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Acute Effects of Hypophysectomy and Injection of Stable Iodide on Iodothyronine Synthesis in Iodine-Depleted Rats[1] (37901)

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Severe iodine deficiency in the rat is associated with high MIT*/DIT*[3] and T_3*/T_4* ratios of thyroid digests after injection of carrier-free radioiodine and a smaller proportion of total thyroid radioactivity present as iodothyronines,* as compared with iodine-replete rats (1, 2). The apparent low rate of iodothyronine* synthesis may be due to decreased efficiency in coupling iodotyrosines* to form iodothyronines* because of the infrequent association of iodinated tyrosyl residues in adequate proximity within severely iodine-deficient thyroglobulin (2). However, because severely iodine-deficient rats have a very high rate of turnover of thyroid radioiodine (1) and because formation of iodothyronines is much slower than that of iodotyrosines, it is possible that iodothyronines may be rapidly synthesized in severe iodine deficiency but even more rapidly secreted. Thyroid iodoamino acid* composition shows only the balance between synthesis and secretion; thus, the actual rate at which iodothyronines* are formed may be obscured. In ingesting colloid for digestion, the thyroid cell does not discriminate between mature thyroglobulin with a high concentration of iodothyronines and immature thyroglobulin containing very little iodothyronine (3). The colloid closest to the apical cell membrane is taken. When there is a very rapid turnover and little stored colloid in the follicular lumen, as in severe iodine deficiency, there may be insufficient time between iodination and secretion for maximum iodotyrosine coupling to occur.

We have therefore studied relative iodoamino acid* synthesis in iodine-deficient rats given carrier-free $^{131}I^-$ 30 min after hypophysectomy. Hypophysectomy causes a more rapid cessation of thyroid secretion than of radioiodine uptake and iodoamino acid synthesis (4–7). The iodothyronines* synthesized after hypophysectomy are retained in the thyroid rather than secreted. Thus a more accurate estimation of the "pure" synthetic rate can be obtained than in intact rats.

Materials and Methods. Sprague–Dawley male rats weighing approximately 200 g were used in all experiments. They were fed a low-iodine diet (LID) containing approximately 30 μg ^{127}I/kg (General Biochemicals, Inc., Chagrin Falls, Ohio) for periods of 13 days to 3 months. In 3 groups, the animals initially received LID containing 0.15% propylthiouracil (PTU) to accelerate iodine depletion. PTU was stopped 7–10 days before the animals were killed and LID alone continued. Hypophysectomy was performed by the parapharyngeal approach in a portion of the animals. Carrier-free $^{131}I^-$ (10–50 μCi) was injected intraperitoneally 30 min postoperatively. Some groups additionally received 1 μg $^{127}I^-$ in the same injection. In one experiment, half of the intact and hypophysectomized rats received 3 mg $NaClO_4$ in 0.5 ml 0.9% saline intraperitoneally 30 min before the $^{131}I^-$. The rats were killed with chloroform 3, 6, or 24 hr after radioiodine administra-

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[3] An asterisk indicates that only the radioiodine-labeled component is being considered.

TABLE I. Thyroid Radioiodine Content (as Percent of Administered $^{131}I^-$) in Various Groups.[a]

	Group	Treatment	Hours after $^{131}I^-$ administration		
			3	6	24
1	LID, 3 months	$\overline{H}$	79.9 ± 0.8	88.2 ± 2.6	92.6 ± 3.2
		Intact	79.6 ± 4.5	66.8 ± 1.9	31.0 ± 2.6
3	PTU, 3 days	$\overline{H}$	46.6 ± 7.6	58.8 ± 0.5	66.3*
	LID, 10 days	Intact	51.3 ± 1.4	60.1 ± 2.4	27.9 ± 2.2
		$\overline{H}$ + $^{127}I^-$	38.2 ± 3.4	42.5 ± 2.0	57.9 ± 4.0
		Intact + $^{127}I^-$	46.2 ± 3.3	47.4 ± 2.3	23.9 ± 1.9

[a] Results are shown as mean ± SE of 4–6 rats per group, except for the value indicated by the asterisk, which represents only 1 rat. H = hypophysectomy. Radioiodine uptake studies were not done in Group 2.

tion. Thyroids were removed and the radioactivity of each was measured at the top of a well scintillation counter and compared with an appropriate standard. The glands were digested in 0.5 ml of pH 8.5 Tris buffer containing 0.02 *M* methimazole and 1% pancreatin. Each hydrolysate was chromatographed individually on paper in ascending butanol–acetic acid–water (BAW) and butanol–ethanol–ammonia (BEA) and the radioiodine-containing components quantified as previously described (8). The hypophyseal fossa was examined with a 10× dissecting microscope at autopsy to ascertain the completeness of hypophysectomy.

