

## Peripheral Tissue Mechanism for Maintenance of Serum Triiodothyronine Values in a Thyroxine-deficient State in Man

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**A**bstract. The present study was undertaken to define the source of endogenous triiodothyronine (T3) production responsible for maintaining serum T3 levels in euthyroid subjects with depressed serum thyroxine (T4) values. After withdrawal from 4 wk of exogenous T3 administration, a 22% decline in serum T3 values (from  $129 \pm 6$  to  $99 \pm 4$  ng/dl) was observed in six euthyroid subjects, despite a twofold reduction in serum T4 concentrations (from  $7.5 \pm 0.5$  to  $3.2 \pm 0.5$   $\mu$ g/dl). This was accompanied by a nearly twofold increase in serum T3/T4 ratio values ( $17 \pm 1$  to  $29 \pm 6$ ) but no significant alteration in reverse T3/T4 ratio values. This phenomenon did not appear to be thyroid stimulating hormone (TSH) dependent, since base-line serum TSH values were subnormal. Nor was it dependent on changes in thyroid gland function, since a blunted T3 response to exogenous bovine TSH occurred and pharmacologic doses of iodide did not influence the phenomenon. The finding in three athyreotic subjects that serum T3/T4 ratio values increased from  $14 \pm 1$  on T4 therapy (mean serum T4,  $9.6 \pm 0.8$   $\mu$ g/dl and T3,  $132 \pm 8$  ng/dl) to  $40 \pm 2$  after withdrawal from 2 wk of T3 administration (serum T4  $1.2 \pm 0.1$   $\mu$ g/dl and T3  $46 \pm 3$  ng/dl) provided direct evidence that an alteration in peripheral thyroid hormone metabolism was probably responsible for these findings previously observed in euthyroid subjects. The results of this study support the possible existence in euthyroid man of a peripheral tissue autoregulatory mechanism for maintaining serum T3 values in states of T4 deficiency. Whether this process

involves an alteration in the efficiency of T4 to T3 conversion or the rate of T3 clearance is presently unknown.

### Introduction

It is axiomatic that thyroid stimulating hormone (TSH)<sup>1</sup> secretion plays a critical role in regulating thyroid gland function and, in turn, circulating thyroid hormone levels (1–5). For example, elevations in serum TSH induced preferential thyroidal triiodothyronine (T3) formation and secretion tend to maintain serum T3 values as circulating thyroxine (T4) levels fall as a result of either thyroid disease or iodine deficiency (2). This centrally controlled “autoregulation” appears to be dependent upon intrapituitary conversion of T4 to T3, which serves to amplify the TSH response to even minimal decreases in circulating levels of T4 (2, 6, 7). The recent demonstration of a TSH inducible thyroidal 5'-deiodinase system acting to increase T3 secretion may be an additional mechanism for maintaining circulating T3 levels (8, 9).

Despite the demonstrated alterations in thyroid glandular secretion in states of T4 deficiency, most of the circulating T3 present in euthyroid man is normally derived from T4 to T3 conversion by peripheral tissue rather than by direct thyroidal secretion (10, 11). Although this peripheral conversion process may be affected by such altered metabolic states as fasting, overfeeding, and various system illnesses (10–16), there is little evidence that this peripheral tissue mechanism is important in maintaining circulating T3 levels when serum T4 concentrations are depressed. This study purports to find evidence that a non-thyroidal, non-TSH-mediated system exists for maintaining circulating T3 levels in a state of T4 deficiency.

### Methods

Studies were performed in 13 normal (10 males, 3 females) and 11 euthyroid athyreotic (females) subjects, ranging in age from 20 to 50 yr. Normal subjects were screened for thyroid disease by history, physical examination, and serum thyroid hormone indices. Those comprising

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1. *Abbreviations used in this paper:* rT3, reverse T3; SSKI, supersaturated solution of potassium iodide; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

the athyreotic group had been shown to have primary hypothyroidism based on serum T4 concentrations of  $<1.0 \mu\text{g/dl}$  and serum TSH values of  $>40 \mu\text{U/ml}$ . The athyreotic subjects had been maintained on exogenous thyroxine replacement therapy for longer than one year, and all were clinically and biochemically euthyroid at the time of study. Written informed consents were obtained from all study subjects before the initiation of the protocol.

