Thiopental and Thyroid Metabolism.* (22177)

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Previous observations(1,2) indicated sodium ethyl (1-methyl-butyl)-thiobarbiturate (thiopental) to reduce the I^{131} uptake by the rat thyroid to 89%. Impairment of thyroid activity was not found related to the anesthetic effect, since anesthetics which did not contain a N – Ċ = S grouping did not change the I^{131} uptake(1). Other anesthetic agents containing a thiocarbamate structure have also been shown to have anti-thyroid activity (3). Widespread use of thiopental as an anesthetic agent suggested that its antithyroid properties be further investigated. This study indicates a relationship between metabolism of thiopental by thyroid and ability of thyroid to accumulate I^{131}.

Methods. The rats used in these studies were of the Sprague-Dawley strain, males, 180-200 g. Hypophysectomized rats were all males, average weight 155 g, and were used 26-30 days post operation. The basal ration consisted of commercial grains and water *ad libitum*. Hypophysectomized animals were given a daily supplement of oranges and lettuce. Not less than 8 nor more than 10 animals were used in each experimental group. The I^{131} uptake and assay procedures have been described previously(1,3). Total iodine content of thyroids was determined by modification of the method of McClendon and Foster(4). S^{35} labeled thiopental was obtained from Abbott Laboratories. It was administered in 10 μc doses diluted with non-radioactive thiopental to give animals a 40 mg/kg dose as used in earlier experiments. Analysis of S^{35} in tissues was achieved following oxidation (HNO_3 and $HClO_4$) of tissue sulfur to sulfate which was precipitated with benzidine hydrochloride and assayed in a gas-flow detector. Sulfur content of precipitate was determined by titration of benzidine sulfate with 0.01 N NaOH. Counting was extended to a 2% statistical error. Corrections for decay and self-absorption were applied by conventional methods. Results are expressed as specific activity, defined here as counts per minute (CPM) per μM. In some preliminary experiments, results were expressed as CPM/mg tissue. In the experiment wherein both I^{131} and S^{35} were used in the same animal, the I^{131} was assayed in the thyroids first using a thick-window (3.5 mg/cm^2) G.M. counter which was insensitive to soft beta radiation of S^{35} as determined by previous trial runs with similar amounts of labelled thiopental. Iodine content was determined on pooled single lobes of thyroid while sulfate content was determined on the remaining pooled lobes. In some cases, it was necessary to add known amounts of carrier to effect chemical separation of the sulfate.

Results. Thiopental inhibited thyroid activity immediately following administration (Fig. 1). Response of thyroid in a 4-hour test period was inversely related to the amount of thiopental given to the animal (Table I). Of perhaps even more interest was the observa-

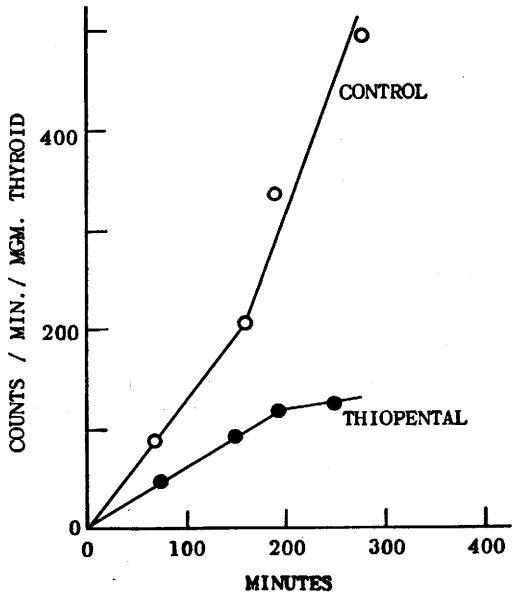

FIG. 1. Effect of thiopental (40 mg/kg) on I^{131} incorporation into rat thyroid; 5 μC I^{131}.

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TABLE I. Four-Hour Uptake of I^{131} by Rat Thyroid in Relation to Amount of Thiopental Administered. 2 μC I^{131} intraperitoneally.

