Alterations in 3,3′,5′-Triiodothyronine Metabolism in Response to Propylthiouracil, Dexamethasone, and Thyroxine Administration in Man

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Abstract

To elucidate the mechanisms involved in altering serum 3,3′,5′-triiodothyronine (rT_3) levels with absolute or relative low 3,5,3′-triiodothyronine (T_3) states in man, agents capable of lowering circulating T_3 levels were sequentially administered to six euthyroid subjects. These agents included propylthiouracil (PTU) (300 mg/6 h × 5 d), dexamethasone (DEX) (2 mg/6 h × 5 d), and thyroxine (T_4) (3.0 mg load and 0.3 mg/d × 5 d). [^{125}I] rT_3 clearance rates and rT_3 production rates were then determined. Increased serum rT_3 levels and rT_3/T_4 values occurred with both PTU and DEX as compared with control, while T_4 increased serum rT_3 but did so without changing rT_3/T_4 values. The rT_3 clearance rate was significantly decreased by PTU without altering production rate, while DEX increased the rT_3 production rate without altering the rT_3 clearance rate. T_4 administration did not change rT_3 clearance but proportionately increased rT_3 production. These responses indicate that circulating rT_3 predominantly originates from a non-PTU inhibitable deiodinase enzyme system located in extrahepatic tissues. This enzyme system appears to have a high capacity and low affinity for T_4 and can be stimulated by DEX administration.

Introduction

The peripheral metabolism of thyroxine (T_4)[1] in man is a complex process appearing to be of central importance in the regulation of thyroid hormone activation and action. Although this process is concerned with the generation of the active metabolite 3,5,3′-triiodothyronine (T_3) via outer ring or 5′-monodeiodination of T_4, an approximately equal portion of T_4 is also deiodinated to the apparently inactive metabolite 3,3′,5′-triiodothyronine (rT_3) by inner ring or 5-deiodination. Further, it is estimated that the combined generation of T_3 and rT_3 from T_4 accounts for ~ 80% of T_4 disposal in the euthyroid state while the remaining 20% apparently occurs by a variety of alternate pathways including sulfate and glucuronide conjugation, conversion to acetic acid analogues, and ether-link cleavage (1–4).

Alterations in the normal pattern of peripheral T_4 metabolism commonly occur in response to a variety of nonthyroidal illnesses, fasting, administration of various pharmacologic agents as well as with T_4 excess states (5–12). In all but the latter case, there is either an absolute or relative fall in T_3 production and, in turn, serum T_3 levels. Concomitant with the fall in serum T_3 levels, there is usually a reciprocal increase in circulating rT_3 values suggesting a shift from activating to inactivating pathways for peripheral T_4 metabolism. However, in those conditions thus far studied, such as nonthyroidal illness, liver disease, and fasting, the rise in serum rT_3 values has been found by tracer kinetic studies to be secondary to a decrease in rT_3 clearance rather than by an increase in the level of rT_3 production (13–16). Since these are also conditions associated with reduced T_3 production, it suggests that there must be a compensatory increase in T_4 metabolism by the alternate pathways.

The purpose of the present study is to determine whether various pharmacologic agents, which have been previously described as producing absolute or relative reductions in serum T_3 levels, raise rT_3 values by increasing its production or decreasing its clearance or both. The agents tested included propylthiouracil (PTU), dexamethasone (DEX), and T_4 (7–12). If the changes observed are similar in character to those previously described in nonthyroidal illnesses and fasting, it can be inferred that a common mechanism for elevating serum rT_3 levels may be involved in all low T_3 states. Further, the administration of these agents may allow a more precise estimation of the magnitude and character of the alternate pathways for T_4 disposal.

Methods

Six healthy euthyroid male subjects, ages 24–56 yr, participated in this study. Written informed consent was obtained from each volunteer before the initiation of the protocol. All studies were approved by the Institutional Review Board of the Los Angeles County/USC Medical Center and conducted on the General Clinical Research Center of that institution.

