Increased Sensitivity of the Thyroid in Iodine-Depleted Rats to the Goitrogenic Effects of Thyrotropin

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ABSTRACT The present studies demonstrate that iodine depletion increases the sensitivity of the thyroid to the goitrogenic effects of thyrotropin. Iodine depletion was induced by feeding rats a low iodine diet containing propylthiouracil for 10–14 days before hypophysectomy. Accumulation of iodine in the thyroid after hypophysectomy was prevented by continuing the antithyroid drugs in the diet. Doses of thyrotropin as low as 3 mU/100 g of body weight per day produced significant thyroid enlargement in 3–7 days in iodine-depleted rats. Adding propylthiouracil or perchlorate to the diet during treatment with thyrotropin did not reduce or augment the goitrogenic response to thyrotropin in iodine-depleted rats. Increasing the level of circulating iodide also did not reduce the goitrogenic response to thyrotropin. The increased sensitivity of the iodine-depleted thyroid gland may provide an explanation for the development of thyroid enlargement without requiring an increased level of circulating thyrotropin.

INTRODUCTION

Thyroid activity is regulated by two mechanisms; it varies directly with the level of circulating thyrotropin (TSH) and inversely with the iodine content of the thyroid gland itself. Raising the level of thyrotropin increases the uptake and release of iodine by the thyroid, causes the gland to hypertrophy, and influences many metabolic processes within the thyroid (1, 2). The level of circulating thyrotropin is in turn regulated by a negative feedback between the pituitary and the level of circulating thyroid hormone (1). This reciprocal relationship between TSH and thyroid hormone has been most elegantly demonstrated by the use of the radioimmunoassay for TSH. When thyroid hormone is low, as in myxedema, TSH is elevated, whereas thyroid hormone replacement reduces the concentration of TSH (3).

The inverse relationship between the concentration of iodine in the thyroid and the activity of the thyroid gland can be demonstrated in intact and in hypophysectomized rats and thus is independent of TSH. In hypophysectomized rats the weight of the thyroid (4) and its uptake of radioactive iodine (5) were higher if the rats had been iodine depleted before hypophysectomy, and administering thyrotropin to these same two groups of rats produces a greater effect in the iodine-depleted animals (6). Thus iodine depletion appears to potenitate the effects of thyrotropin. Stimulation of the thyroid gland of hypophysectomized rats with constant amounts of exogenous thyrotropin produced a greater uptake of radioactive iodine in iodine-depleted glands than in glands with normal iodine content (7). Similar studies in human beings who were acutely depleted of iodine have suggested that the uptake of radioactive iodine by human thyroid may also be regulated, in part, by the intrathyroid content of iodine (8). In the present studies we have explored the possibility that the intrathyroid content of iodine might also

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regulate the TSH-induced growth of the thyroid gland and have found that the goitrogenic effects of thyrotropin are indeed augmented by iodine depletion.

METHODS

In the present experiments, 267 hypophysectomized rats weighing 80–100 g were purchased from Charles River Laboratories, Boston, Mass. A similar protocol was followed for all experiments (see Table I) and minor variations are noted in the legend to each table or figure. Before hypophysectomy 6 rats received a chow diet, 24 rats received a low iodine diet [1] (mildly iodine-depleted group), and 232 rats received a low iodine diet supplemented with 0.1% propylthiouracil (PTU) (severely iodine-depleted groups). From the time of hypophysectomy all rats were maintained on the low iodine diet supplemented, in all but one experiment (see Table II) with 0.1% propylthiouracil, and they all received 100 μg of cortisone acetate intramuscularly and 0.5 μg of triiodothyronine subcutaneously each day, 5 days a week, until autopsied. In addition, in most experiments the rats received, 1% potassium perchlorate in their drinking water. 14–18 days after hypophysectomy, thyrotropin (TSH) was begun and continued for 7 days. During the period of treatment with TSH all rats received a low iodine diet. In some experiments the diet was supplemented with propylthiouracil or sodium perchlorate. At the end of each experiment the animals were sacrificed and the thyroids were carefully dissected out and weighed. Completeness of hypophysectomy was determined by examination of the pituitary fossa under a dissecting microscope and by recording body weight. The thyroid glands from each group were pooled for iodine analysis.[2]

Thyrotropin (Thytropar, Armour Pharmaceutical Co., Kankakee, Ill. lots B-8312 and C-8505) was dissolved in saline and injected in divided doses daily, since preliminary studies had shown that TSH at a rate of 100 mU/100 g of body weight in three divided doses over a 12 hr period each day for 7 days produced a greater enlargement of the thyroid than would the same dose of TSH

[1] Composition of low iodine diet (Diet 30 of Dr. Astwood): To make 1 kg–gluten flour, 300 g; vitamin-free casein, 100 g; corn oil, 80 g; wheat flour, 100 g; sucrose, 370 g; vitaminized casein, 10 g; and salt mixture, 50 g.

