Antithyroid Effects of Lithium

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ABSTRACT Lithium has been reported to be goitrogenic when used for the treatment of manic-depressive psychosis. To investigate the effects of lithium on iodine metabolism, male Sprague-Dawley rats were placed on a low iodine (LID) or normal iodine diet (NID) containing enough Li_2CO_3 to give serum lithium levels of 0.23–0.86 mEq/liter (human therapeutic range is 0.6–1.6 mEq/liter). The following effects were noted with lithium treatment: (*a*) thyroid weight increased concomitant with a slowing of thyroidal iodine release; (*b*) the ability to concentrate iodide was increased only *after* goiters were established; (*c*) on the LID, ^{131}I uptake was elevated throughout all phases of treatment, even when the release rate was normal; (*d*) iodine organification was unaffected but the proportion of ^{131}I present as iodothyronines was decreased; (*e*) the thyroidal ^{127}I content was increased; (*f*) despite these changes, the serum PBI remained normal as did the thyroxine turnover rate; and (*g*) thyrotropin (TSH) levels in serum were the same as controls except for a slight elevation early in the course of treatment; TSH levels did not correlate with goitrogenesis.

When LiCl was injected in large doses into intact rats (giving serum lithium levels of 3.08–3.89 mEq/liter), the iodide concentrating mechanism, ^{131}I uptake, and ^{131}I release rates were depressed. Similar experiments in hypophysectomized rats receiving TSH demonstrated these to be local antithyroid effects not mediated through the pituitary.

The discrepancy between acute and chronic responses to lithium, and the dissociation between the inhibition of iodine release and stimulatory effects is discussed.

INTRODUCTION

Lithium salts were first noted to have calming effects in manic patients in 1949 (1). It was not until 1968 that Schou, Amdisen, Jensen, and Olsen first mentioned the relatively rare occurrence of goiter in lithium-treated patients (2, 3). 12 of 330 patients developed goiter over a 5–24 month period of lithium treatment. Increased iodide clearance rates were demonstrated in these goiters. Discontinuation of lithium led to disappearance of goiter and return of thyroid clearance rates to base line levels. Although the over-all rate of goiter formation was only 3.6%, this was higher than the endemic incidence of 1.1% (3). Sedvall, Jönsson, Pettersson, and Levin reported increased ^{131}I uptake and decreased serum PBI in patients on lithium therapy (4) and in normal volunteers (5). Lithium given to rats (3.0–3.75 mEq/kg per 24 hr) for 7 days also caused a decrease in PBI levels (4).

From a mechanistic point of view it seemed quite remarkable that a simple cation could have "antithyroid" properties at low concentrations. For this reason, acute and chronic effects of lithium administration were studied in rats with the aim of establishing the conditions for goitrogenicity and, in particular, of elucidating the locus of action of lithium in the pathway of iodine metabolism is the thyroid gland.

METHODS

Animals. Male Sprague-Dawley rats were used in all experiments. Intact animals fed special diets were started on the diet when they were weanlings. Body weights at the end of each experiment varied from 100 to 387 g depending on the age of the animal and duration of treatment. Hypophysectomized rats weighing 116–145 g were purchased from Hormone Assay Laboratories, Inc., Chicago, Ill. They were fed the lactating diet and were injected with 1 U of bovine TSH subcutaneously daily for 6 days and were then used for the experiment (12 days postoperative). Hypophysectomies were confirmed by inspection of the sellae at the end of each experiment.

Diets. Four diets were used. (*a*) 75% Remington diet plus 25% vitamin-fortified low iodine diet; the mixture contained 0.034 μg $^{127}I/g$ (Nutritional Biochemicals). Where indicated, Li_2CO_3 (1.11 g/kg = 30 mEq/kg) was added, giving mid-morning serum lithium concentrations of 0.23–0.86 mEq/liter (Table I). Higher doses produced signs of toxicity, such as delayed growth, alopecia, diarrhea, and poly-

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TABLE I

Serum Lithium Concentrations

Conditions	No. of animals	Serum Li^+	Range
		mEq/liter	*mEq/liter*
Acute lithium treatment			
Li^+ 4 mEq/kg i.p.* 4 hr before sample	6	2.19 ±0.03‡	2.16–2.30
Li^+ 4 mEq/kg i.p. 16 and again 4 hr before sample*	6	3.59 ±0.12	3.08–3.89
Animals fed lithium			
LID + Li^+§			
18	6	0.68 ±0.04	0.59–0.86
26	4	0.60 ±0.04	0.55–0.70
44	5	0.39 ±0.03	0.35–0.50
126	5	0.44 ±0.02	0.39–0.50
153	9	0.41 ±0.04	0.23–0.63
NID + Li^+§			
15	4	0.36 ±0.03	0.31–0.43
53	3	0.41 ±0.12	0.24–0.65

* Acute conditions under which [T/S] $^{131}I^-$ was tested.

‡ Mean ±SEM

§ Days on diet.

uria. Human therapeutic levels range from 0.6 to 1.6 mEq/liter (2). Groups fed this diet are designated LID or LID + Li^+. (*b*) A normal iodine-sufficient diet (NID) consisting of 50% low iodine diet and 50% Purina Rat Chow (0.5 μg ^{127}I/g). Lithium carbonate was added in the same proportions as noted for the LID + Li^+. (*c*) A lactating diet containing 0.2 μg ^{127}I/g (General Biochemicals). This was fed to hypophysectomized rats. (*d*) Purina Rat Chow pellets were fed to normal animals used to test acute effects of lithium on the [T/S] $^{131}I^-$. All groups received tap water.

