min/10^7 cells). The selective PKC substrate peptide, MBP (4–14) [28] (Gibco BRL, Life Technologies, Gaithersburg, Md., USA) was also used to measure PKC activity purified from subcellular lymphoid fractions, following the instructions of the PKC assay system of Gibco. PKC specificity was confirmed by means of the PKC pseudosubstrate inhibitor peptide PKC (19–36) provided by Gibco.

Results

Effect of the Thyroid Status on in vivo Modulation and βAR Expression and Function on T Lymphocytes

To analyze the effect of in vivo modulation of the thyroid axis on T-lymphocyte βAR expression, binding assays for the β-adrenergic specific radioligand [^{125}I]-CYP were performed on purified T cells from eu-, hypo- and



Treatment	[^{125}I]-CYP Binding	
	Kd (p M)	Bmax (sites/cell)
None	47.8 ± 3.7	881 ± 56
T4	48.4 ± 4.5	1162 ± 98
PTU	47.4 ± 4.0	429 ± 35*
PTU + T3	50.6 ± 5.2	1018 ± 85

Fig. 1. βAR expression on T lymphocytes from animals with different thyroid hormone statuses. Specific β-adrenergic radioligand [^{125}I]-CYP binding was performed on T lymphocytes (1×10^6 cells/tube) from normal (none, ●), T4 (■)-, PTU (▼)- or PTU+T3 (▲)-treated mice, incubated with increasing concentrations (1–300 p*M*) of the radioligand. Total binding curves were analyzed by the computer program LIGAND. B_{max} and Kd values are the mean of 4 experiments performed in duplicate using a pool of 4 animals for each group per experiment and are depicted in the table adjoined below. * $p < 0.01$ vs. normal .

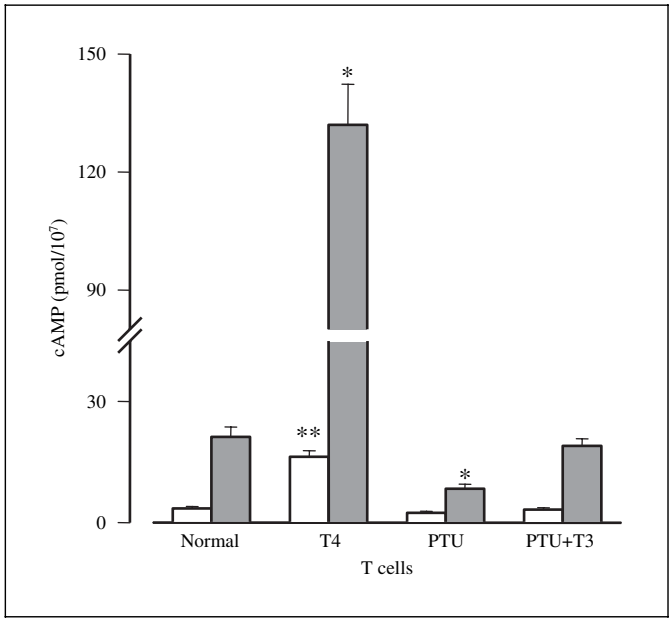


Fig. 2. ISO-induced stimulation of cAMP levels in T lymphocytes from eu-, hypo- and hyperthyroid mice. T lymphocytes purified from normal, T4-treated (T4) or PTU-treated (PTU) mice or hypothyroid (PTU+T3) mice receiving T3 replacement therapy were incubated for 3 min alone (white bars) or in the presence of 10 μ*M* ISO (gray bars). Intracellular cAMP levels were measured as indicated in the Materials and Methods. Results are the mean ± SEM of 4 experiments performed in triplicate. ** $p < 0.01$ vs. ISO-stimulated normal cells, * $p < 0.01$ vs. normal values.

hyperthyroid mice. As shown in table 1 and figure 1, treatment of animals with the anti-thyroid drug PTU significantly diminished both serum levels of T3 and T4 hormones and the βAR number in T lymphocytes compared to control euthyroid animals. Reversion of PTU treatment by T3 administration raised T3 but not T4 serum levels and restored the βAR decrease in T lymphocytes. Moreover, thyroxine treatment despite augmenting T3 and T4 serum levels (table 1) induced a slight, but non-significant, increment in β-adrenergic binding sites in T lymphocytes (fig. 1). No modifications in Kd values were observed among βAR of T lymphocytes from all animals tested.

