The Thyroid Gland Is a Major Source of Circulating T_3 in the Rat

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Abstract

In rats, the respective contribution of the thyroid and peripheral tissues to the pool of T_3 remains unclear. Most, if not all, of the circulating T_3 produced by extrathyroidal sources is generated by 5′-deiodination of T_4, catalyzed by the selenoenzyme, type I iodothyronine 5′-deiodinase (5′D-I). 5′D-I in the liver and kidney is almost completely lost in selenium deficiency, resulting in a marked decrease in T_4 deiodination and an increase in circulating T_4 levels. Surprisingly, circulating T_3 levels are only marginally decreased by selenium deficiency. In this study, we used selenium deficiency and thyroidectomy to determine the relative contribution of thyroidal and extrathyroidal sources to the total body pool of T_3. Despite maintaining normal serum T_4 concentrations in thyroidectomized rats by T_4 replacement, serum T_3 concentrations remained 55% lower than those seen in intact rats. In intact rats, restricting selenium intake had no effect on circulating T_3 concentrations. Decreasing 5′D-I activity in the liver and kidney by > 90% by restricting selenium intake resulted in a further 20% decrease in serum T_3 concentrations in the thyroidectomized, T_4 replaced rats, suggesting that peripheral T_4 to T_3 conversion in these tissues generates approximately 20% of the circulating T_3 concentrations. While dietary selenium restriction markedly decreased intrahepatic selenium content (> 95%), intrathyroidal selenium content decreased by only 27%. Further, thyroid 5′D-I activity actually increased 25% in the selenium deficient rats, suggesting the continued synthesis of this selenoenzyme over selenoproteins in other tissues in selenium deficiency. These data demonstrate that the thyroid is the major source of T_3 in the rat and suggest that intrathyroidal T_4 to T_3 conversion may account for most of the T_3 released by the thyroid. (*J. Clin. Invest.* 1993. 91:2709–2713.) Key words: deiodination • selenium • thyroid • hormone metabolism • T_4 to T_3 conversion

Introduction

In mammals, the relative contribution of thyroidal and extrathyroidal sources to the total body pool of the metabolically active iodothyronine, 3,5,3′-triiodothyronine (T_3), is unclear. T_3 can be derived from conversion of the prohormone thyroxine (T_4) by outer ring (5′-) deiodination in the peripheral tissues, by T_4 to T_3 conversion within the thyroid gland, and by direct secretion of de novo synthesized thyroidal T_3. Estimates of the contribution of extrathyroidal T_4 to T_3 conversion to the total T_3 pool vary from 20% to 100% in the rat (1–3) and the thyroid accounts for the remainder of the T_3 produced daily. Laurberg used in situ thyroid perfusion to directly examine the contribution of the thyroid to the T_3 pool and reported that intrathyroidal T_4 to T_3 conversion accounted for a considerable portion of the T_3 secreted from the dog thyroid (4, 5). Thus, both extrathyroidal and intrathyroidal T_4 to T_3 conversion appear to participate in the daily production of T_3.

T_4 to T_3 conversion is catalyzed by the enzyme, iodothyronine 5′-deiodinase. Two isozymes of iodothyronine 5′-deiodinase have been identified. The most abundant form, type I iodothyronine 5′-deiodinase (5′D-I), is found in liver, kidney, and thyroid (6) and contains the rare amino acid selenocysteine (7–9). Tissue content of 5′D-I in the liver and kidney is proportional to selenium intake (10). The other isozyme, type II iodothyronine 5′deiodinase (5′D-II), is abundant in the brain, pituitary, and brown adipose tissue and does not contain selenium (11, 12). T_3 generated by 5′D-I is released into the general circulation, while the majority of the T_3 produced by 5′D-II remains with the cell. The ability to manipulate 5′D-I levels by altering the dietary intake of selenium provides the means to examine the contribution of 5′D-I to total T_3 production. Selenium deficiency leads to an almost complete loss of 5′D-I in the liver and kidney and a 40–50% increase in the serum T_4 concentration (10, 12–14). This increment in circulating T_4 is completely accounted for by the prolonged metabolic half-life of the iodothyronine due to the loss of 5′D-I (14). Paradoxically, serum T_3 concentrations are not reciprocally affected and decrease by no more than 20%, if at all (12–14). While serum T_3 concentrations are marginally depressed by selenium deficiency, circulating T_3 sulfate concentrations increase nearly twofold (12, 14). Serum TSH levels remain near normal despite the elevated circulating T_4 in the selenium-deficient animal (12–14). Thus, despite the marked decrease in hepatic and renal T_4 to T_3 conversion in the absence of selenium, other sources of T_3 appear to be made available in animals lacking 5′D-I.