Vitaminized casein (1 kg): vitamin-free casein, 827.0 g; riboflavin, 0.5 g; thiamin, 0.5 g; niacin, 2.5 g; inositol, 50.0 g; pyridoxine, 0.5 g; choline chloride, 100 g; biotin, 0.05 g; folic acid, 0.05 g; calcium pantothenate, 2.5 g; *p*-aminobenzoic acid, 10.0 g; menodione, 0.5; tocopherol, 5.0 g; vitamin A acetate, 0.05 g; calciferol, 0.005 g; vitamin B_{12} 1:1000, 1.0 g.

Salt mixture (1 kg): calcium carbonate, 300 g; K_2HPO_4, 150 g; $MgSO_4$, 50 g; NaCl, 500 g; $FeSO_4$, 1.0 g; $CuSO_4$, 0.05 g; $MnSO_4$, 0.05 g; $CoCl_2$, 0.05 g; sodium molybdate, 0.05 g; $ZnSO_4$, 0.05 g.

The iodine content of this diet is less than 100 μg/kg.

[2] Iodine analyses were performed by the Boston Medical Laboratory.

TABLE I

Experimental Design

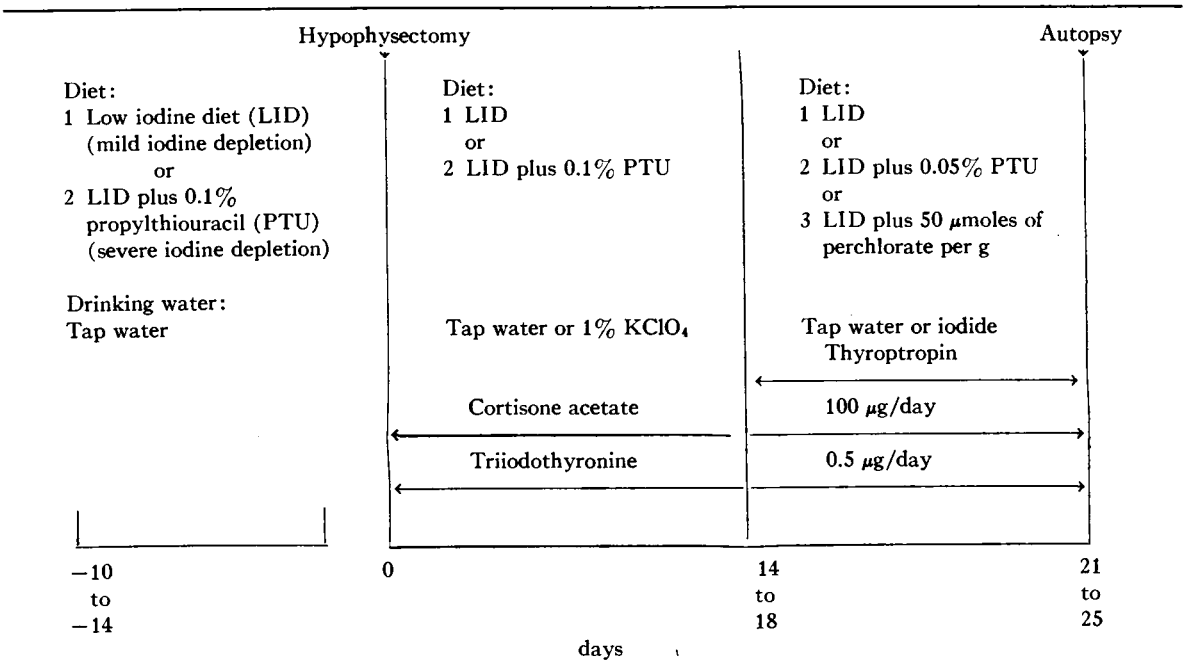

TABLE II

Effect of Diet on Thyroid Weight and Iodine Content

Group	Diet	No. of animal	Additions to diet: Before hypophysectomy	Additions to diet: After hypophysectomy	Day after hypophysectomy	Thyroid weight	Thyroid iodine
						mg/100 g of body wt	*mg/100 g of thyroid*
1	Chow	6	None	None	7	7.6 ± .5‡	55.7
2	Low iodine*	5	None	None	1	12.7 ± 1.2	25.8
3		5	None	None	18	9.0 ± 0.8	34.2
4		6	None	0.1% PTU	25	8.4 ± 0.3	22.3
5		5	0.1% PTU	None	1	32.8 ± 1.8	0.52
6		5	0.1% PTU	None	18	10.0 ± 0.8	19.5
7		9	0.1% PTU	0.1% PTU	19	9.8 ± 0.5	1.4

* Low iodine diet with and without 0.1% PTU was fed for 12 days before hypophysectomy.
‡ Mean ± SEM.

given as a suspension in peanut oil as a single daily dose for 7 days (thyroid weights, 14.5 ± 0.7 mg/100 g of body weight vs. 11.7 ± 0.6 mg/100 g of body weight; $P < 0.05$). Triiodothyronine was dissolved in alkaline saline and 0.5 μg was injected subcutaneously in a volume of 0.1 ml once each day for 5 days/wk after hypophysectomy. Cortisone acetate was diluted with saline and 100 μg was given in a volume of 0.1 ml intramuscularly once each day for 5 days/wk after hypophysectomy. Propylthiouracil was mixed with the low iodine diet to make 0.1%, as described above, or 0.05% and fed to the rats represented in Tables IV and V during the period of administration of thyrotropin. (All other groups received only the low iodine diet during treatment with thyrotropin.) Potassium perchlorate as a 1% solution was given in the drinking water to most groups after hypophysectomy and sodium perchlorate was mixed with the low iodine diet to give 50 μmoles of sodium perchlorate per gram of low iodine diet and was fed during the period of administration of thyrotropin (Tables IV and V). Potassium iodide was dissolved in distilled water to give 0.3, 3, or 30 μg of iodide per 10 ml and given in the drinking water to one or another of the groups in Table V during treatment with thyrotropin.

