Effects of Methimazole and Propylthiouracil on Blood Disappearance and Urinary Excretion of Iodide in the Rat (36729)

AKIRA SATO, MASAO OHTAKE, MASANOBU KOTANI, TOSHIMASA ONAYA AND TAKASHI YAMADA
(Introduced by M. A. Greer)
Department of Medicine, Institute of Adaptation Medicine, School of Medicine, Shinshu University, Matsumoto, Japan

It is well established that methimazole (MT), propylthiouracil (PTU) and related thionamide compounds inhibit organic binding of iodine in the thyroid gland and thus produce goiter (1). An extrathyroidal effect of the drugs has also been recognized. However, it has been reported that PTU blocks deiodination of thyroxine *in vivo* and augments fecal loss of thyroxine but MT does not (2). Studies by Brown (3) have shown that PTU augments urinary excretion of iodide in the rat. In analogy, it might be anticipated that the effect of MT on urinary excretion of iodide might be different from that of PTU.

Materials and Methods. One hundred and twenty-eight male Wistar and Holtzman rats, weighing 152–193 g, were used. The animals were fed Remington low-iodine diet (LID), a moderately low-iodine diet (MLID) and Purina chow, a high-iodine diet (HID) *ad libitum,* beginning 7 days before surgical thyroidectomy. After thyroidectomy, the animals received 4–5 μg of L-thyroxine daily intraperitoneally throughout the experimental period. Seven days after thyroidectomy, the animals were used for the experiment. One to 15 mg MT in 1 ml saline or 5 to 60 mg PTU in 1 ml of 0.5% gelatin was injected subcutaneously (sc) 10 hr and just before intraperitoneal administration of radioiodine (1–5 μCi of ^{131}I). Blood (0.2 ml) was obtained by cardiac puncture, using heparinized syringes 1, 4, 6, 10, 13 and 25 hr after radioiodine administration. Blood radioactivity per 0.2 ml was then expressed as percentage of initial blood radioactivity. At autopsy, the neck was thoroughly examined under the dissecting microscope (10× magnification) for remnants of thyroid tissue. If no thyroid remnant was observed, the following tissue sections were removed for counting in the scintillation well-counter: (a) base of the tongue to beginning of trachea; (b) trachea, pretracheal muscle, and esophagus in the ventral neck region; (c) thymus; (d) heart and great vessels. The ^{131}I concentration in the tissue sections was then determined in relation to that in plasma. The animals that showed appreciable ^{131}I concentration in thyroid region were judged to be incompletely thyroidectomized, and those animals were discarded from statistical analysis. Analysis of the significance of difference between groups was done by means of Student's t test. A p value less than .05 was considered statistically significant. Paper chromatographic analysis of plasma ^{131}I was done according to the method reported previously (14). Iodine content of the diet was 45–70 μg, 90–120 μg and 1–2 mg/kg of the diet in LID, MLID and HID.

Results. Effect of methiamazole and propylthiouracil on blood disappearance of iodide in rats fed LID or HID. Effects of graded doses of MT and PTU on blood disappearance of radioiodide are shown in Fig. 1. In Expts. A, B and C in which the animals were fed LID, the rate of disappearance of radioiodide from the blood was decreased in animals treated with MT. The decrease was significant 10 hr after radioiodine administration ($p < .05$), regardless of the doses of MT (1–15 mg) administered. When the data of Fig. 1A, B and C were plotted on semilog paper against time, the half-life of blood $^{131}I^-$

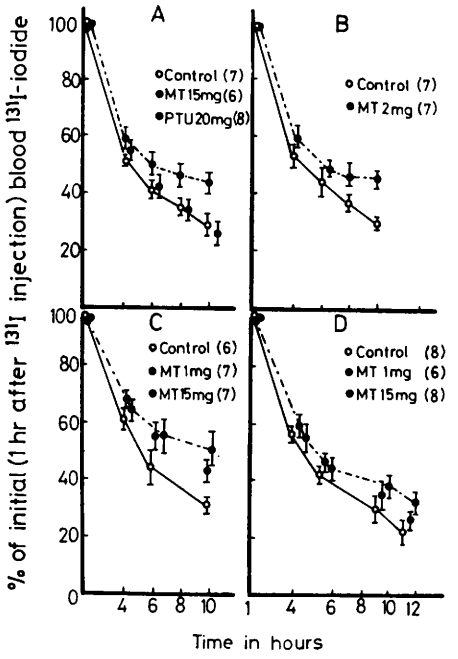

FIG. 1. Thyroidectomized, thyroxine-maintained rats were used. Methimazole (MT) and propylthiouracil (PTU) were injected subcutaneously 10 hr and just before intraperitoneal administration of radioiodine (1–5 μCi of ^{131}I). Circles and vertical lines indicate mean ± SE. Parentheses indicate the number of animals used. The animals of A, B and C were fed LID, while the animals of D were fed HID.