There are several possibilities to account for the discordance between the near complete loss of 5′D-I and the marginal fall in circulating T_3 observed in selenium deficiency. They include (*a*) diminished T_3 clearance, (*b*) increased thyroidal T_3 secretion, and/or (*c*) enhanced recovery of T_3 from sulfo-conjugates released into the gut in the enterohepatic cycle. Previous work has shown that T_3 clearance is only marginally decreased by selenium deficiency and that the 20–25% increase in the metabolic half-life of this iodothyronine is insuffi-

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Part of this work has been presented as an abstract at the 20th meeting of the European Thyroid Association, Dublin, Ireland, 20–25 June 1992. Address reprint requests to Dr. Jack L. Leonard, Department of Nuclear Medicine, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655.

Received for publication 23 October 1992 and in revised form 8 January 1993.

J. Clin. Invest.

0021-9738/93/06/2709/05 $2.00
Volume 91, June 1993, 2709–2713

cient to maintain the steady-state levels of T_3 observed in serum (14). The contribution of the thyroid to the T_3 pool in the selenium-deficient rat remains to be determined. Likewise, the contribution of enterohepatic recycling of T_3 or its conjugates to the circulating T_3 pool is unclear.

In this study, we determined the source(s) of circulating T_3 in selenium-deficient rats. The data show that the thyroid gland serves as a major source of circulating T_3 in the rat and suggest that intrathyroidal T_4 to T_3 conversion accounts for much of the T_3 secreted by the thyroid.

Methods

Animals and reagents. Weanling male Sprague-Dawley rats (40–50 g) supplied by Charles River Laboratories (Wilmington, MA) were used in all experiments. The study was approved by the Animal Research Committee and complies with the institutional assurance certificate of the University of Massachusetts Medical Center. Rats were fed a torula yeast based semisynthetic diet (Teklad Premier Laboratory Diets, Madison, WI) for 5 wk. The selenium-deficient diet (TD 86298) contains less than 16 μg/kg selenium and the selenium-replete diet (TD 91259) is the same base diet supplemented with 200 μg/kg selenium as Na_2SeO_3. Rats were housed in stainless steel cages, and distilled water was available ad lib. Body weight (BW)[1] was monitored biweekly.

Analytical procedures and hormone assays. In all experiments, animals were killed by decapitation and exsanguinated, except where noted. Liver was homogenized in 4 vol (wt/vol) of 20 mM potassium phosphate buffer (pH 7.4), 150 mM NaCl, and in 4 vol (wt/vol) of 250 mM sucrose, 20 mM Hepes buffer (pH 7.0), 1 mM EDTA, and 1 mM DTT and stored at −20°C for determination of glutathione peroxidase activity (GPx) and 5′D-I activity, respectively. Thyroid glands were weighed and homogenized in 800 μl of 250 mM sucrose, 20 mM Hepes buffer (pH 7.0), 1 mM EDTA, and 1 mM DTT for determination of 5′D-I activity.