RESULTS

1. Effect of diet and hypophysectomy on thyroid weight and iodine content. Thyroid glands from six normal male rats weighed 7.6 ± 0.5 mg/100 g

TABLE III

*Effect of Iodine Depletion on the Response of the Thyroid Gland to Thyrotropin**

Dose of thyrotropin	Mild iodine depletion: No. animals	Mild iodine depletion: Thyroid weight	Mild iodine depletion: Thyroid iodine	Severe iodine depletion: No. animals	Severe iodine depletion: Thyroid weight	P‡	Severe iodine depletion: Thyroid iodine
mU/100 g of body wt§		*mg/100 g of body wt*	*mg/100 g of thyroid*		*mg/100 g of body wt*		*mg/100 g of thyroid*
0	6	7.5 ± 0.5‖	36	5	10.4 ± 0.1	<0.01	4.7
10	6	8.0 ± 0.6	37	4	11.6 ± 0.9	<0.05	6.0
100	6	8.2 ± 0.6	26	3	13.7 ± 1.7	<0.05	9.0
1000	7	9.2 ± 0.7	8	4	19.3 ± 1.8‖	<0.01	3.8

* Rats were fed a low iodine diet (mild iodine depletion) or a low iodine diet supplemented with 0.1% PTU (severe iodine depletion) for 14 days before hypophysectomy. After hypophysectomy both groups received a low iodine diet for the remaining 24 days of the study. 1% $KClO_4$ was added to the drinking water for 15 days beginning the day after hypophysectomy, but during treatment with TSH both groups received tap water.
‡ *P*, for comparison between mild and severe iodine depletion.
§ Thyrotropin in saline, in divided doses each day for 7 days was begun on the 17th day after hypophysectomy.
‖ Mean ± SEM.
¶ $P < 0.01$, for difference in thyroid weight between control and thyrotropin-treated rats which were severely iodine depleted.

of body weight and contained 55 μg of iodine/100 mg of thyroid (Table II; group 1). After 12 days on a low iodine diet the weight of the thyroid increased to 12.7 mg/100 g of body weight and the iodine content was reduced by one-half (group 2). Addition of 0.1% propylthiouracil to the low iodine diet before hypophysectomy increased the thyroid weight to 32.8 mg/100 g of body weight and depleted the thyroid of more than 99% of its iodine (group 5). After hypophysectomy the weight of the thyroid declined in all rats (groups 3, 4, 6, 7) but remained consistently heavier than normal (group 1). The iodine content increased substantially after hypophysectomy when the rats were fed only a low iodine diet (Table II; compare groups 5 and 6), but remained almost unchanged if the diet was supplemented with propylthiouracil (Table II [group 7] and Tables III–VI).