Procedures. The following thyroid tests were carried out: (*a*) [T/S] $^{131}I^-$; (*b*) ^{131}I uptake; (*c*) ^{131}I release rate; (*d*) thyroid weight; (*e*) thyroid iodine content and concentration; (*f*) organically bound iodine; (*g*) chromatography of thyroid hydrolysates; (*h*) serum TSH; (*i*) serum PBI; (*j*) serum T_4-^{125}I disappearance rate; and (*k*) thyroid histology. Chronically treated rats were used directly, while acutely treated animals were injected according to the schedules listed in the legends.

[T/S] $^{131}I^-$. This is defined as the ratio of $^{131}I^-$ counts per gram of tissue to counts per milliliter of serum 120 min after $^{131}I^-$ injection. The rats were given methylmercaptoimidazole (MMI) 11.4 mg intraperitoneally. After 1 hr, $^{131}I^-$ was injected intraperitoneally, and the animals were killed 120 min later by exsanguination while under chloroform anesthesia. The thyroids were rapidly weighed, and then serum and thyroids were counted in a well-type scintillation counter.

Thyroid ^{131}I uptake and release. These were measured by the external neck counting technique described by Wolff (6). Thyroid uptake was measured 4–24 hr after the injection of $^{131}I^-$. An intraperitoneal dose of 10 μCi was used for rats on the LID, and 20–25 μCi was used for animals on the NID. During release experiments, the animals were given MMI 11.4 mg intraperitoneally after each measurement. Readings were made at 6- to 12-hr intervals. Discharge slopes were computed by linear regression of semilogarithmic plots fitted by the method of least squares. The initial thyroid count was made 8–36 hr after the injection of radioiodine and was considered as 100% of thyroidal ^{131}I; all subsequent counts were expressed as percentages thereof.

Chromatography. ^{131}I-labeled thyroid homogenates from animals on LID + Li^+ for 77 and 153 days were hydrolyzed with pronase (2 mg/17–20 mg thyroid, wet weight) at 37°C, pH 8.5 with 0.05 M MMI under anaerobic conditions as described by Inoue and Taurog (7). After hydrolysis, the sample was applied to Whatman 3MM paper for ascending chromatography in the following solvents: *n*-butanol, ethanol, 0.5 N NH_4OH (5:1:2), and *n*-butanol saturated with 2.0 N acetic acid. A carrier solution consisting of MIT, DIT, T_3, T_4, and KI was also applied to each strip. Radioactive spots were located by autoradiography on no-screen X-ray film, cut out and counted.

Miscellaneous. The fraction of iodine present in the thyroid as organic compounds was determined in animals on the LID + Li^+ for 44 days by precipitation of labeled thyroid homogenates with 1.0 ml of 10% trichloroacetic acid (TCA) containing 1×10^{-3} M MMI. The precipitate was washed with 3.0 ml of 10% TCA and then counted. Organic iodine content of thyroids from animals on the LID + Li^+ for 77 days was determined by chromatography of ^{131}I-labeled, unhydrolyzed thyroid homogenates using the butanol–acetic acid solvent.

PBI, serum T_4 (by displacement analysis), and total thyroid iodine content were determined by the Boston Medical Laboratory, Inc., Waltham, Mass. (8–10).

Serum T_4-^{125}I disappearance rate was studied in animals on the LID + Li^+ for 25 days. ^{125}I-labeled T_4 (Mallinckrodt) (found to be more than 99% pure by chromatography) was suspended in fresh rat serum diluted 1:8 with normal

TABLE II

Thyroid Weights in Animals Fed Lithium

Days on diet	No. of animals Li+/control	Li+	Control	Thyroid weight ratio Li+/control	P
		mg/100 g	*mg/100 g*		
LID + Li+					
6*	8/9	11.5 ±0.7‡	10.0 ±1.1	1.15	<0.3
11*	8/9	11.3 ±0.7	10.0 ±1.1	1.13	<0.4
15	9/10	10.4 ±0.4	8.5 ±0.4	1.22	<0.01
18	6/6	11.2 ±0.4	8.4 ±0.6	1.33	<0.01
38§	6/6	11.6 ±0.7	7.9 ±0.9	1.47	<0.01
44	5/4	15.5 ±0.7	10.3 ±0.5	1.50	<0.001
50	6/6	15.0 ±1.1	9.5 ±0.8	1.58	<0.01
56	5/5	14.3 ±0.5	11.4 ±0.6	1.25	<0.05
77	6/7	14.8 ±0.7	11.4 ±1.3	1.30	<0.01
95	6/6	13.1 ±0.8	8.9 ±0.2	1.47	<0.001
126	6/6	15.6 ±1.1	15.3 ±3.4	1.02	1
134	6/6	10.4 ±0.7	10.2 ±0.4	1.02	<0.8
153	9/7	14.6 ±1.0	12.3 ±0.8	1.19	<0.2
NID + Li+					
15	10/10	6.5 ±0.3	5.8 ±0.2	1.12	<0.1
25	6/6	6.8 ±0.3	6.9 ±0.3	0.99	<0.8
53	6/6	5.5 ±0.3	4.3 ±0.1	1.28	<0.01
101	9/12	6.2 ±0.3	4.5 ±0.2	1.38	<0.001

* These animals were on the LID 8 wk before addition of Li+. All other animals were placed on the LID + Li+ simultaneously.

