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Effects of sodium ipodate and propylthiouracil in athyreotic human subjects, role of triiodothyronine and pituitary thyroxine monodeiodination in thyrotrophin regulation

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Abstract. To investigate the respective role of triiodothyronine (T_3) and thyroxine (T_4) in the regulation of TSH secretion, we studied the action of sodium ipodate and propylthiouracil (PTU) in 11 athyreotic patients. The LT_4 replacement dose was adjusted to obtain, in each patient, a normal basal TSH level and a normal TSH response to TRH. In the 5 ipodate-treated patients (single 6 g oral dose), the mean serum T_3 level fell by 64% below the baseline value and serum rT_3 rose 180% above the baseline. The free T_4 index (FT_4I) did not change whereas the mean serum TSH concentration increased 280% above baseline values. In the 6 PTU-treated patients (250 mg orally every 6 h for 10 days), serum T_3 levels fell 33%, serum rT_3 increased up to 82% and the FT_4I did not change. The mean serum TSH concentration increased 68% above the baseline value. Thus, the mean percentage increase in serum TSH was less in PTU- than in ipodate-treated patients (68% vs 280%). Statistical analysis of the correlation between the serum T_3 decrease (ΔT_3) and the serum TSH (ΔTSH) increase demonstrated that for the same T_3 diminution, the ipodate-treated group displayed higher increase of TSH than the PTU-treated patients. In the rat, PTU interferes with the 5'-deiodination of T_4 in the liver and kidney but not in the pituitary, while ipodate appears to have the same effect in all tissues. If this holds true for human subjects, our data strongly suggest that circulating T_4 (through its intrapituitary conversion to T_3) shares with serum T_3 the capacity to regulate TSH secretion in man.

Previous studies in animals and in humans have clearly shown that the circulating 3,5,3'-triiodothyronine (T_3) is an important regulator of pituitary thyrotrophin (TSH) secretion (Silva & Larsen 1977; Larsen et al. 1981; Larsen 1982). However, elevated serum TSH levels, normal serum T_3 concentrations and reduced serum thyroxine (T_4) levels may be found in iodine deficiency and in patients with early primary hypothyroidism. These situations lacking a correlation between serum T_3 and TSH levels suggest an important role for T_4 in TSH regulation. The oral cholecystographic agents, iopanoic acid and ipodate have been shown to inhibit T_4-5'-monodeiodination in all tissues that have been studied to date including pituitary and brain (Larsen et al. 1979; Kaplan & Utiger 1978; Crantz & Larsen 1980). 6-n propylthiouracil (PTU) is also a well known inhibitor of T_4 to T_3 conversion (Oppenheimer et al. 1972). However, its failure to decrease the intrapituitary T_3 concentration suggests that in vivo 5'-deiodination of T_4 proceeds in this tissue via a PTU insensitive pathway (Silva et al. 1982).

The present study was carried out to compare the effect of ipodate and PTU in athyreotic T_4 maintained euthyroid patients. The aim was to further investigate the relative importance of the concentration of plasma T_3 and of T_3 generated locally from T_4 within the pituitary, in the regulation of TSH secretion. Our data demonstrate that circulating T_3 concentration and serum T_4 through its intrapituitary conversion are both important in TSH regulation.

Patients and Methods

After informed consent was obtained, 11 patients, 7 women and 4 men (aged 23 to 58 years) with well established primary hypothyroidism were included in the protocol (Table 1). All were selected because of their complete thyroid deficiency with plasma T_4 levels originally below 1 μg/dl. At the time of the study, they had been taking 0.1 to 0.2 mg per day of L-thyroxine for more than 6 months. The L-T_4 replacement dose was adjusted to obtain in each patient a basal TSH level below 10 μU/ml and a TSH response to TRH of more than 100% with a peak increase in TSH above 10 μU/ml. In this study, two TRH tests were performed at intervals of up to 30 days by administering a single iv bolus of 200 μg TRH at 08.00 h after an overnight fast. Blood was sampled immediately before and 15, 30, 60, 90 and 120 min after the TRH injection. Plasma TSH was measured by a double antibody RIA as previously described (Schaison et al. 1981). The sensitivity of the method permits the detection of 0.6 μU/ml and the range of values found in the plasma of normal controls was 0.5–11 μU/ml. The inter-assay coefficient of variation was less that 7%. Blood samples were also analyzed by RIA for T_4 (clinical assay Cambridge, MA, USA). The free T_4 index (FT_4I) represents the product of the serum T_4 concentration and the T_3 resin uptake (Pharmacia Uppsala, Sweden). T_3 and 3,3',5'-triiodothyronine (rT_3) were measured by RIA using materials supplied by respectively Behring (Berlin, W-Germany) and Biodata Serono (Chavannes de Bogia, Switzerland). All plasma samples for a given individual were assayed concurrently

Table 1.
Clinical and biochemical data of 11 hypothyroid patients before and after L-T_4-treatment.