The degree of selenium deficiency in the rats was determined by the decrease in hepatic GPx activity. GPx activity was determined from the oxidation of NADPH in the presence of 0.35 mM *t*-butyl hydroperoxide monitored spectrophotometrically at 340 nm (15). Samples were run in duplicate and results were expressed as nmol NADPH oxidized/min per mg protein. Hepatic GPx activities in intact, selenium-replete and thyroidectomized, T_4 replaced, selenium-replete rats were 598±58 nmol NADPH oxidized/min per mg protein ($n = 9$) and 906±53 nmol NADPH oxidized/min per mg protein ($n = 12$), respectively.

Type I iodothyronine 5′-deiodinase activity was determined by the release of radioiodide from 10 μM $[^{125}I]rT_3$ in the presence of 20 mM DTT (5′D-I) (16). Samples were run in duplicate and results were expressed as units/mg protein; 1 unit of 5′D-I enzyme activity represents the release of 1 pmol radioiodine/min per mg protein at 37°C. Hepatic type I iodothyronine 5′-deiodinase activities in intact, selenium-replete and thyroidectomized, T_4 replaced, selenium-replete rats were 224±15 U/mg protein ($n = 12$) and 114±8 U/mg protein ($n = 9$), respectively.

Serum TSH was measured in duplicate by RIA using materials obtained from the National Pituitary Agency, National Institutes of Health (Bethesda, MD). Serum T_4 and T_3 concentrations were determined in duplicate by species-adapted specific RIAs.

Selenium was quantified by measuring the 162 KeV gamma ray produced during the decay of radioactive ^{77}mSe after irradiation of the sample at a neutron flux. The sensitivity was 0.05 ppm (Research Reactor Facility, University of Missouri–Columbia, Columbia, MO) (17).

Protein was measured by the method of Bradford (18).

Experimental procedures

Effect of altered selenium intake on serum T_4, T_3, and TSH concentrations in T_4 replaced, thyroidectomized rats. 35 rats (22 selenium supplemented and 13 selenium deficient) were used in this experiment. 3 wk before being killed, 12 selenium-supplemented and 6 selenium-deficient rats were anesthetized using 7 mg ketamine and 0.6 mg xylazine/100 g BW and the thyroid glands removed. T_4 replacement was begun one day after thyroidectomy by daily intraperitoneal injections of T_4 (1.1 μg/100 g BW) for 2 wk. For the final 7 d of the experiment, serum T_4 concentrations were maintained at euthyroid levels by the use of an osmotic minipump (Alzet 2001; Alza Corp., Palo Alto, CA) calculated to deliver T_4 at a rate of 1.1 μg/100 g BW per day. T_4 (Sigma Chemical Co., St. Louis, MO) used for hormone replacement was > 99.7% pure as measured by HPLC.

Effect of selenium deficiency on the selenium content and 5′D-I activity in the thyroid gland. 15 rats (8 selenium supplemented, and 7 selenium deficient) were anesthetized as described above and perfused through the aorta with 40 ml of ice-cold saline. The exsanguinated thyroid gland and liver were removed and frozen at −70°C for subsequent determination of selenium content by neutron activation analysis. In a parallel experiment, thyroidal and liver 5′D-I activities were determined in 10 selenium-supplemented and 10 selenium-deficient rats.

Effects of selenium deficiency on intrathyroidal metabolism of ^{131}I. Intrathyroidal metabolism of ^{131}I was determined in groups of 5 rats (5 selenium supplemented and 5 selenium deficient). Animals were killed 2 h after the intraperitoneal injection of 10 μC $Na^{131}I$ (16.2 Ci/μg). Thyroid glands were then dissected free of connective tissue and homogenized in 500 μl of sodium barbital buffer (pH 8.6) containing 20 mM methimazole and 4 mM KI. The percent uptake of radioiodide and the distribution of the ^{131}I between MIT, DIT, T_3, and T_4 was determined by descending paper chromatography after pronase digestion of thyroidal homogenates according to Vagenakis et al. (19).

Statistics

The results are presented as mean±SE. Statistical significance ($P < 0.05$) was determined using the Student's *t* test for unpaired values.

