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PLASMA INORGANIC IODIDE AS A HOMEOSTATIC REGULATOR OF THYROID FUNCTION*

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The enzymatic conversion of iodide to thyroxine and diiodotyrosine is one of the mechanisms enabling the thyroid gland to concentrate iodine. It will be shown in the present study that this mechanism is controlled by the level of plasma inorganic iodine.¹ Organic binding of iodine within the gland can be almost completely blocked by raising the level of plasma inorganic iodine above a certain critical level, which for the rat amounts to about 20 to 35 γ per cent. The inhibition, however, is not permanent, for as soon as the level of plasma inorganic iodine falls below this critical range, the gland again resumes its function of organic binding of iodine. These results, therefore, suggest that plasma inorganic iodine acts as a homeostatic regulator in the formation of the thyroid hormone. This regulator probably serves to prevent the formation of excessive amounts of hormone by the gland when the body is suddenly flooded with iodine.

EXPERIMENTAL

Long-Evans rats weighing 175 to 225 gm. were used throughout. They were injected intraperitoneally with various amounts of iodine in the form of KI labeled with I¹³¹. In no case was the dose of radioactivity great enough to produce deleterious effects on the gland during the intervals studied.² Blood was removed from the heart while the rats were anesthetized with sodium pentobarbital (20 mg. per rat). Equal amounts of plasma from each of five or six animals were pooled, and 2 cc. of plasma were used for duplicate chemical determinations of total plasma iodine (2).

The thyroid glands of the rats used in this investigation weighed 10.8 ± 1.9^3 mg. per 100 gm. of body weight. Each gland contained approximately 5 to 10 γ of iodine.

The thyroid gland of each rat, after it had been rapidly excised and weighed, was ground with 1 cc. of cold 10 per cent trichloroacetic acid in

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¹ A preliminary report of some of the data presented here has appeared (1).

² Feller, D. D., Taurog, A., and Jones, H. B., unpublished observations.

³ Standard deviation = $\sqrt{(\sum_i^n (x_i - \bar{x})^2)/n}$

an all glass homogenizer. The precipitate obtained by centrifugation was then washed twice with 2.5 cc. of 5 per cent trichloroacetic acid. The supernatants were combined for determination of radioactivity; this fraction contains only the inorganic iodine of the gland. The precipitate was dissolved in a minimal amount of 2 N NaOH on a steam bath, and a suitable aliquot was analyzed for radioactivity; this trichloroacetic acid-insoluble fraction of the gland contains only organically bound iodine.

The absolute amount of the *injected* iodine recovered in a given fraction of the thyroid gland, either total or organically bound, was obtained by multiplying the numerical proportion of the injected radioactivity recovered in that fraction by the micrograms of I^{127} injected into the rat. Thus, a recovery of 5 per cent of the administered I^{131} in a fraction prepared from the thyroid of a rat that had been injected with 50 γ of I^{127} would mean that 0.05×50 or 2.5 γ of the *injected* I^{127} had accompanied it. By the use of this labeling procedure, the separation of the amount of injected I^{127} that entered a gland from that present before the injection becomes quite simple. It circumvents the difficulty in making such a separation in glands with variable iodine contents.

In order to test the separation of the gland's iodine into organic and inorganic fractions by the procedure described above, several thyroids were excised from rats and thoroughly ground with 1 cc. of 10 per cent trichloroacetic acid containing 10 γ of I^{127} as KI labeled with I^{131} . The precipitate was washed as described above. Judging from the amount of radioactivity found in the trichloroacetic acid-insoluble fraction, only 0.05 per cent of the added iodide was recovered in what is termed here the organic fraction.

Results

Five levels of iodine administration were studied, namely 10, 50, 100, 200, and 500 γ , and the results obtained in these five experiments are recorded in Figs. 1 to 5. With the exception of the 10 γ dose, the amounts injected greatly exceeded the iodine contents of the thyroids of the rats used here. In each experiment twenty-five to thirty rats were used, all of which were injected with the same amount of labeled I^{127} . Each thyroid value shown in the figures represents the average of five or six closely agreeing measurements obtained from as many rats.

