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Inhibitory Effect of Large Doses of Propylthiouracil and Methimazole on an Increase of Thyroid Radioiodine Release in Response to Thyrotropin (39335)

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Chronic administration of antithyroid drugs lowers circulating thyroid hormone by blocking synthesis of thyroid hormones and thus produces goiter by augmenting thyrotropin (TSH)[1] secretion from the pituitary (1, 2). Although a single injection of antithyroid drug can block hormone synthesis within a few minutes, it is not known how soon pituitary release of TSH increases in response to antithyroid drugs. Thyroidal radioiodine release can be used as a sensitive measure of changes in TSH secretion (3). It is accelerated shortly after TSH (3) or small doses of propylthiouracil (PTU). Since blood TSH increased 24 hr after a single injection of PTU, and since blood PBI was normal during this period, Escobar *et al.* (4) hypothesized that PTU augmented TSH secretion by inhibiting deiodination of thyroxine (T_4) and reducing negative feedback, an argument requiring the assumption that deiodination of T_4 is an obligatory step in its action.

While we were studying some aspects of this hypothesis in rats, we incidentally found that large doses of PTU and methimazole (MMI) failed to augment thyroidal radioiodine release for a period of 29 to 34 hr. This is unexpected finding, since thyroidal radioiodine release is accelerated when recirculation of iodide is blocked, and since large doses of goitrogens are required to inhibit recirculation of iodide to monoiodotyrosine (1). A number of studies were thus performed to shed some light on this unexpected finding.

Materials and methods. One-hundred-thirty-six male Wistar rats, weighing 150 to 200 g, and 72 male DDY mice, weighing 20 to 30 g, were used in this experiment. The animals were fed a Remington low iodine diet (LID) or a moderately low iodine diet[2] (MLID) beginning 7 to 14 days before radioiodine injection. Beginning 28 to 48 hr after the injection of 20 μCi of ^{131}I, thyroidal radioiodine release was measured, with or without injection of anti-thyroid drugs (5). In Experiment 3, blood was obtained by cardiac puncture to measure plasma TSH, $^{131}I^-$ and $PB^{131}I$ during measurement of thyroidal radioiodine release. Plasma TSH was measured according to the McKenzie (3) method, and plasma $^{131}I^-$ and $PB^{131}I$ were measured by the trichloroacetic acid precipitation technique reported previously (6). In Experiment 5, the McKenzie method was also used to assess thyroidal response to exogenous TSH. The data were analyzed for statistical significance by the Student's *t* test. The *P* value less than 0.05 was considered statistically significant.

Results. Experiment 1. Effects of graded doses of methimazole (MMI) on thyroidal radioiodine release in rats fed a low iodine diet. For the first 60 hr, three groups of eight animals each received saline (0.5 ml) ip once daily. The half-life of thyroidal radioactivity during this period ranged from 51 to 56 hr, without a significant difference among the groups (Fig. 1). Seven to nine hours after the administration of MMI (7 or 15 mg), an increase of thyroidal radioiodine release was found in all animals. However, when 40 mg of MMI was administered, a latency of 29 hr was found before any increase of thyroidal radioiodine release could be detected. After the increase of radioiodine release, no difference in half-life of thyroidal radioactivity was found among the three groups.

Experiment 2. Effects of graded doses of propylthiouracil (PTU) on thyroidal radioio-

[1] TSH, Armour Thytropar.

[2] Composition of this diet was shown in Endocrinology **79**, 138 (1966).