The normal subjects were placed on T3 doses of  $50 \mu\text{g}$  daily the 1st wk,  $75 \mu\text{g}$  daily the 2nd wk; and  $100 \mu\text{g}$  daily for the last 10 d. Six of these subjects were on T3 therapy alone and then withdrawn (control group), while seven subjects were given T3 therapy  $500 \text{ mg}$  of iodide daily supersaturated solution of potassium iodide (SSKI). Blood samples were drawn daily at 0800–1200 h or 2–4 h after the daily T3 dose.

Three subjects from the control group had a TSH stimulation test performed before and on the 3rd d after T3 withdrawal. Serum T3 and T4 measurements were performed at 2-h intervals for 8 h after the intramuscular administration of 2 U of bovine TSH (Armour Pharmaceutical Co., Tarrytown, NY).

The athyreotic patients were switched from oral thyroxine replacement to oral T3 (Cytomel; Smith Kline Corp., Philadelphia, PA),  $75 \mu\text{g}$  daily. In three patients, T3 therapy was discontinued after 2 wk, while in 8 patients, the T3 therapy was continued for 6 wk and one subject for 12 wk. After the cessation of T3 all subjects remained off thyroid medication for 8 d.

Total serum T4, T3, and reverse T3 (rT3) measurements were performed in duplicate by a double antibody radioimmunoassay technique (17). The serum T4 assay sensitivity was  $0.25 \mu\text{g/dl}$  with intraassay variabilities 5.1% at  $1.7 \mu\text{g/dl}$  and 1.6% at both  $5.0$  and  $10.4 \mu\text{g/dl}$ , respectively. The serum T3 assay sensitivity was  $10 \text{ ng/dl}$ , with an intraassay variability of 2.9% at  $97 \text{ ng/dl}$  and 1.5% at  $203 \text{ ng/dl}$ . The serum rT3 assay sensitivity limit was  $10 \text{ ng/dl}$ , with an intraassay variability of 3.8% at  $70 \text{ ng/dl}$  and 3.3% at  $195 \text{ ng/dl}$ . The mean normal total serum rT3 was  $34 \pm 1.5 \text{ ng/dl}$  ( $n = 62$ ). The cross reactivity of the rT3 antibody with T4 was 0.019%. Serum TSH measurements were performed by a previously reported modification of a double antibody technique designed to assess low serum TSH concentrations (18). Nominal assay sensitivity was  $0.1 \mu\text{U/ml}$  with an intraassay variability value

of 12.9% at  $0.58 \mu\text{U/ml}$ , 8.4% at  $1.5 \mu\text{U/ml}$ , and 5.8% at  $2.83 \mu\text{U/ml}$ . Serum T3/T4 ratios were expressed by dividing the serum T3 value in nanograms per deciliter by the T4 value in micrograms per deciliter. The molar ratio concentrations of T3 and T4 in the serum can be obtained by multiplying reported values by  $1.194 \times 10^{-3}$ .

## Results

Findings in the euthyroid control group during and after T3 administration are shown in Fig. 1. Mean base-line values of total serum T4 of  $7.5 \pm 0.5 \mu\text{g/dl}$  ( $\pm\text{SEM}$ ), serum T3 of  $129 \pm 6 \text{ ng/dl}$ , and TSH of  $2.0 \pm 0.5 \mu\text{U/dl}$  were all within the normal range. After oral T3, mean TSH values promptly declined to subnormal levels of  $0.4 \pm 0.1 \mu\text{U/ml}$ . Serum T4 concentrations fell gradually, reaching a nadir value of  $3.1 \pm 0.3 \mu\text{g/dl}$  on day 28. Mean serum T3 values progressively rose with increasing T3, reaching peak values of  $498 \pm 51 \text{ ng/dl}$  on day 28. Elevations in serum T3 were a reflection of the ingestion of the daily morning oral T3 dose. After the cessation of T3, serum T3 levels rapidly declined for the first 2 d. Thereafter, mean serum T3 values plateaued and reached a nadir of  $99 \pm 4 \text{ ng/dl}$  on day 33 (5 d after T3 withdrawal). The concurrent mean serum T4 values of  $3.2 \pm 0.5 \mu\text{g/dl}$  and serum TSH concentrations of  $0.56 \pm 0.1 \mu\text{U/ml}$  were not significantly different from values observed during T3 suppression (days 3–28). During days 34 and 36 (6 and 8 d after T3 withdrawal), mean TSH rose to normal range with a parallel rise in serum T4. Subsequently, mean serum TSH rebounded to the upper limits of normal by day 40 and then fell to base line by day 44. During this T3 withdrawal period there was a greater than twofold increase in serum T4, but only a 25% rise in serum T3 levels.