‡ Mean ±SEM.

§ Pair-fed animals.

saline. The final injection volume of 0.5 ml contained 0.041 μg T_4 (2.7 μCi ^{125}I) and was administered into the tail vein 3 hr after 22 mg of MMI was given intraperitoneally. Blood samples were taken from the tail vein at 7- to 15-hr intervals and 11.4 mg MMI was given intraperitoneally immediately after each bleeding. 100 μl of serum was treated with 1.0 ml of 10% TCA containing 1×10^{-3} M MMI. The precipitate was washed once with 1.0 ml of 10% TCA and then counted. Disappearance slopes were plotted semilogarithmically for TCA-precipitable counts and the half-times were determined.

TABLE III

[T/S] $^{131}I^-$ in Animals Fed Lithium

Days on diet	Li+	Control	P‡
LID + LI+			
15	137 ±8.7*	133 ±9.5	<0.8
38§	336 ±20	262 ±31	<0.1
95	249 ±15	163 ±15	<0.01
NID + Li+			
15	54 ±6.8	62 ±7.4	<0.5
53	96 ±17	95 ±12	1

* Mean ±SEM.

‡ Refer to Table II for the number of animals used.

§ Pair fed.

Serum thyrotropin (TSH) was determined by a radioimmunoassay specific for rat TSH (11). We are indebted to Dr. John F. Wilber, Department of Medicine, Northwestern University School of Medicine, Chicago, Ill., for generously performing this assay.

Serum lithium was measured by atomic absorption spectrophotometry (Instrumentation Laboratory, Inc., model 153).

Histology. Thyroids from lithium-treated animals and controls on the LID for 50, 56, 95, and 126 days and on the NID for 101 days were fixed in Bouin's solution, sectioned at 6 μ, and stained with hematoxylin and eosin.

Statistics. All *P* values were obtained by using Student's *t* test for grouped mean data.

RESULTS

Chronic lithium feeding

Goitrogenic response (*Table II*). In rats receiving the LID, chronic lithium feeding resulted in thyroid weights which were significantly larger than controls by 15 days. The difference increased to a maximum of 58% greater than control weights ($P < 0.01$) at 50 days. Thereafter the difference in thyroid weights became smaller, so that by 126 days the glands were no longer

TABLE IV

Thyroid ^{131}I Uptake in Animals Fed Lithium

Days on diet	No. of animals Li^+/control	Uptake interval	Li^+	Control	*P*
		hr	*% of dose*	*% of dose*	
LID + Li^+					
50	6/6	4	77.2 ±1.8*	51.3 ±8.2	<0.02
77	6/7	4	67.8 ±2.4	66.3 ±2.3	<0.8
126	6/6	4	49.9 ±1.6	33.8 ±6.3	<0.05
25	7/8	8	29.5 ±2.3	21.4 ±1.5	<0.01
119	6/6	7.5	52.2 ±1.5	34.6 ±4.6	<0.01
6‡	7/8	10.5	43.8 ±2.3	41.6 ±1.6	<0.5
11‡	8/8	10.5	46.1 ±2.8	41.6 ±1.6	<0.2
25	6/6	10.5	42.1 ±4.8	26.9 ±3.2	<0.05
56	6/6	11.0	55.4 ±3.3	55.8 ±1.5	1
126	6/6	17	57.1 ±2.3	38.6 ±3.0	<0.001
153	5/5	20.5	41.1 ±2.4	31.1 ±3.3	<0.02
119	6/6	24	42.2 ±0.8	23.3 ±2.5	<0.001
NID + Li^+					
25	6/6	9	5.8 ±0.6	5.2 ±0.4	<0.5
101	6/6	21.5	20.3 ±2.4	14.0 ±2.1	<0.1
101	6/6	36	21.6 ±1.7	16.2 ±2.4	<0.1

* Mean ±SEM.

‡ These animals were on the LID 8 wk before addition of Li^+. All other animals were placed on the LID + Li^+ simultaneously.

significantly larger than control thyroids. Although lithium-treated rats fed *ad lib.* tended to be from 5- to 13% smaller, the thyroid weight difference was a true one, as shown in pair feeding experiments. After 38 days, the mean body weights were the same, whereas the relative thyroid weights were enlarged 47% in the group receiving lithium ($P < 0.01$) (Table II). Thyroids from animals fed the NID + Li^+ were 28% larger than controls at 53 days ($P < 0.01$) and 38% larger at 101 days ($P < 0.001$).

Thyroid to serum $^{131}I^-$ concentration ratio (Table III). The [T/S] serves as a measure of the activity of the iodide concentrating mechanism. The ratio was increased in the LID + Li^+-treated groups, but this effect only became significant sometime between 38 and 95 days, i.e., not until *after* goiter had been established. Lithium had no effect on the [T/S] in animals receiving the NID + Li^+ up to 53 days. Thus, inadequate accumulation of iodide is not the cause of goiter induction by lithium.

Radioactive iodine uptake (Table IV). ^{131}I uptake was measured at approximately 4, 8, 11, and 21 hr after different intervals on LID + Li^+, and at 9, 21, and 36 hr after 25 or 101 days on NID + Li^+. Lithium-treated animals usually had significantly higher uptakes when on the LID more than 25 days. Two groups treated for 56 and 77 days respectively, showed no difference from controls in ^{131}I uptake despite having goiters. On the NID, ^{131}I uptakes in the lithium-treated rats were the same as controls despite marked differences in the iodine release rates (see below).

