

Propylthiouracil Blocks Extrathyroidal Conversion of Thyroxine to Triiodothyronine and Augments Thyrotropin Secretion in Man

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ABSTRACT Propylthiouracil (PTU) inhibits peripheral deiodination of thyroxine (T_4) and triiodothyronine (T_3) and decreases the metabolic effectiveness of T_4 in animals. To assess the effect of PTU on extrathyroidal conversion of T_4 to T_3 in man, 15 studies were performed in 7 athyreotic patients treated with 100 or 200 μg of L- T_4 daily for 1 mo before the addition of PTU, 250 mg every 6 h for 8 days. Serum T_3 , T_4 , and thyrotropin (TSH) were measured daily by radioimmunoassay; serum TSH response to 500- μg thyrotropin-releasing hormone (TRH) was measured before and on the last day of giving PTU.

On the 100- μg L- T_4 dose, serum T_3 fell from 120 ± 5 (SE) to 83 ± 6 ng/dl ($P < 0.005$) with return to 113 ± 5 ng/dl after stopping PTU; serum T_4 (4.5 ± 0.3 $\mu\text{g}/\text{dl}$) did not change. Similar results were seen in patients taking 200 μg of L- T_4 daily. On the 100- μg dose of L- T_4 the fall in T_3 was accompanied by a reciprocal rise in serum TSH to $195 \pm 33\%$ of initial concentration ($P < 0.01$) with return to $104 \pm 8\%$ after PTU. The serum TSH response to TRH ($\Delta\mu\text{U}/\text{ml}$ over base line) was greater during PTU therapy than during the control period. On 100- μg L- T_4 , ΔTSH rose from 64 ± 19 to 101 ± 23 $\mu\text{U}/\text{ml}$ ($P < 0.005$). Expressed as percent of base-line TSH concentration, TSH rose from 140 ± 52 to $280 \pm 44\%$ (control vs. PTU) at 15 min, 265 ± 72 to $367 \pm 63\%$ at 30 min, 223 ± 54 to $313 \pm 54\%$ at 45 min, 187 ± 45 to $287 \pm 51\%$ at 60 min, and 145 ± 22 to $210 \pm 28\%$ at 120 min after TRH.

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The data suggest that PTU blocks extrathyroidal conversion of T_4 to T_3 , thus increasing pituitary TSH secretion and augmenting the TSH response to TRH.

INTRODUCTION

Antithyroid drugs of the thiocarbamide type, such as propylthiouracil (PTU),¹ have been used for the treatment of hyperthyroidism for over 30 yr. PTU appears to exert its primary effect on the synthesis of the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), by blocking oxidative iodination within the thyroid gland itself (1, 2). In addition, some of the thiocarbamides alter the metabolism of thyroid hormones outside of the thyroid gland by interfering with the peripheral deiodination of T_4 and T_3 in experimental animals (3-10) and in man (10-13). This extrathyroidal action is independent of the first effect (14). The inhibition of peripheral deiodination is associated with a decrease in the biologic effectiveness of administered T_4 as measured by a decrease in metabolic rate or induction of oxidative enzymes in vivo (15-20) and in vitro (21-23) and an increase in thyrotropin (TSH) secretion (24-28). The thiocarbamide drugs that decrease T_4 deiodination are the ones that also decrease its metabolic effectiveness (14). These same drugs also decrease T_3 deiodination but have no effect on the biologic effectiveness of T_3 or actually potentiate it (5, 14, 19).

Since the reintroduction of the concept that a sig-

¹Abbreviations used in this paper: CPB, competitive protein binding; PBI, protein-bound iodine; PTU, propylthiouracil; RIA, radioimmunoassay; TRH, thyrotropin-releasing hormone; TSH, thyrotropin; T_3 , triiodothyronine; T_4 , thyroxine.

nificant amount of T_3 is produced by the peripheral deiodination of T_4 (29), interest has arisen in the clinical effects of PTU on the peripheral metabolism of T_4 . Oppenheimer, Schwartz, and Surks (23) have demonstrated that PTU decreases the calculated rate of conversion of T_4 to T_3 in thyroidectomized T_4 -treated rats. We have investigated the effect of PTU on the serum concentrations of T_3 , T_4 , and TSH, and the TSH response to thyrotropin-releasing hormone (TRH) in athyreotic patients maintained on L- T_4 .

