EFFECT OF LITHIUM ON THE EEG AND SEROTONIN CONCENTRATION IN THE BRAIN

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A single injection of lithium chloride (200 and 450 mg/kg, intramuscularly, for rats and 100 and 300 mg/kg, intravenously, for rabbits) led to a decrease in the serotonin concentration in the brain stem of rats and in the hypothalamus, reticular formation, and amygdala of the rabbit brain. The compound had a depriming effect on electrical activity of the hippocampus, caudate nucleus, and amygdala which did not correlate with the change in their serotonin concentration.
KEY WORDS: lithium; EEG; serotonin; brain.

Besides the "catecholamine" hypothesis of the pathogenesis of affective disorders [14, 15], the suggestion has been put forward recently that disturbances of serotonin metabolism play an important role in the development of manic-depressive psychosis [8, 9, 11, 13]. One of the most valuable psychopharmacological agents used in the treatment of this disease is lithium. The therapeutic effectiveness of lithium salts is due to a certain extent to their effect on the serotonin metabolism of the brain. Data in the literature on this problem are few in number and conflicting in nature. According to published reports, under the influence of lithium the serotonin concentration in the rat brain is increased [2], unchanged [7, 10], or finally the concentration of this amine is reduced in the brain of rats [12] and mice [3, 4].

Considering possible species-specificity in the effects of lithium on serotonin metabolism and also the differences discovered previously [5, 6] in the distribution of lithium in the brain structures, it was decided to investigate the effect of lithium on the serotonin concentration in the brain stem of rats and in the hypothalamus (with the pituitary), thalamus, mesencephalic reticular formation, hippocampus, caudate nucleus, amygdaloid nucleus, and motor cortex of rabbits. To judge the effect of lithium on the functional state of these brain structures, the corresponding electroencephalographic reactions of these regions were recorded in a separate series of experiments on rabbits.

TABLE 1. Effect of Lithium on Serotonin Concentration in the Rat Brain Stem (M ± m)

Substance injected	Dose (mg/kg)	Time before sacrifice (h)	No. of expts.	Serotinon concn. (μg/g)	P
Physiological saline	—	—	10	0,66±0,012	—
Lithium	200	1	12	0,57±0,21	0,004
"	200	4	12	0,54±0,020	0,001
Physiological saline	—	—	10	0,60±0,032	—
Lithium	450	1	13	0,44±0,017	0,001
"	450	4	12	0,45±0,030	0,003

EXPERIMENTAL METHOD

Experiments were carried out on 69 male rats weighing 170-240 g and on 55 rabbits of both sexes weighing 2-2.5 kg. Lithium chloride was injected intraperitoneally into the rats in doses of 200 and 450 mg/kg and into the marginal vein of the ear of the rabbits as a 10% solution in doses of 100 and 300 mg/kg 1 and 4 h before decapitation. The corresponding volume of physiological saline was injected in control experiments.

Samples of the rabbit brain for analysis containing 200-500 mg tissue were frozen quickly. Serotonin was

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TABLE 2. Effect of Lithium on Serotonin Concentration in Structures of the Rabbit Brain (M ± m)

Region of the brain	Serotonin concentration (μg/g)				
	control	time after injection of lithium			
		100 mg/kg		300 mg/kg	
		1 h	4 h	1h	4 h
Hypothalamus together with pituitary	0,77±0,021 (6)	0,48±0,070 (6)	0,57±0,088 (6)	0,58±0,067 (6)	0,56±0,067 (6)
P		0,003	0,05	0,02	0,01
Mesencephalic reticular formation	0,58±0,070 (6)	0,50±0,060 (7)	0,42±0,033 (8)	0,57±0,065 (7)	0,37±0,026 (8)
P		0,38	0,05	0,9	0,01
Amygdalar nucleus	0,49±0,085 (6)	0,44±0,053 (6)	0,37±0,045 (7)	0,36±0,070 (6)	0,24±0,35 (6)
P		0,6	0,25	0,25	0,02
Hippocampus	0,37±0,035 (6)	0,36±0,035 (6)	0,35±0,070 (7)	0,34±0,060 (6)	0,31±0,017 (6)
P		0,8	0,9	0,7	0,16
Caudate nucleus	0,61±0,053 (6)	0,58±0,030 (7)	0,51±0,053 (7)	0,59±0,086 (6)	0,44±0,10 (6)
P		0,6	0,2	0,8	0,16
Thalamus	0,41±0,053 (6)	0,41±0,044 (7)	0,30±0,045 (7)	0,36±0,060 (7)	0,31±0,026 (8)
P		1,0	0,1	0,6	0,1
Motor cortex	0,45±0,053 (6)	0,48±0,057(7)	0,43±0,044 (6)	0,43±0,088 (6)	0,34±0,038 (7)
P		0,7	0,77	0,8	0,1

Note: Number of experiments given in parentheses.