Administration of 10 γ of I^{127} —Both total and organic iodine of the thyroids rose rapidly after the injection (Fig. 1). In 2.5 hours, 2 γ of the injected iodine had entered the gland, and at this early interval 95 per cent of it was already in the organic form. The maximum amount of iodine (approximately 6 γ) was found at the 5 hour interval; this represents about 60 per cent of the administered iodine.

Not only at the very earliest interval but at all subsequent intervals up to 50 hours after the injection practically the entire amount of the injected iodine acquired by the gland was organically bound.

At the intervals examined, the total plasma iodine in the rats did not

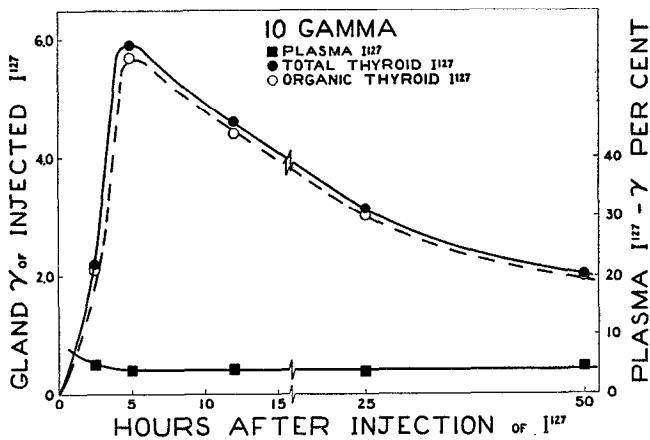


FIG. 1. Changes in plasma and thyroid iodine with time, following the injection of 10 γ of iodide in rats.

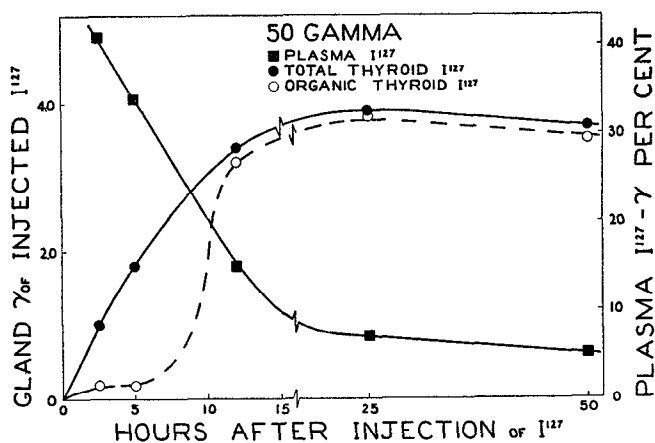


FIG. 2. Changes in plasma and thyroid iodine with time, following the injection of 50 γ of iodide in rats.

attain values in excess of 5 γ per cent. It should be recalled that approximately 3 γ per cent of this total iodine is protein-bound, whereas the remainder is inorganic iodide (2).

Administration of 50 γ of I^{127} —The results shown in Fig. 2 were unexpected, for less of the injected iodine was found in the thyroids of rats

that received 50 γ of I^{127} than in those of rats injected with 10 γ . Even more surprising was the finding that during the first 5 hours (Fig. 2) most of the accumulated iodine was *not organically bound*. Not until after 5 hours did the gland begin to convert significant amounts of the injected iodide into organic forms. Thus at 12, 25, and 50 hours after the injection, 3.4, 3.9, and 3.7 γ of the injected I^{127} were found in the gland, and 95 per cent of these amounts was in the organic form.

During the time when no organic iodine was being formed, the values for plasma iodine exceeded 25 γ per cent.

