EFFECT OF LITHIUM CHLORIDE ON STRUCTURAL ELEMENTS OF THE RAT THYROID GLAND AND CALCITROPHIC HORMONE BALANCE

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It can now be taken as an established fact that lithium affects thyroid function (inhibits thyroid hormone secretion). This property of lithium salts has become widely used for the treatment of hyperthyroid states [1, 2, 8, 9, 11]. The other "endocrine" effects of lithium on the therapeutic plane are being widely studied. Despite intensive research in recent years there is no unanimity regarding the point of application of lithium in the chain of regulation of the hypothalamo-hypophyseothyroid system. Some workers consider that lithium salts have a direct inhibitory effect on hormone production, including on secretion of thyroid hormones [10, 14, 15], whereas others do not rule out an effect of lithium on the peripheral metabolism of thyronines also [4, 12, 13]. Lithium has recently been shown to have the property of affecting calcium metabolism [3, 6, 7]. The appearance of hypercalcemia in some patients receiving lithium preparations for a long time, and the decrease in calcium excretion with the urine during treatment, are usually explained by the onset of hyperparathyroidism. Solitary adenomas of the parathyroid glands have been found in patients treated for a long time with lithium preparations [5]. However, when the causes of lithium hypercalcemia have been analyzed, so important a stage in the regulation of calcium metabolism as the close anatomical and functional connection of the parathyrocytes with the follicular apparatus of the thyroid gland and the C-cells has been overlooked. The inhibitory action of lithium on the follicular apparatus of the thyroid must undoubtedly extend also to some degree or other to the C-cell and parathyroid components of endocrine regulation of calcium metabolism.

The aim of this investigation was an experimental study of morphological and physiological changes arising in the thyroid glands under the influence of lithium chloride (LiCl), and also the possible extrathyroid effects of the compound.

EXPERIMENTAL METHOD

Experiments were carried out on 88 male albino rats weighing 220 ± 15 g, divided into four groups: one control and three experimental (22 animals in each group). The experimental rats received LiCl per os daily for 6 weeks in the following doses: group 1) 0.5 meq/kg, group 2) 1.0 meq/kg, group 3) 2.0 meq/kg. The iodine-accumulating function of the thyroid gland was assessed by the radioindicator method after subcutaneous injection of the isotope ^{131}I into the animals in a dose of 37 Bq/g body weight. After radiometry of the thyroid gland the animals were decapitated and the concentration of thyroid hormones (T_3, T_4), calcitonin (CT), parathyroid hormone (PTH), and pituitary thyrotrophic hormone (TTH) was determined by radioimmunoassay. The serum calcium and lithium levels were measured by flame photometry. For histologic analysis the thyroid glands were fixed in calcium-formol, neutral fixative, and Bouin's fluid. Neutral and acid glucoproteins were detected histochemically by the combined method of Ritter and Oleson, acid and alkaline phosphatases by Gomori's method, DNA by Feulgen's and RNA by Brachet's methods. C cells were detected by impregnation of histologic sections by Grimelins' method. Tissue for general morphology was stained with hematoxylin and eosin. An ocular micrometer was used for morphometry.

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TABLE 1. Serum Levels of Thyroid Hormones, PTH, and Calcium during Administration of TTH and LiCl (M ± m)

