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Propylthiouracil inhibits the conversion of l-thyroxine to l-triiodothyronine: *An explanation of the antithyroxine effect of propylthiouracil and evidence supporting the concept that triiodothyronine is the active thyroid hormone*

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6-*n*-propylthiouracil (PTU) administered to male Sprague-Dawley rats maintained on 2 and 5 μg L-thyroxine (T_4)/100 g body weight resulted in a marked reduction in the rate of conversion of L-thyroxine to L-triiodothyronine (T_3). These effects could not be ascribed to induced hypothyroidism since the group maintained on 5 μg T_4/day had normal levels of liver mitochondrial alpha glycerophosphate dehydrogenase. In confirmation of previous studies, PTU also reduced the fractional rate of deiodination of T_3. These observations provide a possible explanation of the many published observations indicating that PTU antagonizes the tissue effects of T_4 but not of T_3. The data suggest that monodeiodination of T_4 but not of T_3 is essential before hormonal effects can be manifested at the cellular level.

Propylthiouracil Inhibits the Conversion of L-Thyroxine to L-Triiodothyronine

AN EXPLANATION OF THE ANTITHYROXINE EFFECT OF PROPYLTHIOURACIL AND EVIDENCE SUPPORTING THE CONCEPT THAT TRIIODOTHYRONINE IS THE ACTIVE THYROID HORMONE

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ABSTRACT 6-*n*-propylthiouracil (PTU) administered to male Sprague-Dawley rats maintained on 2 and 5 μg L-thyroxine (T_4)/100 g body weight resulted in a marked reduction in the rate of conversion of L-thyroxine to L-triiodothyronine (T_3). These effects could not be ascribed to induced hypothyroidism since the group maintained on 5 μg T_4/day had normal levels of liver mitochondrial alpha glycerophosphate dehydrogenase. In confirmation of previous studies, PTU also reduced the fractional rate of deiodination of T_3. These observations provide a possible explanation of the many published observations indicating that PTU antagonizes the tissue effects of T_4 but not of T_3. The data suggest that monodeiodination of T_4 but not of T_3 is essential before hormonal effects can be manifested at the cellular level.

INTRODUCTION

In addition to its well recognized effects on intrathyroidal iodine metabolism, 6-*n*-propylthiouracil (PTU)[1] inhibits the peripheral hormonal manifestations of injected T_4. Thus, in rats PTU and many related thiouracil-type compounds reduce the capacity of a given dose of T_4 to increase the oxygen consumption of the whole animal (1–6) and isolated tissues (7, 8), to raise the activity of mitochondrial alpha glycerophosphate dehydrogenase (α-GPD) in heart, liver, and kidney (5, 8–10), to inhibit the pituitary release of TSH (7, 11–14), and to decrease the heart rate (15). The peripheral tissue effects of PTU have been attributed to the capacity of this drug to inhibit T_4 deiodination (7, 15–20). Curiously, however, PTU does not antagonize the peripheral effects of injected T_3; a variety of studies show either no change, or in fact a slight increase in the tissue effects of T_3 when administered to PTU-treated animals (4–6, 10, 14, 21). although the biological effects of T_3 are not decreased, PTU inhibits its deiodination as effectively as it does the deiodination of T_4 (15, 17, 20).

The recent demonstration that T_4 is converted to T_3 under physiological conditions both in man (22–24) and in the rat (25) afforded a possible explanation of these findings. Quantitative considerations based on the biological potency ratio of T_3 to T_4 and the extent of T_4 to T_3 conversion in the rat raised the possibility that all of the hormonal effect of injected T_4 may be derived from its peripheral conversion to T_3 (25). Thus, if PTU inhibited the monodeiodination of T_4 to form T_3, a marked

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[1] *Abbreviations used in this paper:* α-GPD, alpha glycerophosphate dehydrogenase; PTU, propylthiouracil; T_3, L-triiodothyronine; T_4, L-thyroxine; TSH, thyroid-stimulating hormone.

TABLE 1

Effect of PTU on Conversion of T_4 to T_3

Group	n	(T_3/T_4) Observed	(T_3/T_4) Corrected	λ_4	K	CR
				hr^{-1}	hr^{-1}	%
PTU + 2 μg T_4/100 g body wt.	12	0.0262*±0.0030	0.0224*±0.0031	0.0344*±0.0013	0.0026*±0.0004	7.51*±0.90
PTU + 5 μg T_4/100 g body wt.	6	0.0174*±0.0041	0.0153*±0.0070	0.0456±0.0170	0.0028*±0.0008	6.20*±1.76
Control‡	11	0.1000±0.0038	0.0873±0.0038	0.0492±0.0020	0.0083±0.0008	16.9±1.0

Explanation of symbols: n, number of animals in each group; T_3/T_4, the ratio of istopic T_3 to T_4 in the carcass; λ_4, fractional removal rate of T_4; K, fractional rate of nonradioactive T_4 to T_3 conversion; CR, conversion ratio = $(K/\lambda_4) \times 100$.