Results. The data of the first three experiments are shown in Tables I and II. Thyroid radioiodine accumulation was the same in the hypophysectomized and intact controls at 3 hr (Table I). Radioiodine progressively accumulated in the thyroids of the hypophysectomized rats up to 24 hr. Thyroid radioiodine kinetics were variable in the control rats, depending on the degree of iodine deficiency, but the 24-hr ^{131}I content of the thyroid was always approximately half of that at 6 hr. Acute injection

TABLE II. Temporal Changes in Labeled Iodothyronine Content (as Percent of Total Thyroid Radioactivity) in Various Groups.[a]

	Group	Treatment	Hours after $^{131}I^-$ administration					
			3		6		24	
			T_4	T_3	T_4	T_3	T_4	T_3
1	LID 3 months	$\overline{H}$	7.0 ± 0.9	8.0 ± 1.0	4.9 ± 0.0	12.1 ± 2.7	8.9 ± 2.3	15.9 ± 1.1
		Intact	6.9 ± 1.2	12.9 ± 1.1	8.3 ± 1.3	16.6 ± 1.5	5.4 ± 0.3	15.2 ± 0.4
2	PTU, 13 days	$\overline{H}$	—	—	9.3 ± 2.1	5.4 ± 3.3	12.1 ± 3.4	9.8 ± 0.4
	LID, 10 days	Intact	—	—	17.0 ± 2.9	12.9 ± 1.8	10.1 ± 1.5	12.5 ± 0.8
		$\overline{H}$ + $^{127}I^-$	—	—	19.6 ± 3.0	8.3 ± 0.3	16.3 ± 2.0	7.6 ± 2.3
		Intact + $^{127}I^-$	—	—	21.7 ± 3.9	9.1 ± 1.9	16.0 ± 0.4	12.8 ± 0.5
3	PTU, 3 days	$\overline{H}$	9.4 ± 0.8	6.7 ± 0.2	13.4 ± 2.8	5.4 ± 2.5	28.4*	12.9*
	LID, 10 days	Intact	12.2 ± 2.1	7.3 ± 0.1	20.2 ± 2.4	6.0 ± 1.5	24.0 ± 1.0	13.8 ± 0.3
		$\overline{H}$ + $^{127}I^-$	20.6 ± 0.3	4.8 ± 0.2	24.4 ± 0.8	5.5 ± 0.9	30.7 ± 1.4	6.9 ± 0.5
		Intact + $^{127}I^-$	24.3 ± 1.3	8.1 ± 1.4	28.4 ± 1.1	8.3 ± 0.6	26.0 ± 2.7	13.3 ± 2.0

[a] Results are shown as mean ± SE of 4–6 rats per group, except for the values indicated by an asterisk, which represent only one rat. $\overline{H}$ = hypophysectomy.

of stable iodide did not change the pattern of thyroid radioiodine kinetics in either the hypophysectomized or intact rats, but it did produce a lower thyroid ^{131}I content at each interval than when it was not given.

Iodothyronine* content was lower in the hypophysectomized rats at 3 and 6 hr than in the controls. This difference disappeared by 24 hr. Acute injection of $^{127}I^-$ resulted in an increase in iodothyronine* content in both the intact and hypophysectomized iodine-deficient groups. This was most marked at 3 and 6 hr. The increase in iodothyronine* content was primarily in the form of T_4*.

The thyroid iodothyronine* content in the intact rats was higher than anticipated in the first three experiments. To obtain a more definite decrease in T_3* and T_4*, a fourth experiment was performed with rats fed LID-PTU for 2 weeks followed by LID alone for 1 week. Half of both the intact and hypophysectomized rats received 3 mg sodium perchlorate 30 min before radioiodine injection to make certain that there would be a depressed iodothyronine* content (2).

The results are shown in Table III and Fig. 1. Perchlorate pretreatment profoundly depressed ^{131}I uptake and iodothyronine* content at 3 hr in both the intact and hypophysectomized groups. At 24 hr, ^{131}I uptake was significantly higher and iodothyronine* content lower in the hypophysectomized than in the intact perchlorate-treated group; differences were presumably due to continuing turnover of thyroglobulin* in the latter. The data of both the intact and hypophysectomized groups not given perchlorate were similar to the first two experiments.

Discussion. The present data confirm earlier findings that acute hypophysectomy in iodine-deficient rats causes a much more severe depression of thyroid secretion than of radioiodine accumulation (4–7). In the present studies, hypophysectomy also depressed the rate of iodothyronine* synthesis within 3 hr after hypophysectomy. Several days after hypophysectomy there is little detectable formation of iodothyronines* within a few hr after radioiodine adminis-

TABLE III. Radioiodine Studies in Iodine-Deficient Intact and $\overline{H}$ Rats: Effect of Perchlorate Pretreatment.[a]