Protocol. Subjects underwent a series of four studies over a period of 3 wk as outlined in Fig. 1. 1 d before and daily throughout the duration of the study, each subject received 10 drops of a saturated solution of potassium iodide orally to prevent thyroidal uptake and recycling of radioiodine. At 0900 hours on the morning of each study period, the subject was given 1 liter of water orally to insure adequate urine flow. A 21-gauge scalp vein needle was placed in a peripheral arm vein and maintained patent with a heparin solution (25 U/ml). At 1000 hours an intravenous bolus injection of 20 μCi of [^{125}I]rT_3 (~ 700 μCi/μg; Abbott Laboratories, North Chicago, IL) was given. Before the injection, the [^{125}I]rT_3 had been passed through a 0.22-μm millipore filter (Millipore Corp., Bedford, MA) to insure sterility. Blood samples were obtained at −15, 0, 2, 10, 20, 30, 60, 90, 120, 180,

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1. *Abbreviations used in this paper:* DEX, dexamethasone; PTU, propylthiouracyl; T_4, thyroxine; rT_3, 3,3′,5′-triiodothyronine; T_3, 3,5,3′-triiodothyronine.

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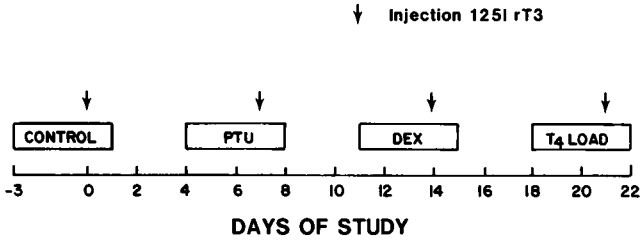

Figure 1. Experimental protocol for determining the effects of PTU, DEX, and T_4 on rT_3 clearance and production. Each arrow represents an injection of [^{125}I] rT_3. Serial blood and urine samples were obtained to assess serum disappearance and total deiodination.

240, 300, 360, 600, and 720 min after each injection to determine the disappearance pattern of the labeled rT_3. Serial urine samples were collected in 2-liter plastic bottles containing 2 ml of 25% human serum albumin (Travenol Laboratories, Inc., Glendale, CA) to bind and stabilize excreted thyronines. The collections were made every 2 h for the first 6 h and then every 6 h for the next 24 h to estimate the total deiodination of the tracer rT_3. This 30-h urinary collection period was utilized as > 90% of the total ^{125}I activity excreted had been recovered. All urine samples were refrigerated during the collection period and stored for processing. All blood samples were allowed to clot fully at room temperature before the serum was separated and stored at −20°C for processing. After the completion of the control period, the subjects were given sequentially PTU (300 mg every 6 h), DEX (2 mg every 6 h), and then an oral 3.0 mg T_4 load followed by a maintenance dose (0.30 mg every day). Each study agent was administered for a 3-d period before the rT_3 tracer studies to allow peripheral thyronine status to approach a new equilibrium. At least 3 d were allowed between each study period to minimize the influence of the previous study agent.

Sample processing. To separate labeled thyronines from radioiodine and iodoproteins, the serum samples were processed using C18 Sep-Pak cartridges (Waters Associates, Milford, MA). Each Sep-Pak cartridge was activated with 10 ml of a 50% tetrahydrofuran: 20 mM ammonium acetate (THF:NH4Ac) solution followed by 10 ml of 10% THF:NH4Ac. Serum samples, volumes ranging from 3.0 to 5.0 ml, were incubated for 3 min with an equal volume of 0.2 N NaOH and passed through an activated Sep-Pak. This was followed by a 5.0 ml wash of 10% THF:NH4Ac to eliminate radioiodide. The bound radioiodothyronines were then eluted from the Sep-Pak with 4 ml of 50% THF:NH4Ac and collected in 12 × 75 mm culture tubes, and counted on a dual channel gamma counter (TM Analytic, Elk Grove Village, IL). The average recovery of [^{125}I]rT_3 from serum was 85±1.1% (±SEM, n = 6). Less than 1% of the radioiodide, as assessed by sodium ^{131}I studies, was recovered in the thyronine elution fraction (n = 6). Greater than 99% of the iodoproteins, as assessed by radiolabeled albumin studies, were recovered in the void volume (n = 6). After appropriate corrections for recovery, individual serum tracer rT_3 disappearance curves were analyzed by noncompartmental analysis (13). Serum disappearance curve data were fitted to the sums of two or three exponentials. The data from five of the six curves in each of the control, PTU, DEX, and T_4 groups fit the sums of two exponentials better than three. The rT_3 production rates were estimated as the product of the metabolic clearance rate and the respective serum rT_3 concentration. In addition, mean serum disappearance curves for each of the groups were analyzed by both noncompartmental as well as compartmental calculations (17). The rate constants generated were used to calculate the mean serum rT_3 clearance and appearance rates. The urine samples, after acidification to a pH of 3.5 with 1.0 N HCl, were processed by the identical Sep-Pak method as detailed above to estimate the total radioiodine and radiothyronine content of each urine sample. The average recovery of [^{125}I]rT_3 from urine was 74.5±2.5% (±SEM, n = 6).