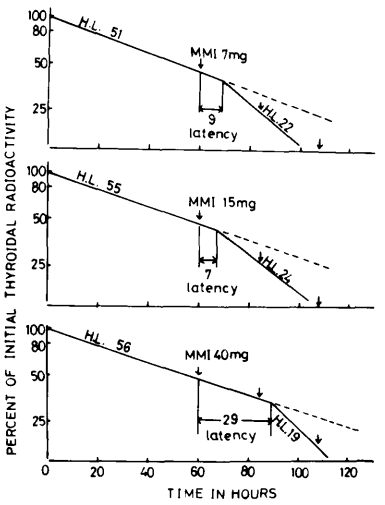

FIG. 1. Typical curve of thyroidal radioiodine release before and after methimazole. In this and subsequent figures: H.L., half-life of thyroidal radioactivity; latency, hours elapsed before an increase of thyroid secretion was detected; MMI, methimazole.

dine release in rats fed a low iodine diet. For the first 60 hr, four groups of eight animals each received gelatin solution (2%) sc daily. There was no significant difference in the thyroidal release among them (Fig. 2). When 1 or 5 mg of PTU was administered, a marked increase of thyroidal radioiodine release occurred immediately after the PTU. However, only a smaller increase of secretion occurred with 30 mg of PTU, which was followed by a final increase 30 hr later. The half-life of thyroidal radioactivity during intermediate and final increase was 31 and 15 hr, respectively. When 60 mg of PTU was administered, 34 hr elapsed before a significant increase was detected. There was no significant difference in the final release rate among the four groups.

Experiment 3. Effects of graded doses of propylthiouracil on thyroidal radioiodine release, plasma $^{131}I^-$, PB^{131}I, and TSH in rats fed a moderately low iodine diet. In the gelatin-injected controls, the half-life of thyroidal radioactivity was 104 ± 21 hr (mean ± SE) (Fig. 3). The administration of 5 mg of PTU produced a slight increase of thyroidal radioiodine release with a half-life of 67 ± 9 hr, which was followed by a final increase 12 hr later. When 60 mg of PTU was administered, a 34-hr latency was found before any increase of thyroidal radioiodine release occurred. The half-life of thyroidal radioactivity was slightly longer in the 5-mg PTU group than in the 60-mg PTU group.

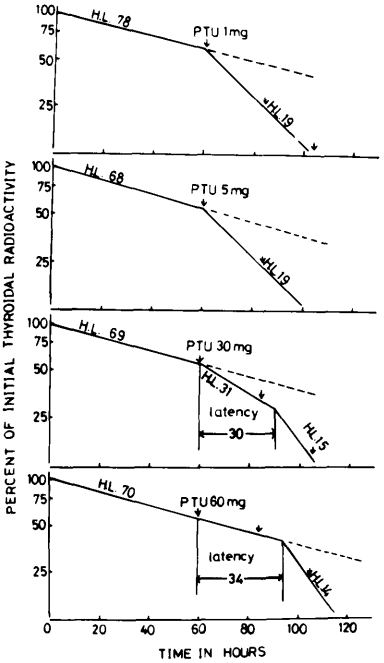

FIG. 2. Typical curve of thyroidal radioiodine release before and after propylthiouracil. PTU, propylthiouracil.

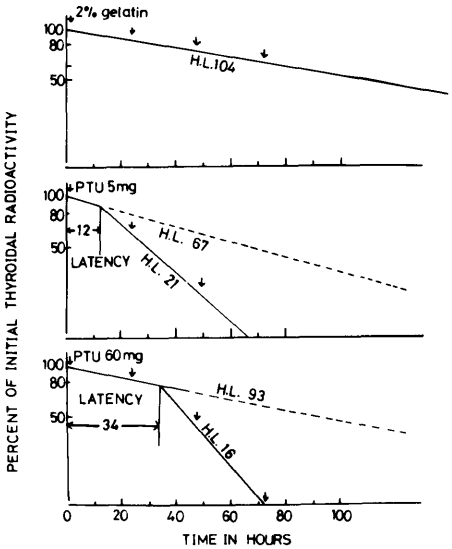

FIG. 3. Typical curve of thyroidal radioiodine release before and after propylthiouracil. Arrow indicates injection of gelatin or PTU. PTU, propylthiouracil.