To analyze βAR coupling to the AC system in T lymphocytes from eu-, hypo- or hyperthyroid mice, cAMP levels in response to the β-agonist ISO were measured. Figure 2 shows that after hypothyroid treatment diminished ISO-stimulated cAMP levels were obtained, an effect that was impaired by the reversal of the hypothyroid condition in vivo. Despite the non-significant increase in T-lymphocyte βAR from T4-treated mice, higher basal as well as ISO-stimulated levels of cAMP were obtained compared to euthyroid normal animals.

Effects of the Thyroid Status on T-Lymphocyte Mitogen-Induced Proliferation

As βAR expression and function was demonstrated to exert a neuroendocrine control of T lymphocyte proliferation, selective T-cell mitogen-mediated proliferation of lymph node cells from mice with in vivo modulation of

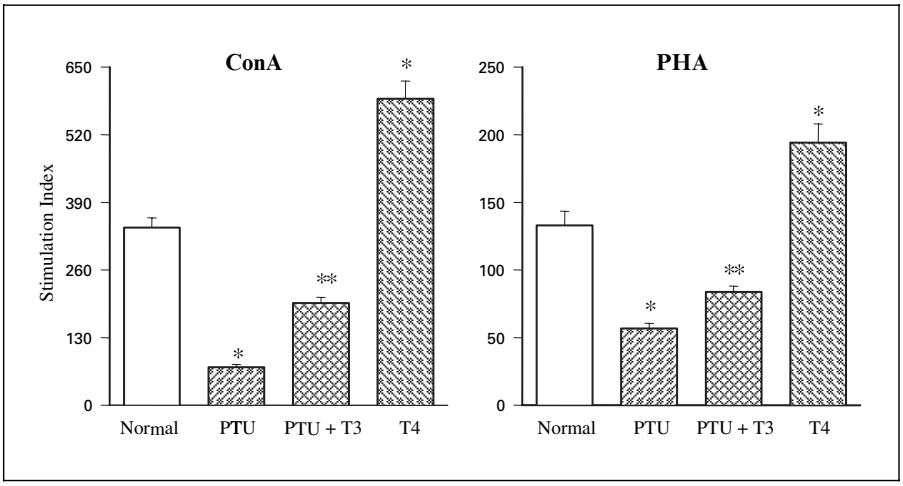


Fig. 3. T-selective mitogenic stimulation of lymphocytes from animals with in vivo modulation of the thyroid status. Lymph node cells were obtained from control (normal) or T4-, PTU- or PTU+T3-treated animals. Cells (1×10^6 cells/ml) were cultured as described in the absence or presence of the following T-selective mitogens: ConA (2 μg/ml) or PHA (25 μg/ml) for 72 h. Proliferation was evaluated by [^{3}H]-thymidine incorporation, and stimulation indexes were calculated as the ratio between dpm values in experimental cultures and dpm from control values of unstimulated cells. Results are the mean ± SEM of n = 4. * $p < 0.01$ vs. corresponding normal values, ** $p < 0.05$ vs. corresponding PTU values.

Table 2. Expression of βAR in ConA-stimulated T lymphocytes from mice with in vivo modulation of the thyroid hormone status

Treatment	[^{125}I]-CYP binding	
	B_{max}, sites/cell[a]	decrease in B_{max}[b]
None	468 ± 40	46.8 ± 5.3
T4	349 ± 38	70.0 ± 6.2*
PTU	335 ± 32	18.7 ± 3.0*

* $p < 0.05$ vs. the decrease in untreated mice. Mice were treated as described. Lymph node lymphocytes from T4-, PTU- or vehicle (none)-treated animals were cultured alone or in the presence of 2 μg/ml of ConA for 3 days as indicated in the Materials and Methods.

[a] [^{125}I]-CYP binding was performed on cultured cells as indicated before and B_{max} values were obtained using LIGAND. Results are the mean ± SEM of 4 experiments performed in duplicate for each group.