2. The effect of iodine content and the dose and duration of treatment with thyrotropin on the weight of the thyroid gland. The effect of mild and severe iodine depletion on the weight of the thyroid in rats given graded doses of thyrotropin

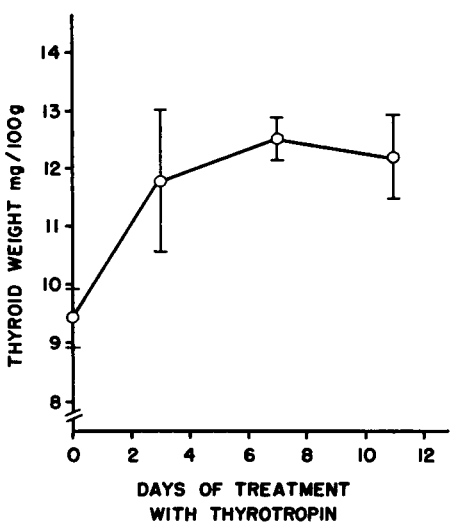

FIGURE 1 Effect of duration of treatment with thyrotropin on thyroid weight. Rats were fed a low iodine diet supplemented with 0.1% PTU for 10 days before hypophysectomy. After hypophysectomy they received the same diet and drinking water with 1% perchlorate for 17 days. Thyrotropin in saline, 100 mU/100 g, was given s.c. in divided doses for 3, 7, or 11 days, starting 25, 21, or 17 days after hypophysectomy, respectively. Rats received tap water and a low iodine diet during the period of thyrotropin injections. Each point is the mean of 6–8 rats and the vertical bars represent ± 1 SEM.

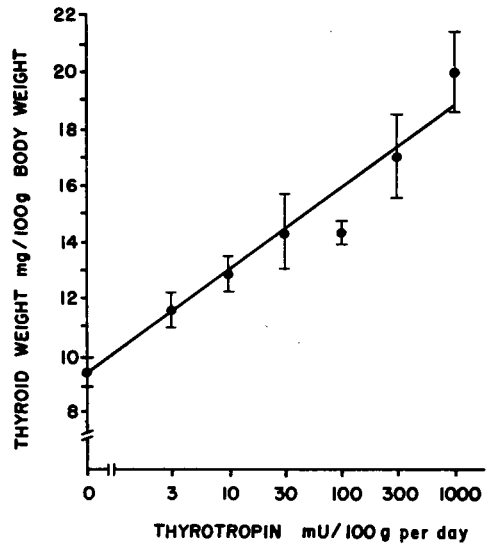

FIGURE 2 Log-dose response curve of thyroid weight against dose of thyrotropin. Rats were fed a low iodine diet supplemented with 0.1% propylthiouracil for 12 days before hypophysectomy. After hypophysectomy they received the same diet and drinking water with 1% perchlorate for 9 days and were then switched to a low iodine diet without PTU and tap water. Thyrotropin in saline was given s.c. in divided doses each day for 7 days beginning 17 days after hypophysectomy. Each point is the mean of 5–8 rats and the vertical bars represent ± 1 SEM.

is shown in Table III. Doses of TSH up to 1000 mU/100 g of body weight each day for 7 days produced only a small increase in the weight of the thyroid gland of rats with mild iodine depletion, but in rats with severe iodine depletion the thyroid increased in weight with each dose level of thyrotropin. In Fig. 1, the effect of duration of treatment with thyrotropin on the increase in thyroid weight was examined. Rats receiving 100 mU of tryrotropin per 100 g of body weight showed an increase in thyroid weight as early as 3 days after beginning treatment, and there was no further increase in weight after 7 days. For this reason a 7 day period of treatment was chosen for the subsequent experiments. Fig. 2 shows the thyroid weight as a function of the dose of thyrotropin on a log scale. A dose of TSH as low as 3 mU/100 g of body weight each day for 7 days produced a significant increase in the weight of the thyroid gland ($P < 0.05$). A dose of 100 mU/100 g of body weight produced a 50% increase in thyroid weight and was selected for most of the remaining experiments.