Blood was obtained by cardiac puncture for plasma iodine analysis and TSH bioassay, just before and 24 as well as 52 hr after the initial dose of PTU. As shown in Fig. 4, plasma $PB^{131}I$ and $^{131}I^-$ were fairly constant throughout the experimental period in the gelatin-injected controls. PTU administration produced a marked increase of plasma $^{131}I^-$ and a slight decrease of $PB^{131}I$. As compared with the 5-mg PTU group, an increase of plasma $^{131}I^-$ in the 60-mg PTU group was less at 24 hr ($P < 0.05$).

Finally, plasma TSH activity was measured in 42 mice fed MLID for 7 days (Fig. 5). As compared with the control plasma, a marked increase of plasma radioactivity was found 24 and 52 hr after administration of 5 mg of PTU ($P < 0.001$ at 24 hr). An increase of plasma radioactivity was also found 24 hr after administration of 60 mg of PTU (control vs PTU 60-mg, $P < 0.01$), although the magnitude of the response was slightly less in the 60-mg PTU group than in the 5-mg PTU group.

Experiment 4. Effects of propylthiouracil and methimazole on thyroidal response to TSH in rats treated with thyroxine. In the first experiment, 27 animals were divided into three equal groups (Control, PTU, and MMI groups) and were fed MLID for 10 days before the experiment. Beginning 48 hr after ^{131}I injection, thyroidal radioiodine release was measured while the animals were receiving 15 μg of T_4 once daily ip. Thyroidal radioiodine release was exponential but slow because of depression of TSH. Administration of PTU (5 mg) or MMI (5 mg) once daily for 2 days had no consequence on thyroidal radioiodine release. With the last dose of goitrogens, 1 U of TSH was administered sc. Just before and 20 hr after the injection of TSH, blood was obtained for plasma $PB^{131}I$ analysis. As shown in Fig. 6 (left), the increase of plasma $PB^{131}I$ was less in the PTU group than in gelatin-injected controls ($P < 0.02$). Such a depression of thyroidal response to TSH was marked in animals injected with MMI (PTU vs MMI, $P < 0.01$).

In the second experiment, 20 animals were divided into two groups (Control and PTU 60-mg groups). Administrations of MLID, $^{131}I^-$, T_4, and measurement of thyroidal radioiodine release were the same as in the first experiment. Administration of 60 mg of PTU failed to augment thyroidal radioiodine release under T_4. With the last dose of PTU, 0.3 U of TSH was administered sc. Just before and 4 hr after TSH, blood was obtained for ^{131}I analysis. As shown in Fig. 6 (right), the increase of plasma $PB^{131}I$ was significantly less in the

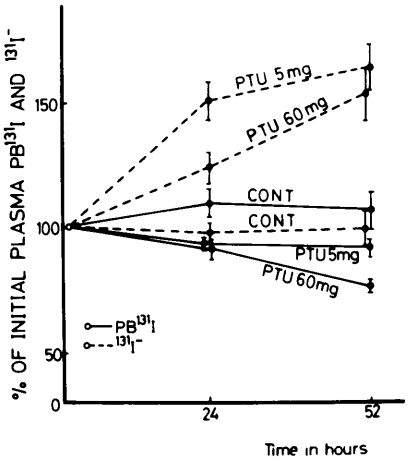

FIG. 4. Blood was obtained from the animals in Fig. 3 just before and 24 as well as 52 hr after PTU administration. $PB^{131}I$ and $^{131}I^-$ were expressed as percentage of initial plasma radioactivity. Circles and vertical lines indicated mean ± SE. Experimental procedures were the same as in Fig. 3.