	Sex	Age (years)	Aetiology	Before treatment		After treatment	
				FT_4I	TSH μU/ml	TSH basal	Peak (TRH)
Ipodate							
1	F	23	Lingual ectopy	1	80	3	14
2	F	50	Chronic autoimmune thyroiditis	0	90	3.6	18
3	M	33	Thyroid agenesis	0.5	56	2.8	12
4	F	58	Primary idiopathic hypothyroidism	0.25	100	7.4	24
5	M	30	Lingual ectopy	0.5	72	3	15
Mean		39		0.45	79.6	4.2	16.6
PTU							
1	F	31	Post thyroidectomy	0	76	5	13
2	F	57	Primary idiopathic hypothyroidism	0	60	4.7	12
3	F	44	Primary idiopathic hypothyroidism	0.5	66	5.5	15
4	M	30	Thyroid agenesis	0.25	80	9.5	20
5	F	44	Chronic autoimmune thyroiditis	0.9	54	3.4	14
6	M	33	Thyroid agenesis	0.6	78	9	21
Mean		40		0.37	69	6.2	15.8

and in duplicate for each hormone. Normal ranges for control subjects in this laboratory are 4.5–11.5 μg/dl for T_4, 0.81–1.14 for T_3 resin uptake, 3.6–13.1 for FT_4I, 70–220 ng/dl for T_3 and 9–35 ng/dl for rT_3. During the study, the 11 patients were continuing L-thyroxine therapy. They were divided into 2 groups in a non-random fashion. The 2 groups were however comparable and studied during the same period (Table 1).

Ipodate-treated patients

Five patients were given a single 6 g oral dose of sodium ipodate (Oragrafin) at 08.00 h. Blood was drawn from each patient, immediately before and on days 1, 2, 3, 4, 5, 7 and 10 after ipodate administration and was analyzed for FT_4I, T_3, rT_3 and TSH. In these patients, total plasma iodine was measured by a classic chemical method (Piette et al. 1966).

PTU-treated patients

Six patients received PTU (250 mg orally every 6 h) for 10 days. Blood was drawn before and during the treatment period for measurement of FT_4I, T_3, rT_3 and TSH.

Student's *t*-test was used to evaluate the hormone level changes from pre-treatment values. In order to assess whether the ΔTSH difference between ipodate- and PTU-treated patients was due only to the difference in T_3, or in part to a differential effect of treatment on the pituitary, linear regression lines of TSH vs ΔT_3 within each group were calculated by the least square method, and compared by analysis of covariance[1] (Snedecor & Cochran 1967).

Results

Table 2 shows the sequence of the changes in TSH and iodothyronines and total iodine concentration in ipodate-treated patients.

After ipodate administration, the mean serum T_3 concentration significantly decreased from the pre-treatment (day 0) level of 100 ± 3 ng/dl to 36 ± 3 ng/dl by day 4 ($P < 0.001$). Ten days later, the serum T_3 values returned to a mean level of 79 ± 14 ng/dl, not significantly different from the initial level. The mean serum rT_3 level increased

Table 2.
Changes in serum T_3, rT_3, T_4, FT_4I, TSH and Ti (total plasma iodine) values in 5 hypothyroid patients treated with L-T_4, and given a single dose of ipodate on day 0. Each value represents mean ± SEM.

	Days after ipodate							
	0	1	2	3	4	5	7	10
T_3, ng/dl	100 ± 3	63 ± 5***	56 ± 6***	39 ± 3***	36 ± 3***	39 ± 4***	47 ± 7***	79 ± 14
rT_3, ng/dl	24 ± 3	37 ± 5*	55 ± 7.8*	67 ± 7***	66 ± 5***	59 ± 4***	51 ± 7**	39 ± 8
T_4, μg/dl	8.6 ± 0.7	7.4 ± 0.4	7.8 ± 0.9	8.9 ± 0.8	8.9 ± 1.1	9.1 ± 1.2	10.4 ± 1.1	9.7 ± 1.3
FT_4I	8.8 ± 0.5	7.3 ± 0.8	8.1 ± 1.3	9.1 ± 1.2	9.7 ± 1.3	9.8 ± 0.9	10.2 ± 1.4	10.5 ± 1.3
TSH, μU/ml	4.2 ± 2.0	7.1 ± 2.6	8.4 ± 3.0	10.9 ± 3.4	11.7 ± 3.6*	14.2 ± 4.7*	16.1 ± 4.5*	12.2 ± 3.7*
Ti	6 ± 0.3	4400 ± 1267	2267 ± 891	1820 ± 650	1405 ± 512	1074 ± 416	748 ± 324	511 ± 204

Asterisks indicate a significant difference from the values at day 0 (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$).