Group	Hr after ^{131}I	ClO_4^-	% ^{131}I uptake	% of total chromatograph radioactivity					
				O	I	MIT	DIT	T_4	T_3
$\overline{H}$	3	+	5.8 ± 0.3	2.1 ± 0.2	7.0 ± 0.6[b]	72.4 ± 1.1[c]	13.6 ± 1.3	0.8 ± 0.1[a]	1.1 ± 0.1[b]
Intact	3	+	4.7 ± 0.4	2.8 ± 0.4	10.4 ± 0.6	65.3 ± 1.0	15.0 ± 1.4	1.3 ± 0.2	1.9 ± 0.2
$\overline{H}$	3	−	70.0 ± 10.6	3.1 ± 0.3	5.8 ± 0.4[b]	58.0 ± 1.7[c]	19.1 ± 0.6	3.4 ± 0.4[c]	5.3 ± 0.6[a]
Intact	3	−	73.8 ± 3.1	3.3 ± 0.1	8.6 ± 0.6	46.4 ± 1.2	20.2 ± 1.2	6.2 ± 0.3	9.0 ± 1.1
$\overline{H}$	24	+	32.0 ± 2.2[c]	1.2 ± 0.2[c]	3.0 ± 0.6[c]	67.9 ± 3.1[c]	20.6 ± 2.6	1.8 ± 0.5[c]	2.3 ± 0.4[b]
Intact	24	+	7.2 ± 0.5	8.4 ± 0.6	11.3 ± 1.1	39.4 ± 0.6	21.6 ± 1.1	7.4 ± 0.5	5.7 ± 0.7
$\overline{H}$	24	−	83.8 ± 0.9[c]	2.6 ± 0.1[c]	2.8 ± 0.3[c]	52.1 ± 3.7[a]	20.8 ± 2.0	5.4 ± 1.4	8.5 ± 1.2
Intact	24	−	29.3 ± 2.7	5.8 ± 0.6	10.6 ± 0.8	39.9 ± 1.2	19.0 ± 1.2	8.7 ± 1.6	8.9 ± 1.2

[a] Data presented as mean ± SE of 6 rats per group. $\overline{H}$ = hypophysectomy. Statistical comparison: [a] = $P < 0.05$, [b] = $P < 0.01$, [c] = $P < 0.001$ compared with appropriate intact controls (Student's t test). All other such comparisons not statistically different ($P > 0.05$). $\overline{H}$ and/or administration of 3 mg ClO_4^- intraperitoneally was performed 30 min before ^{131}I injection.

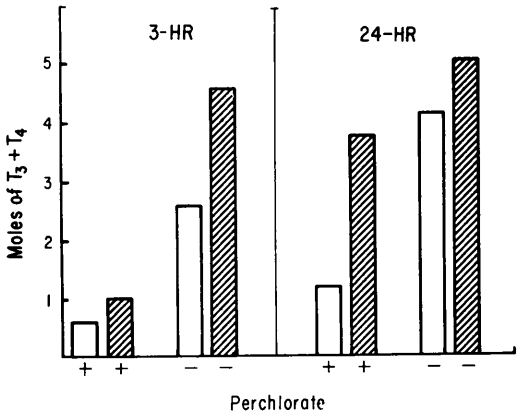

FIG. 1. Relative iodothyronine* formation in hypophysectomized (open bars) and intact (hatched bars) rats at 3 and 24 hr after ^{131}I injection is shown. Data are plotted from the values shown in Table III. The percent of total chromatograph radioactivity in T_3* and T_4* was divided by 3 and 4, respectively, in each group, then added together to give the values plotted on the ordinate. A (+) or (−) on the abscissa indicates whether or not perchlorate was given.

tion (9, 10) but a slow rate of T_4 synthesis and accumulation can be demonstrated in long-term studies (5). In our experiments and those of others (2), the more severe the iodine depletion, the lower the amount of iodothyronine* synthesis. As Inoue and Taurog (2) have reported, acute injection of stable iodide increased T_4* synthesis within 3 hr. These effects were seen in both intact and hypophysectomized rats in our experiments and support the hypothesis (2, 10) that decreased coupling of DIT to form T_4 in iodine-deficient rats is due to an inadequate number of DIT residues within the thyroglobulin matrix to permit ready coupling.

There was a progressive increase in the quantity of total thyroid radioactivity present as iodothyronines* in the thyroids of the hypophysectomized rats up to 24 hr after ^{131}I administration. At no point did it exceed that of the intact controls. However, when calculated as percent of administered radioiodine, iodothyronines* were higher in the hypophysectomized than in the intact rats at 24 hr, presumably reflecting only the cessation of thyroid secretion in the former.

Summary. The hypothesis was examined that one reason severely iodine-deficient rats have a lower thyroidal labeled iodothyronine content than iodine-replete rats after ^{131}I administration may be because thyroid iodine turnover is too rapid in the iodine-deficient rats to permit maximal labeled iodothyronine accumulation. Thyroid radioiodine accumulation and relative labeled amino acid distribution was examined between 3 and 24 hr after ^{131}I administration to iodine-deficient rats. Half the animals were hypophysectomized to inhibit thyroid secretion 30 min before giving ^{131}I. No increase in the proportion of thyroid ^{131}I present as iodothyronines was produced by thus acutely inhibiting secretion. Our data therefore do not support the hypothesis. Addition of 1 μg $^{127}I^-$ to the ^{131}I injection increased labeled iodothyronine synthesis (primarily as T_4) in both intact and hypophysectomized iodine-deficient rats.

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