Parameter	Control	P	Experimental group					
			1	P	2	P	3	P
TTH, IU/liter	3,3±0,25		5,3±0,50	0,01	5,4±0,53	<0,001	6,0±0,64	<0,001
	7,8±0,53	<0,001	7,6±0,59	<0,001	7,9±0,61	<0,001	8,4±0,66	<0,001
T_3, ng/ml	0,78±0,08		0,75±0,11		0,63±0,04		0,54±0,02	<0,025
	2,1±0,14	<0,001	1,8±0,09	<0,05	1,3±0,07	<0,01	1,1±0,12	<0,001
T_4, μg/100 ml	3,25±0,54		2,75±0,37		2,45±0,12		2,05±0,08	<0,05
	10,3±0,21	<0,001	6,5±0,44	<0,001	5,7±0,35	<0,001	5,2±0,26	<0,001
CT, ng/ml	0,39±0,03		0,71±0,05	<0,001	0,79±0,07	<0,001	0,68±0,05	<0,001
	0,93±0,08	<0,01	0,97±0,09	<0,01	1,24±0,13	<0,001	1,47±0,15	<0,001
PTH, IU/ml	6,2±0,40		5,4±0,52		4,2±0,29	<0,001	3,1±0,35	<0,001
	5,8±0,41		11,6±0,95	<0,001	9,5±0,57	<0,01	7,6±0,43	<0,05
Calcium, mg/ liter	94,4±2,26		105,1±3,51	<0,01	116,2±3,35	<0,001	127,3±3,64	<0,001
	98,6±2,33		104,2±2,35		120,5±2,37	<0,001	117,6±2,45	<0,01

Legend. Significance of differences calculated relative to data for intact animals. First value in control refers to intact animals, second to animals receiving TTH. First value in experimental animals denotes administration of LiCl, second value LiCl + TTH.

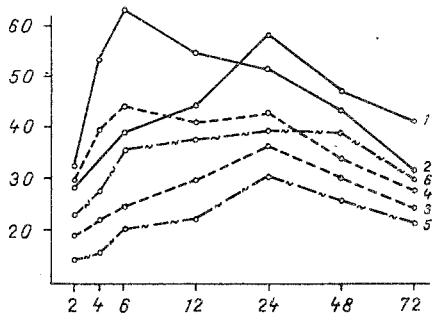

Fig. 1. Parameters of ^{131}I uptake by albino rat thyroid gland during "lithium therapy" and during stimulation by TTH against the background of lithium. Abscissa, time (in h); ordinate, uptake of ^{131}I (in %). 1) Control, 2) stimulation by TTH (5 IU/kg), 3) LiCl (1.0 meq/kg), 4) LiCl (1.0 meq/kg) + TTH, 5) LiCl (2.0 meq/kg), 6) LiCl (2.0 meq/kg) + TTH.

EXPERIMENTAL RESULTS

Depending on the dose given LiCl had different actions on the parameters of thyroid function. For instance, when low concentrations of lithium (0.5 meq/kg) were given to the rats the morphological picture of the thyroid gland was characteristic of the organ in a state of hyperfunction: the ratio between the structural components of the thyroid tissue was changed in the direction of enlargement of the follicular epithelium, accompanied by a decrease in bulk density of the colloid and an increase in the intensity of oxidation-reduction processes in the thyrocytes. Administration of higher concentrations of lithium (1.0-2.0 meq/kg), on the other hand, caused physiological and morphological changes in the thyroid complexes corresponding to a state of hypofunction of the gland. With blood Li^+ concentrations in excess of 0.8 meq/liter, a decrease in the content of neutral glycoproteins was found very constantly in the cytoplasm of the follicular cells, and acid phosphatase was detected in the thyrocyte nuclei in the form of pale or dark brown granules; staining nuclei of the follicular epithelium for DNA and their cytoplasm for RNA was weaker than in the control.

Lithium did not affect uptake of iodides by the thyroid gland, but considerably increased the half-elimination time of ^{131}I from the gland into the blood stream (Fig. 1). Blocking of release of hormonal iodine in the thyroid gland is evidently the principal stage in the mechanism of the effect of lithium on iodine metabolism.

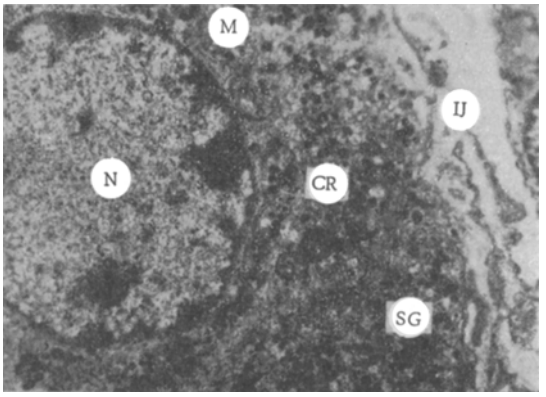

Fig. 2. Perifollicular thyroid gland cell of rat treated with LiCl (4200×). Large cell nucleus. Cytoplasm abundantly filled with secretory granules of varied electron density; N) nucleus, M) mitochondria, CR) cytoplasmic reticulum, IJ) intercellular junction, SG) secretory granules.