After 119 days on LID + Li^+, ^{131}I uptake was examined over a 96 hr period. Uptake reached a peak at 7 hr (Li^+ 52% of dose, control 35%, $P < 0.01$), and the difference in uptake was greatest at 29 hr (Li^+ 36%, control 17%, $P < 0.001$). Uptake remained elevated in the lithium group at 96 hr (Li^+ 19%, control 9%, $P < 0.05$). 3 days after the conclusion of this uptake experiment, the same animals were again injected with $^{131}I^-$ and the radioiodine release rates were determined as described above. There was no significant difference from controls in the release rates (see below, Fig. 2 D). Despite this lack of difference, there was a persistent elevation in the ^{131}I uptake at 17 hr (controls = 39% and lithium-treated rats = 57% of the injected dose; $P < 0.001$). Thus the higher uptake is not due to delayed ^{131}I release in this group.

Organically bound ^{131}I and chromatography. Deter-

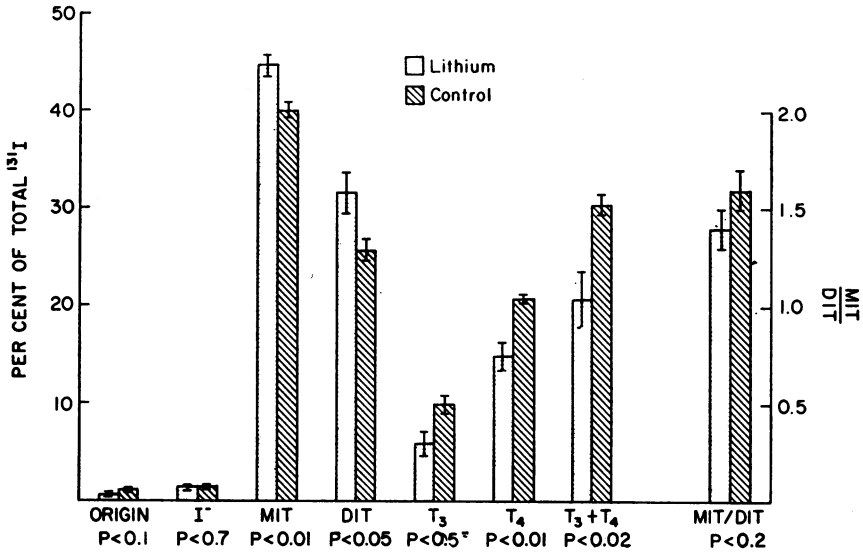

FIGURE 1 Chromatographic analysis of hydrolysates of thyroids labeled for 21 hr from rats on LID + Li^+ for 153 days. The solvent was butanol-ethanol-ammonia. There were five animals in each group.

mination of TCA-precipitable ^{131}I 4 hr after injection revealed that more than 99% of the counts were precipitated in both control and lithium-treated rats, and, therefore, were presumably organic iodine. Chromatography of unhydrolyzed thyroid homogenates in the butanol-acetic acid solvent also showed more than 99% protein-bound ^{131}I in both lithium-treated animals and controls. Therefore, chronic feeding of lithium does not prevent organification of iodide.

As seen in Fig. 1, chromatography of thyroid hydrolysates from animals on LID + Li^+ for 153 days revealed decreased labeled iodothyronines and increased

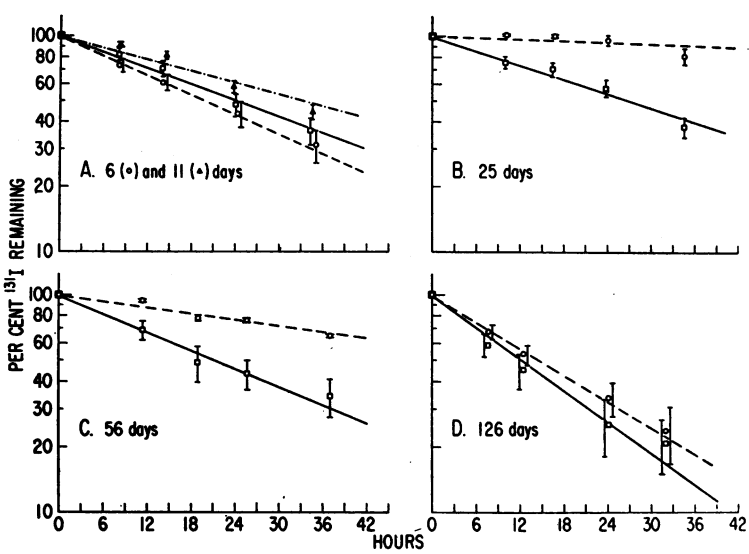

FIGURE 2 The release of ^{131}I from the thyroids of rats on LID + Li^+. □——□ control, ○- - -○ or △—·—△ Li-treated. In panel A, the animals were on the LID for 8 wk before being placed on Li^+ and then received Li^+ for 6 or 11 days. All other groups were started directly either on LID or LID + Li^+ for the periods noted. The "zero time" counts were made 8–36 hr after the injection of ^{131}I. Vertical lines denote ±SEM. There were six to eight animals in each group.