METHODS

Subjects. 16 studies were carried out on 7 totally athyreotic male patients. Six patients had had total surgical thyroidectomies followed by ablative doses of radioactive iodine, and one patient had idiopathic myxedema. Proof of the athyreotic state was based on lack of significant radioiodine uptake and no evidence of its accumulation on scan, serum T_4 less than 1 $\mu\text{g}/\text{dl}$ and T_3 less than 50 ng/dl, and lack of T_4 or T_3 elevation in response to the TRH-mediated rise of serum TSH concentration.

Three patients had atherosclerotic cardiovascular disease, one of whom was taking digoxin during the time of study. One patient had a transitional cell carcinoma of the bladder resected a year before the study with no evidence of recurrence or of renal insufficiency. One patient had Parkinson's disease and was taking L-dopa and trihexyphenidyl hydrochloride during the study. None of the others was taking any medication known to affect thyroidal or pituitary function. The patients gave their informed consent to participate in the studies.

All patients were treated daily with 100 μg of a commercial preparation of sodium levothyroxine (L- T_4) for at least 1 mo before admission to the metabolic unit. In addition, five of the patients were restudied after they had been taking 200 μg of L- T_4 daily for at least 1 mo. A single commercial preparation of L- T_4 (lot ZE040) was kindly supplied by Flint Labs., Morton Grove, Ill., and used throughout the study. The T_3 content was 0.76% (by weight) of the T_4 content.

Bloods were collected daily for determination of serum TSH, T_4 , and T_3 during hospitalization. The patients' white cell counts and liver function were also monitored. After a control period of several days to determine basal concentrations, the L- T_4 -treated patients were given PTU, 250 mg every 6 h, for 8 days. TSH, T_4 , and T_3 concentrations were also determined before, and on the 7th day of, PTU treatment at 2, 6, 10, and 14 h after administration of the L- T_4 dose. TRH testing of pituitary TSH responsiveness was carried out at least once before, and on the last day of, PTU administration.

Serum determinations. T_3 (30) and TSH (31) were measured by radioimmunoassay (RIA). T_4 was determined by both RIA (32) and competitive protein binding (CPB) (33). Protein-bound iodine (PBI) (done by Bio-Science Laboratories, Van Nuys, Calif.), total protein, albumin, and T_3 resin index (using the Thyopac-3 of Amersham/Searle Corp., Arlington Heights, Ill.) were determined on selected sera.

Infusions. Synthetic TRH was kindly supplied by Abbott Laboratories, North Chicago, Ill. It was administered in the morning after an overnight fast. A 19-gauge butterfly needle was inserted in an antecubital vein for collection of blood specimens 15 min before, at the time of, and 15, 30,

45, 60, 120, and 240 min after injection of a 500- μg bolus of TRH.

Statistics. Change in serum concentrations of T_3 , T_4 , and TSH were evaluated for significance by the method of paired *t* testing (34).