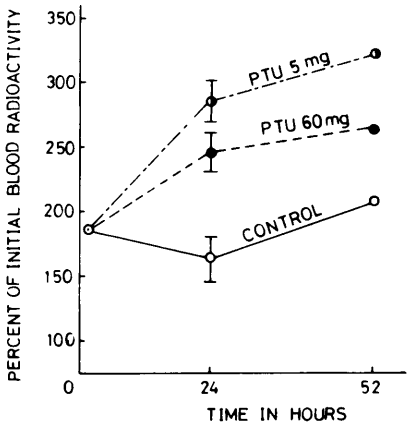

FIG. 5. TSH activity of rat plasma, as judged by mouse bioassay. Blood was obtained from rats shown in Fig. 3 just before and 24 as well as 52 hr after the administration of PTU. Plasma at 0 and 52 hr was pooled before TSH assay. Circles and vertical lines indicates mean ± SE. Statistical analysis at 24 hr: control vs PTU 5-mg, $P < 0.001$; control vs PTU 60-mg, $P < 0.01$; PTU 5-mg vs PTU 60-mg, $0.05 < P < 0.1$.

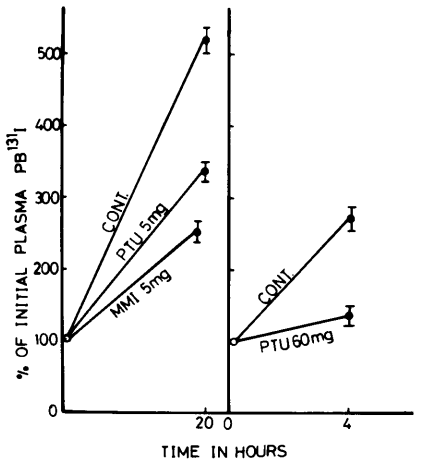

FIG. 6. On the left, 1 U of TSH was injected sc to rats treated with T_4 (15 μg) and goitrogens. Blood was obtained just before and 20 hr after TSH injection. On the right, 0.3 U of TSH was administered sc to rats treated with T_4 (15 μg) and PTU 60 mg. Blood was obtained just before and 2 hr after TSH administration. Circles and vertical lines indicated mean ± SE.

60-mg PTU group (Control vs 60-mg PTU, $P < 0.005$).

Experiment 5. Effects of graded doses of propylthiouracil or methimazole on thyroidal response to TSH in mice. Thirty mice fed MLID for 7 days were used to measure thyroidal response to TSH under the influence of goitrogens. Graded doses of PTU (0.1, 1, and 5 mg) or 5 mg of MMI in 0.5 ml of gelatin (0.5%) were administered ip 45 min before iv injection of 5 mU of TSH. Blood was obtained just before and 2 hr after TSH administration. As shown in Fig. 7, administration of TSH produced a marked increase of blood radioactivity. Administration of gelatin had no effect on thyroidal response to TSH. This increase of plasma radioactivity was augmented by 0.1 mg of PTU. However, the thyroidal response to TSH decreased progressively with increasing doses of PTU administered. MMI apparently depressed thyroidal response to TSH.

Discussion. In accordance with the previous studies (4, 5), our present data indicated that thyroidal radioiodine release increased shortly after a single injection of 1 to 5 mg of PTU into animals fed LID, and this increased rate of release continued as long as PTU injection was continued. Since PTU and MMI failed to augment thyroidal radioiodine release in rats treated with T_4, TSH was essentially linked with the manifestation of this goitrogen effect on thyroidal radioiodine release. Escobar *et al.* (4) hypothesized that PTU might cause an acute increase of pituitary TSH secretion by blocking the deiodination of T_4, a process presumably required for the manifestation of hormonal action. However, this explanation is not satisfactory, since a similar increase of thyroidal radioiodine release is also produced by moderate doses (7 to 15 mg) of MMI which is known not to block deiodination of T_4 *in vivo* (7). Simultaneous measurements of thyroidal radioiodine release, plasma $^{131}I^-$ and plasma $PB^{131}I$ indicate that a marked increase of thyroidal $^{131}I^-$ release is responsible for an increase of thyroidal radioiodine release. Two processes are undoubtedly involved in this increased release of iodide produced by goitrogens. First, goitrogens augment thyroidal radioiodine release by blocking intrathyroidal recirculation of iodide. Second, iodide release is augmented by an increased secretion of TSH produced by a reduction of thyroid hormone synthesis under goitrogen treatment. Since both processes are accentuated by increasing the doses of goitrogen admin-