Administration of 100 γ of I^{127} —Two separate effects produced by the injection of 100 γ of iodine are brought out in Fig. 3: (1) inhibition of organic binding of the injected iodine by the thyroid gland during the early

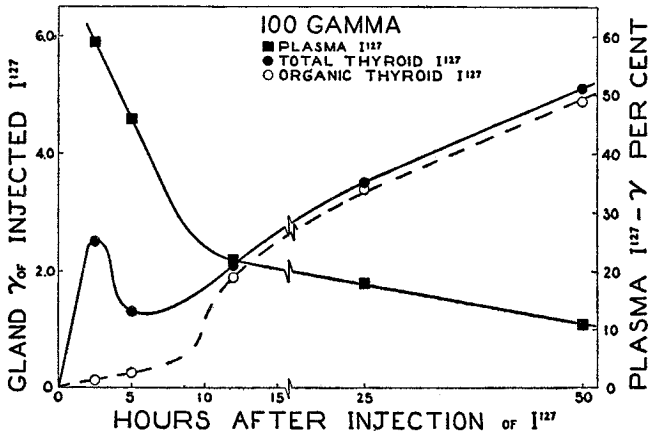


FIG. 3. Changes in plasma and thyroid iodine with time, following the injection of 100 γ of iodine in rats.

hours, and (2) early concentration of the injected iodine in the gland *in non-organic form*.

Here, as in the preceding experiment, significant amounts of organic iodine were not synthesized in the gland for the first 8 to 9 hours, during which time the level of plasma iodine exceeded 25 γ per cent.

Table I shows quite definitely that the normal gland possesses a mechanism for concentrating iodine that is not dependent upon its organic conversion. During the first 6 hours the concentration of iodine in the gland appeared to parallel roughly that in plasma (Fig. 3). A concentration ratio of approximately 100 to 300 seems to have been maintained during this time between gland and plasma inorganic iodine.

After 12 hours, when the levels of plasma iodine had receded, a gradual accumulation of the injected iodine occurred in the gland, but this time

94 per cent of the injected iodine present in the gland was organically bound.

Administration of 200 γ of I^{127} —The more striking effects observed in this experiment were to be expected in view of the high plasma iodine levels attained in the rats. The failure of the gland to convert any of the injected iodine to organic forms during the first 12 to 13 hours is clearly brought out in Fig. 4. Although in 2.5 hours 3.4 γ of the injected iodine were present in the gland, practically all of it was inorganic iodide. The early accumulation of the injected iodine in the thyroid and its loss reflect the changing

TABLE I
Iodine-Concentrating Capacity of Thyroid Gland While Organic Binding of Iodine Is Inhibited

Dose injected	Interval	Plasma iodine	Gland inorganic I^{127} Plasma inorganic I^{127}
γ	<i>hrs.</i>	γ per cent	
50	2.5, inhibited*	41	100
	5, inhibited	34	250
	7, escape†	29	290
100	2.5, inhibited	59	210
	5, inhibited	46	130
	9, escape	27	190
200	2.5, inhibited	108	160
	5, inhibited	93	100
	13, escape	20	150
500	2.5, inhibited	330	160
	5, inhibited	253	130
	17, escape	32	220

* Refers to periods in Figs. 2 to 5 during which organic binding of iodine was inhibited in the gland.

† Interpolated from Figs. 2 to 5; it is the point of inflection in the organic curve and represents the time at which inhibition was released.

level of inorganic iodine in the plasma. During this period the concentration of inorganic iodide in the gland was 100 to 300 times that of plasma (Table I).

When plasma iodine had dropped to concentrations at or below 20 γ per cent (approximately 12 to 13 hours after the injection), the mechanism involving the formation of organic iodine in the gland was no longer inhibited and organic iodine rapidly accumulated. At the 50 hour interval about 7 γ of iodine had entered the gland and nearly all of it was found organically bound.