RESULTS

Effect of PTU on T_3 , T_4 , and TSH. Fig. 1 shows the response to PTU in a typical patient taking 100 $\mu\text{g}/\text{day}$ of L- T_4 and a month later 200 $\mu\text{g}/\text{day}$ of L- T_4 . Fig. 2 depicts the average daily T_3 , T_4 , and TSH concentrations during nine studies in the patients taking 100 μg of L- T_4 each day. Serum T_3 concentration decreased significantly after the 2nd day of PTU administration. T_3 fell from a mean of 120 ± 5 (SE) to 83 ± 6 ng/dl by the 7th day on PTU ($P < 0.005$). After discontinuation of PTU, T_3 rose rapidly to initial serum concentrations (113 ± 5 ng/dl). Serum T_4 concentrations did not change significantly, remaining at about 5.5 ± 0.3 (by RIA) or 4.5 ± 0.2 $\mu\text{g}/\text{dl}$ (by CPB). Average serum PBI was 4.6 ± 0.5 before PTU and 4.9 ± 0.5 $\mu\text{g}/\text{dl}$ on the 7th day of PTU. Serum TSH rose to $195 \pm 33\%$ of average basal TSH concentrations during PTU ad-

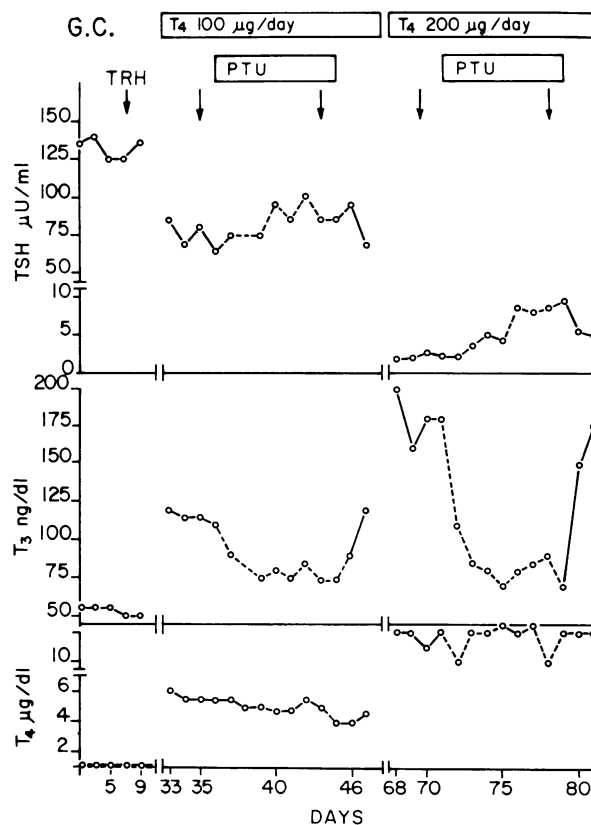


FIGURE 1 The effect of PTU 250 mg every 6 h on daily serum TSH, T_3 , and T_4 , measured by RIA in an athyreotic patient who had been receiving 100 and then 200 μg of L- T_4 a day for 1 mo before study. Arrows indicate tests with TRH.