Dose (mg/kg)	I^{131} CPM/mg	%
0	214 ± 19*	100
5	138 ± 15	64.4
10	112 ± 14	52.3
20	76 ± 9	35.5
40	44 ± 7	20.6
70	26 ± 5	12.2

* Stand. error of the mean.

tion of impairment of thyroid activity following administration of a single 40 mg/kg dose of thiopental (Table II). It required 6 to 7

TABLE II. Recovery of I^{131} Trapping Ability of Thyroid following a Single Dose of Thiopental (40 mg/kg).

Hr	I^{131} uptake (% controls)
4	18
12	33
24	47
48	56
72	62
96	64
168	96
192	100

days for complete recovery. To obtain information on the nature of the inhibition, I^{131} uptakes were performed on hypophysectomized animals. The results shown in Table III indicate that thiopental reduces the uptake

TABLE III. Effect of Thiopental on I^{131} Uptake by Thyroids of Hypophysectomized and Normal Rats.

Group	CPM/mg	%
Hypox	28.8 ± 5.7*	100
Hypox + thiopental	6.8 ± 0.7	23.6
Normal	258.0 ± 25.4	100
Normal + thiopental	30.1 ± 4.7	11.6

* Stand. error of the mean.

of I^{131} in the absence of the pituitary and suggest that the principal mode of action is via interference with iodine uptake, probably by reduction of I_2 to I^-(5). In another experiment, normal animals were given I^{131} and samples were taken for thyroid assay at 24 hours. Remaining groups were given thiopental (40 mg/kg) and thyroids assayed(1-3) 24 hours later. Compared to controls the treated animals lost I^{131} rapidly (Fig. 2). A final experiment was performed wherein S^{35} labelled thiopental was administered along with carrier-free I^{131} to intact and hypophysectomized rats. The results indicated that recovery of the thyroid was related to disappearance of S^{35} from thiopental in the thyroid (Fig. 3). The S^{35} content of pituitary and adrenal seemed to bear no relation to thyroid iodine metabolism. Specific activities of the normal rat adrenal S^{35} at 2, 24, 48, 120, and 144 hours post thiopental were 93.5, 7.9, 2.4, 2.0, and 1.8; of the pituitary 4.1, 2.6, 1.9, 2.2. The levels of S^{35} from thiopental in the endocrines of the hypophysectomized rats were lower than controls and a constant level of S^{35} in the thyroid of hypophysectomized rats appeared to be related to a constant I^{131} uptake (Fig. 3). The specific activities of the hypophysectomized rat adrenal S^{35} were 4.4, 2.0, and 1.8 at 24, 48, and 120 hours.

Discussion. The data presented here suggest that thiopental possesses properties of an antithyroid substance predictable by its thiocarbamate structure. That it also possesses anesthetic properties is indeed most interesting. Prolonged inhibition of thyroid activity demonstrated by a single dose is of interest in view of the observations of others(6,7) that thiopental is rapidly removed from the blood stream and stored in body fat from which it is slowly released. Further, studies on metabolism of thiopental(7,8) indicate it to be diversely attacked by the organism, thiourea being one of the many metabolic products. It may be that thiourea or substituted thioureas formed by metabolism of thiopental may be ultimately responsible for the prolonged in-

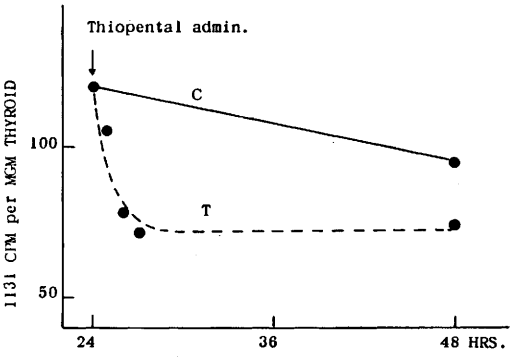

FIG. 2. Reduction of I^{131} content by administration of thiopental (40 mg/kg) to rats given 1 μC I^{131} 24 hr previously.