TABLE IV

*Effect of Perchlorate and Propylthiouracil on the Goitrogenic Response to Thyrotropin**

Treatment	No. animals	Thyroid weight	Thyroid iodine
		mg/100 g of body wt	*mg/100 g of thyroid*
Control	8	10.3 ± 0.3‡	1.25
Propylthiouracil, *0.05%*	8	11.8 ± 0.7	0.74
Perchlorate, 50 *μmoles/g of diet*	8	11.2 ± 0.6	0.78
TSH§	8	15.0 ± 1.3‖	6.05
TSH plus PTU	9	16.4 ± 1.1‖	0.52
TSH plus perchlorate	9	15.5 ± 0.8‖	0.44

* Rats were fed a low iodine diet supplemented with 0.1% PTU for 8 day before hypophysectomy. After hypophysectomy they received the same diet for 15 days and 1% $KClO_4$ in the drinking water for 10 days. On the 11th day after hypophysectomy the rats were switched to tap water for the remaining 11 days of the experiment and 15 days after hypophysectomy food was changed to a low iodine diet supplemented with 0.05% PTU or sodium perchlorate, 50 μmoles/g of diet.

‡ Mean ± SEM.

§ Thyrotropin in saline, 100 mU/100 g of body weight, in divides doses each day for 7 days was begun on the 15th day after hypophysectomy.

‖ $P < 0.05$, for comparison between thyrotropin-treated and appropriate control group.

3. Effect of propylthiouracil, perchlorate and iodide on the response to thyrotropin. The addition of propylthiouracil or perchlorate to the diet of hypophysectomized, iodine-depleted rats did not change the weight of their thyroid glands, and neither drug inhibited or augmented the thyroid enlargement produced by thyrotropin (Table IV). To test the effect of circulating levels of iodide on the TSH-induced enlargement of the thyroid gland, iodide was added to the drinking water and both perchlorate and propylthiouracil were added to the food to prevent the uptake of iodide by the thyroid gland. Iodide alone had no effect on thyroid weight, and it did not prevent enlargement of of the thyroid gland in rats treated with thyrotropin (Table V).

4. The effect of thyrotropin on iodine uptake and intrarat-thyroidal iodine content. During treatment with thyrotropin the iodine content increased in thyroid glands from rats that had been severely depleted of iodine before hypophysectomy (Tables IV and VI). Supplementing the diet with propylthiouracil prevented the accumulation of iodine, but did not augment the response to thyrotropin (Table IV).

DISCUSSION

The present studies demonstrate the extreme sensitivity of the iodine-depleted thyroid to the goitrogenic effects of thyrotropin, and support the concept that enlargement of the thyroid is inversely related to iodine content. 3 mU of thyrotropin (TSH) were given to 100 g rats in divided doses each day, such that each dose contained only 1 mU of TSH. If this entire dose were immediately absorbed into a blood volume equivalent to 10% of the body weight (i.e., 10 ml), the concentration could reach a level of 0.1 mU/ml, a value five times higher than that of 0.02 mU/ml for serum

TABLE V

*Effect of Iodine on the Enlargement of the Thyroid Gland in Rats Treated with Thyrotropin**

Iodine added to drinking water	Vehicle				Thyrotropin‡				
	No. animals	Thyroid weight	Thyroid iodine	Total Plasma iodine	No. animals	Thyroid weight	Thyroid idoine	Total plasma iodine	*P*§
μg/10 ml		*mg/100 g of body wt*	*mg/100 g of thyroid*	*μg/100 ml*		*mg/100 g of body wt*	*mg/100 g of thyroid*	*μg/100 ml*	
0	6	11.5 ± 1.3‖	0.49	0.6	7	14.9 ± 0.8	0.16	0.8	<0.05
0.3	5	12.0 ± 1.4	0.44	1.0	6	14.3 ± 0.7	0.15	1.0	NS
3.0	6	10.4 ± 0.9	0.43	2.0	6	15.0 ± 1.2	0.18	1.4	<0.05
30.0	7	12.0 ± 0.6	0.51	28.0	6	15.0 ± 1.4	0.41	14.0	=0.05

* Rats were fed a low iodine diet supplemented with 0.1% propylthiouracil for 10 days before hypophysectomy. After hypophysectomy they received the same diet and 1% $KClO_4$ in the drinking water for 9 days. On the 10th day they were switched to low iodine diet and tap water. On the 15th day after hypophysectomy the low iodine diet was supplemented with 0.05% propylthiouracil and 50 μmoles of perchlorate per gram of diet.