Selected serum and urine thyronine Sep-Pak eluates were analyzed by HPLC. Separation of the radiothyronines was accomplished on a reverse-phase C18 column (Water Associates) run with a gradient system ranging from 16 to 26% THF:NH4Ac and then purged of any remaining radiothyronines with a 50% THF:NH4Ac wash. Standards of labeled rT_3, 3,3′-diiodothyronine (3,3′-T_2), 3,5,3′-triiodothyronine sulfate, 3,3′-T_2 diiodothyronine sulfate and iodide were run concomitantly in the appropriate media to identify the radiothyronines in the patient sample.

Serum total T_4, T_3, rT_3, and TSH concentrations were determined by previously described radioimmunoassay procedures (6). A highly specific rT_3 antibody kindly provided by Dr. Theo J. Visser (Rotterdam, The Netherlands) was employed in the rT_3 radioimmunoassay (18).

Statistical analysis was by paired t test and results reported as mean±SEM.

Results

Table I summarizes the response of the serum thyroid hormone values after administration of each agent. After 3 d of PTU treatment, mean serum T_4 concentrations were not altered relative to control. In contrast, DEX administration decreased the mean serum T_4 levels while the oral T_4 load increased serum T_4 values. PTU administration did not significantly lower the serum T_3 levels but DEX administration did produce a decrease in T_3 levels as compared to control. As expected, serum T_3 levels were increased with the oral T_4 load. Total serum rT_3 values were increased by PTU, DEX, and oral T_4 administration, as compared to the control group. Of all the agents studied, only oral T_4 administration decreased serum TSH levels at the end of the 3-d treatment period as compared to control. Serum T_3/T_4 and rT_3/T_4 ratios are also shown in Table I. Treatment with PTU did not change the serum T_3/T_4 ratio as compared to control. DEX administration also did not decrease the T_3/T_4 ratio despite significantly lowering T_3

Table I. Serum Thyroid Function Tests

Study period	TT_4	TT_3	T_3/T_4	TrT_3	$rT_3/T_4 \times 10^{-3}$	TSH
	nmol/liter	*nmol/liter*		*nmol/liter*		*μU/ml*
Control	90.1±5.5	2.3±0.1	0.026±0.002	0.23±0.02	2.4±0.12	2.0±0.4
PTU	89.6±6.3	2.2±0.1	0.025±0.001	0.37±0.04*	3.9±0.29‡	3.6±0.8
DEX	73.2±10.2*	1.9±0.1‡	0.027±0.002	0.33±0.03§	4.7±0.59§	1.5±0.5
T_4 load	204.2±11.8‖	3.3±0.3‖	0.016±0.002‖	0.40±0.04¶	2.0±0.24	<0.01

Data presented as mean±SEM. TT_4, total serum T_4 concentration; TT_3, total serum T_3 concentration; TrT_3, total serum rT_3 concentration. * $P < 0.05$, ‡ $P < 0.03$, § $P < 0.04$, ‖ $P < 0.005$, ¶ $P < 0.02$.

values, while oral T_4 loading did decrease the T_3/T_4 ratio. This latter finding is consistent with the previously reported data showing an "autoregulatory" decrease in T_4 conversion to T_3 in man in high T_4 states (11, 12). Both PTU and DEX significantly increased serum rT_3/T_4 ratios, while no significant influence on rT_3/T_4 was found with the oral T_4 load as compared to control.

The mean serum tracer rT_3 disappearance curves in each study period are plotted in Fig. 2. Only PTU significantly altered the disappearance pattern of tracer rT_3. Estimates of rT_3 metabolic clearance rates are summarized in Table II. PTU administration decreased the clearance of tracer rT_3 while treatment with DEX and oral T_4 load had no significant influence on clearance as compared to control. PTU did not alter the rT_3 production rate while DEX administration increased the daily production rate of rT_3 as compared to control. Oral T_4 administration substantially increased the daily rT_3 production rate.