[b] Values represent the mean ± SEM of the percent decrease in B_{max} values obtained in the presence of ConA compared to the corresponding values obtained in the absence of ConA.

the thyroid hormone status was assessed. As shown in figure 3, modification of the thyroid status altered both ConA- and PHA-mediated lymph node cell proliferation, with PTU treatment decreasing, and T4 treatment increasing T lymphocyte proliferation, respectively, compared to control animals. Reversion of the hypothyroid state by T3 also restored the PTU-induced decrease in T-cell growth.

Regulation of βAR Expression by Mitogenic Treatment and PKC Activity in Lymphocytes from Mice with Distinct Thyroid Hormone Serum Levels

We have previously reported on the downregulation of βAR in T lymphocytes during the peak of mitogenic ConA stimulation [15]. As βAR expression and function in T lymphocytes from hypo- and hyperthyroid mice seem to be directly related to mitogen-induced proliferation of corresponding T cells, fluctuations in the βAR number upon mitogen stimulation were studied. Table 2 shows the downregulation of βAR binding sites after 3 days of culture with ConA on T lymphocytes from eu-, hypo- and hyperthyroid mice. However, the percent decrease was significantly higher in hyper- and lower in hypothyroid lymphocytes, respectively, compared to euthyroid cells. Also, hyperthyroid T lymphocytes depicted high levels of PKC activity in cytosol and membrane fractions, with a higher percentage of membrane-bound enzymatic activity compared to controls. In contrast, in hypothyroid T lymphocytes, low levels of PKC activity were found (fig. 3).

Discussion

Complex bidirectional interactions between the cells of the immune and the neuroendocrine system contribute to regulatory mechanisms that influence the function of cellular activities associated with both systems. In the present work, we investigated if thyroid hormone regulation of T-lymphocyte growth would be related to alterations in βAR expression and function.

Measurements of βAR-binding sites in T lymphocytes from PTU-treated mice, displaying low serum levels of T3 and T4 hormones, showed a decreased number of receptors, while a non-significant increase was observed in T cells from T4-treated animals showing high serum levels of thyroid hormones. Reversion of PTU treatment by T3 administration restored both βAR number and T3 serum levels, but T4 levels were still under basal values. It is worth noting that T3 reversion of anti-thyroid PTU treatment was demonstrated to maintain low levels of T4 by other authors using similar drug administration schedules [29, 30]. Furthermore, lower ISO-mediated stimulation of lymphoid cAMP levels were found in hypothyroid animals that were restored by T3 treatment, while higher basal and β-agonist-induced cAMP levels were observed in hyperthyroid T lymphocytes. The agonist response is probably related to βAR expression in hypothyroid lymphocytes. Concerning the values obtained in lymphocytes from T4-treated mice, basal increase in AC activity was also described in mononuclear cells from hyperthyroid patients [31]. However, agonist-induced stimulation of cAMP might be related to a high non-significant number of βAR or to a more efficient coupling to the effector system.

Some previous reports described unaltered βAR number in lymphocytes purified by density gradient centrifugation from hyperthyroid humans and rats [32–34]. It is worth noting that in the study performed in rats, treatment consisted of a daily subcutaneous injection of T3 for 3 days only, and no measurement of serum thyroid hormone levels confirming the thyroid status were shown. Additionally, in humans, Andersson et al. [31] found increases in the number of βAR and catecholamine-mediated AC activity in mononuclear purified leukocytes from hyperthyroid patients compared to those obtained after restoration of the euthyroid state by antithyroid treatment. Also, a decrease in human lymphocyte βAR density and T3, but not T4, serum levels in thyroidectomized patients was demonstrated [35], thus indicating that only the decrease in T3 levels accounted for the βAR fall [35, 36].

