

# PLASMA INORGANIC IODIDE, A CHEMICAL REGULATOR OF NORMAL THYROID FUNCTION<sup>1</sup>

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IN AN EARLIER communication (Wolff and Chaikoff, 1948) it was shown that the administration of large amounts of iodine temporarily inhibits the capacity of the *normal* thyroid gland to bind iodine organically. This inhibition appeared to be related to the level of plasma iodine. So long as the concentration of plasma iodine exceeded 20–35% per cent, no organic binding of iodine occurred in the gland, and only when the concentration fell below this critical range did the gland resume its function of depositing iodine in an organic form. On the basis of these findings it was postulated that the level of plasma iodine is part of a homeostatic mechanism governing hormone synthesis in the normal gland. Thus, when a large amount of iodine is ingested, the prevention of its deposition as organically bound compounds in the thyroid gland keeps the ingested iodine circulating as inorganic iodide, in which form it is readily excreted by the kidney. In this way, it was argued, the formation of toxic amounts of the thyroid hormone is prevented.

In the experiments described above, the inhibition of thyroid function was temporary, lasting some 8–17 hours, i.e. during the time when the concentration of plasma iodine remained well above 35% per cent. The experiments described here provide additional proof that plasma iodine, probably by influencing the level of inorganic iodide in the gland, is an inhibitor of normal thyroid function. It is shown in the present study that the period of inhibition of thyroid function imposed by high iodine administration can be prolonged by preventing the escape of the administered iodine by excision of the kidneys.

## EXPERIMENTAL

Long-Evans rats ranging from 171 to 240 gms, were used throughout. The animals were fed until the time of the operation but afterwards were permitted access to water only. The rats were first injected intraperitoneally with 6 mg. of sodium pentobarbital and were then completely anesthetized with ether. The kidneys were exposed by a lateral incision and the perirenal fat peeled off, care being taken

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to avoid damage to the adrenals. The ureter and renal vessels were then tied close to the hilum and the kidneys removed. After the operation the animals were kept in a warm room (28–30°C.). Approximately 1–2 hours after they had recovered from the anesthesia, they were injected with  $I^{127}$  labeled with  $I^{131}$  and sacrificed at various intervals thereafter. Blood was removed by heart puncture, and total plasma iodine was determined for each rat on 2 cc. of plasma, as de-

TABLE 1. THE UPTAKE OF IODINE BY THYROIDS OF NEPHRECTOMIZED RATS FOLLOWING INJECTIONS OF 10 AND 500 $\gamma$  OF  $I^{127}$  AS KI AND THEIR CONVERSION TO DIODOTRYOSINE AND THYROXINE

Time after $I^{127}$ injection	10 $\gamma$ $I^{127}$ Injected				500 $\gamma$ $I^{127}$ Injected			
	Total amount of injected $I^{127}$ found in thyroid	Per cent of injected $I^{127}$ found in thyroid as		Plasma total iodine*	Total amount of injected $I^{127}$ found in thyroid	Per cent of injected $I^{127}$ found in thyroid as		Plasma total iodine*
		In-organic	Or-ganic			In-organic	Or-ganic	
hours	$\gamma$			$\gamma$ per cent	$\gamma$			$\gamma$ per cent
4	0.87	11	89	12.3	4.6	99	1.0	178
4	1.5	5	95	13.2	7.5	99	0.39	200
4	1.4	7	93	12.8	5.5	99	0.93	215
10	2.4	3	97	8.9	12.5	99	0.36	225
10	0.91	16	84	8.9	7.0	99	0.84	230
10	0.70	11	89	9.5	11.5	99	0.64	150
18	2.9	4	96	10.5	6.3	99	1.3	161
18	2.0	5	95	12.4	8.9	99	0.79	313
18	1.9	6	94	15.0	2.6	96	3.8	195
26	1.4	3	97	8.8	7.9	99	1.4	185
26	1.9	6	94	9.2	7.6	99	0.92	306
26	2.4	3	97	9.2	5.8	98	2.1	146
32	5.5	2	98	8.9	9.2	99	0.67	105
32	4.1	2	98	9.5	6.8	97	2.9	173
32	4.3	2	98	8.9	8.0	95	4.9	225
40	4.7	2	98	8.5	1.8	74	26	218
40	3.8	2	98	8.0	9.9	96	3.7	180
40	4.4	2	98	8.8	3.9	81	14	200

\* At time thyroids excised.

scribed by Taurog and Chaikoff (1946). The gland iodine was separated into organic and inorganic fractions as previously described (Wolff and Chaikoff, 1948).

## RESULTS

The rats were injected with either 10 or 500 $\gamma$  of  $I^{127}$  as KI one to two hours after removal of both kidneys and groups of them sacrificed at intervals of 4, 10, 18, 26, 32, and 40 hours after the injection. Values for total plasma iodine and for the amounts of injected  $I^{127}$  recovered in the gland are recorded in table 1. The amounts of injected  $I^{127}$  present in the inorganic (trichloroacetic-acid soluble) or the organic (trichloroacetic-acid insoluble) fractions of the gland were obtained by multiplying the numerical proportion of the injected  $I^{131}$  recovered in the respective fraction by the gamma of  $I^{127}$  injected.