[1] Comparison of regression lines by analysis of covariance consists of 3 successive steps: 1) test for the significance of correlation between TSH and T_3 within each group, 2) test for the difference between slopes of regression lines, 3) test for the difference between intercepts of regression lines.

significantly ($P < 0.001$) from the pre-treatment level of 24 ± 3 ng/dl to 67 ± 7 ng/dl on day 3 and then gradually declined. However, the value was still higher than the initial level on day 7 and even on day 10. The serum T_4 and FT_4I increased slightly, but the change in the mean value was too small to be significant. The serum TSH concentration increased significantly from the pre-treatment level of 4.2 ± 2.0 μU/ml to 16.1 ± 4.5 μU/ml by day 7 ($P < 0.05$). From day 5 to day 10, the change in the plasma TSH mean value was not significant. On day 10, total plasma iodine was still elevated (511 ± 204 μg/dl).

Table 3 illustrates the results in PTU-treated patients. The mean serum T_3 concentration decreased significantly ($P < 0.001$) from the pre-treatment value of 91 ± 6 ng/dl to 61 ± 3 ng/dl by day 4 and thereafter varied minimally.

The mean serum rT_3 increased from 27 ± 5 ng/dl and reached a peak of 49 ± 5 ng/dl on day 3. Afterwards rT_3 gradually declined returning to the pre-treatment level by day 10.

The serum T_4 and FT_4I remained unchanged during the study period.

The serum TSH concentration increased from the pre-treatment level of 6.2 ± 1.9 μU/ml to 10.2 ± 1.6 μU/ml by day 5. This slight but significant TSH increase ($P < 0.05$) was the same on days 5 and 10.

Thus, after sodium ipodate administration, the maximum per cent decrement in T_3 (64%) and the maximum per cent increment in rT_3 (180%) were greater than those in the PTU-treated patients (33% and 82%, respectively). Likewise, the enhanced TSH secretion was greater in the ipodate-treated (280%) than in the PTU-treated patients (68%). The comparison of ipodate- and PTU-treated patients by analysis of covariance showed:

1) a significant correlation between TSH and T_3 in the ipodate ($r = -0.30$, $P < 0.01$)[2] and PTU ($r = -0.05$, $P < 0.01$)[2] groups; 2) no significant difference between slopes but 3) a significant difference between intercepts of the two regression lines[3] ($P < 0.01$) (Fig. 1). In other words, the lower serum T_3 levels in ipodate-treated patients did not fully account for their higher serum TSH levels. For the same ΔT_3 decrease, a higher ΔTSH increase was observed in these patients.

Table 3.
Changes in serum T_3, rT_3, T_4, FT_4I and TSH values in 6 hypothyroid patients taking L-T_4 and treated with PTU for 10 days.
Each value represents mean ± SEM.

	Days during PTU treatment							
	0	1	2	3	4	5	7	10
T_3, ng/dl	91 ± 6	72 ± 4*	67 ± 3**	64 ± 3**	61 ± 3***	70 ± 2**	67 ± 3**	68 ± 3**
rT_3, ng/dl	27 ± 5	46 ± 3**	46 ± 3**	49 ± 5**	43 ± 3**	39 ± 2*	37 ± 2*	33 ± 2
T_4, μg/dl	10.1 ± 0.4	9.6 ± 0.7	9.8 ± 0.5	9.4 ± 0.6	11.2 ± 0.6	9.3 ± 0.4	9.7 ± 0.5	10.1 ± 1.1
FT_4I	9.9 ± 0.6	9.7 ± 0.4	10.1 ± 0.4	10.2 ± 0.5	10.3 ± 0.5	10.3 ± 0.5	9.9 ± 0.3	10.3 ± 0.7
TSH	6.2 ± 1.9	7.1 ± 0.4	8.5 ± 0.9	9.1 ± 0.9	9.5 ± 1.2*	10.2 ± 1.6*	9.4 ± 1.3*	10.4 ± 1.5*

Asterisks indicate a significant difference from the values at day 0 (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$).