Administration of 500 γ of I^{127} —The results of this experiment, shown

in Fig. 5 and Table I, are one of the clearest demonstrations of the capacity of *normal* thyroid tissue to concentrate iodine in an inorganic form. 10 γ of the injected iodine were present in the thyroid gland in 2.5 hours, and

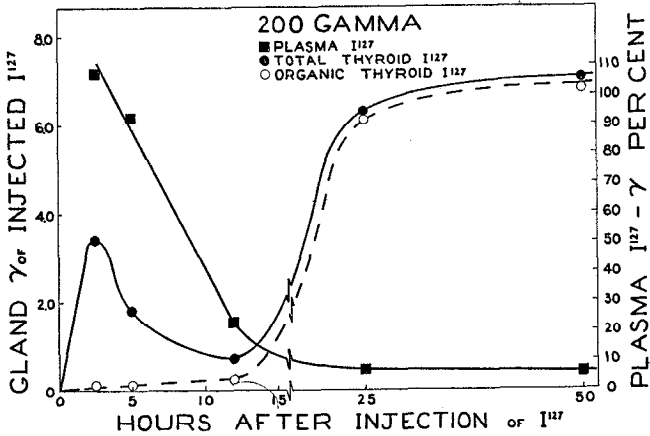


FIG. 4. Changes in plasma and thyroid iodine with time, following the injection of 200 γ of iodine in rats.

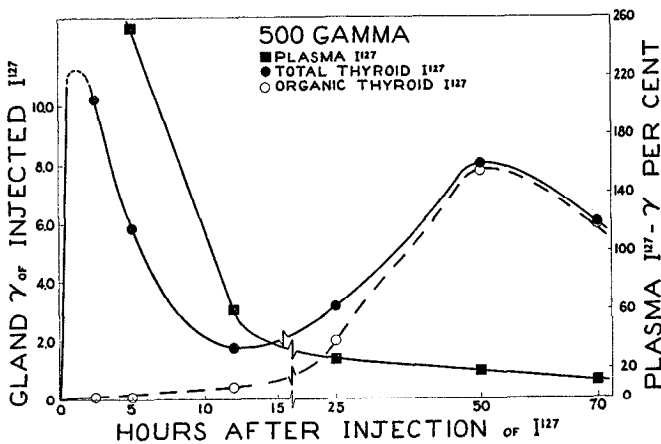


FIG. 5. Changes in plasma and thyroid iodine with time, following the injection of 500 γ of iodine. The plasma value for the 2.5 hour interval is not shown; it was 330 γ per cent.

practically all of it was recovered in the trichloroacetic acid-soluble fraction prepared from the gland. In 5 hours the amount of the injected iodine in the gland fell to 5.8 γ , but again nearly all of it was in the inorganic form. By 12 hours the amount of the injected iodine in the gland fell to 1.7 γ ,

nearly all of which was still inorganic. This precipitous rise and fall in the concentration of *inorganic iodine* in the gland during the first 12 hours paralleled the rapid rise and fall in the levels of plasma iodine during this time. Thus at 2.5 hours, when the plasma contained 330 γ per cent, the gland contained 10.2 γ of the injected iodine; at the 5 hour interval plasma iodine fell to 253 γ per cent and the gland iodine to 5.8 γ ; at 12 hours plasma and gland contained respectively 61 γ per cent and 1.7 γ .

The more prolonged inhibition in organic binding of iodine by the gland is in keeping with the very large dose of iodine injected. When 50, 100, and 200 γ were administered, nearly all of the injected iodine that had accumulated in the gland at the 25 hour interval was organically bound. This was not the case when 500 γ of iodine were injected; even as late as 25 hours only two-thirds of the injected iodine in the thyroid was organically bound. This prolongation of the period of inhibition is related, of course, to the level of plasma iodine. Since we were attempting to determine at precisely what level of plasma iodine the gland is inhibited, it is of interest to note that, when plasma contained 19 γ per cent, all of the injected iodine in the gland, namely 8.0 γ , was organically bound. Apparently the critical plasma level at which the gland's activity was inhibited was above 19 γ per cent.