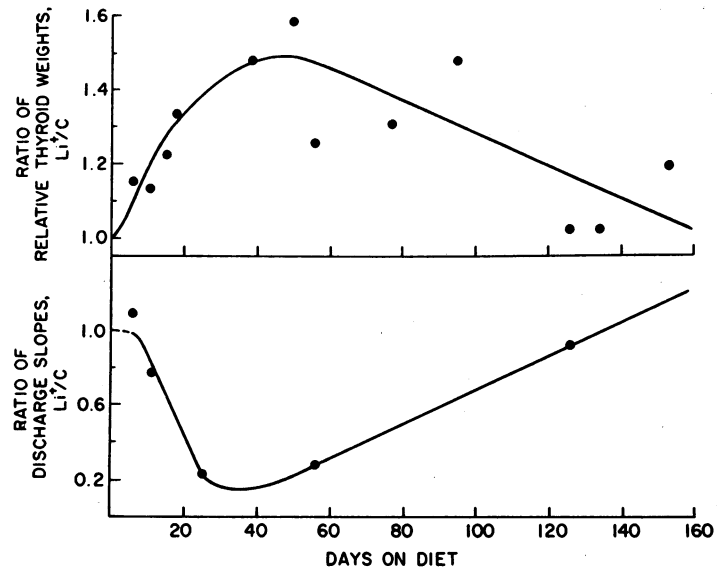

FIGURE 3 Relative thyroid weights and ^{131}I discharge slopes (Li-treated/control) as a function of duration on LID + Li^+.

iodotyrosines with an unchanged MIT/DIT ratio. This combination of findings suggests that lithium may inhibit the coupling of iodotyrosines, but not enough is known of this reaction to draw any definite conclusions. Results after 77 days on the diet were similar. A normal MIT/DIT ratio also suggests that lithium does not embarrass over-all iodination. These changes in thyroidal iodoamino acids were present irrespective of gland size.

Release of ^{131}I from the thyroid. Since the effects of lithium on the iodide concentrating mechanism and on thyroidal iodothyronine synthesis were unlikely to be the principle causes of goiter formation, ^{131}I release from the thyroid was examined. The rate of ^{131}I secretion from the thyroids of rats prelabeled for 8–36 hr was markedly decreased by lithium feeding (Fig. 2). This was evident at 11 days after starting treatment and was maximal at 25 days (91% slower than in control rats, $P < 0.001$ testing the final two points on the graph, Fig. 2 B). Like the goitrogenic response, the effect on iodine release diminished with time; at 126 days control and lithium-treated discharge slopes were identical. This relationship in the time course of goitrogenic response and slowing of ^{131}I discharge is depicted in Fig. 3. The greatest difference from control in iodine release rate occurred between 25 and 56 days on the LID, and the greatest difference in thyroid weights was at 56 days. Whether or not these "peaks" occurred at significantly different times cannot be determined with the present data. In rats on a normal iodine intake, persistence of the goiter at 101 days was accompanied by persistence in the delay of iodine release (Fig. 4: 46% difference in slopes at 25 days, $P < 0.01$, and 54% difference at 101 days, $P < 0.05$; P values were obtained by testing the last two points on the graphs).

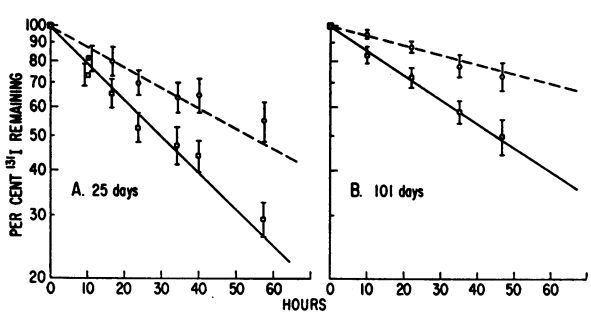

FIGURE 4 The release of ^{131}I from the thyroids of rats fed NID + Li^+ for 25 or 101 days. □——□ control, ○---○ Li-treated. Vertical lines denote ±SEM. There were six animals in each group.

Thyroid ^{127}I content. In view of the markedly delayed release of ^{131}I from the thyroid in conjunction with normal or increased iodide trapping, we anticipated an elevated thyroid iodine (TI) content and concentration in the lithium-treated rats. This was, in fact, observed in animals on both normal and low iodine intakes (Table V). Both thyroid iodine *content* and *concentration* were increased in the lithium-treated rats fed the low iodine diet. On a normal iodine diet this increase became apparent only at 101 days.

Serum TSH and PBI levels. It is well established that iodine release from the thyroid is very sensitive

TABLE V

Thyroid Iodine in Animals Fed Lithium

Days on diet	Total iodine content/thyroid			Iodine concentration		
	Li^+	Control	*P*	Li^+	Control	*P*
	μg	μg		μg/mg	μg/mg	
LID + Li^+						
56 (5)*	4.8 ±0.4‡	3.9 ±0.5	<0.3	0.17 ±0.03	0.13 ±0.02	<0.4
95 (6)	7.4 ±0.7	4.2 ±0.6	<0.01	0.23 ±0.04	0.15 ±0.01	<0.1
134 (6)	7.4 ±0.7	1.6 ±0.3	<0.001	0.30 ±0.03	0.04 ±0.01	<0.001
NID + Li^+						
53 (6)	17.0 ±2.1	13.2 ±0.8	<0.2	1.09 ±0.15	1.02 ±0.06	<0.7
101 (6)	21.2 ±1.3	12.1 ±1.6	<0.01	1.11 ±0.07	0.80 ±0.11	<0.05

* Numbers in parentheses indicate number of animals in each group.