Despite the reduced number of βAR expressed in T lymphocytes from PTU-treated animals, selective T mitogen stimulation of hypothyroid lymph node cells was found to induce a diminished proliferative response, while a higher response to both ConA and PHA was found in cells from T4-treated mice. Similarly, decreases in PHA- or ConA-induced proliferation were reported in splenic or peripheral blood lymphocytes from hypothyroid animals [18, 21]. However, contradictory results exist in the literature on the effect of in vivo thyroid hormone administration on the proliferative responses of lymphocytes to T-selective mitogens, with different studies showing either enhancing or suppressing effects on cell proliferation [21, 37]. T lymphocyte responses in mixed lymphocyte reactions were found decreased and enhanced in cells from hypothyroid and hyperthyroid mice, respectively [19]. These effects are apparently not related to lymphoid βAR expression modified by the thyroid status, as βAR were demonstrated to exert negative control of lymphocyte proliferation [10, 11, 13], and in hypo- or hyperthyroid lymphocytes a direct relationship between the βAR number and cell growth was found. As we have previously described the downregulation of T-lymphocyte βAR during the peak of mitogen stimulation [15], fluctuations in the βAR number after 3 days of culture with ConA were analyzed. The mitogen-induced decrease in the βAR number was increased and decreased in hyper- and hypothyroid T lymphocytes, respectively, thus indicating that the magnitude of the βAR decrease would be related to the different proliferative patterns of lymphocytes from T4- or PTU-treated animals.

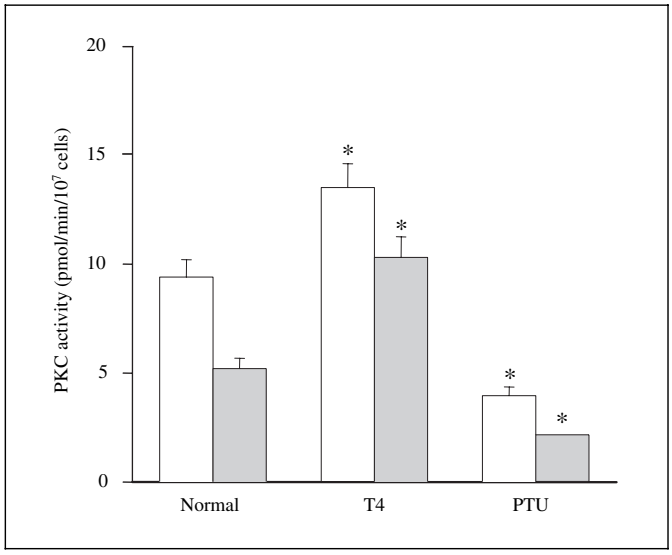


Fig. 4. PKC activity in T lymphocytes from eu-, hypo- and hyperthyroid mice after 72 h of culture in the presence of ConA. PKC was purified from subcellular cytosol (white bars) and membrane (gray bars) fractions from normal and T4- or PTU-treated murine T lymphocytes and assayed on the specific PKC peptide MBP [4-14] as substrate. It is worth noting that similar values (data not shown) were obtained when using histone H_1 as substrate. Results are the mean ± SEM of 3 experiments performed in duplicate. * $p < 0.01$ vs. corresponding normal values.

Downregulation of β_2AR has been demonstrated as a consequence of several intracellular signals, including PKC activation [38]. Analysis of PKC activity on ConA-stimulated lymphocytes from hyper- and hypothyroid mice showed higher and lower cytosolic and membrane enzymatic activity, respectively. Furthermore, the percentage of membrane-associated PKC activity was higher (≈43%) in T4-treated animals and similar to euthyroid controls in PTU-treated mice (≈36%). However, lower membrane-associated PKC activity was found in T lymphocytes from hypothyroid mice compared to control animals. These results suggest that mitogen activation of PKC would account for differential regulation of βAR expression in eu-, hyper- and hypothyroid animals thus contributing to the distinct proliferative responses of their lymph node cells. In fact, PKC-dependent increases in βAR kinases, both at protein and mRNA levels, were found after 48 h mitogenic stimulation of T lymphocytes [16, 39]. Because βAR kinases regulate the levels of βAR [40], their activation may account for βAR downregulation. Moreover, thyroid hormones were demonstrated to increase PKC expression or activity in several tissues [41–43], while hypothyroidism was demonstrated to decrease PKC activity in both membrane and cytosol in rat liver [44].

Although the direct effect of thyroid hormones on T-lymphocyte βAR expression is still under study, our results indicate that the cross-talk between intracellular signals triggered by neuroendocrine modulation of lymphocyte function may play a contributory role in their actions on T-lymphocyte proliferation.

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