The mean serum rT_3 clearance and production rates as calculated by noncompartmental analysis were compared to the mean serum clearance and appearance rates generated by compartmental analysis. Noncompartmental analysis slightly overestimated serum clearance values in all groups as compared with those generated by compartmental analysis (8.8% in normals, 4.5% with PTU, 2.9% with DEX, and 7.8% with T_4). A similar pattern was seen when mean serum production rates calculated by each method were compared (6.3% in normals, 6.3% with PTU, 4.3% with DEX, and 8.3% with T_4).

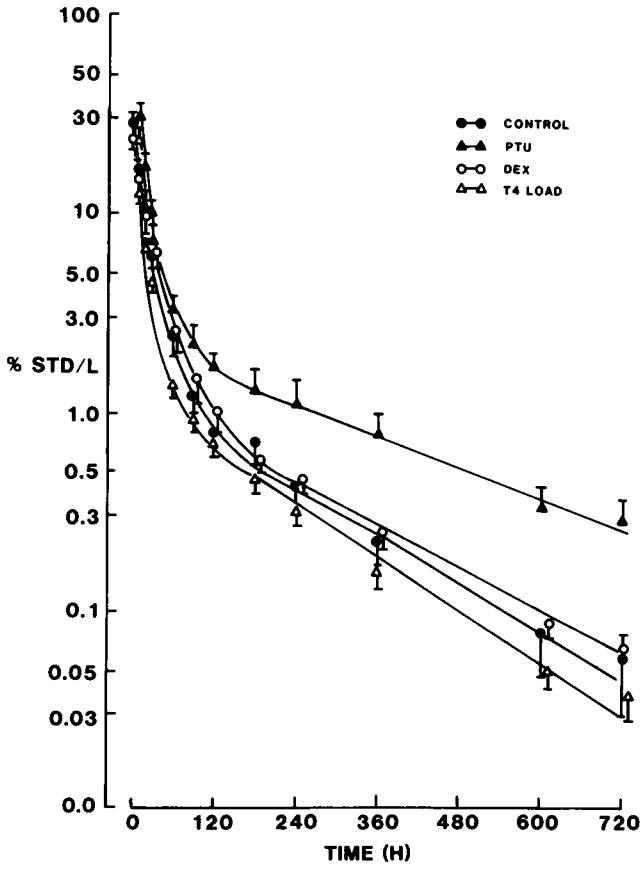

Figure 2. The serum disappearance curve of [^{125}I] rT_3 in each study group (control ●, PTU ▲, DEX ○, T_4 △). The percent dose per liter is plotted against time in minutes. The vertical bar represents mean±SEM.

Table II. Serum rT_3 MCR and Production Rates

Study period	rT_3 MCR	rT_3 PR
	liters/d	*nmol/d*
Control	156.8±22.3	29.1±3.4
PTU	105.1±16.2*	31.5±4.1
DEX	161.6±22.7	51.8±6.2*
T_4 Load	187.6±6.3	69.7±6.2‡

Data presented as mean±SEM.
MCR, metabolic clearance rate; PR, daily blood production rate (MCR × serum rT_3 concentration).
* $P < 0.02$; ‡ $P < 0.006$.

Estimates of total deiodination of tracer rT_3 in each study group are shown in Fig. 3. The fraction of rT_3 undergoing deiodination decreased both with PTU administration and after the oral T_4 load while treatment with DEX had no effect as compared to control.

Some of the urine samples, after Sep-Pak concentration, were further analyzed by reverse-phase HPLC. Note that the passage of urine through the Sep-Pak eliminated any free radioiodide present. Fig. 4 depicts the elution profile of [^{125}I]rT_3, [^{125}I]3,3'-T_2, [^{125}I]3,5,3'-triiodothyronine sulfate (T_3SO_4), [^{125}I]3,3'-diiodothyronine sulfate (T_2SO_4), and ^{125}I-Na when added to an unlabeled urine sample. A representative elution pattern of a patient's urine sample is also shown in Fig. 4 for comparison. Despite the intravenous administration of labeled rT_3, no labeled rT_3 was detected in the urine. The major urinary peak co-migrated with the 3,3'-T_2 standard and is presumably the primary deiodinative product of rT_3, 3,3'-T_2. Interestingly, a peak migrating just before the T_3SO_4 standard was found suggesting formation of an rT_3 conjugate. In this context, Mol and Visser (2) reported that the sulfate of rT_3 elutes before T_3 sulfate when using a similar mobile phase.