The three euthyroid subjects who had been administered 2 U of bovine TSH intramuscularly demonstrated a rise in mean serum T4 from  $7.8 \pm 0.8$  to  $11.9 \pm 1.6 \mu\text{g/dl}$  at 8 h. Repeat TSH stimulation testing, performed 3 d after T3 withdrawal, showed

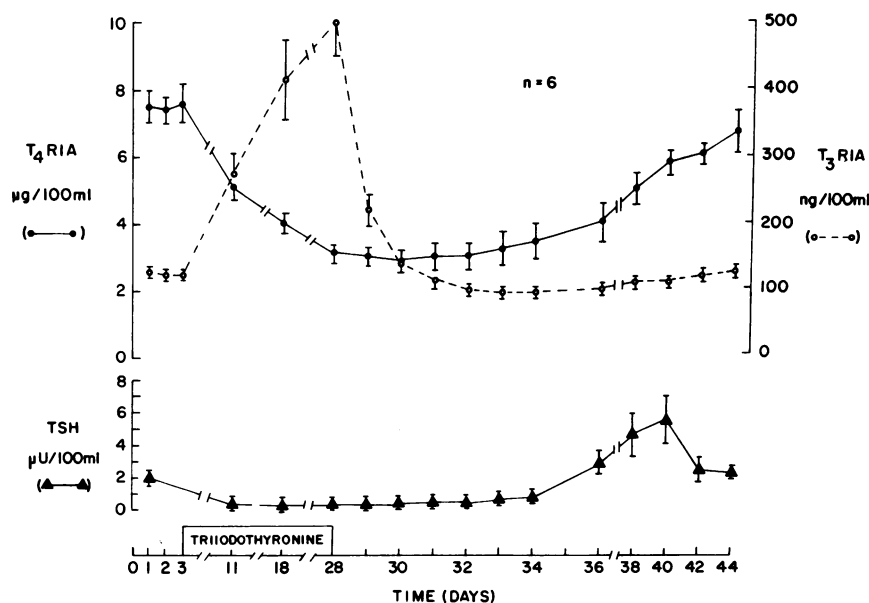


Figure 1. Serum T3, T4, and TSH concentrations (mean  $\pm$  SE) in six euthyroid subjects before, during, and after withdrawal of T3.

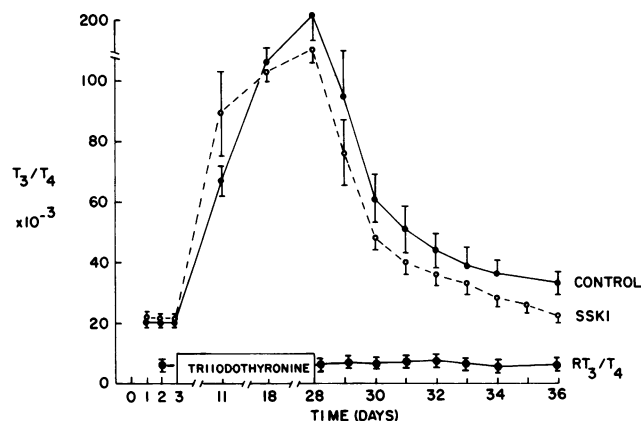


Figure 2. Comparison of T<sub>3</sub>/T<sub>4</sub> ratio values (mean±SE) in the two groups of euthyroid subjects administered T<sub>3</sub> with and without SSKI supplementation during the post-T<sub>3</sub> withdrawal period. Changes in serum rT<sub>3</sub>/T<sub>4</sub> ratio values for the control group were plotted in the lower portion of the slide.

a blunted response in mean serum T<sub>4</sub> from  $3.7 \pm 0.19$  to  $4.7 \pm 0.3$   $\mu\text{g}/\text{dl}$ . Similarly, the mean serum T<sub>3</sub> response to TSH showed an increase from  $119 \pm 12$  to  $173 \pm 16$  ng/dl during the control period, but only rose from  $114 \pm 13.9$  to  $128 \pm 4.2$  ng/dl with repeat testing 3 d post-T<sub>3</sub> withdrawal. In terms of percentages, serum T<sub>4</sub> response fell from 53 to 27% and serum T<sub>3</sub> response fell from 45 to 12%.