* Statistically different from control group at $P < 0.01$ level (Student's t test). Conversion ratios for 2 μg and 5 μg T_4 groups were not significantly different from each other.

‡ Control data has previously been published (25). Mean ±SE are indicated.

reduction in T_4 hormonal effects would be anticipated. On the other hand, inhibition of deiodination of T_3 would not be expected to result in a diminution in hormonal effect. The following studies were therefore undertaken to determine whether in fact PTU inhibits the conversion of T_4 to T_3.

METHODS

Methods for quantitating the conversion of T_4 to T_3 in PTU-treated male Sprague-Dawley rats (100–150 g) were identical to those described in a previous communication dealing with this phenomenon in untreated animals (25). In brief, animals were killed 48 hr after the injection of tracer ^{125}I-T_4. The carcass was homogenized and extracted with ethanol. After addition of authentic ^{131}I-T_3, T_3 in the extract was isolated and purified by serial chromatography in three paper and one thin-layer cycles. The final eluate of the T_3 region was chromatographed on paper in three different solvent systems. The ratio of ^{131}I-T_3 to ^{125}I-T_3 was determined and the content of ^{125}I-T_3 in the carcass calculated. Account was taken of artifactual in vitro T_4 to T_3 conversion by repeating similar procedures in animals killed within 1 min after the intravenous injection of tracer ^{125}I-T_4. The fractional removal rate of T_4 (λ_4), was determined from the residual T_4 in the carcass. The fractional removal rate of T_3 (λ_3), was measured in a separate series of paired animals as previously described (26). It was possible to calculate K, the fractional rate of nonradioactive T_4 to T_3 conversion, and the conversion ratio (CR), the percentage of nonradioactive T_4 ultimately converted to T_3, by appropriate substitution of carcass ^{125}I-T_3/^{125}I-T_4, λ_4, and λ_3, and $t = 48$ hr into the following equation derived in reference 25,

$$CR = \frac{K(100)}{\lambda_4} = \frac{200\left(\frac{^{125}\text{I-T}_3}{^{125}\text{I-T}_4}\right)\left(\frac{\lambda_3}{\lambda_4} - 1\right)}{1 - e^{-(\lambda_3 - \lambda_4)t}}.$$

In some animals, fecal and urinary radioactivity were also measured. The fraction of total radioactivity disposed of via the deiodinative pathways, F_u, and the fraction of total radioactivity disposed via the fecal route, F_f, were calculated as previously described (26). The fractional fecal excretion rate (λ_f) and the fractional deiodinative removal rate (λ_u) were calculated respectively from the product of λ and F_f and λ and F_u.

Animals were maintained on 0.10% PTU in their drinking water from 3.5 to 8 wk. During this period, T_4 was administered daily by subcutaneous injection in 0.01 N NaOH solution (2 and 5 μg/100 g body weight). The animals were in good health during this period and gained weight normally. Since the present series of studies followed immediately upon our analysis of T_4 to T_3 transformation in untreated animals and since an identical strain of rats and identical techniques were used, the results of the previously published study were considered adequate as controls in determining the T_4 to T_3 transformation under the influence of PTU. The level of the mitochondrial enzyme α-GPD was determined by the method of Lee and Lardy (27).

RESULTS

PTU effects a marked reduction in the fractional conversion of T_4 to T_3 (Table I). In both groups of PTU-treated animals, the conversion ratio was reduced to at least 40% of the control value.[2] There was no statistical difference between the conversion ratio of the PTU-treated group supplemented with 2 μg T_4/100 g body weight and those PTU-treated animals supplemented

[2] Since PTU is known effectively to block thyroidal synthesis of T_4 and T_3, the theoretical possibility arises that the lower T_3 content in the PTU-treated animals is attributable to a more effective thyroidal blockade provided by the PTU than by the 1 mg NaI alone administered daily to the control group. This explanation, however, is not tenable since less than 0.06% of the radioactivity in the injected ^{125}I-T_4 dose was found in the thyroid of control animals 48 hr after injection. The release rate of total thyroidal radioactivity from the gland in animals treated with a high iodine diet is small, less than 20% per day. Thus, the amount of free T_3, either in the gland or in the carcass derived from recycled labeled iodine, is several orders of magnitude less than the ^{125}I-T_3 actually observed.

