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著者	AKIBA Yukio, MATSUMOTO Tatsuro
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## Biosynthesis of Thyroid Hormone Affected by Three-Day Administrations of (-)-5-Vinyl- 2-oxazolidinethione in Chicks

Yukio AKIBA and Tatsuro MATSUMOTO

*Department of Animal Science, Faculty of Agriculture,  
Tohoku University, Sendai, Japan*

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### Summary

The changes in the biosynthesis of the thyroid hormone in the early period of  $^{131}\text{I}$  administration were investigated in chicks injected with goitrin (20 mg/day) or PTU (20 mg/day and 12 mg/day) for 3-days. In both goitrin and PTU injected chicks, the thyroidal  $^{131}\text{I}$  uptake was depressed and the plasma level of thyroid hormone decreased. In the intrathyroidal biosynthesis of hormone, the oxidation of iodide, the iodination of tyrosine and the synthesis of the iodothyronines were intensively depressed by the injections of goitrin or PTU. The synthetic ability of iodothyronines was, however, restored at 24 hours after administration of  $^{131}\text{I}$  and the rebound phenomenon was observed. It is suggested that there is no distinct difference in the mechanism of the antithyroid action between goitrin and PTU in the case of 3-day administrations and that the antithyroid effects and action of goitrin are affected by the length of the administration period.

It has been well known that (-)-5-vinyl-2-oxazolidinethione (goitrin), a naturally occurring goitrogen in rapeseed, affects the thyroid hormone biosynthesis. It was suggested that feeding of goitrin for 14 days to chicks produced thyroid enlargement (about 5 times that of the control) and depressed the synthesis of iodothyronines, though monoiodination of tyrosine was not inhibited and a greater amount of iodothyronines was found in the goitrin-fed chicks than that of the control (1-3). On the other hand, different features of the depressing mechanism in the thyroid hormone biosynthesis were observed in chicks fed 0.05% propylthiouracil (PTU) for 14 days.

The purpose of the work described below is to determine the effect of goitrin on the biosynthesis of thyroid hormone in the case of 3-day administrations, particularly immediately after the administration of radioiodine in growing chicks.

### Materials and Methods

One-hundred and twenty day-old male Single Comb White-Leghorn chicks were fed a basal diet (about 0.67  $\mu\text{g}$  iodide/g of diet) throughout the experiment.

From the 11-th day, 10 mg of goitrin or PTU or 6 mg PTU were intramuscularly injected into the thigh twice a day for 3 days. This dosage of 6 mg PTU seems to have the same potency as 10 mg goitrin in hypertrophy of thyroid gland. One hour after the last injection of goitrogens, all chicks were injected subcutaneously in the thigh with carrier-free  $\text{Na}^{131}\text{I}$  ( $10 \mu\text{C}/100 \text{ g}$  body weight). At 0.5, 1, 2, 4, 8, and 24 hours after administration of  $^{131}\text{I}$ , five chicks in each group were killed by heart puncture and the thyroid glands and plasma were analyzed. Determination of plasma per cent  $\text{PB}^{131}\text{I}$ , distribution of radioactive iodinated substances in thyroid lobes and preparation of goitrin from rapeseed were stated in our previous reports (2, 4).

### Results

Goitrogen injection for 3 days had no effect on the thyroid weight (Table 1). The thyroidal  $^{131}\text{I}$  uptake of the control chicks was gradually increased and a maximum uptake (about 8 per cent of administered  $^{131}\text{I}$ ) was found at 8 hours after administration of  $^{131}\text{I}$  (Fig. 1). Otherwise, the thyroidal  $^{131}\text{I}$  uptake of

TABLE 1. *The Effect of Three-Day Administrations of Goitrogen upon Thyroid Weight in Chicks*

Treatment	Number of chicks	Body weight (g)	Thyroid weight (mg/100 g bw)
Control	15	115±14	7.4±0.8
Goitrin 20 mg	15	101±10	6.5±0.8
PTU 20 mg	15	110±12	6.8±1.0
PTU 12 mg	15	113±12	6.8±0.8

± Standard deviation of the mean.

