EFFECT OF LITHIUM CHLORIDE AND TRIIODOTHYRONINE ON THE OXYGEN CONSUMPTION OF RATS AND TISSUE RESPIRATION

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Lithium chloride (200 mg/kg, intraperitoneally), triiodothyronine (0.1 mg/kg, by mouth), or both preparations together were administered for 5-7 days to intact and thyroidectomized rats. The effect of lithium chloride and triiodothyronine on the oxygen consumption and tissue respiration of the rat liver was studied in vitro. The inhibitory action of lithium on the gas exchange was shown to be due to its direct effect on oxidative metabolism of the cell. In experiments on rabbits the oral administration of 490 mg/kg lithium chloride modified the dynamics of I^{131} accumulation and its release from the thyroid gland. The thyrostatic effect of lithium chloride may be the result of inhibition of tissue respiration in the thyroid cells.

Lithium salts are used in the treatment of manic-depressive psychoses and the prophylaxis of affective disturbances [1, 2, 8]. In recent years the development of diffuse nontoxic goiter [6, 7, 9] and disturbance of iodine metabolism [10, 11] have been described in patients treated with lithium.

In this investigation the effect of lithium chloride on thyroid function was studied by estimating the changes in oxygen consumption and tissue respiration of the rat liver and also the changes in I^{131} metabolism in the thyroid gland of rabbits.

EXPERIMENTAL METHOD

Experiments were carried out on 139 albino rats of both sexes weighing 160-210 g and 10 male rabbits weighing 2-2.3 kg. For 5-7 days intact and thyroidectomized rats received lithium chloride (200 mg/kg per animal, intraperitoneally), triiodothyronine (0.1 mg/kg per animal, by mouth), or both preparations together. In special experiments intact rats received lithium chloride for 6 days and on the first day of the experiment received triiodothyronine (1 mg/kg), or rats were given triiodothyronine for 14 days (0.1 mg/kg) and lithium chloride (200 mg/kg) from the 8th to the 16th days of the experiment. The oxygen consumption of the rats was determined on various days of the experiment by means of a closed-circuit apparatus [3] 1 h after administration of the above preparations. The rabbits received a single dose of lithium chloride (490 mg/kg) by mouth and of I^{131} (5 μCi) intravenously. Pulses were counted above the thyroid gland by means of the DSU-60 instrument 2, 24, 48, 72, 96, and 120 h after the beginning of the experiment. The tissue respiration of the rat liver in 5% glucose solution (pH 7.4) was studied in a Warburg apparatus [5] in the presence of lithium chloride (0.05, 0.125, 0.5, and 1 M), triiodothyronine (4×10^{-5}M), or both together (a total of 140 experiments). 3,3,5-Triiodo-L-thyronine (Berlin-Chemie, East Germany) was used in the experiments.

The numerical results were subjected to statistical analysis [4].

EXPERIMENTAL RESULTS AND DISCUSSION

The oxygen consumption of the intact rats was 3.53 ± 0.22 ml/min/100 g. Lithium chloride inhibited while triiodothyronine stimulated the gas exchange of the rats (Fig. 1). The longer the preparations were

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TABLE 1. Effect of Lithium Chloride and Triiodothyronine on Tissue Respiration of Rat Liver

Molar concentration		Number of experiments	Oxygen consumption (in μl/min/100 g wet wt.)		
LiCl	triiodothyronine		$M \pm m$	% of control	P
Control		25	1,71±0,076	100	—
—	$4 \cdot 10^{-5}$	24	1,93±0,075	113	0,05
0,05	—	10	1,83±0,053	107	0,2
0,125	—	24	1,45±0,066	85	0,02
0,125	$4 \cdot 10^{-5}$	20	1,79±0,062	105	0,5
0,5	—	11	1,29±0,179	75	0,05
0,5	$4 \cdot 10^{-5}$	10	1,61±0,100	94	0,5
1,0	—	8	0,72±0,169	42	0,001
1,0	$4 \cdot 10^{-5}$	8	1,12±0,152	65	0,002