‡ Mean ±SEM.

to TSH (7, 12), and an altered level of TSH could have accounted for the release effects described above. The serum TSH concentration was therefore of considerable interest (Table VI). Except for the first interval tested (15 days on LID + Li^+) serum TSH levels of lithium-fed rats were the same as in control rats throughout the period of observation. This was true even at times when there were marked differences in thyroid weights. TSH levels did not, therefore, correlate with goitrogenesis.

The serum PBI was never significantly different from controls (Table VII). We found this puzzling since an estimate based on the discharge rates, thyroid iodine, and labeled iodothyronine content (and disregarding heterogeneity of thyroid iodine) suggested that lithium-treated animals on the LID would deliver only about one-half as much T_4 to the circulation as would controls. This suggested the possibility that thyroxine turnover might be delayed by lithium-treatment and thus keep the PBI at normal levels. To evaluate this further, the serum T_4-^{125}I disappearance rate was determined and found to be the same as controls after 25 days on LID + Li^+ ($t_{\frac{1}{2}}$ for lithium group = 13.75 hr, controls 14.0 hr). Thus, the reason for the normal PBI under these conditions remains obscure.

Histology. Histologic examination failed to reveal any consistent differences between lithium-treated animals and controls, despite significant differences in thyroid weight and iodine metabolism.

Acute administration of lithium

[T/S] $^{131}I^-$ (Table VIII). In intact animals there was no demonstrable effect on the [T/S] 4 hr after

TABLE VI

Serum TSH in Animals Chronically Fed Lithium*

Days on diet	Li^+	Control	*P*
	μU/ml	μU/ml	
LID + Li^+			
15	46 ±2‡ (9)§	37 ±3 (10)	<0.05
50	73 ±9 (6)	94 ±17 (6)	<0.3
77	108 ±9 (6)	103 ±4 (6)	<0.7
153	77 ±7 (9)	93 ±8 (7)	<0.2
NID + Li^+			
15	34 ±2 (10)	36 ±3 (10)	<0.6
56	33 ±2 (6)	36 ±7 (6)	<0.8

* The radioimmunoassay for rat TSH was performed by Dr. John F. Wilber.

‡ Mean ±SEM.

§ Number in parentheses is number of animals in each group.

TABLE VII

Serum PBI in Animals Fed Lithium

Days on diet	Li^+	Control	*P*
	μg/100 ml	μg/100 ml	
LID + Li^+			
18 (6)*	2.3 ±0.2‡	2.7 ±0.1	<0.2
50 (6)	1.6 ±0.1	1.7 ±0.1	<0.3
77 (6)	1.5 ±0.1	1.2 ±0.1	<0.1
153§	1.8 ±0.2	1.7 ±0.1	<0.7
NID + Li^+			
15 (10)	2.5 ±0.1	2.6 ±0.2	<0.7
25 (6)	2.2 ±0.1	2.3 ±0.1	<0.5
53 (6)	2.8 ±0.2	3.1 ±0.2	<0.4

* Number in parentheses indicate number of animals in each group.

‡ Mean ±SEM.

§ For LID + Li^+ 153 days, there were nine LiCl-treated animals and seven NaCl-treated controls. T_4 (displacement analysis) was the same in both groups.

TABLE VIII

[T/S] $^{131}I^-$ with Acute Lithium Treatment

Conditions	No. of animals Li+/control	Li+	Control	P
4 hr after Li+ injection*	6/6	47 ±3.5‡	47 ±3.3	1
16 hr after Li+ injection*	15/14	38 ±2.9	54 ±3.7	<0.01
Hypophysectomized rats,§ 16 hr after Li+ injection*	7/8	38 ±4.5	58 ±4.7	<0.01

* LiCl 4 mEq/kg i.p. was given at the times indicated. In the 16-hr groups, a second dose was given 4 hr before the animals were killed.
‡ Mean ±SEM.
§ Injected with 1.0 U/day of bovine TSH for 2 days.

TABLE IX

Thyroid ^{131}I Uptake with Acute Lithium Treatment

Conditions	Li+	Control	P*
	% of dose	% of dose	
Li+ 2 mEq/kg i.p. × 2, uptake at 11 hr‡	26.1 ±2.4§	38.5 ±3.1	<0.02
Li+ 4 mEq/kg i.p., uptake at 8 hr‖	22.9 ±2.1	43.7 ±2.2	<0.001

* There were six animals in each group.
‡ LiCl was given 9 hr before and again with ^{131}I.
§ Mean ± SEM
‖ LiCl was given 12 hr before ^{131}I.

lithium was injected, but by 16 hr the [*T/S*] was significantly decreased ($P < 0.01$). Thus, the effect on the iodide concentrating mechanism is not immediate and involves a latency of more than 4 hr. The [T/S] measured after 16 hr of lithium treatment in hypophysectomized rats given TSH showed a significant decrease compared to the control hypophysectomized group ($P < 0.01$), suggesting that this effect was not mediated by the pituitary. This acute decrease in the [T/S] is in marked contrast to the late stimulatory effects seen in the animals chronically treated with the low dose of lithium (see above).

^{131}I uptake. Uptake of ^{131}I over the neck was significantly lowered (Table IX) in intact animals given a total of 4 mEq/kg in a single or in two divided doses.

