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Role of thyrotropin in metabolism of thyroid hormones in nonthyroidal tissues

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Abstract

T_4 conversion into T_3 in peripheral tissues is the major source of circulating T_3. However, the exact mechanism of this process is ill defined. Several in vitro studies have demonstrated that thyrotropin facilitates deiodination of T_4 into T_3 in liver and kidneys. However, there is a paucity of in vitro studies confirming this activity of thyrotropin. Therefore, this study was conducted to examine the influence of thyrotropin on thyroid hormone metabolism in nonthyroidal tissues. We assessed T_4, T_3, reverse T_3 (rT_3), and T_3 resin uptake (T_3RU) responses up to 12 hours at intervals of 4 hours in 6 thyroidectomized female mongrel dogs rendered euthyroid with LT_4 replacement therapy before and after subcutaneous (SC) administration of bovine thyrotropin (5 U) on one day and normal saline (0.5 mL) on another in a randomized sequence between 08:00 and 09:00 AM. Euthyroid state after LT_4 replacement was confirmed before thyrotropin administration. Serum T_4, T_3, rT_3, and T_3RU all remained unaltered after SC administration of normal saline. No significant alteration was noted in serum T_3RU values on SC administration of thyrotropin. However, serum T_3 rose progressively reaching a peak at 12 hours with simultaneous declines being noted in both serum T_4 and rT_3 concentrations ($P < .05$ vs prethyrotropin values for all determinations). The changes after SC administration were significantly different ($P < .001$) in comparison to those noted on SC administration of normal saline. Thyrotropin may promote both the conversion of T_4 to T_3 and metabolism of rT_3 into T_2 in nonthyroidal tissues via enhancement of the same monodeionase.

1. Introduction

Several in vitro studies have documented that thyrotropin facilitates deiodination of T_4 into T_3 in several peripheral tissues including both the hepatic and renal parenchyma [1-3]. However, in intact humans or animals, this activity of thyrotropin on T_4 monodeiodination in nonthyroidal tissues is not well documented. We have previously demonstrated a positive correlation between serum thyrotropin concentration and T_3/T_4 ratio, a reliable index of T_3 generation from T_4 in nonthyroidal tissue, in subjects with hypothyroidism of both the primary and central type [4]. This finding may indicate the role of thyrotropin in facilitating T_3 generation from T_4 in nonthyroidal tissues especially in the absence of adequate functioning thyroid tissue. Therefore, we examined the influence of exogenous thyrotropin administration of serum T_4, T_3, reverse T_3 (rT_3), and T_3 resin uptake (T_3RU) values in thyroidectomized dogs rendered euthyroid with LT_4 replacement therapy. Euthyroid thyroidectomized dogs were studied to eliminate the contribution of the thyroid gland itself to circulating thyroid hormone concentrations.

2. Materials and methods

The study protocol was approved by both the research and development committee and the animal research subcommittee at the medical center. Six healthy female mongrel dogs were used. Euthyroid status of these dogs was established by determination of serum T_4, T_3RU, and thyrotropin levels. The dogs underwent near total thyroidectomy with preservation of parathyroid glands after administration of general anesthesia. LT_4 replacement therapy, 1.5 μg/kg (body weight [BW]), was initiated on the next day after the thyroidectomy. The dose of LT_4 was adjusted to attain and maintain serum T_4, T_3RU, and thyrotropin levels within the range of values noted before thyroidectomy. The daily dose of LT_4 was then continued