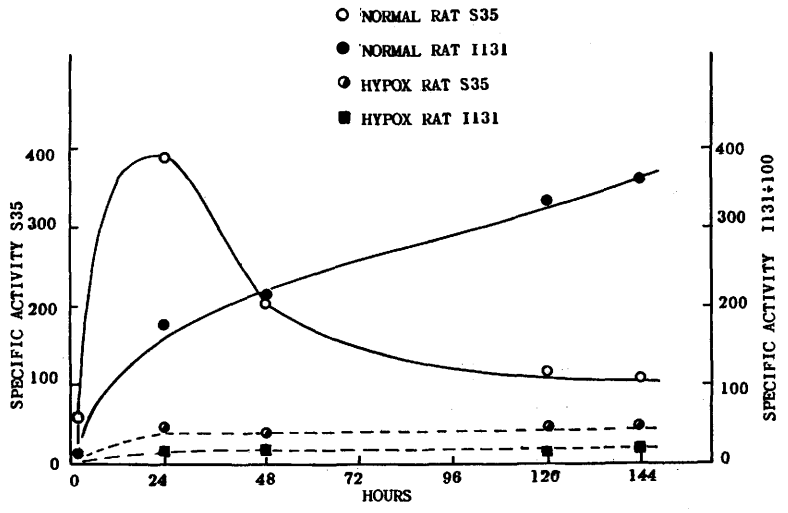

FIG. 3. Thyroid I^{131} in relation to S^{35} from thiopental in normal and hypophysectomized rats.

hibition. The relatively long period wherein activity from the S^{35} thiopental was found in the thyroid (Fig. 3) supports this hypothesis. The S^{35} activities of the pituitary and adrenal show no obvious relation to inhibition of the thyroid suggesting that other endocrines are not involved. The S^{35} and I^{131} specific activities of thyroids of hypophysectomized rats were both low and did not change during the experiment. Since thyroid in these animals was not functioning properly due to absence of the thyrotrophic hormone, these results were not unexpected.

In vitro studies by investigators indicated that aqueous thiopental solutions reduced I_2 to I^-. The reduction was not stoichiometric, more than molar equivalents of I_2 were reduced by thiopental. These observations suggest that the reaction is quite complex. This phenomenon is characteristic of many antithyroid agents(9). It would appear that thiopental could deprive the thyroid of I_2 by reducing it to I^- in the organism. This view is supported further by the reduced uptake of I^{131} in the hypophysectomized rat treated with thiopental. The ratio of inorganic I^{131} to diiodotyrosine I^{131} to thyroxine I^{131} was 54; 33; 13, and 57; 28; 15 in treated and nontreated animals respectively (4-hour uptake). These nearly identical ratios of activities indicated that thiopental did not interfere with thyroxine synthesis but functioned by depriving the thyroid of iodine. Plasma PBI^{131} in thiopental-treated rats was also reduced to 49% of control values, another indication that the primary action is a reduction of available I_2 for synthetic purposes.

Summary. 1. Thiopental influences thyroid metabolism primarily by depriving the thyroid of available I_2. 2. The prolonged inhibition of thyroid activity by thiopental is probably related to accumulation of its metabolic products in the thyroid.

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1. Wase, A. W., Repplinger, E., and Foster, W. C., *Endocrinology,* 1953, v53, 630.

2. Wase, A. W., Foster, W. C., and Repplinger, E., *XIXth Internat. Physiol. Congress,* 1953, 870.

3. Wase, A. W., and Greenspan, J., PROC. SOC. EXP. BIOL. AND MED., 1953, v84, 154.

4. McClendon, J. F., and Foster, W. C., *ibid.,* 1938, v39, 230.

5. Miller, W. H., Roblin, R. O., Jr., and Astwood, E. B., *J. Am. Chem. Soc.,* 1945, v67, 2201.

6. Brodie, B. B., Mark, L. C., Popper, E. M., Lief, P. A., Bernstein, E., and Rovenstein, E. A., *J. Pharm. Exp. Therap.,* 1950, v98, 85.

7. Brodie, B. B., *Fed. Proc.,* 1952, v11, 632.

8. Taylor, J. D., Richards, R. K., and Tabern, D. L., *J. Pharm. Exp. Therap.,* 1952, v104, 93.

9. Astwood, E. B., *Ann. N. Y. Acad. Sci.,* 1949, v50, 419.

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