Results

Effects of selenium status on serum T_4, T_3, and TSH concentrations in T_4 replaced, thyroidectomized rats. During the 5-wk experimental period, body weights increased from 55 to 330 g in the euthyroid rats (intact) ($n = 17$) and from 55 to 289 g in the thyroidectomized rats replaced with T_4 (T_4 replaced) ($n = 18$), indicating that hormone replacement was almost complete in the thyroidectomized animals. No differences in growth were observed between the selenium-deficient and selenium-supplemented rats. Selenium deficiency resulted in a 97% decrease in hepatic GPx activity and a parallel 93% decrease in hepatic 5′D-I activity in both the intact and T_4-replaced rats indicating that the animals were selenium deficient. As shown in Fig. 1, in selenium-supplemented rats, serum T_4 concentrations were similar in the intact and T_4 replaced groups (*A*). Selenium deficiency resulted in the expected increase in the serum T_4 concentrations in both the intact and T_4 replaced groups ($P < 0.05$, *A* vs. *B*).

Although the serum T_4 concentrations were identical in the selenium-supplemented intact and T_4 replaced rats, serum T_3 concentrations were not normalized and T_3 concentrations in the T_4 replaced rats remained 55% lower than those in the intact group (Fig. 1 *C*). Selenium deficiency did not significantly affect serum T_3 values in the intact rats (1.23 nM±0.14 vs. 1.11±0.10, selenium-supplemented vs. selenium-deficient

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[1] *Abbreviations used in this paper:* BW, body weight; GPx, glutathione peroxidase activity.

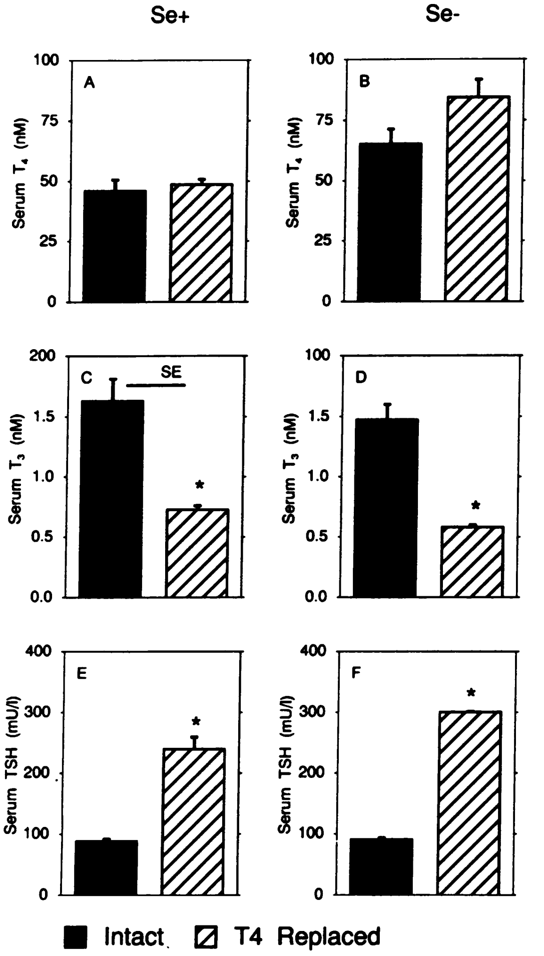

Figure 1. Effect of selenium and thyroidectomy on serum concentrations of T_4, T_3, and TSH in the rat. Rats were fed a defined diet, thyroidectomized, and replaced with T_4 as described in Experimental procedures. Blood was obtained at the time of killing and analyzed for T_4, T_3, and TSH. Intact, nonthyroidectomized rats; T_4 replaced, rats thyroidectomized and replaced with exogenous T_4. $^*P < 0.05$.

rats, respectively) but decreased the serum T_3 concentrations by 20% in the T_4 replaced group (*C* and *D*) (0.55±0.03 nM vs. 0.44±0.02 nM, $P < 0.05$ selenium-supplemented vs. selenium-deficient rats, respectively).