In selected serum extracts, HPLC analysis revealed a single peak, which comigrated with the injected rT_3 tracer (data not shown). Less than 10% of labeled rT_3 added to urine samples

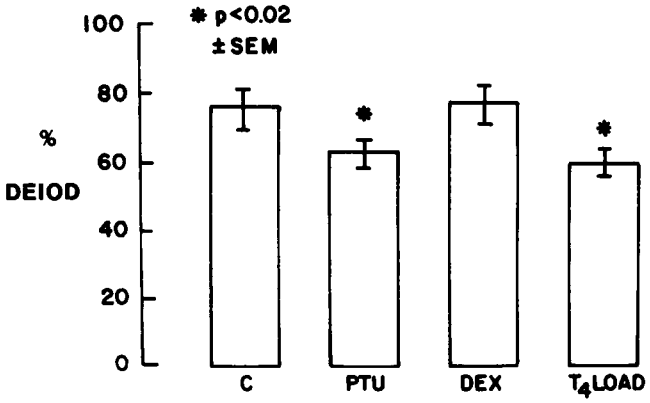

Figure 3. The percentage of total rT_3 injected that is recovered in the urine as radioiodine in each study group. Results are presented as mean±SEM.

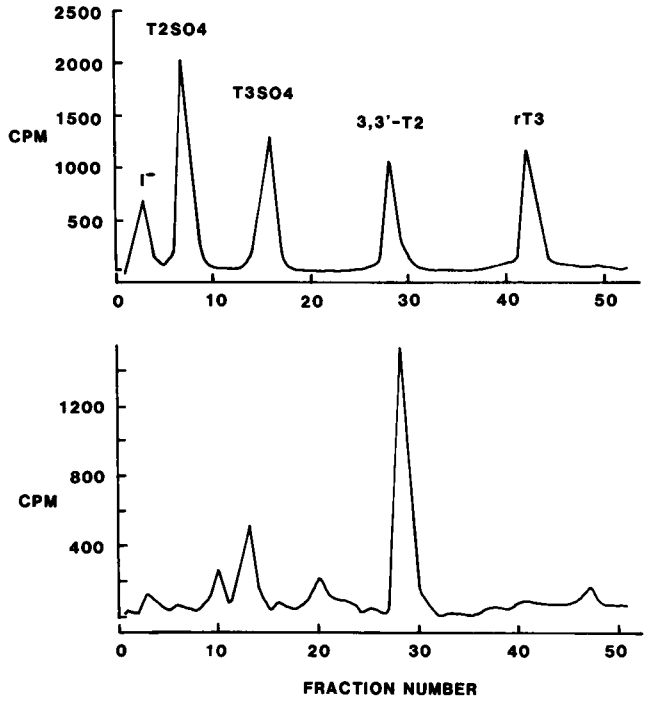

Figure 4. Reverse phase HPLC analysis of a urine labeled with a mixture of ^{125}I labeled NA, T_2SO_4, T_3SO_4, 3,3'-T_2 and rT_3 (*top*). The lower panel depicts a reverse-phase HPLC analysis of a Sep-Pak extracted urine sample from a patient receiving intravenous [^{125}I] rT_3.

was degraded to 3,3'-T_2 and I^- as shown by HPLC analysis. The remainder comigrated with the injected tracer (data not shown).

Discussion

The major finding in the present study was that PTU, DEX, and T_4 administration all produced significant elevations in serum rT_3 levels, but did so by different mechanisms. PTU, a known type I 5'-deiodinase inhibitor slowed the clearance of rT_3, which in turn, led to an increase in circulating rT_3 and the rT_3/T_4 ratio values without altering the daily rT_3 production rate (19). This is consistent with the previous work of Kaplan and co-workers who demonstrated that the administration of PTU to T_4-replaced hypothyroid patients produced a similar rise in serum rT_3 values (20). These changes are also analogous with findings previously described with fasting, liver disease, and nonthyroidal illnesses (13–16). DEX, a previously reported type I 5'-deiodinase inhibitor, also increased the circulating rT_3 and rT_3/T_4 ratio values (21). However, this appeared not to result from decreased rT_3 clearance, but rather from increased rT_3 production. T_4 administration also increased serum rT_3 values presumably by increasing substrate availability (T_4) since serum rT_3/T_4 ratio values and clearance rates remained constant. This confirms the work of Kaplan et al. who showed circulating rT_3 values vary directly with serum T_4 levels (20).