‡ Thyrotropin in saline, 100 mU/100 g of body weight in divided doses each day for 7 days, was begun on the 15th day after hypophysectomy.

§ *P*, comparison of thyroid weight between vehicle-treated and thyrotropin-treated rats.

‖ Mean ± SEM.

TABLE VI

*Effect of Thyrotropin on the Iodine Content of the Thyroid Gland**

Experiment	Control			Thyrotropin-treated‡		
	No. animals	Thyroid weight	Thyroid iodine	No. animals	Thyroid weight	Thyroid iodine
		mg/100 g of body wt	*mg/100 g of thyroid*		*mg/100 g of body wt*	*mg/100 g of thyroid*
7	9	10.2±0.65	2.80	8	13.1±0.80	8.47
8	8	9.6±0.44	1.39	9	14.5±0.66	2.52
9	6	10.3±0.8	1.3	6	14.2±0.7	5.9

* Rats were fed a low iodine diet supplemented with 0.1% PTU for 10 or 11 days, (expt. 7) before hypophysectomy. After hypophysectomy they received the same diet and 1% perchlorate in the drinking water for 8 (expt. 8) or 10 days. On the 11th day they were switched to tap water and low iodine diet for the remainder of the experiment. Thyrotropin in saline, 100 mU/100 g of body wt in divided doses each day for 7 days was begun on the 14th or 15th day (exept. 9) after hypophysectomy.

‡ Mean ± SEM.

TSH of normal rats, as measured by Bakke and Lawrence (9). In all likelihood, however, the TSH was not absorbed immediately, and with a half-time in rat serum of only 12 min (9) the levels achieved by a single injection of TSH would probably be less than normal. Moreover, the estimated secretion of TSH from the pituitary each day was 16.8 mU/day (9) or more than five times the quantity of thyrotropin we used to produce significant thyroid enlargement. Further support for the sensitivity of our preparation comes from the observations of Averill (10) who injected or infused TSH and measured the release of radioactive iodine from the thyroid. An infusion of 2.4 mU/hr (i.e., 58 mU/day) significantly increased the release of radioactive iodine from the thyroid, but subcutaneous injection required 4–10 times as much TSH to get comparable results. Thus, the demonstration that thyroid enlargement can be produced by 3 mU/day of TSH given by the subcutaneous route indicates a very high degree of sensitivity.

In contrast to the data on the rats which were severely depleted of iodine are the data on mild depletion and iodine supplementation. When the content of iodine in the thyroid was only slightly depleted, 1000 mU/day of thyrotropin did not increase the weight of the thyroid, a finding which confirms the obesrvations of previous investigators that doses of TSH in excess of 1000 mU/day (or more than 1 mg/day) are usually necessary to produce goiters in normal rats (see Table VII, where the only exception is the study of Albert, Rawson, Riddle, Merrill, and Lennon (11) in which chicks were used). Further support for the inverse relationship between the content of iodine in the thyroid and its growth in response to TSH was presented by Katakai, Yamada, and Shichijo (12) who showed that rats receiving 200 μg of iodine daily had a significantly reduced goitrogenic response to 4000 mU of TSH daily.

Iodine depletion not only augments the potential of the thyroid for cellular growth, but also increases its capacity to accumulate and metabolize iodine (4–8), even in the absence of TSH. Conversely, high iodine intake suppresses the uptake and metabolism of iodine independently of thyrotropin (13, 14). VanderLaan and Caplan (7) were the first to suggest that some intracellular iodinated component was acting as a regulator of

TABLE VII

Data from the Literature on the Effect of Thyrotropin on Enlargement of the Thyroid Gland

Authors and reference	Animal studied	Dose of thyroptropin	Duration of treatment	Thyroid weight		
				Control	TSH	TSH plus thiourylene
		mg or U/day	*days*			
Astwood and Bissell (17)	rat	20 mg	4	9.3	22.9	19.1*
Albert et al. (11)	chick	0.4 mg	3	4.0	6.50	9.14*
Vander Laan and Caplan (7)	rat	1 mg	10		13.4	12.6‡
Taurog et al. (30)	rat	3–4 mg	4	14.5	38.3	
Alexander and Wolff (18)	rat	10 U	14	5.5	8.0	10.3‡
Katakai et al. (12)	rat	4 U	10	13.0	19.9	
Bray (this study)	rat	0.1 U	7	10.3	15.0	16.4‡

* Thiouracil.