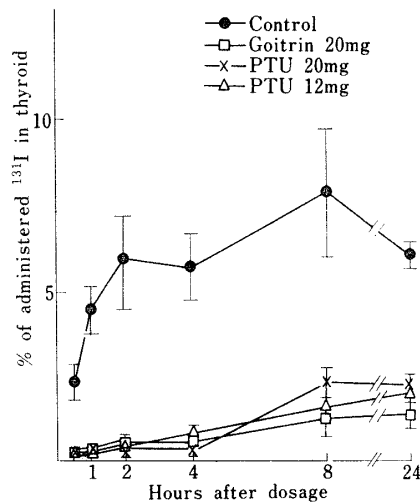


FIG. 1. The changes of thyroidal  $^{131}\text{I}$  uptake after administration of  $^{131}\text{I}$ .

Each point represents an average value for 5 animals. The vertical bars represent the standard deviation of the mean.

TABLE 2. The Effect of Three-Day Administrations of Goitrogen upon Plasma %  $PB^{131}I$  in Chicks

Treatment	Number of chicks	Hours after administration of $^{131}I$	
		8	24
Control	5	11.2±4.0	50.8±7.4
Goitrin 20 mg	5	2.3±1.0	38.3±3.6
PTU 20 mg	5	1.7±0.6	37.4±4.7
PTU 12 mg	5	1.1±0.2	36.0±4.2

goitrogen-injected chicks was intensively depressed in the early period of  $^{131}I$  administration and thereafter a little increase was observed. There was no distinct difference in the thyroidal  $^{131}I$  uptake between the goitrin-injected and PTU injected groups.

The changes of plasma per cent  $PB^{131}I$  were given in Table 2. Injection of goitrogen for 3 days induced a depression of circulating thyroid hormone. Plasma per cent of  $PB^{131}I$  in the goitrogen-injected groups was about 70 per cent that of the control group at 24 hours after administration of  $^{131}I$ .

Percentages of  $^{131}I$ -iodide in the components of radioiodinated substances in the thyroid lobes (Fig. 2A) of the goitrin-injected chicks increased considerably (60–80 per cent of total thyroid  $^{131}I$ ) immediately after the administration of  $^{131}I$ . The increased percentage of  $I^-$  in the goitrogen-injected groups decreased rapidly and reached the same level as the control group at 8 hours after administration of  $^{131}I$ .

Inversely, the percentages of  $^{131}I$ -iodotyrosines (monoiodotyrosine, MIT and diiodotyrosine, DIT) of the goitrogen-injected chicks were greatly depressed in the early period after  $^{131}I$  injection and increased to the level of the control chicks at 8 hours after administration of  $^{131}I$  (Fig. 2B). The lowest percentage of iodotyrosines was observed in the goitrin group, followed by the PTU 20 mg and 12 mg injected groups in the early period after administration of  $^{131}I$ . These percentages of iodotyrosines were inversely correlated with the percentages of iodide mentioned above.

The ratios of iodide and iodotyrosines are illustrated in Fig. 2C. The lower value was demonstrated immediately after administration of  $^{131}I$  in the control chicks. In goitrin 20 mg and PTU 20 mg injected chicks the maximum ratios of  $I^-$ /iodotyrosines (about 10–11) were found at 1 hour after administration of  $^{131}I$  and then dropped to the same level as the control group. There was a little increase in the ratio of  $I^-$ /iodotyrosines in the PTU 12 mg injected group and it situated between the goitrin-injected chicks and the control chicks.