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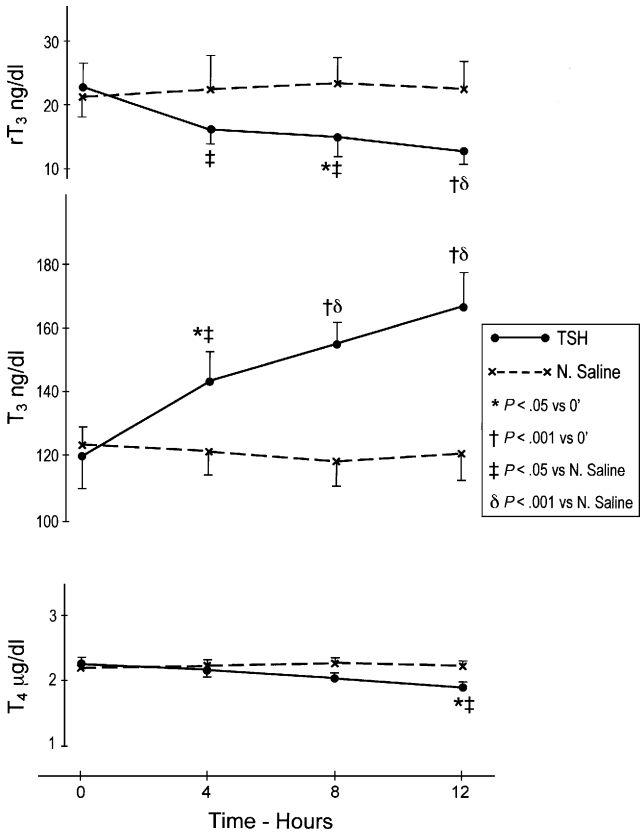

Fig. 1. Serum T_4, T_3, and rT_3 before and after SC administration of either bovine thyrotropin (5 U) or normal saline (0.5 mL) between 08:00 and 09:00 AM in 6 thyroidectomized female mongrel dogs rendered euthyroid with LT_4 replacement therapy.

for the next 3 months. The dogs were caged individually and fed ad libitum Purina Dog Chow (Nestle Purina Pet Care, St Louis, MO). Experimental procedure involving subcutaneous (SC) administration of thyrotropin or normal saline was conducted only after attainment and maintenance of euthyroid eucalcemic state documented by normal serum concentrations of T_4, T_3, and T_3RU. The 2 procedures were conducted on different days in a randomized sequence. On the day of the procedure, bovine thyrotropin (5 U) or normal saline (0.5 mL) was administered subcutaneously between 08:00 and 09:00 AM (Fig. 1). Blood (6 mL) was then drawn from an antecubital vein before and again at 4, 8, and 12 hours after administration of either bovine thyrotropin or normal saline. The blood samples were immediately centrifuged at 20°C, and serum was separated and stored at −4°C for later determination of T_4, T_3, rT_3, T_3RU, and thyrotropin levels using well-established commercial kits. Coefficients of variations for both interassay and intra-assay determinations for all parameters were 7% to 12% in our laboratory. Comparisons were conducted between pre- and postthyrotropin serum concentrations of all parameters by statistical analyses using Student t test and analyses of variance. All data are reported as mean ± SEM.

Table 1
Serum T_4, T_3, T_3RU, and thyrotropin concentrations before thyroidectomy and after LT_4 replacement, 2.7 ± 0.2 µg/kg BW, in 6 female mongrel dogs

	Prethyroidectomy	Post−LT4 replacement
T4 (µg/dL)	2.3 ± 0.2	2.4 ± 0.4
T3 (ng/dL)	127 ± 10	123 ± 9
rT_3 (ng/dL)	22 ± 4	24 ± 5
T_3RU (%)	57.3 ± 0.8	58.4 ± 0.8
Thyrotropin (mU/L)	1.8 ± 0.3	1.6 ± 0.4
Calcium (mg/dL)	6.8 ± 0.3	6.4 ± 0.3

Table 2
Change (Δ) in serum level of T_4, T_3, rT_3, and T_3RU after SC administration of thyrotropin (5 U) and normal saline (1 mL) in 6 female mongrel thyroidectomized dogs rendered euthyroid with LT_4 replacement therapy

	Thyrotropin	Normal saline
ΔT_4 (µg/dL)	−0.36 ± 0.08*	0.05 ± 0.01
ΔT_3 (ng/dL)	49 ± 7*	3 ± 1
ΔrT_3 (ng/dL)	−10 ± 3*	−1 ± 1
ΔT_3RU (%)	1.1 ± 0.04	0.9 ± 0.03

* $P < .001$ vs. normal saline.