As can be seen in Fig. 2, identical serum T<sub>3</sub>/T<sub>4</sub> ratio values were observed in the control and SSKI pretreated groups. Thus, prior exposure to pharmacological levels of iodides did not alter the pattern of serum T<sub>3</sub> and T<sub>4</sub> after withdrawal of exogenous T<sub>3</sub>. In contrast to the variability in serum T<sub>3</sub>/T<sub>4</sub> ratio values,

serum rT<sub>3</sub>/T<sub>4</sub> ratios were constant (range 5.1–7.8) and did not significantly vary throughout the study.

Comparison of mean serum T<sub>3</sub> in athyreotic subjects who had been withdrawn from 6 wk of oral T<sub>3</sub> with the euthyroid control group is shown in Fig. 3. The mean serum T<sub>4</sub> values in the athyreotic group were  $0.4 \pm 0.1$   $\mu\text{g}/\text{dl}$ , indicating that residual T<sub>4</sub> was present from previous T<sub>4</sub> therapy. After T<sub>3</sub> withdrawal, mean serum T<sub>3</sub> levels plateaued at 27 ng/dl, in contrast to 102 ng/dl for the euthyroid group. Final serum T<sub>3</sub> values for euthyroid and athyreotic subjects on day 8 were  $104 \pm 5$  and  $21 \pm 1$  ng/dl, respectively. In one athyreotic subject placed on oral T<sub>3</sub> for 12 wk, the serum T<sub>4</sub> value was below the assay limit of 0.1  $\mu\text{g}/\text{dl}$ . Serum T<sub>3</sub> levels fell below the assay limit of 10 ng/dl by day 4 after T<sub>3</sub> withdrawal.

Fig. 4 shows a comparison of serum T<sub>3</sub>/T<sub>4</sub> ratio values in a euthyroid control group with three euthyroid athyreotic subjects placed on T<sub>3</sub> for 2 wk and then withdrawn. Nearly identical serum T<sub>3</sub>/T<sub>4</sub> ratios were observed before study, during T<sub>3</sub> administration, and for the first 3 d after T<sub>3</sub> withdrawal. Subsequently, the athyreotic subjects maintained elevated serum T<sub>3</sub>/T<sub>4</sub> ratios, while those in the control group declined as the serum T<sub>4</sub> levels rose. On day 8 after T<sub>3</sub> withdrawal, the athyreotic subjects had mean T<sub>3</sub>/T<sub>4</sub> ratios of  $40 \pm 2$  as compared with control group values of  $29 \pm 4$ . On day 2 of T<sub>3</sub> withdrawal, serum TSH values gradually rose from  $0.3 \pm 0.2$  to  $6.3 \pm 2.6$   $\mu\text{U}/\text{ml}$  on day 8 post-T<sub>3</sub> withdrawal in the athyreotic subjects. Since three of the athyreotic subjects participated in both the 2- and 6-wk treatment protocols, comparison of the serum TSH, T<sub>4</sub>, and T<sub>3</sub> responses could be obtained. Mean serum T<sub>3</sub> values were  $51 \pm 3$ ,  $50 \pm 3$ ,  $46 \pm 3$ , and  $46 \pm 3$  ng/dl on days 4–8, while mean serum T<sub>4</sub> values were  $1.5 \pm 0.2$ ,  $1.3 \pm 0.1$ ,  $1.2 \pm 0.1$ , and  $1.2 \pm 0.1$   $\mu\text{g}/\text{dl}$ , respectively, in the 2-wk T<sub>3</sub> protocol. In contrast, on the 6-wk T<sub>3</sub> protocol, the serum T<sub>3</sub> values were  $28 \pm 2$ ,  $25 \pm 3$ ,