‡ Propylthiouracil.

thyroid function, independently of thyrotropin. This suggestion has subsequently been made by several other groups of investigators (13, 15, 16). Our studies showing that the goitrogenic effect of thyrotropin was not blocked by high levels of circulating iodide are consistent with the hypothesis that it is the intracellular iodine that is regulating the response to TSH. The nature and mechanism by which this intrathyroidal substance influences thyroid function, however, must await further study.

The question of whether propylthiouracil potentiates the goitrogenic effects of thyrotropin has received divergent answers (11, 17, 18). Astwood and Bissell (17) noted that increase in the weight of thyroid in rats treated with 10 mg of TSH twice daily for 4 days was unaffected by thiouracil, and our findings that PTU did not affect the enlargement of the thyroid in iodine-depleted rats are in agreement with theirs. Albert et al (11), on the contrary, found that thiouracil potentiated the effects of 400 μg of TSH in chicks fed the goitrogen, and Alexander and Wolff (18) observed that 10 U of TSH daily for 14 days produced somewhat larger thyroid glands in rats which were also receiving propylthiouracil. The apparent potentiation of thyroid enlargement attributed to thiouracil (11, 18) or PTU may have resulted from the increased sensitivity of the iodine-depleted thyroid gland to TSH, rather than to any direct effect of the antithyroid drug on the response to TSH.

Finally, the present experiments may provide some insight into a mechanism for enlargement of the thyroid that does not require an increased release of thyrotropin. The usual sequence of events in the development of thyroid enlargement has been depicted as follows: (*1*) Some disturbance occurs in one of the steps of thyroid hormone biosynthesis with a reduction in the formation of thyroid hormone. (*2*) This results in a decreased secretion of thyroid hormone and a decrease in the level of circulating thyroid hormone. (*3*) The reduced level of circulating thyroid hormone, in turn, stimulates the pituitary to secrete thyrotropin, which leads to enlargement of the thyroid gland (19). There is substantial experimental evidence supporting this sequence of events. A number of mechanisms can reduce the quantity of hormone synthesized by the thyroid gland, including drugs (20), iodine deficiency (21), and genetic or acquired defects in hormone synthesis (22, 23). Moreover, removal of the pituitary prevents the development of goiter in animals fed antithyroid drugs and markedly slows the secretion of hormones from the thyroid gland (1, 20). Reduction of the levels of circulating thyroid hormone leads to an increased output of thyrotropin by the pituitary (1).

As impressive as the data for this hypothesis appear, many patients with nontoxic nodular goiter do not have demonstrable reductions in the level of circulating thyroid hormone (23) and recent studies using the radioimmunoassay for measuring plasma TSH in patients with nontoxic goiter have failed to find increased levels of thyrotropin in the plasma in many patients (24). In addition, studies on goiter formation in iodine-depleted rats by Studer and Greer (25) indicated that the early phases of thyroid enlargement occurred without a measurable increase in TSH or a decrease in PBI, although they did observe a decrease in the iodine content of the thyroid. These authors argued that TSH was probably still elevated during this early period, but that their methods were not sensitive enough to detect it. It is also conceivable, however, that TSH was not elevated, but rather the thyroid had become more sensitive to TSH as a result of the decrease in its iodine content. The concept that elevated levels of TSH may not be necessary to produce some forms of thyroid enlargement might be extended to nodular goiter in man. There is direct evidence that the iodine concentration in nodular tissue is reduced, when compared with paranodular tissue (26). Moreover, nodular tissue incorporated less radioactive iodine into diisotyrosine and thyronines than paranodular tissue (27–29). The mechanism for the decreased iodine content and functional capacity of nodular tissue to synthesize iodothyronines is unknown. However, such a reduction in iodine content could increase the sensitivity of these regions of the thyroid to the goitrogenic effects of thyrotropin and lead to nodular growth. Thus it seems possible that two mechanisms may be involved in thyroid enlargement. The first mechanism involves stimulation of the thyroid by increased levels of circulating thyrotropin and leads to diffuse glandular enlargement. The second mechanism suggested by the present studies is one in which nodular thyroid enlargement occurs with

normal levels of circulating thyrotropin due to the loss of iodine from localized regions of the thyroid and subsequent increased sensitivity of these regions to the goitrogenetic effects of thyrotropin.

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