The ratio of MIT/DIT in the control group was about 0.8 at 2 hours after administration of  $^{131}I$  (Fig. 2D). A distinct increase of MIT/DIT ratio was found in the goitrogen-injected chicks though difference was insignificant at 0.5 hours after administration of  $^{131}I$ . A higher ratio of MIT/DIT than that of the PTU-

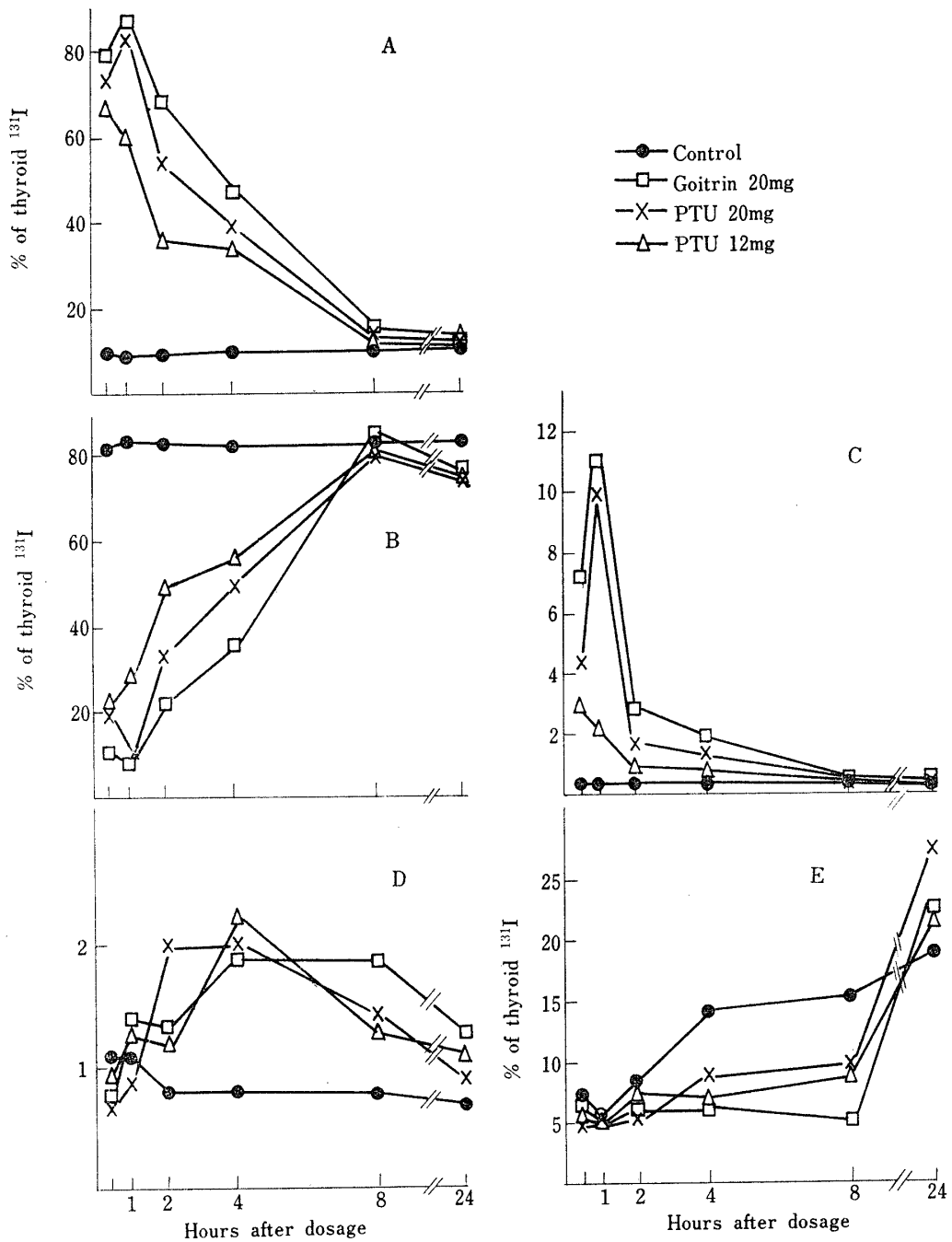


FIG. 2. The changes of percentage or ratio of radioactive iodinated substances in the thyroid lobes. (A) Percentages of I<sup>-</sup> to total thyroid <sup>131</sup>I. (B) Percentages of iodotyrosines to total thyroid <sup>131</sup>I. (C) I-/iodotyrosines ratios. (D) MIT/DIT ratios. (E) Percentages of iodothyronines to total thyroid <sup>131</sup>I.

injected groups was found in the goitrin-injected chicks at 8 hours and 24 hours after administration of <sup>131</sup>I.

