EFFECT OF LITHIUM CHLORIDE ON THE THYROID GLAND IN ALBINO RATS

V. A. Glumova, N. M. Petrov, and V. N. Markov

UDC 612.441.014.46:546.34'131

The character of morphological and functional changes in the thyroid tissue of albino rats was studied by radiometric, histological, and biochemical methods during administration of lithium chloride to the animals for three weeks in doses of 0.5 meq/kg (Group 1), and 1 meq/kg (Group 2) daily. The inhibitory action of lithium chloride on hormone production in the thyroid gland and on the secretion of thyroid hormones into the blood stream was shown to be directly dependent on the dose of the compound and the lithium concentration in the blood. The results of intravital radiometry and morphological analysis of the organs of the animals of group 1 showed some activation of the gland, but secretion of hormones into the blood stream was inhibited. An increase in the lithium concentration inhibited hormone production and the secretion of thyroid hormones into the blood stream.

KEY WORDS: thyroid gland; thyroid hormones; lithium.

A new property of lithium has recently been discovered, namely its ability to influence thyroid hormonal function in persons who have been treated with lithium compounds for a long time [7, 11]. Most workers who have observed the goitrogenic effect of lithium during treatment of psychiatric patients [3, 4, 6, 8, 12, 13] consider that, during treatment, lithium prevents thyroxine production in the thyroid gland, with the result that a deficiency of this hormone develops. The effect of lithium on the thyroid gland has been explained [9] by inhibition of thyroglobulin breakdown and depression of the stimulating effect of thyrotrophic hormone. Some workers [5, 10, 14] consider that lithium has a direct inhibitory action on liberation of hormones from the thyroid gland tissue and on the excretion of thyroxine from the body.

The absence of any clear and consistent ideas in the literature of the mechanism of action of lithium salts on thyroid function, and also the practical interest of clinicians in lithium during recent years motivated this study of the character of the morphological and functional changes in the thryoid gland during the experimental administration of various doses of lithium chloride.

EXPERIMENTAL METHOD

Experiments were carried out on 53 albino rats of both sexes with a mean weight of 204.5 ± 26.5 g. After administration of lithium chloride for 3 weeks per os to the rats in a daily dose of 0.5 meq/kg (group 1) or 1 meq/kg (group 2) a thyroid function test was performed: ^{131}I was injected subcutaneously in a dose of 0.02 μCi/kg, after which the iodine-assimilating function of the thyroid gland was studied by means of the DSU-61

TABLE 1. Radioindication Indices of Albino Rat Thyroid Gland during Lithium Treatment

Time, h	Accumulation of ^{131}I in thyroid gland, %				
	control (n = 10)	group 1 (n = 8)	P	group 2 (n = 8)	P
2	25,6±2,3	24,3±1,9	>0,50	15,7±2,6	<0,025
4	30,1±2,1	32,3±3,1	>0,50	19,2±2,2	<0,005
6	36,8±4,1	37,2±4,9	>0,50	20,1±1,9	<0,005
12	39,3±6,6	41,6±5,9	>0,50	21,0±2,5	<0,01
24	49,0±5,9	53,3±5,3	>0,50	29,4±4,5	>0,05
48	39,7±4,4	44,2±2,8	>0,50	20,9±3,2	<0,005
72	32,2±3,9	38,8±2,8	>0,50	16,9±1,7	<0,005

Department of Biology and Department of Internal Medicine, Izhevsk Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. P. Avtsyn.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 87, No. 6, pp. 604-607, June, 1979. Original article submitted July 31, 1978.

 0007-4888/79/8706-0640$07.50

TABLE 2. Effect of Lithium Chloride on Hormone-Forming Function of the Thyroid Gland (M ± m)

Index studied	Control (n = 22)	Group 1 (n = 15)	P	Group 2 (n = 16)	P
Plasma protein-bound iodine, %/liter	0,26±0,025	0,25±0,09	>0,50	0,18±0,022	<0,05
Serum triiodothyronine, conventional units	0,61±0,045	0,51±0,02	<0,05	0,68±0,057	>0,50
Total serum thyroxine, mg%	5,6±0,730	4,34±0,54	>0,25	4,9±0,08	>0,50
Free serum thyroxine, conventional units	0,95±0,026	0,76±0,06	<0,02	0,88±0,048	>0,25