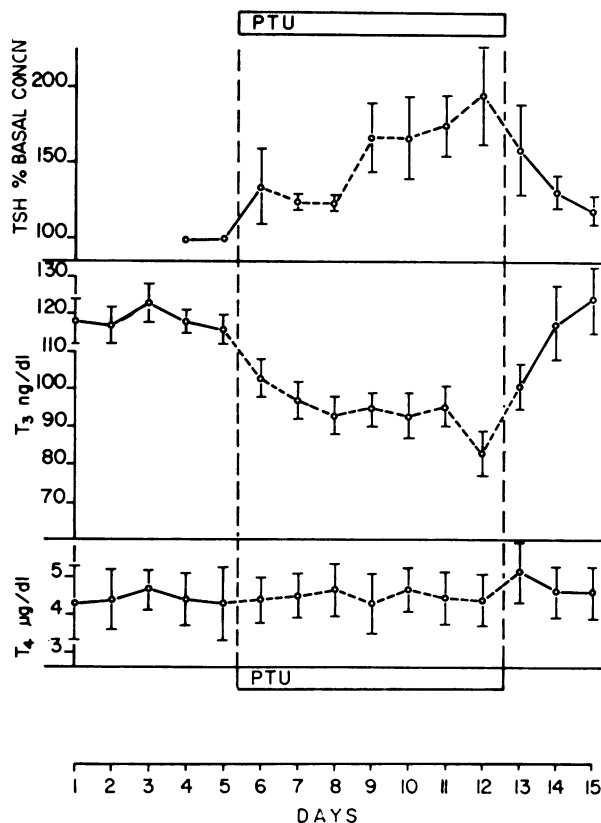


FIGURE 2 The effect of PTU 250 mg every 6 h on average daily serum concentrations of TSH, T_3 , and T_4 measured by RIA during nine studies in athyreotic patients who had been receiving 100 μg of L- T_4 a day for 1 mo before study. Vertical bars represent SE.

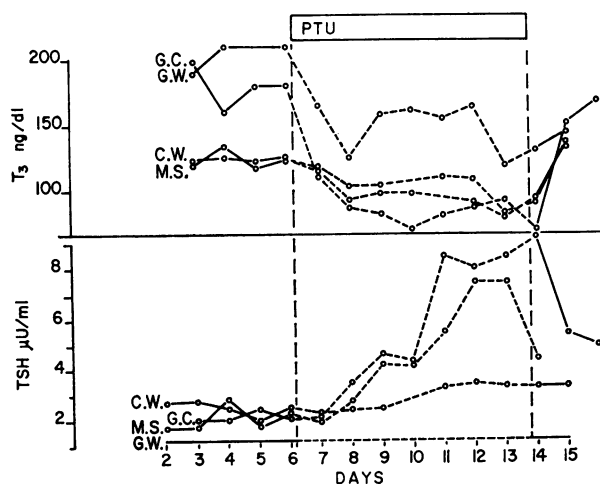


FIGURE 3 The effect of PTU 250 mg every 6 h on daily serum concentrations of T_3 and TSH in four athyreotic patients who had been receiving 200 μg of L- T_4 a day for 1 mo before study.

ministration. Based on analysis by paired *t*-testing of individual values in microunits per milliliter on the 5th and 12th days of the protocol, there was a significant increment in serum TSH ($P < 0.01$). TSH returned to basal concentrations ($104 \pm 8\%$) upon discontinuation of PTU.

Fig. 3 depicts individual values of several of the patients taking 200 μg of L- T_4 a day whose serum TSH concentrations were detectable in our assay. T_3 fell from a mean of 150 ± 19 to 97 ± 9 ng/dl during PTU administration. Serum T_4 concentration (RIA) rose from 10.5 to 11.5 $\mu\text{g}/\text{dl}$; this change was not significant in this small group of patients. There was no change in serum PBI or T_3 resin uptake before and during PTU administration in either group.

Effect of PTU on TSH response to TRH. Fig. 4 shows the TSH response to TRH during eight studies carried out in the patients taking 100 μg of L- T_4 a day. Expressed as a percent of initial TSH concentrations, the TSH response in the control period compared with the response during PTU administration was significantly augmented from 140 ± 52 to $280 \pm 44\%$ at 15 min; 265 ± 72 to $367 \pm 63\%$ at 30 min; 223 ± 54 to $313 \pm 54\%$ at 45 min; 187 ± 45 to $287 \pm 51\%$ at 60 min, and 145 ± 22 to $210 \pm 28\%$ at 120 min after TRH. The ΔTSH , defined as the maximal increase in TSH above basal TSH concentration, rose from 64 ± 19 before PTU to 101 ± 23