The changes of percentages of <sup>131</sup>I-iodothyronines (triiodothyronine, T<sub>3</sub> and thyroxine, T<sub>4</sub>) to total thyroid <sup>131</sup>I in the lobes are given in Fig. 2E. The percent-

ages of iodothyronines in the control group were increased as a function of time after 1 hour. A decrease of percentages of iodothyronines was observed after 2 hours in the goitrogen-injected groups. At 8 hours after administration of  $^{131}\text{I}$ , the highest value is found in the control chicks, followed by the PTU 20 mg and 12 mg injected groups and the lowest value in the goitrin-injected group. The percentages of iodothyronines in the goitrogen-injected groups increased considerably thereafter and exceeded that of the control group at 24 hours after administration of  $^{131}\text{I}$ . The most striking increase was observed in the PTU 20 mg injected group.

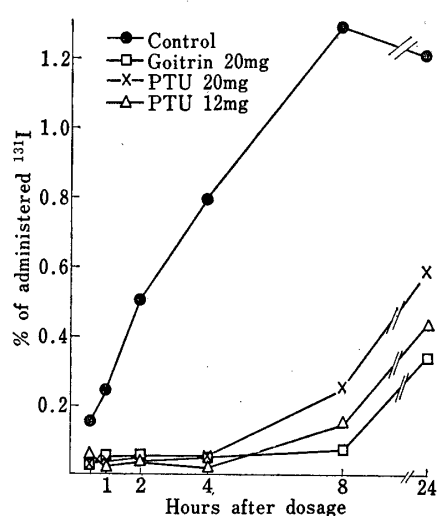


FIG. 3. The changes in amounts of iodothyronines synthesized in the thyroid gland (percentages of iodothyronines per dosage of  $^{131}\text{I}$ ).

The amount of  $^{131}\text{I}$ -iodothyronines synthesized in the thyroid gland is shown as percentage of total administered  $^{131}\text{I}$  in Fig. 3. The amount of iodothyronines in the control group was about 0.15 per cent of the total administered  $^{131}\text{I}$  at 0.5 hours and rapidly increased to 1.3 per cent at 8 hours after administration of  $^{131}\text{I}$ . On the other hand, the amount of iodothyronines was markedly depressed by 3-day injections of goitrogen though its increase was observed at 24 hours after administration of  $^{131}\text{I}$ .

### Discussion

Since the thyroidal radioiodine uptake was depressed immediately after administration of  $^{131}\text{I}$ , it was thought that the thyroid function was markedly depressed by 3-day injections of goitrin or PTU. The depressed thyroidal  $^{131}\text{I}$  uptake in the goitrin or PTU injected chicks are in good agreement with the results of Krusius and Peltola in goitrin-administered rat (5) and those of Sugita et al. in MTU-injected rats (6), respectively. At 24 hours after administration of  $^{131}\text{I}$ , the thyroidal  $^{131}\text{I}$  uptake of the goitrogen-injected groups were slightly increased.

It is suggested that the blocking effect of the goitrogen was diminished gradually and that the thyroidal  $^{131}\text{I}$  uptake in the goitrogen-injected groups increased by degrees.