^{131}I release. In order to demonstrate an acute effect on release of ^{131}I from the thyroid, it was necessary to inject large doses of lithium. Thus 4 mEq/kg led to a 112% decrease in the release slope, whereas two injections of 2 mEq/kg given at 9-hr intervals caused no significant change in the slope (Table X). Hypophysectomized rats receiving TSH also had much slower release after receiving a 4 mEq/kg initial dose. The discharge for the lithium-treated group was 65% slower than controls ($P < 0.001$ comparing final points on the graph, Fig. 5). When release was examined immediately before and after an injection of LiCl in hypophysectomized rats on TSH, slowing was evident with 7 hr of the first dose of lithium ($P < 0.02$ comparing final points on the graph, Fig. 6).

DISCUSSION

The effects of lithium on thyroid function are summarized in Table XI. Chronic treatment of rats with low doses of lithium resulted in thyroid enlargement that was accompanied by markedly slower release of radioiodine from the gland. In animals on the LID, both effects reached a peak at 25–56 days and then diminished despite continued treatment and maintenance of serum lithium levels. Iodide concentrating ability increased after the goiter was formed, whereas ^{131}I uptake and gland size increased *pari passu*. The increased ^{131}I uptake was not *necessarily* associated with a slowing in release of iodine from the thyroid; this was seen in the last LID + Li+ group tested (Fig. 2 D) in which the uptake was elevated but the release rate was the same as in controls. Conversely, the ^{131}I uptake was not necessarily elevated if the release rate was slowed; thus, in

TABLE X

^{131}I Release Slopes with Acute Lithium Treatment

Conditions	Li+	Control	P
Li+ 2 mEq/kg i.p. × 2, then 1 mEq/kg every 8 hr*	−0.04220‡ ±0.00766§	−0.03625 ±0.00866	<0.7‖
Li+ 4 mEq/kg i.p., then on LID + Li+¶	+0.00414 ±0.00223	−0.03513 ±0.00318	<0.001‖

* LiCl was given 9 hr before and again with ^{131}I.
‡ The slope (fraction/hour) for each animal was calculated by linear regression using $Y = \log_e$ of the per cent ^{131}I remaining in the thyroid.
§ Mean ±SEM.
‖ There were six animals in each group and five points for each slope.
¶ LiCl was given 12 hr before ^{131}I.

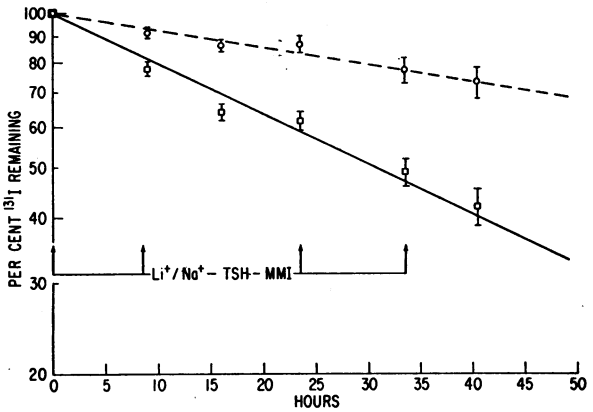

FIGURE 5 The effect of acute lithium treatment on thyroid ^{131}I release in hypophysectomized rats. □——□ control, ○---○ Li-treated. Vertical lines denote ±SEM. The animals were hypophysectomized 12 days earlier, received the lactating diet and 1 U TSH/day subcutaneously for 6 days, and LiCl or NaCl 4 mEq/kg intraperitoneally 12 hr before the injection of ^{131}I. The "zero time" measurement was made 14 hr after ^{131}I was given. Injections of LiCl or NaCl 1 mEq/kg intraperitoneally, MMI 11.4 mg intraperitoneally, and TSH 0.5 U subcutaneously were given at the times indicated by arrows. There were eight Li-treated animals and seven Na-treated controls.

the NID + Li$^+$ group the release was delayed but the ^{131}I uptake was the same as in controls.

These changes in iodine metabolism occurred without any consistent or sustained alteration in the circulating TSH levels compared to controls. The present TSH data are consistent with observations in lithium-treated patients which show a small, early rise in serum TSH but normal levels upon prolonged treatment.[1]

Several unresolved problems in the present data merit attention. (*a*) Unlike the effects of most other goitrogens on thyroidal iodine content, lithium treatment leads to an increase in both iodine content and iodine concentration. Since Bray (13) has demonstrated that iodine depletion in rats increased the sensitivity of the thyroid to the goitrogenic effects of TSH, it is possible that the increased iodine concentration in the thyroids of lithium-treated rats is responsible for the waning of goiter when therapy is prolonged.

(*b*) Despite the slower fractional rate of iodine release and the decrease in the proportion of ^{131}I present as iodothyronines in short-term labeling experiments,[2] the PBI of lithium-treated rats was the same as in untreated controls. This surprising finding may, in part, be due to the increased iodine concentrations in the thyroids of treated animals. However, the concentration changes are not sufficient to compensate for the decrease in release of iodine. Another possible mechanism for the persistence of the normal PBI might have been a decrease in thyroxine disposal rate. However, we showed that T_4 turnover was not changed by lithium treatment. Thus we have no explanation at present for the similarity of PBI in control and treatment groups. Copper and Simpson (15) described an early, transient drop in PBI in patients on lithium therapy and it is possible that we missed such a change for technical reasons.