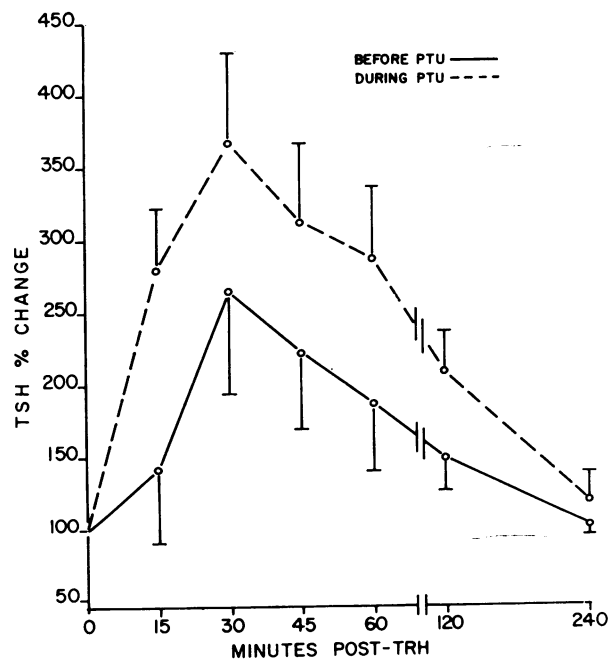


FIGURE 4 The effect of PTU 250 mg every 6 h for 8 days on the TSH response to TRH (500- μg i.v. bolus) during eight studies in athyreotic patients who had been receiving 100 μg of L- T_4 a day for 1 mo before study. Vertical bars represent SE.

$\mu\text{U/ml}$ during PTU administration ($P < 0.005$). Similar findings of augmented TSH response to TRH are depicted in Fig. 5 for three patients who had detectable levels of TSH while taking 200 μg of L-T₄ a day.

DISCUSSION

PTU significantly decreased serum T₃ concentrations in the athyreotic patients taking 100 or 200 μg of L-T₄ a day. The fall in serum T₃ derived exclusively from administered T₄ is consistent with the PTU-induced decrease in total deiodination of T₄ previously described in experimental animals (3–10) and in man (10–13). In clinical studies of the metabolism of [¹²⁵I]T₄, PTU decreased the urinary excretion of urinary ¹²⁵I by 30–40%, increased hepatic accumulation of ¹²⁵I, increased biliary secretion and fecal excretion of organic ¹²⁵I by 40–70%, raised PBI and [¹²⁵I]PBI slightly, and decreased the rate of disappearance of [¹²⁵I]PBI from the serum (10–14). Another mechanism to explain our findings might be that PTU increases the metabolic clearance of T₃. Oppenheimer et al. (23) showed that PTU reduced the calculated rate of conversion of T₄ to T₃ in thyroidectomized rats and also reduced the fractional rate of deiodination of both T₃ and T₄. To conclusively establish the mechanism for the reduction of serum T₃ induced by PTU in man, direct kinetic analysis of T₄ and T₃ metabolism must be carried out.

The PTU-induced decrease in the peripheral deiodination of T₄ to T₃ has been shown to be associated with a decrease in biologic activity of T₄ in vivo (15–20) and in vitro (21–23). Methimazole and other thiocarbamide drugs which do not affect the deiodination of T₄ do not interfere with its metabolic effectiveness (14). This extrathyroidal effect of PTU probably contributes to its effectiveness in the treatment of hyperthyroidism. Abuid and Larsen (35) demonstrated a significantly greater fall in T₃ concentration and T₃/T₄ ratio in hyperthyroid patients being treated acutely with PTU plus iodine compared with those treated with methimazole plus iodine suggesting that the inhibition of T₄ to T₃ conversion by PTU may play a significant role in its therapeutic effectiveness.

We did not measure absolute free thyroid hormone concentrations. However, it has been shown previously that PTU has no effect on thyroid hormone binding to human plasma proteins (10, 13). There was no significant change in T₃ resin uptake or plasma protein concentration during PTU administration in our patients.