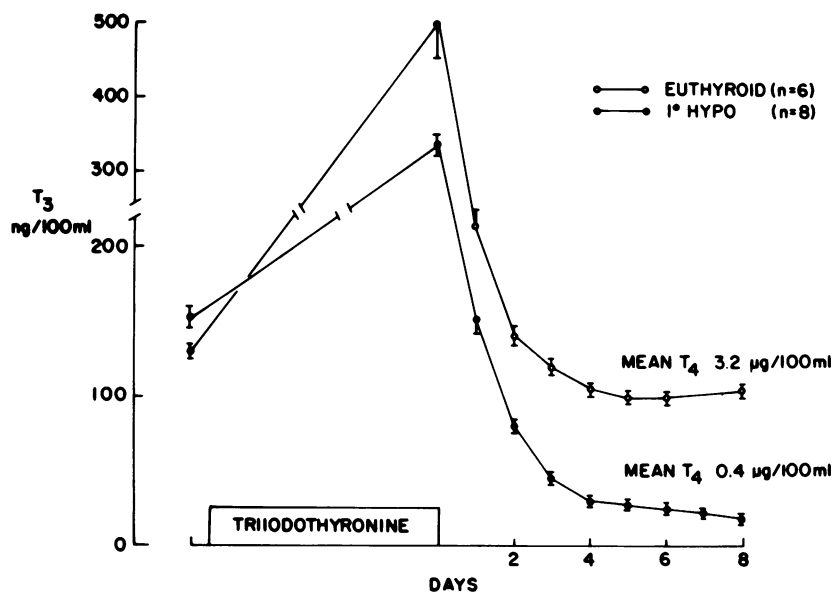


Figure 3. Serum T<sub>3</sub> concentration (mean±SE) in euthyroid and athyreotic subjects during and after T<sub>3</sub> administration. After 4 wk of T<sub>3</sub> suppressive therapy, mean serum T<sub>4</sub> value for euthyroid subjects was 3.2  $\mu\text{g}/\text{dl}$ . Mean serum T<sub>4</sub> value after 6 wk of T<sub>3</sub> administration was 0.4  $\mu\text{g}/\text{dl}$  in the athyreotic subjects.

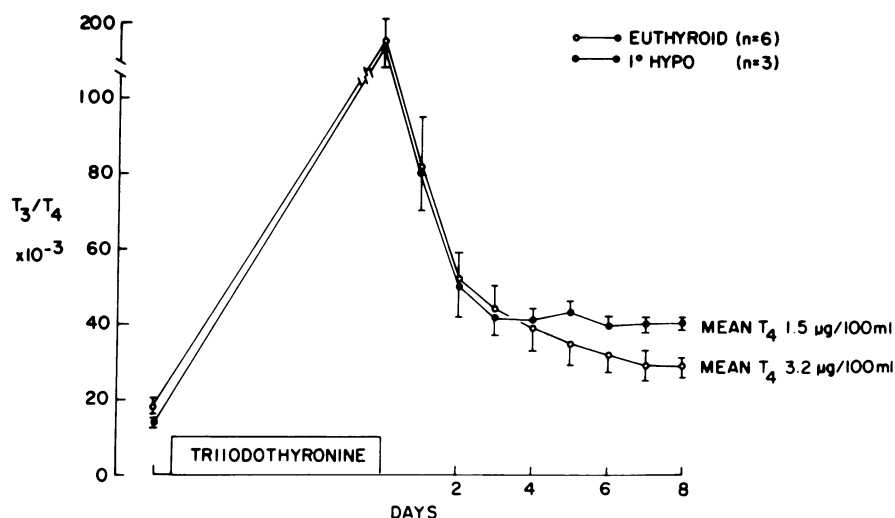


Figure 4. Comparison of the T<sub>3</sub>/T<sub>4</sub> ratio value (mean±SE) in euthyroid subjects placed on T<sub>3</sub> daily for 4 wk and then withdrawn and three athyreotic T<sub>4</sub>-treated subjects maintained on T<sub>3</sub> alone for two weeks before stopping.

22±3, and 21±3 ng/dl, while the corresponding mean T<sub>4</sub> values were 0.4±0.1, 0.4±0.1, 0.4±0.1, and 0.4±0.1, respectively. Serum TSH values were consistently >10 µU/ml in this latter study. These observations are consistent with the view that the circulating T<sub>3</sub> values measured in these subjects originated from peripheral T<sub>4</sub> conversion rather than T<sub>3</sub> secreted by TSH stimulation from a thyroid gland remnant.

## Discussion

This study describes a phenomenon whereby serum T<sub>3</sub> values are maintained when there is a deficient source of circulating T<sub>4</sub> in eumetabolic subjects. Although the precise mechanism responsible for this phenomenon is unknown, it does not appear to result from alterations in the pituitary-thyroid axis for the following reasons: (a) Serum TSH values were subnormal in euthyroid subjects throughout the initial 6 d after T<sub>3</sub> withdrawal; (b) intramuscular bovine TSH produced a blunted rise in serum T<sub>3</sub> and T<sub>4</sub> during this period, thus indicating reduced thyroid sensitivity to TSH; and (3) prior administration of pharmacologic iodides, which would be expected to inhibit thyroidal hormone release, had no influence on serum T<sub>3</sub>. In contrast, the finding of sustained elevations in serum T<sub>3</sub>/T<sub>4</sub> ratios in three athyreotic subjects partially withdrawn from T<sub>4</sub> therapy provided direct evidence of an extrathyroidal mechanism being responsible for this process.