[2] r = standard correlation coefficient.

[3] by Fisher's F-test with 1 and 78 degrees of freedom ($F_{78} = 10.2$).

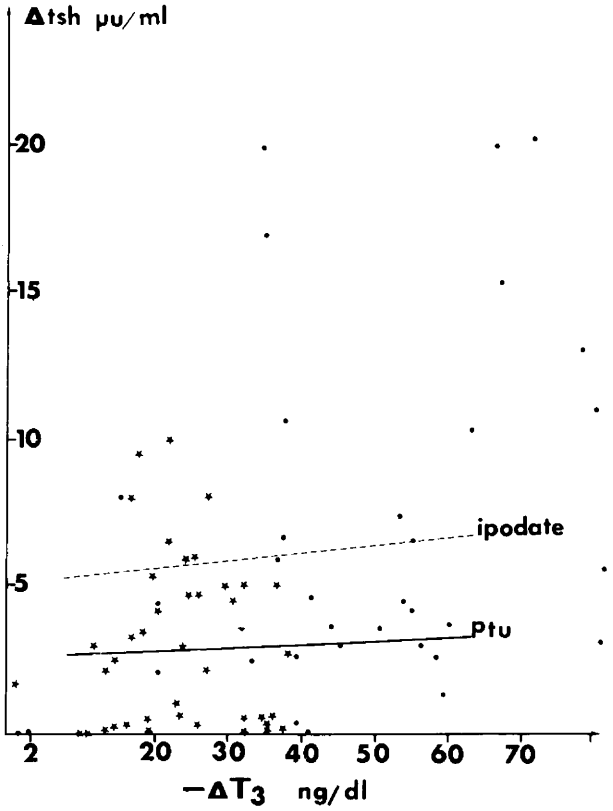

Fig. 1.
Correlation between TSH and T_3 in the ipodate (●) and PTU (✱) treated patients. The difference between intercepts of the two regression lines is significant ($P < 0.01$). See text and footnotes.

Discussion

The aim of our study was to evaluate the relative importance of circulating T_3 and T_4 in the regulation of TSH secretion in man.

It has now been clearly demonstrated that circulating T_3 is an important regulator of TSH secretion. Clinical observations indicate, however, that circulating T_4 might also play a significant role: thus, in iodine deficiency and in the early stages of thyroid failure, a low serum T_4 concentration is associated with an increased level of TSH and a normal serum T_3 level (Larsen 1982).

In the present study, we chose to investigate hypothyroid patients in order to avoid any interference with thyroid hormonal secretion. In addition, the replacement doses of T_4 were carefully adapted for each patient so that the basal and TRH stimulated TSH levels were within the normal range. Our data shows that PTU-treated patients have a smaller decrease in serum T_3 levels and a smaller increase in TSH levels than the ipodate-treated group. It has been reported that PTU was less potent than ipodate in inhibiting the conversion of T_4 to T_3 (Sharp et al. 1981; Wu et al. 1982). Therefore, in order to compare the two protocols, we attempted to find out if the serum TSH values were similar in both groups of patients for the same serum T_3 levels.

The shape of the dose-response curves for T_3 and TSH is not well known. However, Silva & Larsen (1978) have shown that, 3 h after iv injection of increasing doses of T_3 into hypothyroid rats, the plasma T_3 concentration correlated with the change in TSH. There was a linear relationship between the nuclear occupancy by T_3 and TSH

release in rats. Moreover, for a plasma T_3 level between 20 and 200 ng/dl, the TSH suppression was linearly related to the increase in plasma T_3. Therefore, for both groups in the present study, we assumed a linear relationship between the decrease in serum T_3 and the rise in TSH levels. If this assumption is not completely valid, however, analysis of covariance has been shown to be robust with respect to deviation from linearity (Snedecor & Cochran 1967).