The possibility that the results obtained were due to a differential extraction of T_3 in control and PTU-treated animals was considered. Successive extractions were performed in two PTU and two control animals sacrificed within 2 min after the injection of a combined dose of ^{131}I-T_4 and ^{125}I-T_3. The extraction characteristics were the same for both iodothyronines and there was no difference between control and PTU-treated animals.

TABLE II

Mitochondrial α-GPD in PTU-Treated Rats

	α-GPD	P
	ΔOD/mg per min	
Normal	0.1355±0.0135	
PTU + 5 μg T_4	0.1294±0.0087	NS
Normal	0.0981±0.0106	
PTU + 2 μg T_4	0.0483±0.0028	< 0.001
Thyroidectomized	0.0396±0.0038	< 0.001

Mean ±SE are indicated. Statistical comparisons are made with simultaneously run untreated intact rats.

with 5 μg/100 g body weight. As indicated in Table II, administration of 2 μg T_4/100 g body weight, however, was insufficient to maintain the animals in the euthyroid state. This was inferred from the reduced activity of hepatic mitochondrial α-GPD, an enzyme which has been shown to be a sensitive index of the thyroidal state of tissues (*27*). Since the daily dose of T_4 required to maintain the euthyroid state is probably 2 μg/100 g body weight or less (8, 28), the finding of a low α-GPD is probably an example of the well documented antagonism between PTU and T_4 which prompted this study. Since the administration of 5 μg T_4/100 g body weight led to a normal liver activity of α-GPD, the reduction in the fractional conversion of T_4 to T_3 in this group cannot be ascribed to hypothyroidism.

Table III summarizes kinetic data obtained in those groups which were studied primarily in order to determine the fractional removal rate of T_3, (λ_3), in the treated animals. As pointed out above, this value is necessary in the calculation of T_4 to T_3 conversion. In confirmation of previous studies (15, 17, 20), PTU effected a marked reduction in the fraction of labeled iodine from T_3 and T_4 which was disposed of via deiodinative pathways (F_u). PTU caused a modest reduction in the fractional removal rate of T_4 (λ_4). In the case of T_3, PTU appeared to reduce slightly the fractional removal in the animals treated with 2 μg/100 g body weight and to increase slightly the fractional removal rate in the animals treated with 5 μg/100 g body weight. In all cases, however, the fractional rate of deiodination (λ_u) was markedly reduced in PTU-treated animals. Of interest was the slight but consistent increase in the fractional rate of fecal excretion (λ_f) in all groups. An increase in the fractional disposition via the fecal route offsets the decreased fractional rate of deiodination, thus stabilizing the overall fractional removal rate ($\lambda = \lambda_u + \lambda_f$). It is entirely probable that the increase in the fraction of hormone iodine excreted via the fecal pathway (F_f) is related to the increase in biliary clearance of T_4 and T_3 previously reported by Lang and Premachandra (*29*). A decrease in distribution space, especially in the case of T_3 was noted. Unfortunately, no plasma binding studies were performed in order to assess the contribution of alterations in plasma binding to the reduction of distribution volume. Increased binding of rat plasma proteins associated with hypothyroidism (30), however, could not explain the reduced distribution volume of T_3 since this change was also found in the group of animals treated with 5 μg T_4/100 g body weight, a dosage regimen which maintained animals in the euthyroid condition.

DISCUSSION

The most important result of these studies is the demonstration that PTU causes a marked reduction in the fractional conversion of T_4 to T_3. No information is currently available regarding the site of inhibition, nor is it known where monodeiodination of T_4 occurs. In this connection, however, it is of interest to evaluate the ratio K/λ_u,

TABLE III

Effect of PTU on Tracer T_3 and T_4 Metabolism

	n	V_T	F_u	F_f	λ	λ_u	λ_f
		ml/100 g body wt.			hr^{-1}	hr^{-1}	hr^{-1}
^{125}I–T_3							
Control	10	213.0±29.2	0.49±0.03	0.51±0.03	0.122±0.0020	0.0600±0.0039	0.0626±0.0031
PTU + 2 μg T_4	10	107.8*±8.1	0.16*±0.01	0.84*±0.01	0.0982*±0.0036	0.0158*±0.0011	0.0823*±0.0037
PTU + 5 μg T_4	8	119.7*±16.3	0.22*±0.02	0.78*±0.02	0.1384±0.0092	0.0294*±0.0036	0.1090*±0.0061
^{125}I–T_4							
Control	10	21.2±1.0	0.40±0.02	0.60±0.02	0.0461±0.0013	0.0183±0.0012	0.0278±0.0010
PTU + 2 μg T_4	10	18.1*±0.4	0.13*±0.01	0.87*±0.01	0.0398*±0.0016	0.0050*±0.0003	0.0347*±0.0015

* Significant difference from control at $P < 0.01$ level.