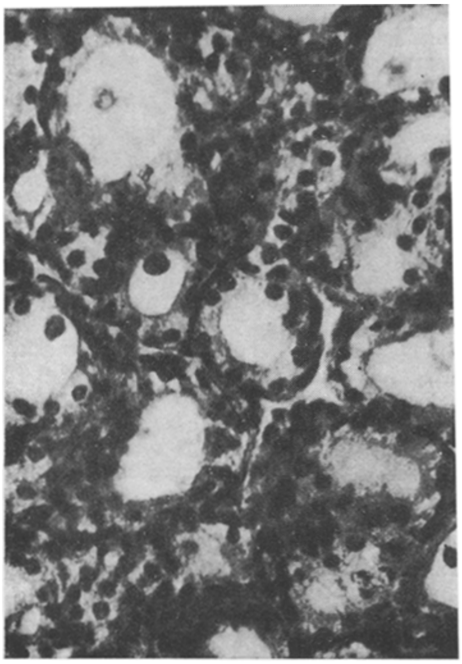

Fig. 1

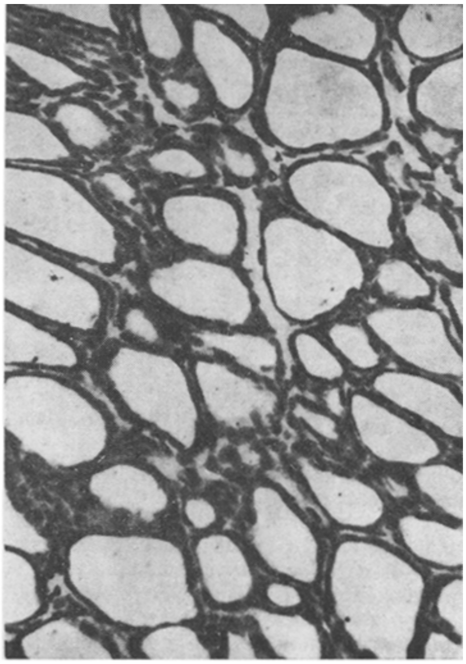

Fig. 2

Fig. 1. Thyroid gland of intact albino rats. Injection of ink in gelatin, counterstained with Ehrlich's hematoxylin, 200 ×.

Fig. 2. Changes in dimensions of follicles and flattening of thyroid epithelium during lithium treatment. Hematoxylin-eosin, 90×.

apparatus in animals in a fixed position 2, 4, 6, 12, 24, 48, and 72 h after administration of the isotope. A group of 22 rats not receiving lithium served as the control. After intravital radiometry of the thyroid gland the animals were decapitated and the protein-bound ^{131}I, the concentration of thyroid hormones (by means of RES-O-MAT and KET kits), and the lithium concentration were determined in blood collected from each rat separately. The biological specimens were measured in an NZ-138 well counter, connected to a type NK-350 energy-selective scaler (Gamma, Hungary). Glucose-6-phosphate dehydrogenase activity was determined in the thyroid glands by Dische's method [2]. For histological analysis the thyroid glands were fixed in Carnoy's mixture and embedded in paraffin. Sections 5-7 μ thick were stained with hematoxylin-eosin and subjected to stereologic analysis [1]. The combined method of Ritter and Oleson was used for histochemical determination of acid and neutral mucopolysaccharides. The experimental results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

The use of different doses of lithium chloride has different effects on the thyroid function of albino rats. Administration of lithium chloride to the rats in a daily dose of 0.5 meq/kg increased the ability of the thyroid gland tissue to take up ^{131}I from the blood (Table 1), but the rate of excretion of the isotope was somewhat

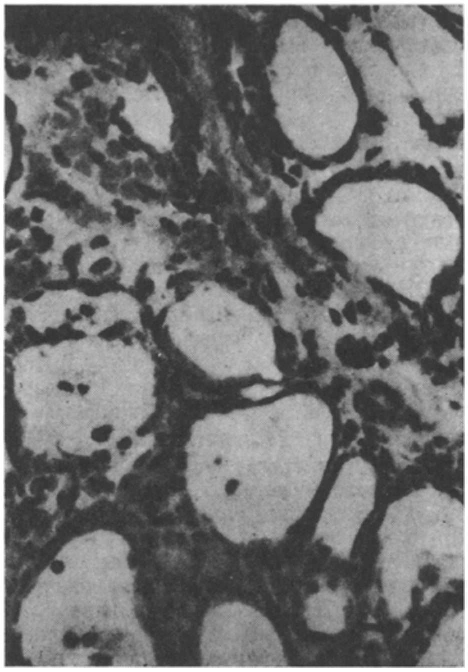

Fig. 3. Desquamation of thyrocytes in cavity of follicles, groups of cells with intensive basophilic granulation in stroma of gland. Hemaxotylin-eosin, 200×.

TABLE 3. Changes in Bulk Density of Tissue Components of Thyroid Gland during Administration of Lithium Chloride in a Dose of 1 meq/kg

Group	Bulk density			
	follicular epithelium	colloid	connective tissue	interfollicular eyelets
Control	$0{,}305\pm8{,}5\cdot10^{-3}$	$0{,}268\pm8{,}1\cdot10^{-3}$	$0{,}224\pm7{,}7\cdot10^{-3}$	$0{,}204\pm7{,}4\cdot10^{-3}$
Receiving lithium chloride	$0{,}313\pm7{,}1\cdot10^{-3}$	$0{,}416\pm6{,}9\cdot10^{-3}$	$0{,}155\pm5{,}6\cdot10^{-3}$	$0{,}116\pm5{,}4\cdot10^{-3}$

reduced, indirectly suggesting the possible inhibition of hormone formation in the gland by lithium. This suggestion was confirmed by the results of determination of the endogenous thyroxine, triiodothyronine, and protein-bound iodine concentration in the plasma, given in Table 2, where the dynamics of the decrease in the thyroid hormone concentration in the rats under the influence of lithium compared with the group of intact animals (control) can be clearly seen. No significant changes were observed, however, in the plasma protein-bound ^{131}I concentration. The mean blood lithium concentration in the animals of group 1 varied between 0.05 and 0.30 meq/liter.