The totality of our data shows that for a similar decrease in serum T_3, the rise in serum TSH was higher in the ipodate-treated group than in the PTU-treated patients. The TSH increase and the T_3 decrease ratio through day 4 was similar in both groups. However, after day 4, while plasma T_3 was already returning to normal in the ipodate-treated group, plasma TSH was not decreasing. This discrepancy argues against a simple relationship between TSH secretion and circulating T_3 at that time. It is clear from the assays of total plasma iodine that ipodate was still present on day 7. It can be hypothesized that its effect on the pituitary persisted for a longer period than on peripheral deiodination. A more satisfactory explanation might be that the role of the locally produced T_3 on TSH regulation in the pituitary is overpowered by the presence of very low circulating T_3 levels. This is the case during the first 4 days for the ipodate-treated group. The pituitary T_3 produced by deiodination of T_4 becomes important for TSH regulation when plasma T_3 increases towards normal levels. This would occur during the last 6 days. This hypothesis would be valid if 50% of the intrapituitary T_3 in man originates from plasma T_3 and 50% from local production as is the case in rats (Larsen 1982). Regardless of the mechanism, the fact that from day 5 to day 7, serum TSH did not respond to increasing T_3 levels, is a strong argument against plasma T_3 being the exclusive regulator of TSH production.

In man, previous studies have attempted to assess the role of T_3 and T_4 in TSH regulation, with partially conflicting conclusions. Thus, Wu et al. (1978) studied the effects of ipodate on normal subjects and hypothyroid patients on T_4 replacement therapy. No increase in serum TSH was measurable in either group. However, the replacement doses of T_4 were probably too high. Other investigators have reported increased serum TSH levels in hypothyroid patients on T_4 replacement therapy, when their serum T_3 levels were lowered by inhibition of T_4 deiodination, either by administration of sodium iopanoate (Bürgi et al. 1976) or by PTU (Saberi et al. 1975; Geffner et al. 1975). Serum T_4 values did not change. Several of these patients were undertreated, however, as evidenced by the basal TSH levels. Overall, the results indicate that circulating T_3 is one of the factors regulating TSH secretion. Finally, Kleinmann et al. (1980) and Suzuki et al. (1981) showed that, in normal subjects, the iopanoic acid-induced decrease in serum T_3 is accompanied by an increase in serum TSH. Furthermore, in both studies, administration of T_3 sufficient to restore almost normal serum T_3 levels prevented or reversed the effects of iopanoic acid on TSH. T_4 replacement was ineffective. However, the authors stress that no definite conclusion can be drawn concerning the relative importance of extrapituitary T_3 sources and intrapituitary T_3 generation in the regulation of TSH secretion in patients receiving iopanoic acid (Kleinmann et al. 1980). These results are in accordance with our present study using PTU administration and suggest that circulating T_3 is the main regulator of TSH secretion. However, if sodium ipodate inhibits the intrapituitary T_4 to T_3 conversion in humans as it does in rodents, the augmented TSH levels obtained with this drug for the same diminution in circulating T_3 levels strongly suggests a role for circulating T_4 in the regulation of TSH secretion. This conclusion would be in agreement with the data obtained from earlier animal studies.

In animals, Silva & Larsen (1977), Larsen et al. (1979), Crantz & Larsen (1980), and Silva & Larsen (1978) measured the plasma concentrations of TSH, T_3 and T_4 as well as intracellular levels and nuclear receptor bound iodothyronines in the pituitary and peripheral tissues of the rat. These parameters were compared in controls and in hypothyroid animals before and after treatment with T_3 or T_4. The authors also made use of the specific actions of propylthiouracil and of iopanoic acid on the conversion of T_4 to T_3. They showed that PTU interferes with the 5'-deiodination of T_4 in the liver and kidney but not in the pituitary (Silva et al. 1978). 5'-deiodination of T_4 proceeds via a PTU insensitive pathway in the central nervous system and the pituitary (Silva et al. 1982). On the other hand, iopanoic acid inhibits T_4 5'-monodeiodination in all tissues and in particular blocks the enzyme activity in the rat anterior pituitary (Obregon et al. 1980). These studies demonstrated

that TSH secretion is regulated by the level of nuclear-receptor bound T_3 in the pituitary. Only 40–50% of nuclear T_3 in this organ originates from plasma T_3. Conversion of T_4 to T_3 within pituitary tissue accounts for the remainder (Larsen 1982). On the contrary, nearly all the nuclear T_3 present in the liver and kidney is derived from plasma T_3. Thus, the mixed origin of T_3 in the pituitary explains how TSH secretion can be a function of by both plasma T_3 and T_4 (Crantz et al. 1982).

In conclusion, the effects of PTU or ipodate administration on the serum TSH and iodothyronine levels in hypothyroid patients on T_4 replacement therapy were investigated. For the same decrease in serum T_3, ipodate treatment elecited a higher rise in the serum TSH than PTU. If the specific properties of these drugs are the same in animals and humans, our data suggest that circulating T_3, as well as circulating T_4, as a result of its intrapituitary deiodination to T_3, are important in the regulation of TSH secretion in man.

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