The increase in basal concentrations of serum TSH and the increased TSH response to TRH associated with the decrease in serum T₃ is of great interest. It occurred at a time when there was no significant change in serum T₄ concentration. Previous investigators have shown that PTU administration increased the amount of bioassayable TSH in the serum of thyroidectomized

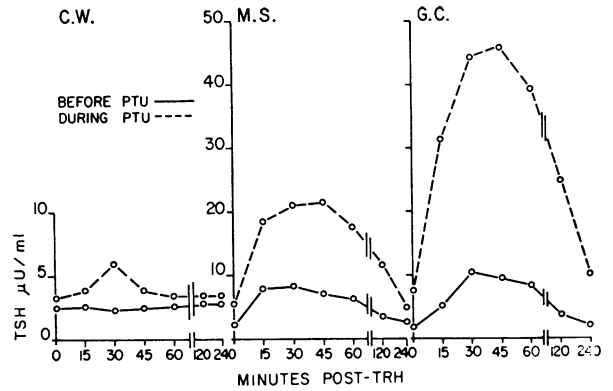


FIGURE 5 The effect of PTU 250 mg every 6 h for 8 days on the TSH response to TRH (500- μg i.v. bolus) in three athyreotic patients who had been receiving 200 μg of L-T₄ a day for 1 mo before study.

animals maintained on L-T₄ replacement at a time when serum PBI was unchanged or actually increased (24–28). In our patients, there was no significant change in PBI or T₄ (CPB or RIA) during PTU treatment in agreement with the findings of other clinical studies (14). The 30% decrease in serum T₃ concentration is equivalent to about 14 μg of T₃, assuming a volume of distribution of 35 liters for T₃. In athyreotic patients, this would arise from 16 μg of administered T₄. Since T₄ has a volume of distribution of 10 liters, the increment in T₄ would be only 0.15 $\mu\text{g}/\text{dl}$, or about a 3% rise in serum T₄, a change which is too small to be detected reliably because of the variability of the measurement of serum T₄.

Intravenous administration of TRH results in a prompt rise in serum TSH (36, 37). This response is also regulated by the circulating concentrations of thyroid hormones (38). The relative contributions of serum T₄ and T₃ concentrations to this regulation have not been defined precisely, in part, because of the conversion of T₄ to T₃ in peripheral tissues (29). Recent studies show that pituitary nuclei possess high affinity, low capacity binding sites for iodothyronines; the affinity of the binding site for T₃ is much greater than that for T₄ (39, 40). Presumably this specific binding plays a role in the control of pituitary TSH secretion.

When patients with primary hypothyroidism who have low circulating levels of thyroid hormone, high serum TSH, and exaggerated TSH response to TRH are fed small doses of L-T₄ plus L-T₃ in increasing amounts, there is eventual obliteration of the TSH response to TRH at a time when serum T₃ concentrations increase and before there is a significant increase in serum T₄ concentrations (41). Conversely, treatment of hyperthyroid patients who have elevated serum concentrations of T₄ and T₃ with antithyroid drugs has been reported to result in a return of TSH responsiveness

to TRH at a time when in some patients serum T_4 is elevated but T_3 has fallen to normal concentrations (42). Our findings are consistent with these observations. In our patients presumed blockade of deiodination of the administered L- T_4 to T_3 resulted in increasing serum TSH concentration and augmentation of the TSH response to TRH at a time when serum T_3 concentration fell, but T_4 concentration remained unchanged. The TSH response was relatively consistent in those patients who were tested with TRH on two occasions before administration of PTU. Thus the larger response during administration of PTU is not attributable to the previous test with TRH.

We cannot completely exclude a direct stimulatory effect of PTU on TSH release by the pituitary. Bioassay data concerning the effect of thiocarbamides on thyroid hormone suppression of TSH release from the pituitary indicate that, although PTU decreases the effectiveness of a given dose of L- T_4 , it has no effect on the ability of L- T_3 to suppress TSH release (14). Therefore we suggest that the augmentation in basal TSH level and the TSH response to TRH in our patients was most likely due to the fall in serum T_3 concentration caused by the effect of PTU on blocking the peripheral conversion of T_4 to T_3 . Our data are consistent with the hypothesis that T_3 is more important than T_4 for modulation of pituitary TSH secretion.

Addendum. Saberi, Sterling, and Utiger (43) have recently presented findings similar to those reported here.

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