In both selenium-supplemented and selenium-deficient thyroidectomized rats, T_4 replacement did not normalize the serum TSH concentrations, and they remained 2 to 3 times higher than those observed in the intact rats (Fig. 1, *E* and *F*). Selenium deficiency did not affect serum TSH concentrations in the intact rats.

Effect of selenium deficiency on selenium content and 5'D-I activity in the thyroid. The failure of T_4 replacement to normalize serum T_3 concentrations in the selenium-supplemented rats, despite the availability of normal T_4 levels to the 5'D-I containing tissues, suggested that the thyroid gland may contribute up to 55% of the T_3 found in the circulation. Similarly, the thyroid appeared to contribute as much as 60% of the circulating T_3 in the selenium-deficient rats, animals that lack the selenoprotein 5'D-I in the liver and kidney. Since earlier work suggested that intrathyroidal T_4 to T_3 conversion was a major contributor to the T_3 found in the dog thyroid effluent (4, 5), and thyroidal 5'D-I appears to be a selenoprotein (7), the near normal serum T_3 concentrations found in intact, selenium-deficient animals raised the possibility that thyroidal 5'D-I was unaffected by selenium deficiency. Thus, we determined the effects of selenium deficiency on thyroidal selenium content (Fig. 2) and on 5'D-I activity in the thyroid (Fig. 3). Rats fed the selenium-deficient diet had a > 97% fall in selenium content in the liver and a corresponding > 93% decrease in liver 5'D-I activity. However, in the thyroid, the selenium-deficient diet resulted in only a modest 27% decrease in selenium content, and paradoxically, the 5'D-I activity was increased by 25% ($P < 0.05$).

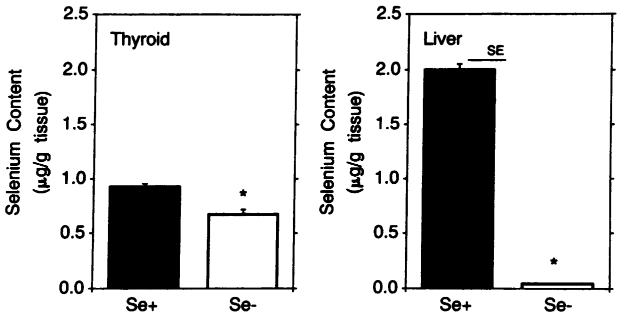

Figure 2. Effect of selenium deficiency on the selenium content in the thyroid and liver. Rats were fed a selenium-supplemented (Se+) or selenium-deficient (Se−) diet for 5 wk then were killed. Selenium content was determined as described in Experimental procedures. $^*P < 0.05$.

Effects of selenium deficiency on intrathyroidal metabolism of ^{131}I. To evaluate the influence of altered selenium intake on intrathyroidal iodine metabolism, we determined the effects of selenium deficiency on the thyroid gland's ability to concentrate and organify iodine. Thyroidal uptake of ^{131}I was unaffected by selenium intake, and there were no differences in the synthesis of the ^{131}I-labeled iodotyrosines (MIT and DIT) or iodothyronines (T_4 and T_3) between selenium-deficient and selenium-supplemented rats (Table I).

Discussion

Controversy surrounds the contribution of the various tissues to T_3 production in the rat. DiStefano (1) estimated that 47% of T_3 originates from both thyroidal secretion and extrathyroidal T_4 to T_3 conversion in liver and kidney, while the remain-

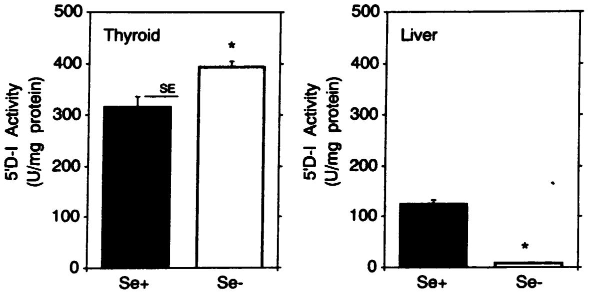

Figure 3. Effect of selenium deficiency on 5'D-I activity in the thyroid and liver. Rats were fed a selenium-supplemented (Se+) or selenium-deficient (Se−) diet for 5 wk then were killed. 5'D-I activity was assayed as described in Experimental procedures. $^*P < 0.05$.