There were minor but important differences observed in rT_3 clearance and production rate estimates in euthyroid subjects. The mean normal rT_3 plasma clearance rate of 157±22 liters/d observed in this study is slightly higher than the mean values of 76 to 140 liters/d previously reported (22–25). This variance may reflect the improved isolation methods for tracer rT_3 from serum employed in this study. Some of the previous isolation techniques may have been hampered by incomplete elimination of radioiodine and iodoprotein during the extraction process (26). In the present study, the use of Sep-Pak processing for tracer rT_3 isolation virtually eliminated any contaminating radioiodine and iodoprotein. In turn, this led to a somewhat higher and presumably more accurate rT_3 clearance estimate. Despite the somewhat greater rT_3 clearance rate values, the calculated mean daily rT_3 production rate of 29 nmol/d was at the lower end of the previously reported normal range of 26 to 89 nmol/d (22–25). The principal reason for this finding appears to be that the total serum rT_3 values were systemically lower than have been generally reported. This is apparently the result of the highly specific rT_3 radioimmunoassay employed in the present study (18). This dependency of serum rT_3 estimates on antibody specificity characteristics has been previously documented by Eisenstein and co-workers (15).

This study also may shed light on the source of circulating rT_3 in man. It has been postulated that circulating rT_3 may arise from the liver as the type I-5'-deiodinase in rat liver is equally adept at removing either an inner or outer ring iodide from T_4 (27). However, the subsequent rapid intrahepatic degradation of locally produced rT_3 would prevent the liver from being a net exporter of rT_3 into the circulation (21). Recent studies by Visser et al. have shown that the 5'-deiodinase located in normal human liver has almost identical enzymatic characteristics to that present in rat liver and would presumably behave in a similar fashion (28). Further, Faber and colleagues, who estimated serum rT_3 values in the hepatic artery and portal vein in man, were unable to demonstrate a gradient of rT_3 across the liver (29). This suggests that the human liver, like the rat liver, is also not a net producer of circulating rT_3. Thus, functionally, the liver acts more as an rT_3 disposal organ rather than a producer of rT_3.

Perhaps a more likely source of circulating rT_3 would be from extrahepatic tissues where T_4 to rT_3 conversion is catalyzed by the so-called type III or 5-deiodinase enzyme system. Such a specific inner ring deiodinase system has been documented in rat skin, brain, and placenta as well as in the human placenta (30–33). Whatever the specific tissue deiodinase system responsible for rT_3 generation from T_4 in man, it does not appear to be inhibited by PTU since rT_3 production rates were not altered by the amount of PTU employed (1,200 mg/d). It is of interest that such PTU dosages will inhibit 80% of outer ring T_4 deiodination in man (34). Although the lack of PTU inhibition in vivo is consistent with the observations in rat brain and skin in vitro, a possible exception may exist in rat and human placenta where rT_3 generation is inhibited (32, 33). It would appear that a differential inhibitory effect of PTU exists at various tissue sites. Clarification of this discrepancy will have to await the full biochemical characterization of this enzyme system.

DEX administration had no effect on rT_3 clearance, but did increase the total daily rT_3 production rate. To our knowledge, this is the first reported instance where increased levels of circulating rT_3 resulted from augmented production rather than by decreased clearance. In turn, this suggests that DEX

may directly stimulate the type III 5-deiodinase. The finding by Osathanondh and colleagues of an increase in amniotic fluid rT_3 levels in pregnant women administered DEX is consistent with this observation (35). However, McCann et al. were unable to show any influence of corticosterone acetate on the type III 5-deiodinase system in rat liver in vitro (36). This may reflect either species variability or tissue specific regulation of type III 5-deiodinase enzyme activity.

Both compartmental and noncompartmental analysis of mean serum rT_3 tracer disappearance curves were performed in the present study. Computation of blood rT_3 clearance rate estimates differed by < 10% using these two methods. More importantly, these differences did not alter the basic conclusions reached regarding the changes in the calculated rT_3 production rates observed in the various study groups. Because of the multiple assumptions required for the compartmental approach (i.e., number of compartments, source of production, sites of degradation, so forth), noncompartmental analysis was used for calculation of the production estimates. Although compartmental analysis may potentially provide some information regarding the source of the increased rT_3 production noted with glucocorticoid administration, without independent validation of this model separate from serum rT_3 disappearance curves, such analysis would appear to be highly problematical.