The plasma level of the thyroid hormone was also depressed by 3-day injections of goitrin or PTU (Table 2). That intensively depressed level of thyroid hormone in the plasma at 8 hours after injection returned to 75 per cent of the control group at 24 hours after administration of  $^{131}\text{I}$  in the goitrogen-injected groups. A similar restoration of the thyroid function at 24 hours after administration of  $^{131}\text{I}$  has been observed in the MIT/DIT ratios (Fig. 2D) and I-/iodotyrosines ratios (Fig. 2C). Furthermore, a restoration in the percentage of iodothyronines (Fig. 2E) was striking and the rebound phenomenon, which exceeded the level of the control group, was clearly demonstrated at 24 hours after administration of  $^{131}\text{I}$  in the goitrogen-injected groups. The increase (restoration) and the rebound phenomenon of thyroid function at 24 hours after administration of  $^{131}\text{I}$ , namely 25 hours from the last injection of goitrin, can best be understood on the basis of the observations by Maloof and Soodak (7) that the administered goitrogen disappeared rapidly from the blood. A similar rebound phenomenon in thyroid function was previously reported in rat by withdrawal of PTU administration (8) and in chicks by withdrawal of PTU (4).

The biosynthesis of the thyroid hormone in the gland was depressed by 3-day injections of the goitrogens as is evident from the increased MIT/DIT ratios (Fig. 2B). It is considered that the oxidation of the iodide and the iodination of the tyrosine were greatly inhibited by the injection of goitrin or PTU, since an increase of iodide (Fig. 2A) and I-/iodotyrosines ratios (Fig. 2C) was clearly observed from 0.5 hours after administration of  $^{131}\text{I}$ . These results are different from those in chicks that, when fed 0.05 per cent goitrin for 14 days, no inhibition in the oxidation and iodination processes in the gland occurred (2, 3). It is, therefore, speculated that the mode of action of goitrin is different in respect to immediate effects after 3-days injections and to accumulated effects after relatively long term administration.

The activity of iodothyronines synthesis and the amount of iodothyronines synthesized in the gland were intensively depressed by 3-day injections of goitrin or PTU and it was striking at 8 hours after administration of  $^{131}\text{I}$  in the goitrin-injected group. The differences between the goitrin and PTU in mechanism of antithyroid action in the gland after 3-day injections were not observed since both goitrogens depressed each step in biosynthesis of hormone in the gland similarly; i.e., oxidation of iodide, iodination of tyrosine and iodothyronine synthesis.

In view of the above results, it can be suggested that the antithyroid effects of goitrin on chicks may be affected by the method (route) of administration or by the length of administration in respect to mechanism of antithyroid action. It

is, however, not apparent in this study whether the difference between the results obtained by 3-day injections of goitrin and those obtained by 14-day feedings of goitrin in our previous reports (2, 3) is attributable to the difference in method (route) of administration (intramuscularly injection and oral administration) or the difference in the length of the administration period (3 days and 14 days). An additional experiment was conducted to elucidate this problem.

Single Comb White-Leghorn chicks were used, and at 14 days of age, 10 mg or 1 mg of goitrin was administered orally for 2 days. Thereafter, radioiodine ( $\text{Na}^{131}\text{I}$ , 10  $\mu\text{C}/100$  g body weight) was injected subcutaneously in the thigh and the thyroidal  $^{131}\text{I}$  uptake was observed at 24 hours after administration of  $^{131}\text{I}$ . The thyroidal  $^{131}\text{I}$  uptake was depressed by 2-day oral administrations of 1 mg goitrin (about 88 per cent that of the control) and 10 mg goitrin (about 60 per cent that of the control) as in Table 3. These depressions of thyroidal  $^{131}\text{I}$  uptake by 2-day oral administrations of goitrin are in good agreement with that obtained by 3-day intramuscular injections of goitrin (Fig. 1).

TABLE 3. *The Effect of Oral Administrations of Goitrogen for Two Days upon Thyroidal  $^{131}\text{I}$  Uptake*

Treatment	Number of chicks	Thyroid $^{131}\text{I}$ uptake (%)
Control	5	7.3 $\pm$ 0.5
Goitrin 1 mg	5	6.4 $\pm$ 0.5
Goitrin 10 mg	5	3.0 $\pm$ 0.3

It may be concluded that the difference of antithyroid action of goitrin between 3-day injections and 14-day feedings is attributable to the length of administration period of goitrin and it is not due to the method (route) of administration.

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