(*c*) Differences between chronic and acute experiments. In contrast to the chronic lithium effects of both inhibition and stimulation of certain thyroid functions, *acute* lithium treatment led to suppression of all functional parameters measured. Thus, the [T/S], ^{131}I uptake and release of ^{131}I from prelabeled thyroid glands were depressed below their respective control values. These are local antithyroid effects which were not mediated through changes in pituitary function. This difference from chronically treated animals appears to be largely one of dose since these acute effects occurred at blood

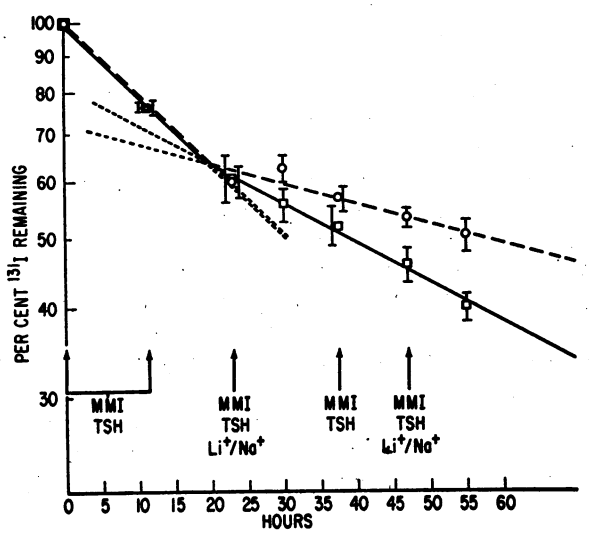

FIGURE 6 The effect of acute lithium treatment on thyroid ^{131}I release in hypophysectomized rats. □——□ control, ○---○ Li-treated. Vertical lines denote ±SEM. The animals were hypophysectomized 12 days earlier and received the lactating diet and 1 U TSH/day subcutaneously for 6 days. The "zero time" measurement was made 33.5 hr after ^{131}I was given. MMI 11.4 mg intraperitoneally, TSH 0.5 U subcutaneously, and LiCl or NaCl intraperitoneally were given at the times indicated by the arrows. The first dose of LiCl or NaCl was 4 mEq/kg, and the second dose was 1 mEq/kg. There were nine Li-treated animals and seven Na-treated controls.

[1] Berens, S. Unpublished observations.

[2] Cooper, Wagner, and Kline (14) have found that the distribution of iodoamino acids in equilibrium-labeled rats was not altered by lithium therapy although these animals showed a 24% enlargement of the thyroid glands. We should like to thank the authors for supplying us with this manuscript before publication.

TABLE XI

*Effects of Lithium on Tests of Thyroid Function**

Measurement	Chronic	Acute
Thyroid weight	Increased	
[T/S]	Late increase	Decreased
Uptake	Increased	Decreased
Organification	Unchanged % $T_3 + T_4$ decreased	
Release	Slowed	Slowed
Iodine content	Increased	
PBI	Unchanged	
TSH	Unchanged‡	

* All comparisons are with respect to untreated controls.
‡ TSH was slightly elevated in one group early in treatment.

levels which were about six times greater than those attained during chronic lithium feeding. Serum lithium in excess of 1.5 mEq/liter results in toxicity in rats after 72 hr. Toxicity was not observed in our rats probably because the acute experiments lasted less than 48 hr. For these reasons, it seems likely that the decreased PBI levels reported by Sedvall et al. (4) are the result of toxic doses of lithium since serum levels (1.71 mEq/liter) were 3–4 times those reported here in chronically treated animals.

Thyroid lithium levels were measured in an attempt to correlate such levels with the physiological effects. This is the subject of another paper (16) and the results will only be summarized here. Animals receiving the LID + Li^+ had thyroid lithium levels ranging from 1.05 to 1.85 mEq/kg of wet tissue weight. This gave thyroid/serum lithium concentration ratios in the range of 2.7. Acutely treated animals had higher tissue levels (6–10 mEq/kg wet weight) but the lithium concentration ratios were the same as in the chronically treated animals. This ratio is higher than for any other tissue reported to date (17).

A peculiar feature of the lithium effect on the thyroid gland is the apparent dissociation produced by this cation in the response to TSH. Most of the measurements summarized in Table XI can be augmented by TSH, yet release of iodine from the gland, which is one of the more sensitive responses to TSH, was inhibited by Li^+, whereas other parameters of iodine metabolism were stimulated. Furthermore, there is reversal in the time course of response of some of these parameters. Halmi, Spirtos, Bogdanove, and Lipner (18) have shown that stimulation of iodide concentration precedes, and is more sensitive than, thyroid enlargement in response to TSH. Yet the TSH stimulus resulting from the low iodine diet + Li^+ was expressed first in thyroid enlargement and only much later by an increase in the [T/S]. We have recently demonstrated that lithium has an inhibitory effect on thyroid adenyl cyclase in concentrations similar to those found in the thyroids of animals *acutely* treated with high doses of LiCl (19). This may provide an explanation for the depression of function observed under *acute* treatment conditions. In chronically treated arts, however, it seems unlikely that thyroid adenyl cyclase is inhibited in view of the stimulation of some TSH-dependent functions. Because of the dissociation of functions, it is more likely that lithium is affecting iodine metabolism at a point subsequent to the formation of cyclic-AMP.

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