Several possible peripheral tissue mechanisms could account for the increases in circulating T<sub>3</sub>/T<sub>4</sub> with depressed T<sub>4</sub> values. These include a slow back-diffusion of T<sub>3</sub> into the blood of T<sub>3</sub> stored in peripheral tissues during the period of oral T<sub>3</sub> administration. However, this explanation appears unlikely since athyreotic subjects were unable to maintain serum T<sub>3</sub> levels after T<sub>3</sub> withdrawal, despite having similar elevations in serum T<sub>3</sub> during T<sub>3</sub> administration. Thus, it is essential that circulating

T<sub>4</sub> be present to generate the T<sub>3</sub> found in the circulation. Another possible factor is that a marked slowing of T<sub>3</sub> clearance relative to T<sub>4</sub> might account for the increased serum T<sub>3</sub>/T<sub>4</sub> ratios observed at low serum T<sub>4</sub> levels. Such a divergence in serum T<sub>3</sub> and T<sub>4</sub> clearance rates has been previously described in hypothyroidism (19). Whether these changes are a reflection of an altered state of metabolism or related to circulating T<sub>4</sub> levels is unknown. In any case, it is doubtful that such differential changes in T<sub>3</sub> and T<sub>4</sub> clearances could account for the twofold increase in T<sub>3</sub>/T<sub>4</sub> ratios. What appears to be the most likely explanation is that an autoregulatory mechanism exists for altering peripheral T<sub>4</sub> to T<sub>3</sub> conversion. The recent evidence for such autoregulatory 5'-deiodinase systems in rat pituitary, brain and brown adipose tissue which respond to T<sub>4</sub> substrate levels provides independent evidence to support this possibility (7, 20–22).

A peripheral tissue mechanism for increasing T<sub>4</sub> to T<sub>3</sub> conversion in primary hypothyroidism and the reverse in states of chronic T<sub>4</sub> excess has been previously described by Shimizu and co-workers (23) and Inada and co-workers (24). Further, Braverman and co-workers (25) have shown a decrease in T<sub>4</sub> to T<sub>3</sub> conversion occurring in euthyroid subjects after chronic oral T<sub>4</sub> loads. Whether these apparent changes in T<sub>4</sub> to T<sub>3</sub> conversion are a result of an autoregulatory mechanism or are related to the metabolic consequences of hypo- or hyperthyroidism is unclear. It is unlikely that the changes observed in the present study resulted from hypothyroidism, since the subjects were essentially euthyroid at the time of study.

The mechanism responsible for producing alterations in serum T<sub>3</sub> to T<sub>4</sub> ratios after acute T<sub>3</sub> withdrawal does not seem to influence rT<sub>3</sub> metabolism, as rT<sub>3</sub> to T<sub>4</sub> ratios remained constant despite variable serum T<sub>4</sub> levels. This is in contrast to the findings reported by Kaplan and co-workers (26) who observed an increase in rT<sub>3</sub>/T<sub>4</sub> ratio values in association with

depressed T4 concentrations associated with hypothyroidism. The exact cause for this disparity is unknown but may be a reflection that hypothyroidism per se may influence rT3 metabolism.

That a peripheral tissue mechanism may exist for maintaining circulating T3 levels in a state of T4 deficiency would seem compatible with the general pattern of evolution of human thyroid metabolism. For example, the evolutionary development of thyroxine binding globulin with its associated large extrathyroidal T4 pool is a reflection of the dominance of peripheral over central control in man. Further, TSH-induced changes in thyroid glandular secretion appear to play a relatively minor role in altering serum thyroid hormone indices found in association with fasting or systemic illnesses (13–16, 27) as contrasted to smaller mammals (28). However, the apparent importance of peripheral thyroid hormone metabolism should not be interpreted as indicating that there is only a minor role for the pituitary-thyroid axis in human physiology. Clearly, in states of iodine deficiency or thyroid gland failure, there is adaptive significance of the hypersecretion of TSH in promoting thyroidal T3 formation and secretion and in turn, maintaining serum T3 (2, 8, 9). What seems most likely is that these two systems, peripheral tissue and pituitary-thyroid, act in a complementary manner to prevent decreases in serum T3 as circulating T4 values fall. The discovery of these multiple systems for sustaining circulating T3 levels underscores the physiologic importance placed on the precise control of circulating T3 concentrations in man.

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