The lack of detectable tracer rT_3 in the urine as analyzed by HPLC was also a surprising finding. This phenomena was not due to breakdown of rT_3 as minimal degradation of labeled rT_3 occurred when added to fresh unlabeled urine samples that were incubated at 37°C overnight. This observation is consistent with the findings of Rogowski and colleagues and Faber et al. who were unable to detect stable rT_3 in urine using a specific radioimmunoassay (37, 38). The lack of rT_3 in urine may be due to either tubular reabsorption of filtered rT_3 and/or rapid deiodination of rT_3 by renal tubular 5'-deiodinase enzyme systems (39). The predominance of 3,3'-T_2 in the urinary thyronine metabolite fraction suggests that the tracer rT_3 had been deiodinated, which is consistent with the observations in a perfused rat kidney where rapid deiodination of [^{125}I]rT_3 occurs with the identifiable urinary excretory products being iodide and 3,3',T_2 (40).

Another somewhat unexpected by-product was the minimal effect that PTU administration had on circulating T_3 levels and T_3/T_4 ratio values in our subjects. This was surprising since PTU is known to inhibit the hepatic type I-5'-deiodinase system. This contrasts with other studies where dramatic falls in circulating T_3 and T_3/T_4 ratios have occurred in subjects administered similar doses of PTU. Abuid and Larsen and Croxson et al. observed an ~ 50% decrease in circulating T_3 levels in hyperthyroid patients administered PTU (41, 42). Further, Saberi et al. and Geffner and co-workers showed a less striking decrease of serum T_3 in T_4-replaced hypothyroid patients administered up to 1,000 mg of PTU per day (7, 8). One possible explanation for the failure of serum T_3 concentrations to fall in the present study may be due to a compensatory increase in TSH-mediated T_3 secretion by the thyroid gland. However, this seems unlikely as serum TSH levels were only modestly but not significantly increased. Another interpretation would be that the source of circulating T_3 varies with the level of serum T_4 concentration (43). Silva et al. have suggested that up to 40% of the circulating T_3 in the adult rat is generated from the type II 5'-deiodinase pathway and that an even greater proportion is derived from this pathway in the neonatal rat (44, 45). Similar estimates of T_3 generation in the rat have also been made by DiStefano and colleagues employing kinetic models suggesting that ~ 50% of the circulating T_3 is derived from the so-called "slow pool" where type II 5'-deiodinase enzyme systems predominate (46).

DEX administration also produced lower serum T_3 values, but did so in proportion to the decline in circulating T_4 levels. This may reflect a vascular-tissue redistribution effect of DEX on T_4 and T_3 rather than an alteration in T_4 to T_3 conversion efficiency. This contrasts with the rapid fall in circulating T_3 levels seen in thyrotoxic Graves' patients treated with DEX (11). Thus, as with PTU, the effectiveness of DEX in lowering T_3 levels may be related to the circulating T_4 values. Supporting this view were the findings of Ferguson and Jennings who observed that a marked decrease in the conversion efficiency of T_4 to T_3 could only be demonstrated when pharmacological doses of T_4 were employed in a perfused liver preparation from DEX-treated rats (47). Cavalieri et al. reported that whole body conversion rates of tracer T_4 to T_3 were reduced in intact T_4-replaced hypothyroid rats treated with DEX (48). However, these results were complicated by the unexpected alterations in the metabolism of tracer T_3, including changes in T_3 distribution and tissue binding as well as slowing of its clearance. This contrasts with the apparent lack of effect that DEX administration has on tracer T_3 distribution and clearance in man (49). Thus, it would appear that the intact rat and man may not be comparable models in studying the effects of glucocorticoids on peripheral thyroid hormone metabolism.

Clearly the present study revealed that peripheral rT_3 metabolism in man is somewhat more complex than has been previously appreciated. Specifically, the source of circulating rT_3 most likely orginates from extrahepatic tissues containing the type III 5-deiodinase, that the activity of this enzyme system is not influenced by PTU but stimulated by DEX, and that the proportion of T_4 metabolized to circulating rT_3 does not vary with substrate availability indicating that this is a low affinity, high capacity enzyme system.

Acknowledgments

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