was 7.3–8.6 hr in the controls and was 12.3–14.0 hr in MT groups. In contrast, PTU failed to affect the rate of disappearance of radioiodide from the blood (Fig. 1A). In Expt. A, blood was obtained at autopsy for radioiodine analysis. Iodide was the only one that was found by paper chromatographic analysis. In Expt. D, the animals were fed HID (Fig. 1D). One milligram of MT did not affect disappearance of radioiodide from the blood for up to 12 hr after radioiodine injection. However, the slope of disappearance curve was somewhat slower in the 15 mg MT group than in the saline injected control, although the difference was not significant [at 12 hr: control–MT (15 mg) $0.05 < p < 0.1$].

Effect of propylthiouracil and methimazole on early and late stages of disappearance of radioiodide from the blood in rats fed MLID. In animals fed MLID and injected with saline, MT (15 mg) and graded doses of PTU (5–60 mg), we compared blood radioactivity by obtaining blood samples 1 hr after radioiodine injection to see if the early stage of disappearance rate was affected by goitrogens. No difference in blood radioactivity was found between control and MT groups (Fig. 2A). When PTU was given, a dose-related decrease of blood radioactivity was found (Fig. 2A). The decrease was statistically significant with 10 and 60 mg PTU. Additional blood samples were also obtained to see if at later stages of disappearance the rate was affected by goitrogens. When blood radioactivity at 13 and 25 hr was expressed as percentage of 1 hr radioactivity (Fig. 2B), the later stages of disappearance were not affected by graded doses of PTU. In accordance with the previous data, 15 mg MT apparently slowed the disappearance rate of radioiodide, however.

Effect of methimazole on urinary excretion

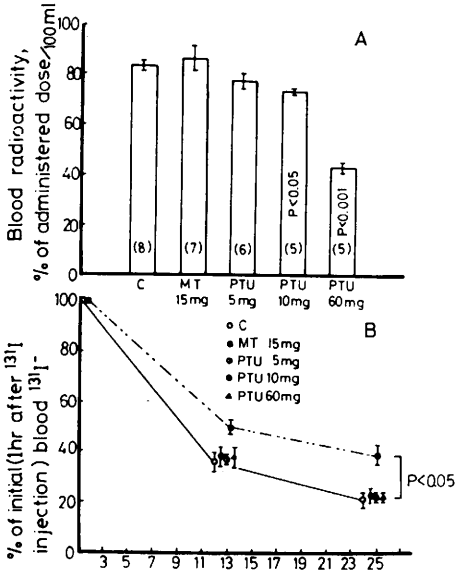

FIG. 2. Experimental conditions were the same as in Fig. 1, except that the animals were fed MLID. (A) Blood ^{131}I– concentration 1 hr after radioiodine injection. Bars and vertical lines indicate mean ± SE. Parentheses indicate the number of animals used. (B) Blood ^{131}I– concentration at the later stage. Circles and vertical lines indicate mean ± SE. C = control, MT 15 mg = 15 mg methimazole was injected. PTU 5 mg = 5 mg PTU was injected.

and blood concentration of radioiodide. In this experiment, the animals were fed LID. Immediately after injection of radioiodide, each animal was placed in a metabolic cage. Water was given but food was omitted during the 10-hr experiment. At the end of the experiment, urine and blood were obtained for radioiodine analysis. In saline injected control, 74.6% of radioiodide administered was found in the urine, while 62.1% of the injected radioiodide was recovered in the urine of the animals injected with MT (Fig. 3A). As expected, blood radioiodide was apparently greater in the MT group than in saline injected controls (Fig. 3B).