TABLE 2. Effect of Lithium Chloride (490 mg/kg) on Uptake and Elimination of I^{131} by the Rabbit Thyroid Gland

Time after injection of I^{131} (in h)	Concentration of I^{131} in thyroid gland (in % of dose injected; M ±m)		
	distilled water	lithium chloride	P
2	16,0±0,9	7,2±0,2	0,001
24	14,2±1,0	15,8±1,6	0,5
48	11,4±1,2	15,8±2,7	0,5
72	8,2±0,9	13,2±1,5	0,05
96	2,8±0,4	10,0±0,3	0,001
120	0,4±0,1	7,4±0,4	0,001

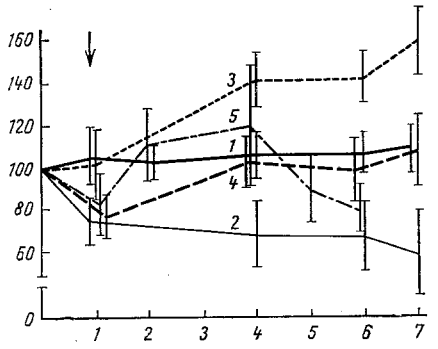

Fig. 1. Oxygen consumption of rats receiving lithium chloride and triiodothyronine: 1) control; 2) lithium chloride (200 mg/kg daily); 3) triiodothyronine (0.1 mg/kg daily), 4) triiodothyronine (0.1 mg/kg daily) and lithium chloride (200 mg/kg daily); 5) triiodothyronine (single dose of 1 mg/kg) and lithium chloride for 6 days (200 mg/kg daily). Values of M ± m given. Arrow marks beginning of administration of lithium chloride. Abscissa, days of experiments; ordinate, oxygen consumption (in % of initial level.

administered, the more marked these effects. During combined administration of lithium chloride and triiodothyronine the oxygen consumption of the rats fell on the first days of the experiment and then returned to its initial level. In the rats receiving a single large dose of triiodothyronine on the first day of this experiments, followed by lithium chloride the oxygen consumption fell only after the first injection of lithium, but later, on the 2nd and 4th days of the experiment, it exceeded the control level. This last effect is evidently due to the development of hyperthyroidism, for on the subsequent days the inhibitory effect of lithium was clearly defined.

The ability of triiodothyronine to abolish the inhibitory effect of lithium on the oxygen consumption was also confirmed by another series of experiments. Injections of lithium chloride started after the 8th dose of triiodothyronine (when hyperthyroidism was well marked) did not prevent the increase in gas exchange resulting from continued injections of the hormone. However, after the injections of the hormones were discontinued the oxygen consumption in the rats receiving lithium chloride fell more rapidly than in the control animals (receiving distilled water), and the difference after 6 days was 21% ($P < 0.005$).

Thyroidectomy had no significant effect on the ability of lithium to reduce the oxygen consumption of the rats. If lithium chloride and triiodothyronine were given to the thyroidectomized animals, the gas exchange was reduced on the first day of the experiment, but after the accumulation of the hormone in the tissues lithium no longer had any effect.

The hypothesis that lithium salts depress the secretion of thyroid hormone [10] appears improbable, for the decrease in the oxygen consumption of the rats began a few minutes after the administration of lithium, before any substantial deficiency of the hormone could have arisen on the tissues. This hypothesis is also contradicted by the fact that the gas exchange was reduced to the same degree in the intact and thyroidectomized rats under the influence of lithium. Lithium and triiodothyronine evidently have an antagonistic action on energy processes in the cell. This is confirmed by the results of experiments in vitro in which the inhibitory effect of lithium on the respiration of the rat liver tissue was not manifested when triiodothyronine was added to the incubation medium (Table 1).

Neither the data in the literature nor the results of the present experiments (Table 2) to study I^{131} metabolism in the thyroid gland contradict the hypothesis of the competitive action of lithium and triiodothyronine on energy processes in the cell. Lithium, which depresses oxidative processes in the thyroid (as also in other tissues), evidently inhibits biochemical reactions concerned in the synthesis and secretion of thyroid hormones, and this is manifested as a disturbance of iodine metabolism.

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