Explanation of symbols: n, number of animals in group; V_T volume of distribution; F_u, fraction of labeled hormone iodine excreted in urine; F_f, fraction of labeled hormone iodine excreted in feces; λ, fractional removal rate of hormone (per hour); $\lambda_u = (\lambda)(F_u)$; $\lambda_f = (\lambda)(F_f)$. Mean ±SE indicated.

where K is fractional rate of conversion of T_4 to T_3 and λ_u, the fractional deiodinative removal rate of T_4. From the data in Tables I and III, one can calculate that in control animals $K/\lambda_u = 0.45$ and in PTU-treated animals, 0.52. These results suggest that one-half of all T_4 which is deiodinated is converted to T_3. Recent data from our laboratory are compatible with the idea that iodine atoms are detached from both the inner and outer ring of T_4 in a random fashion (31). If deiodination occurs more rapidly than transformation of other parts of the thyronine molecule, random deiodination would result exactly in a 50% conversion of T_4 to T_3. These considerations raise the interesting possibility that T_3 formation is an obligatory step in all biological deiodination of T_4 regardless of the tissue involved.

If one assumes that the entire hormonal potency of injected T_4 is derived from its conversion to T_3, it is possible to provide an estimate of the degree of inhibition of T_4 activity expected to result from the concurrent administration of PTU. Within a restricted range, hormonal tissue effects appear to be grossly proportional to the exchangeable hormonal tissue pool (32). Since only 5% of total body T_3 in the rat is bound to plasma protein, and the rest is contained within the cells (26), the total exchangeable body pool of T_3 can be regarded as a first approximation of the tissue pool. Thus, the following equation can be written:

$$\Delta E = \alpha P_3 = \frac{\alpha(CR)S_4}{100\lambda_3}$$

where ΔE is the increment in a given hormonal tissue effect over base line hypothyroid levels produced by S_4, the daily dose of injected T_4; α, a proportionality constant; P_3, the exchangeable body pool of T_3; CR, the conversion ratio expressed in per cent; and λ_3, the fractional rate of T_3 removal. It is assumed that in this system, the only source of T_3 is the injected T_4. If PTU exerts its effects by inhibiting the conversion of T_4 to T_3, it follows that

$$\frac{\Delta E_{PTU}}{\Delta E_{CON}} = \frac{(CR)_{PTU}}{(CR)_{CON}} \cdot \frac{(\lambda_3)_{CON}}{(\lambda_3)_{PTU}}$$

where the subscripts refer to control and PTU-treated groups.

If we substitute in the expression the average value for the conversion ratio in PTU-treated (6.9%), control animals (16.9%), and the corresponding average λ_3 in control animals (0.122/hr) and PTU-treated animals (0.118/hr), the predicted value for $\Delta E_{PTU}/\Delta E_{CON}$ would be 0.42. Experimentally, the value for $\Delta E_{PTU}/\Delta E_{CON}$ can be estimated best from the data of Hoffman, Richert, and Westerfield (5) in which the effect of PTU on the increase in tissue mitochondrial α-GPD is measured at various doses of injected T_4. For liver, $\Delta E_{PTU}/\Delta E_{CON}$ is 0.37 and for kidney, $\Delta E_{PTU}/\Delta E_{CON}$, 0.47. The anticipated decrease in T_4 activity brought about by PTU is thus in general agreement with the experimentally observed values. Because the effect of PTU on the fractional turnover of T_3 is not marked, it is apparent that PTU would be expected to have no major effect on the effectiveness of injected T_3. In fact, a slight slowing of the fractional turnover might explain the enhanced effectiveness of T_3 reported in some of the published studies.

The internal consistency of this formulation lends additional credence to the concept that most, if not all, of the hormonal effect of T_4 is due to its conversion to T_3. This proposal was first advanced by Gross and Pitt-Rivers (33) and was supported specifically by the studies of Maclagan, Sprott, and Wilkinson (34) and Wilkinson and Maclagen (35). Nevertheless, the report by Lassiter and Stanbury negating T_4 to T_3 conversion in man (36) led to an abandonment of the concept that T_3 was the active thyroid hormone. Renewed interest in the problem was aroused by the demonstration by Braverman, Ingbar, and Sterling (22) that T_4 to T_3 conversion did in fact occur in man and that the earlier conclusion by Lassiter and Stanbury was premature. Additional evidence favoring the concept that T_3 is the active hormone has been the finding of limited capacity anterior pituitary sites for T_3 but not T_4 (37) and the demonstration of stereospecific binding of T_3 but not T_4 by rat hepatic and renal nuclei (38).

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