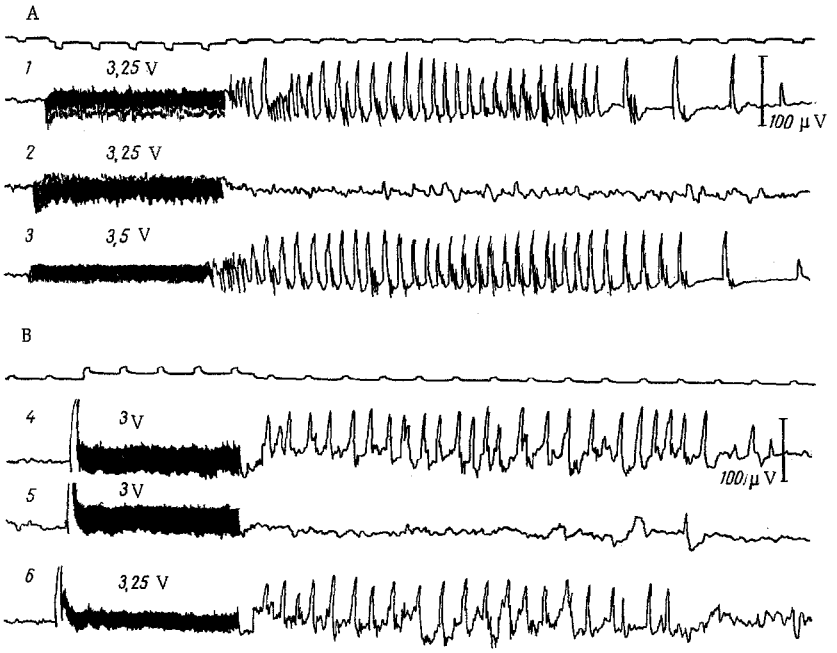

Fig. 1. Effect of lithium chloride (100 mg/kg) on threshold of afterdischarges in hippocampus (A) and caudate nucleus (B): 1, 4) before injection; 2, 3, 5, 6) 1 h after injection of the peparation.

determined [17] on a spectrofluorimeter with a sensitivity of $1 \cdot 10^{-8}$ g/ml. In each series of experiments 10-13 rats and 6-8 rabbits were used.

Potentials were recorded by nichrome electrodes inserted into the above-mentioned brain structures. The indicator of the functional state of the hippocampus, caudate nucleus, amygdaloid nucleus, and motor cortex was the threshold of paroxysmal activity of these structures and the duration of the seizure afterdischarges; the recruiting reaction from the sensomotor cortex during stimulation of the medial thalamus and the activation reaction from the mesencephalic reticular formation and hypothalamus were recorded. Electrical stimulation of the corresponding structures was carried out with the ÉST-10 stimulator, using the generally accepted parameters of the current.

EXPERIMENTAL RESULTS AND DISCUSSION

Lithium chloride in doses of 200 and 450 mg/kg, 1 and 4 h after injection, significantly reduced the serotonin concentration in the rat brain stem (Table 1).

In the experiments on rabbits, lithium chloride in doses of 100 and 300 mg/kg, 1 and 4 h after the injection, led to a statistically significant decrease in the serotonin level in the hypothalamus +pituitary (Table 2). A similar effect was discovered 4 h after injection of 100 and 300 mg/kg lithium in the mesencephalic reticular formation and in the amygdaloid nucleus (dose 300 mg/kg). In the other brain structures studied (hippocampus, caudate nucleus, thalamus, motor cortex), under the influence of doses of lithium used a tendency was observed for the serotonin concentration to fall in the thalamus and motor cortex (after 2 h; $P = 0.1$).

The decrease in the serotonin concentration discovered in the brain stem of the rats and in the hypothalamus, reticular formation, and amygdaloid nucleus of the rabbits is in harmony with the results obtained by Ho et al. [12], who found a decrease in the serotonin concentration in the hypothalamus and brain stem of rats during a course of lithium chloride (2 meq/kg daily for 28 days). Similar results were obtained by Oksenkrug [3] after administration of 200/kg lithium carbonate to mice; the compound also prevented the increase in the serotonin level induced by injection of 5-hydroxytryptophan.

The decrease in the concentration of serotonin in some brain structures of intact rabbits and rats induced by lithium evidently takes place as a result of the activation of its breakdown, for lithium does not affect 5-hydroxytryptophan decarboxylase activity [4]. Meanwhile, under the influence of lithium the concentration of deaminated products of serotonin metabolism [16] and in monoamine oxidase activity in vitro [1] has been observed.

In experiments in which the electroencephalograph reactions were recorded 60-90 min after intravenous injection of 100 mg/kg lithium chloride into rabbits an increase in the seizure threshold was found in the the hippocampus ($P = 0.001$), the caudate nucleus ($P = 0.05$), and the amygdaloid nucleus ($P = 0.06$), reaching a maximum (by 30-40%) toward the end of the first hour and persisting for 3-4 h of observation (Fig. 1). In the other structures no significant changes in the threshold of stimulation were found, although the duration of the activation reaction to stimulation of the mesencephalic reticular formation was reduced under the influence of lithium ($P = 0.001$) throughout the period of observation. In control experiments the EEG responses showed no significant change during repeated stimulation of these structures at intervals of 30-60 min for 3-4 h.

No correlation was found between the depriming effect of lithium on electrical activity of the hippocampus, caudate nucleus, and amygdaloid nucleus and the change in their serotonin concentration.

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