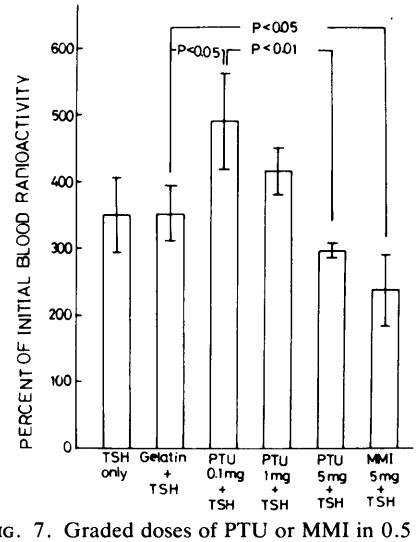

FIG. 7. Graded doses of PTU or MMI in 0.5 ml of gelatin (0.5%) were injected ip 45 min before TSH administration. Blood was obtained just before and 2 hr after TSH (5 mU) administration. gelatin + TSH vs PTU 0.1-mg + TSH, $P < 0.05$; PTU 0.1-mg + TSH vs PTU 5-mg + TSH, $P < 0.01$; gelatin + TSH vs MMI 5-mg + TSH, $P < 0.05$.

istered (1), it can be suspected that thyroidal radioiodine release is augmented with increasing doses of goitrogen administered. In contrast to this speculation, the following three unexpected findings were observed. First, when 30 mg of PTU was administered daily, an intermediate increase of thyroidal radioiodine release appeared shortly after a single injection of PTU, and this release was then followed by a final increase 30 hr later. Second, when 60 mg of PTU was administered, 34 hr elapsed before any increase of thyroidal radioiodine release was detected. Finally, when 40 mg of MMI was administered, 29 hr elapsed before any increase of thyroid secretion was detected. Since these unexpected effects of goitrogens were short-lasting, and since the final release rate was slightly faster in the 30-mg and 60-mg PTU groups than in the 5-mg group, it seemed that these findings were not simply due to general toxic actions of goitrogens.

It is possible that large doses of goitrogens depress thyroidal radioiodine release by inhibiting an increased secretion of TSH in response to goitrogens. This is unlikely, however, since a possible difference of plasma TSH between 5-mg and 60-mg PTU group is too small to account for the observed marked difference of thyroidal radioiodine release and plasma $^{131}I^-$. Also, normal increase of thyroidal radioiodine release resumes in response to this concentration of TSH after a certain period of latency. An alternative hypothesis would then be that large doses of goitrogens make the thyroid less responsive to TSH for a certain period. In order to test this hypothesis, we have measured thyroidal response to TSH in rats and mice treated with T_4. As shown in Figs. 6 and 7, large doses of PTU and MMI apparently reduced the effectiveness of TSH. It is concluded that large doses of PTU and MMI make the thyroid less responsive to TSH for a certain period through some unknown mechanism.

Summary. Thyroidal radioiodine release increased shortly after a single injection of small doses of PTU, while moderate doses of MMI produced a similar increase of thyroidal radioiodine release with a latency of 7–9 hr. Large doses of PTU and MMI failed to augment thyroidal radioiodine release for at least 29 to 34 hr after the initial administration of goitrogens, although plasma TSH increased significantly because of goitrogen administration. An increase of thyroid hormone release in response to exogenous TSH was depressed by PTU and MMI in rats and mice treated with T_4. Since this depression of TSH action only continued for a short period in spite of continuous administration of goitrogens, and since final thyroidal radioiodine release rate was similar to that produced by small doses of PTU, the effects mentioned were not simply due to general toxic action of goitrogens. It is suggested that large doses of PTU and MMI not only block thyroid hormone synthesis but also interfere with the action of TSH on thyroid hormone secretion.

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