DISCUSSION

The first indication that conversion of inorganic iodide to diiodotyrosine and thyroxine can be blocked in *normal* thyroid tissue by excessive amounts of iodide came from the *in vitro* experiments of Morton *et al.* (3). These workers demonstrated that, when 300 mg. of sheep thyroid tissue were incubated in 3 cc. of a bicarbonate-Ringer's medium containing 1, 5, 10, 15, 20, and 50 γ of I^{127} as inorganic iodide, an inhibitory effect on the conversion of the Ringer's I^{127} to diiodotyrosine and thyroxine occurred when the amount of I^{127} exceeded 20 γ .

The results of the present investigation confirm and extend the observations of Morton *et al.* (3). They show that the activity of the normal thyroid gland, even *in situ*, is inhibited in the presence of excessive concentrations of inorganic iodide. During the first 6 to 12 hours after the injection into normal rats of 50, 100, 200, and 500 γ of iodine, the formation of organically bound iodine is almost completely blocked. The time relations shown in Figs. 2 to 5 suggest that this block in the conversion of the injected iodide to organic forms is related to the level of plasma inorganic iodide. This relation between plasma iodine and thyroid activity is more clearly brought out in Fig. 6, in which the concentrations of plasma iodine were plotted against the amounts of injected iodine that were organically bound in the thyroid glands. Fig. 6 shows that no organic binding of the

injected iodine occurred in our experiments so long as the level of plasma iodine remained above 20 to 35 γ per cent, and only when the level of plasma iodine fell below this range did the gland show any capacity for organically binding the injected iodine.

Thus, the inhibitory effect of excessive amounts of iodide upon *normal* thyroid function has now been established *in vivo* as well as *in vitro* and for rat thyroid as well as for sheep thyroid.

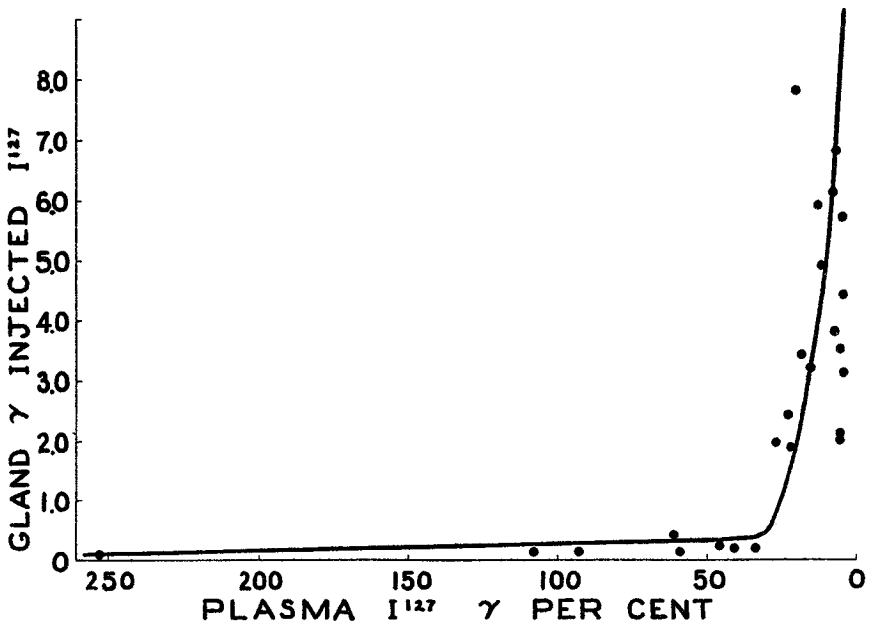


FIG. 6. The relation of the level of plasma iodine to the inhibition of organic binding of iodine in the thyroid gland. The ordinates represent the micrograms of the injected I^{127} present in the organic fraction of the gland. This figure shows that organically bound iodine can form in the gland only when the concentration of plasma iodine does not exceed 35 γ per cent.