Table I. Effect of Selenium on Intrathyroidal ^{131}I Metabolism

	Se+	Se−
% Uptake	9.4±1.3	12.7±3.2
% MIT	27.4±0.6	27.0±2.2
% DIT	41.4±1.6	36.9±1.5
MIT/DIT	0.74±0.08	0.67±0.03
% T_3	1.0±0.3	1.1±0.2
% T_4	4.1±0.5	3.1±0.3
T_3/T_4	0.33±0.06	0.25±0.06

Intrathyroidal metabolism of ^{131}I was determined in 5 selenium-supplemented (Se+) and 5 selenium-deficient (Se−) rats as described in Experimental procedures. Results are expressed as mean±SE.

ing 53% comes from T_4 to T_3 conversion in the slowly equilibrating pools, such as brain, skin, and muscle. Kinlaw et al. (3) revised their earlier estimate that only 20% of T_3 is produced by extrathyroidal T_4 to T_3 conversion in the rat (2) and suggested that essentially all T_3 is produced by T_4 to T_3 conversion. They also speculated that there is little or no direct secretion of T_3 by the thyroid.

The current data demonstrate that at least 55% of circulating T_3 comes from the thyroid gland in the intact, selenium-supplemented rat. Since liver and kidney 5′D-I still contribute to the pool of circulating T_3 in these rats, it is difficult to estimate the relative contribution of the thyroid to total body T_3 concentrations. Moreover, the failure of T_4 replacement to normalize serum T_3 concentrations in thyroidectomized rats, resulting in reduced liver 5′D-I activity, further complicates the analysis of the sources of circulating T_3. However, in the selenium-deficient rat, liver and kidney 5′D-I are virtually absent (12), and the contribution of the thyroid to the serum T_3 pool can be approximated. The contribution of thyroidal T_3 derived from thyroglobulin and that from thyroidal T_4 to T_3 conversion to the circulating T_3 pool in these animals, as estimated from the data presented in Fig. 1 panel *D*, is approximately 65% and the residual serum T_3 concentrations present in these rats lacking both the thyroid and extrathyroid 5′D-I is in excellent agreement with previously measured values (12). The source of the residual T_3 in the serum of thyroidectomized rats with essentially undetectable serum T_4 concentrations and no hepatic and renal 5′D-I remains unclear. Taken together, extrathyroidal T_4 to T_3 conversion contributes 20–25%, and thyroidal T_4 to T_3 conversion and T_3 derived from thyroglobulin contributes 55–65% of the total body pool of T_3. Thus, nearly all the circulating T_3 derived from T_4 appears to be produced by the selenoenzyme, 5′D-I.

Thyroidectomy resulted in a marked increase in serum TSH concentrations in both selenium-supplemented and selenium-deficient rats despite the maintenance of serum T_4 concentrations identical to those observed in the respective intact groups. The presence of increased serum TSH concentrations, decreased serum T_3 concentrations, and normal or elevated serum T_4 concentrations indicates that circulating T_3 plays an important role in regulating TSH secretion (12, 20, 21). Previously, we found a modest increase in serum TSH concentrations (12) in selenium-deficient rats that was proportional to the fall in circulating T_3 suggesting that TSH levels may actually be slightly elevated for some period during dietary restriction of selenium.