*Rats Injected with 10 $\gamma$  of  $I^{127}$ .*—The highest concentration of  $I^{127}$  found in the plasma of rats that had been injected with 10 $\gamma$  of  $I^{127}$  was 15 $\gamma$  per cent. Since the kidney is the main pathway of excretion

for inorganic iodide (Keating, Power, Berkson, and Haines, 1947; Nelson, Palmer, Park, Weymouth, and Bean, 1947; Spector, Mitchell, and Hamilton, 1945; Perlman, Chaikoff, and Morton, 1941), the finding of plasma-iodine values of 8–9 $\gamma$  per cent in nephrectomized rats as late as 40 hours after the injection is not surprising.

In this experiment the amounts of the injected  $I^{127}$  recovered in the thyroid gland increased with time. At the later intervals about 4 $\gamma$  or 40 per cent of the injected dose were found in the gland. *At all intervals studied, approximately 90 per cent of the newly accumulated iodine was organically bound.*

TABLE 2. RELATION OF THE LEVEL OF PLASMA IODIDE TO ORGANIC BINDING OF IODINE BY THE THYROID GLAND  
(All values are the averages of the results recorded in table 1)

Interval after injection of $I^{127}$ as KI hours	Plasma iodine $\gamma$ per cent	Injected $I^{127}$ recovered in gland		
		Total $\gamma$	Organically bound	
			Amount $\gamma$	Per cent of total
4	13	1.3	1.2	92
	198	5.8	0.04	0.69
10	9	1.3	1.2	92
	202	10.3	0.06	0.58
18	13	2.3	2.2	96
	223	5.9	0.08	1.4
26	9	1.9	1.8	95
	212	7.1	0.10	1.4
32	9	4.6	4.5	98
	168	8.0	0.22	2.7
40	8	4.3	4.2	98
	199	5.2	0.46	8.9

*Rats Injected with 500 $\gamma$  of  $I^{127}$ .*—The levels of plasma iodine in these rats were always in excess of 100 $\gamma$  per cent and in some were over 300 $\gamma$  per cent. The concentration of plasma iodine remained fairly constant during the entire period of observation (average, 210 $\gamma$  per cent).

Larger amounts of  $I^{127}$  were recovered from the glands of the rats that received 500 $\gamma$  than from those of rats injected with 10 $\gamma$ . But in this experiment practically none of the newly accumulated  $I^{127}$  was organically bound. For example, in the rats that were sacrificed 26 hours after the injection of 500 $\gamma$  dose, from 5.6 to 7.9 $\gamma$  of the injected  $I^{127}$  was found in the gland; yet only 0.07–0.12 $\gamma$  or at most 2 per cent of this iodine was organically bound.

#### DISCUSSION

In the present investigation 2 plasma levels of iodine, one in the neighborhood of 10 $\gamma$  per cent, the other of 200 $\gamma$  per cent, were estab-

lished and maintained for a period of 40 hours by a single injection of KI into nephrectomized rats. As shown in table 2, which summarizes the results of these experiments, so long as plasma iodine remained in the neighborhood of 200 $\gamma$  per cent, the gland failed to convert iodine to organic forms; even after 40 hours, only 9 per cent of the injected I<sup>127</sup> found in the gland had been converted to organic forms. That the thyroid gland of the nephrectomized rat retained its capacity to bind iodine organically during the entire period of observation is brought out in the experiments in which the levels of plasma iodine were kept below 15 $\gamma$  per cent. More than 90 per cent of the iodine found in the thyroids of these rats was organically bound. The present investigation thus shows that the period of inhibition of organic binding by the thyroid gland can be extended at will by maintenance of a high plasma-iodine level.

It was pointed out earlier that the inhibition of organic binding of iodine by the gland offers a rational explanation for the response of the thyrotoxic patient to iodine treatment (Wolff and Chaikoff, 1948). This view is fully supported by the results of the present investigation. Since the findings in the normal and nephrectomized rats show that the gland is inhibited only so long as the plasma concentration of iodine is kept high, it is suggested that the failure to maintain high enough levels of plasma iodine may account for the exacerbation of the hyperthyroid state sometimes noted during the treatment of patients suffering from hyperthyroidism.

#### SUMMARY

The relation of the level of plasma inorganic iodide to the organic binding of iodine in the thyroid gland was investigated. A single injection of 500 $\gamma$  of iodide into bilaterally nephrectomized rats made possible the maintenance of a plasma iodine level of approximately 200 $\gamma$  per cent for a period of 40 hours. Although the injected iodine readily entered the gland, practically none of the newly accumulated iodine was converted to organic forms even after 40 hours. On the other hand, when 10 $\gamma$  of iodine were injected into nephrectomized rats, the level of plasma iodine remained low enough (below 15 $\gamma$  per cent) to permit incorporation of nearly all the newly accumulated iodine into organic forms. The significance of these findings for iodine treatment of thyrotoxic patients is pointed out.

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