3. Results

Daily LT_4 dose required to maintain euthyroid state as confirmed by the laboratory testing was 2.7 ± 0.2 µg/kg BW. Body weight as well as serum T_4, T_3, rT_3 thyrotropin, T_3RU, and calcium levels noted at the time before procedures were not significantly different in comparison to those noted before thyroidectomy (Table 1). Serum thyrotropin concentration progressively rose after SC thyrotropin administration reaching a peak at 4 hours (45 ± 11 mU/L) followed by a decline, although not attaining baseline concentration by 12 hours (4 ± 1 mU/L), whereas it remained unchanged after SC normal saline administration (peak level, 1.7 ± 0.2 mU/L). Serum T_3 concentration rose progressively reaching a peak at 12 hours, whereas serum T_4 and rT_3 levels declined attaining their nadirs at 12 hours after SC administration of thyrotropin with no significant change in T_3RU. After SC administration of saline, no significant changes were noted in serum levels of T4, T3, rT3, and T_3RU. Finally, changes in serum T4, T3, and rT3 levels from baseline were significantly different after SC administration of thyrotropin as compared with those noted after SC normal saline administration, whereas the change in T_3RU values was not significantly different (Table 2).

4. Discussion

The effect of thyrotropin on synthesis and release of T_4 and T_3 by the thyroid gland is well established [5,6]. Moreover, the role of T_3 as the main biologically active thyroid hormone is also well documented [5]. Finally, almost 80% of circulatory T3 is generated by conversion of T_4 in nonthyroidal tissues in healthy subjects [5]. Therefore, it is conceivable that thyrotropin may also be responsible for promoting the final step in generation of the biologically

active T_3 in peripheral tissues. This study demonstrates that SC thyrotropin administration induced a progressive rise in serum T_3 levels with simultaneous declines in serum T_4 and rT_3 concentrations in thyroidectomized dogs rendered euthyroid by oral LT_4 replacement therapy.

These thyroid hormone alterations after SC thyrotropin administration may be explained by various physiologic mechanisms. The rise in serum T_3 may be attributed to its release by the residual thyroid tissue, after thyroidectomy, by exogenous thyrotropin administration. However, the lowering of both serum T_4 and rT_3 levels cannot be explained by this mechanism because thyrotropin administration is likely to induce a rise in serum T_4 secondary to enhanced release by the remnant thyroid tissue, and the contribution to circulating rT_3 even by the normal thyroid gland is minimal or none. The likelihood of thyroid gland being a major contributor to these thyroid hormone changes in response to thyrotropin administration is even more remote in these thyroidectomized dogs because of the suppression of this minimal remnant thyroid tissue by exogenous LT_4 administration. Alternatively, altered clearance of these thyroid hormones induced by thyrotropin may be responsible for the changes in their levels. However, this mechanism seems improbable because thyrotropin is unlikely to influence the clearance of these hormones in opposite directions, that is, lowering the clearance of T_3 while raising the clearance of T_4 and rT_3. Moreover, such an effect of thyrotropin on clearance of these hormones has not been documented. Finally, these thyroid hormone alterations after thyrotropin administration can be explained by a single mechanism of enhanced activity of the same deiodinase, promoting conversion of T_4 into T_3 and rT_3 into diiodotyrosine (T_2) in peripheral extrathyroidal tissues as documented in several previous reports [1-3,7-10]. Moreover, our finding is consistent with other studies that demonstrated the influence of thyrotropin in facilitating conversion of T_4 to T_3 in hepatic and renal parenchyma in vitro studies as well as in intact dogs [1-3]. A distinct significant correlation between thyrotropin level on one hand and T_3/T_4 ratio, a reliable index of T_3 generation from T_4 in nonthyroidal tissue on the other, documented in subjects with both primary and central hypothyroidism may add further credence to this hypothesis [4]. It is therefore likely that thyrotropin may regulate the generation of T_3, the major biologic active thyroid hormone from T_4 in nonthyroidal tissues especially in the absence of adequately functioning thyroidal tissue, in addition to its effect on their synthesis and release by the thyroid gland.

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