As a result of accumulation of iodides in the gland tissue the distribution of organic iodine in the gland tissue was disturbed (an increase in the MIT/DIT ratio), and consequently, hormone production speeds up due to the action of iodides on the critical microenvironment of the follicles (the Wolf–Tchaikov effect). There are other possible mechanisms of inhibition of hormone production by lithium, for example, slowing of the response of the adenylate cyclase of the thyrocytes to TTH under the influence of lithium. It will be clear from the data given in Fig. 1 and Table 1 that stimulation of the thyroid glands of intact animals by injection of exogeneous TTH always caused an equal response of the thyrocytes in the form of stimulation of their function, whereas against the background of prolonged administration of LiCl to the animals, the stimulating action of TTH on the thyroid gland gradually weakened. The degree of leveling of the effect of TTH on the thyrocytes in this case correlated directly with the dose of the preparation and the blood lithium level.

One other interesting rule was discovered in these observations: During long-term administration of LiCl to the animals the C-cell apparatus of the thyroid was activated. This was shown both by a significant increase in the basal CT level in the animals' blood serum with an increase in the blood lithium level, and also by the results of morphological investigation of the thyroid glands, which in some cases revealed an increase in the number of C-cell populations in the gland tissue, and also an increase in the number of secretory granules in them (Fig. 2). Histochemical reactions for enzymes showed increased activity of phosphatases in them and an increase in the concentrations of DNA and RNA in their nuclei.

The increase in CT secretion, incidentally, took place against the background of a higher serum calcium level. According to data in the literature [5, 6], in patients treated for a long time with lithium hypercalcemia also is frequently found, and is linked with a decrease in calcium excretion with the urine [3, 7]. In the present experiments positive correlation was found between the serum Ca^{++} level and the Li^{+} concentration in the animals' blood. For instance, while the Li^{+} concentration in the blood was between 0.2 and 0.4 meq/liter the serum calcium concentration was 11.2% higher than in the control, whereas with a blood lithium level of 0.5–0.8 meq · $liter^{-1}$ the calcium was increased by 22.8%, and with Li^{+} concentrations of over 1.0 meq/liter, it was 34.5% higher. Since calcium and phosphorus metabolism in the body is regulated by the negative feedback principle between the formation of two hormones (CT and PTH), the discovery of increased CT secretion and inhibition of PTH secretion is the logical result of the hypercalcemia arising during prolonged administration of lithium salts.

To determine more precisely the possible effect of pituitary TTH on calcium homeostasis, a series of experiments was carried out in which, during prolonged administration of LiCl to rats, additional injections of TTH in a dose of 5 U/kg were given. Rats not receiving lithium served as the control. It will be clear from Table 1 that injection of exogenous TTH into intact animals did not affect the serum calcium level and did not change the PTH level, but significantly increased the concentrations of thyroid hormones and CT. Against the background of a long-lasting high blood lithium level (experimental groups of animals), injection of TTH was accompanied by an increase in the basal level of both physiological calcium antagonists (CT and PTH), whereas

the serum calcium level of the animals was relatively stable. The results of this series of experiments thus showed that the participation of TTH in calcium metabolism can be reduced to potentiation of the stimulating effect of Ca^{++} on the thyroid C-cell apparatus. In the writers' opinion the small fall in the calcium level in the animals of group 3 must be interpreted as the results of predominance of the action of calcitonin. The rise in the basal PTH level after an increase in the blood level of its antagonist CT must be regarded as compensatory, and aimed at maintaining the serum calcium concentration within physiological limits.

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