Histologically, slight evidence of excitation was found in the thyroid glands of most animals of group 1: hypertrophy of the epithelium, liquefaction of colloid, an increase in the diameter of the interfollicular capillaries. However, the changes in the volume density of the tissue components were not statistically significant.

After administration of high concentration of lithium chloride (1 meq/kg) its blood level varied from 0.25 to 0.65 meq/liter. The dynamics of the radiometric levels of the thyroid gland were more clearly defined and indicative of depression of the functional activity of the gland. For instance, the absolute quantity of ^{131}I assimilated by the thyroid gland in the inorganic phase of the iodine cycle (during the first day) was 9.9-19.6% lower than in the control group; the rate of elimination of the isotope from the thyroid gland also was slowed. The "neck/thigh ratio" was significantly reduced (on average by 5-12 conventional units), further evidence of a reduction in the concentration function of the thyroid gland with respect to iodides. The inhibitory effect of lithium chloride in a dose of 1 meq/liter was more clearly demonstrated in the transport-organic phase. This was shown by a significant decrease in the plasma protein-bound iodine ($P < 0.05$); the decrease in the blood thyroxine concentration, however, was not statistically significant, and the triiodothyronine level actually rose a little.

An increase in the blood lithium concentration caused marked morphological changes in the structure of the thyroid gland (Figs. 1 and 2). Medium-sized and large polygonal follicles, lined with flat thyroid epithelium, predominated in the sections. The colloid was homogeneous, with no sign of resorption, and gave a strong reaction for mucopolysaccharides. The mean diameter of the follicles increased from $56.3 \pm 2.7\ \mu$ in the control to $81.5 \pm 4.3\ \mu$ in the experiment ($P < 0.05$). Desquamated cells with degenerative changes of varied severity in their nuclei (Fig. 3) were frequently found in the cavity of the peripheral follicles. In three of 16 sections examined, intensive basophilic granules were found in the cytoplasm of the interfollicular cells.

The results of stereologic analysis (Table 3) showed changes in the bulk density of the colloid and a parallel decrease in the bulk density of the interfollicular eyelets and stroma under the influence of lithium. The decrease observed in glucose-6-phosphate dehydrogenase activity, as an indicator of the pentose shunt (to 42.5% of the control level) also points to an inhibitory effect of lithium salts on oxidative processes in the thyrocytes.

It can be concluded from a comparison of the results of the radiometric and histological analysis that different doses of lithium chloride have different effects on the morphology and physiology of the thyroid gland. Lithium chloride in a dose of 0.5 meq/kg causes some activation of the gland, reflected in hypertrophy of the epithelium and an increase in the diameter of the interfollicular capillaries. The iodine-accumulating power of the thyroid gland also increases. However, the hormone-forming function of the gland is depressed under these circumstances, as shown by lengthening of the half-life of ^{131}I in the gland and decrease in the thyroxine and triiodothyronine concentrations in the blood. With an increase in the concentration of lithium chloride to 1 meq/kg both hormone formation in the thyroid gland tissue and secretion of hormones into the blood stream are depressed.

LITERATURE CITED

1. G. G. Avtandilov, N. I. Yabluchanskii, and V. G. Gubenko, Byull. Éksp. Biol. Med., No. 1, 93 (1977).
2. V. S. Asatiani, Enzymic Methods of Analysis [in Russian], Moscow (1969), pp. 596-601.
3. J. F. J. Cade, Med. J. Aust., 2, 349 (1949).
4. J. Candy, Brit. Med. J., 3, 277 (1972).
5. H. E. Carlson, R. Temple, and J. Robbins, J. Clin. Endocrinol., 36, 1251 (1973).
6. T. B. Cooper and G. M. Simpson, Curr. Ther. Res., 11, 603 (1969).
7. R. R. Fieve and S. Platman, Am. J. Psychiat., 125, 119 (1968).
8. J. H. Lazarus and E. H. Bennie, Acta Endocrinol. (Copenhagen), 70, 266 (1972).
9. A. Radvilla, R. Roost, H. Burgi, et al., Acta Endocrinol., (Copenhagen), 81, 496 (1976).
10. A. Rifkin, F. Quitkin, A. G. Blumberg, et al., J. Psychiat. Res., 10, 115 (1974).
11. M. Chou, A. Andisen, E. E. Jensen, et al., Brit. Med. J., 3, 710 (1968).
12. G. Sedvall, B. Jonsson, U. Petterson, et al., Life Sci., 7, 1257 (1968).
13. B. Shopsin, Dis. Nerv. Syst., 31, 237 (1970).
14. R. Temple, M. Berman, H. E. Carlson, et al., Proc. Mayo Clin., 47, 872 (1972).