Dietary restriction of selenium intake had only a marginal effect on the selenium content and levels of the selenoenzyme 5′D-I in the thyroid gland. Thus, while there was a near complete loss in hepatic selenium content and 5′D-I activity, the thyroid preserves its selenium stores and 5′D-I activity was increased by 25% in selenium-deficient rats. This increase in thyroidal 5′D-I may be due to TSH mediated stimulation of 5′D-I activity (22, 23) resulting from small increases in circulating TSH that may occur in selenium-deficient rats. Thus, despite the loss of extrathyroidal T_4 to T_3 conversion, the thyroid retains the ability to catalyze the 5′deiodination of T_4.

Similar preservation of thyroidal selenium stores was recently observed in rats fed a selenium-deficient diet for two generations. Behne and co-workers have observed that the thyroid gland and brain exhibited the highest avidity for selenium (24). Arthur et al. (25) recently found that thyroidal GPx activity fell by ~ 50% after 5 wk of selenium deficiency. Since the 25% increase in thyroidal 5′D-I occurred during this same time period in our studies, these data suggest that the thyroid is resistant to the effects of selenium deficiency and that thyroidal 5′D-I is preserved over other selenoproteins in selenium-deficient animals. The thyroid is not unique in this regard since the testis and brain also preferentially preserve selenium over other organs (26).

In this study, intrathyroidal iodine metabolism was also unaffected by selenium deficiency, whereas inconsistent results have been reported on the effects of selenium deficiency on intrathyroidal metabolism by others. Goldstein et al. observed a decrease in PB^{131}I after in vitro incubation of thyroid glands from selenium-deficient rats with ^{131}I (27). Arthur et al. (25) found a decrease in both T_4 and T_3 content in the thyroid gland from selenium-deficient rats, while Meinhold et al. (28) found no change in T_4 and T_3 content in the thyroid from rats fed a selenium-deficient diet. Taken together, these data suggest that secretion of de novo synthesized T_3 is unaffected by selenium deficiency. It is generally assumed that 70–80% of the circulating T_3 concentrations (29, 30) is derived from T_4 to T_3 conversion in human and similar, albeit, more variable estimates have been made for the rat and that the liver, kidney, and thyroid contain nearly all the 5′D-I activity in the body (6, 30). Since extrathyroidal 5′D-I contributes 10–25% of the T_3 production (see above), then more than 50% of the T_3 in the thyroidal effluent is likely to be derived from intrathyroidal T_4 to T_3 conversion of T_4 liberated from thyroglobulin.

The finding that the majority of T_3 in the rat derives from the thyroid provides a potential explanation for the apparent discordance between the observed K_m of 5′D-I and the concentration of T_4 available to extrathyroidal tissues. In vitro estimates of the K_m for T_4 for 5′D-I range between 0.5 and 1 μM (6, 30), while the T_4 available to the tissues ("free hormone") is 3–4 orders of magnitude less, indicating that catalysis by 5′D-I in peripheral tissues is very inefficient. However, intracellular T_4 levels in the thyroid would be expected to be much greater than those in the circulation, and the K_m for T_4 of 5′D-I may reflect the substrate available in the thyroid rather than that in the circulation.

In conclusion, the current study demonstrates that the thyroid gland is a major source of circulating T_3 in rats, accounting for approximately 55% of total T_3 production. The contribution of intrathyroidal T_4 to T_3 conversion to T_3 homeostasis appears to be important, but the exact contribution remains to be determined.

Acknowledgments

We thank J. S. Morris, V. L. Spate, and C. L. Reams from the University of Missouri Research Reactor, University of Missouri–Columbia, Columbia, MO, for determination of tissue selenium content.

J.-P. Chanoine is the recipient of a Public Health Service Fogarty International Research Fellowship (1 F05 TW04373-01) and Aspirant at the Fonds National de la Recherche Scientifique, Belgium. This work was supported by grants DK-38772, DK-18919, and DK-02005 from National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, and by a grant from North Atlantic Treaty Organization.

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