Despite an almost complete block in the gland's capacity to bind iodine organically during the first 6 to 12 hours after the injection of massive doses of iodide, the gland does not lose its ability to concentrate iodine at such times. The concentrations of *inorganic iodine* found in the blocked gland⁴ were roughly 100 to 300 times those in plasma (Table I). There can no longer be any doubt, therefore, that *even the normal thyroid* possesses a mechanism for concentrating iodine which is not dependent upon its conversion to organic forms. A similar mechanism for concentrating iodine in

⁴ The thyroid glands of the rats contained comparatively small amounts of *inorganic* iodine before the injections were made.

the inorganic form has been demonstrated by Vanderlaan and Vanderlaan (4) and by Taurog *et al.* (5) in the thyroids of rats made goitrous by treatment with propylthiouracil. Thus, whether the organic binding of iodine in the gland is blocked by a goitrogenic substance or by excessive amounts of inorganic iodine the thyroid can still concentrate iodine.

It is plausible to assume that the level of plasma iodine is part of a homeostatic mechanism governing hormone synthesis in the gland. This level was found to be approximately 20 to 35 γ per cent. Since the concentration of inorganic iodine in the thyroid is approximately 100 to 300 times that in plasma, the inhibitory level inside the gland (undoubtedly the immediate agent responsible for this homeostatic control of hormone synthesis by the gland) amounts to approximately 2 to 10 mg. per cent. Whenever large amounts of iodine are ingested, the animal limits the conversion of inorganic iodine to thyroid hormone and is thereby afforded sufficient time to rid itself of the excess iodine. By means of this homeostatic regulator the formation of toxic amounts of thyroid hormone is prevented.

What is the mechanism by which organic binding of iodine in the *normal* thyroid gland is inhibited by excessive amounts of inorganic iodide? That the inhibition operates by suppressing the secretion of thyrotropic hormone of the anterior hypophysis would appear to be ruled out by the *in vitro* experiments of Morton *et al.* (3). But the possibility that the excess iodide interferes with the action of the thyrotropic hormone already present within the thyroid gland is not excluded. Other explanations, namely (1) iodination of enzymes concerned in the conversion of inorganic iodide to diiodotyrosine and thyroxine and (2) inhibition of the formation of an intermediate in thyroxine synthesis, have been considered by Morton *et al.*

Ever since the introduction of iodine therapy for the treatment of Graves' disease by Plummer in 1923 (6), the mechanism by which iodine brings about a dramatic remission of signs and symptoms in patients suffering from this disease has attracted considerable attention. There can be no doubt that under the influence of therapeutic doses of iodine thyroid hormone in excessive amounts ceases to be delivered to the circulation (7-12). A reversal in the direction in which the hormone is secreted, *i.e.* secretion into the follicle rather than into the blood stream, has been offered as an explanation for this iodine effect upon the hyperthyroid state (13). It has also been postulated that the therapeutic action of iodine is due to the inhibition of the proteolytic enzyme system responsible for the release of the follicular colloid (14). While we shall not attempt to evaluate these theories, we do believe that our findings, even though they deal with normal thyroid tissue, justify the conclusion that an interference in organic binding of iodine by the gland is an integral part of the mechanism by which iodine brings about a remission in Graves' disease. According to this concept,

inhibition of hormone synthesis by excess iodide is a general property of thyroid tissue regardless of its state of activity.

SUMMARY

1. Rats were injected with 10, 50, 100, 200, and 500 γ of iodine in the form of KI labeled with I^{131} . The radioactivity served as a measure of the amounts of injected I^{127} that entered the gland.

2. So long as plasma iodine remained above 20 to 35 γ per cent, organic binding of the injected iodide in the gland was blocked. Organic binding of the newly accumulated iodine began to occur only when the level of plasma iodine fell below the critical range of 20 to 35 γ per cent.

3. A homeostatic mechanism is postulated in which excessively high levels of plasma iodine inhibit formation of the hormone in the thyroid gland. This mechanism helps to explain the beneficial effect produced in patients suffering from thyrotoxicosis (Graves' disease) when large amounts of iodine are administered.

4. While the organic binding of iodine is blocked, the gland is still able to concentrate iodine. The results presented here thus establish that the normal thyroid gland possesses a mechanism for concentrating iodine that does not depend upon its conversion to thyroxine and diiodotyrosine.

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