Discussion. Theoretically, serial measurements of blood radioactivity should indicate the disappearance of $^{131}I^-$ from the blood under our experimental conditions, since the animals were thyroidectomized and injected with 4–5 μg L-thyroxine, and since no significant concentration of radioactivity was found in the neck. This was ascertained by the fact that we failed to detect radioactive materials other than iodide in the blood. Thus our present data clearly indicated that MT retarded the rate of disappearance of radioiodide from the blood in animals fed LID and MLID. This was statistically significant 10 hr after radioiodine injection, regardless of the doses of MT used. Since disappearance of blood iodide is largely governed by the kidney in the absence of the thyroid, the slow disappearance rate of $^{131}I^-$ might possibly be related to the kidney. In support of this concept, urinary excretion of iodide was significantly less in the MT group than in saline injected control. However, there is an additional factor which influences this MT effect, since the MT effect is markedly lessened in rats fed HID.

In contrast, the rate of disappearance of iodide from the blood was not influenced by PTU in animals fed LID (Fig. 1A). Escobar del Rey and Morreale de Escobar (6) also found that PTU did not influence urinary excretion of iodide in rats. Thus these data did not agree with the previous report by Brown (3) who found an acceleration of the rate of loss of $^{131}I^-$ from the blood after repeated injections of PTU in rats. However, it should be noted that Wollman and Scow (7) reported an increase of disappearance of blood $^{131}I^-$ within 30 min after intraperitoneal administration of radioiodine in mice previously injected with PTU. This increase was apparently related to the dose of PTU administered, and the effect disappeared within 120 min when small doses of PTU were administered. In agreement with these findings, we found that disappearance of blood iodide increased within 60 min after intraperitoneal injection of radioiodine in rats previously injected with PTU, and that the increase of disappearance of blood radioactivity was actually related to the doses of PTU. Since the later stage of iodide disappearance was not influenced by

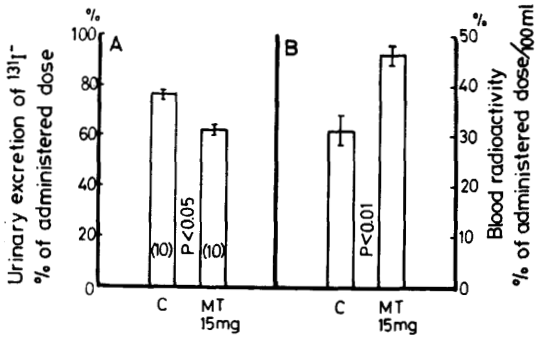

FIG. 3. Animals were fed LID. Experimental procedures were the same as in Fig. 1, except that the animals were kept in the metabolic cages for 10 hr, beginning soon after radioiodine injection and blood samples were obtained 10 hr later. Bars and vertical lines indicate mean ± SE. Parentheses indicate the number of animals used. C = control, MT 15 mg = 15 mg methimazole was injected.

PTU, this PTU effect was only short lasting under our experimental conditions. Since Brown has shown that repeated injections of PTU was required to produce a constant increase of disappearance of blood iodide (3), repeated injection of PTU may be required to produce a long lasting effect of PTU on renal excretion of iodide in the rat.

Summary. Regardless of the dose of MT administered, MT decreased the rate of disappearance of radioiodide from the blood for at least 25 hr by depressing urinary excretion of iodide in thyroidectomized, thyroxine-maintained rats fed LID. This effect of MT was lessened in rats fed HID. In contrast, PTU augmented disappearance of blood iodide during the first 60 min after radioiodine injection. This effect was apparently related to the dose of PTU administered. It is concluded that MT and PTU have different mode of action on extrathyroidal iodine metabolism in the rat.

1. Astwood, E. B., N.Y. Acad. Sci. **50**, 419 (1949).

2. Morreale de Escobar, G., and Escobar del Rey, F., *in* "Recent Progress in Hormone Research" (G. Pincus, ed.), Vol. 23, p. 87. Academic Press, New York (1967).

3. Brown, J., Endocrinology **58**, 68 (1956).

4. Kobayashi, I., Yamada, T., and Shichijo, K., Metabolism **15**, 694 (1966).

5. Brown-Grant, K., Physiol. Rev. **41**, 189 (1961).

6. Escobar del Rey, F., and Morreale de Escobar, G., Endocinology **69**, 456 (1961).

7. Wollman, S. H., and Scow, R. O., Endocrinology **56**, 448 (1955).

Received Apr. 5, 1972. P.S.E.B.M., 1972, Vol. 141.