EFFECT OF LITHIUM CHLORIDE ON THE NEUROSECRETORY SYSTEM OF THE RAT HYPOTHALAMUS

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The response of the hypothalamic-pituitary neurosecretory system (HPNS) of rats to a single and repeated injection (200 mg/kg each time) of lithium chloride was studied by quantitative cytochemical analysis. The response of the HPNS was found to depend directly on the dose of lithium given and to consist of activation of synthesis and liberation of neurosecretion after a single dose of LiCl or inhibition of hormone formation in the hypothalamus and exhaustion of the reserves of neurosecretion in the neurohypophysis after a course of injections. In the recovery period (7-30 days after stopping the course of injections of LiCl) the previous state of the HPNS was gradually restored.

KEY WORDS: lithium; hypothalamic-pituitary neurosecretory system.

Lithium salts are widely used for the prevention and treatment of manic-depressive psychosis [1]. An important role in the pathogenesis of this disease is played by changes in the hypothalamic region of the brain [2]. After administration of its salts lithium accumulates electively in the pituitary and, to a considerable degree also, in the hypothalamus [6], where marked changes are observed in the concentration of biogenic amines [8] and the activity of oxidative enzymes [5].

However, the question of the state of the most important part of the hypothalamus – the hypothalamic-pituitary neurosecretory system (HPNS) – during the action of lithium salts has not previously received special study and the investigation described below was carried out for that purpose.

EXPERIMENTAL METHOD

Experiments were carried out on 52 male albino rats weighing 180-220 g. Lithium chloride (200 mg/kg, 0.22 LD_{50}) was injected intraperitoneally as the 5% solution. Control animals received an injection of the same volume of distilled water. The rats were decapitated 3, 24, and 72 h after the single injection or 1, 7, and 30 days after the end of the 6-day course of injections of the compound. The hypothalamus and pituitary were fixed in Bouin's fluid. Serial paraffin sections were stained: with paraldehyde–fuchsin by the Gomori–Gabe method for neurosecretion; with gallocyanin by Einarson's method for nucleic acids (RNA). The functional morphology of the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus was assessed by counting the various types of neurosecretory neurons [3] and determining their relative percentages and their RNA content was assessed from the mean histochemical coefficient [7]. The content of neurosecretion in the median eminence (ME) and the main posterior lobe of the pituitary (PLP) was assessed by a five-point system [3].

EXPERIMENTAL RESULTS AND DISCUSSION

Signs of activation of HPNS were clearly recorded 3 h after a single injection of LiCl into the rats. The number of neurons actively producing neurohormones, characterized by hypertrophy of their bodies and nuclei

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TABLE 1. Effect of Single Intraperitoneal Injection and Course of Injections of LiCl (200 mg/kg each) on Percentages of Different Types of Neurons in Neurosecretory Nuclei of Rat Hypothalamus (mean of 5-7 observations, M ± m)

Content of neurosecretion in cytoplasm of neurons	Control	Time of investigation after injection of compound					
		Single injection (h)			Course of 6 injections (days)		
		3	24	72	1	7	30
		Supraoptic nucleus					
Rich	4±0,4	10±1,1*	14±1,1*	7±0,6*	1±0,4*	10±0,9*	6±0,6*
Average	17±1,7	26±2,1*	29±1,9*	18±1,7	7±0,8*	24±1,3*	15±1,1
Poor	73±1,7	56±0,6*	48±1,9*	69±1,9	75±1,9	57±1,7*	72±1,1
Pycnomorphic neurons	6±0,8	8±1,1	9±1,6	6±0,8	17±1,3*	9±1,3	7±0,6
		Paraventricular nucleus					
Rich	11±0,8	11±1,1	13±1,1	13±1,1	1±0,4*	14±1,1*	12±1,1
Average	20±1,5	31±1,7*	30±1,3*	21±1,5	14±0,6*	25±1,3*	17±1,3
Poor	65±1,7	52±1,3*	51±1,1*	62±1,7	74±1,3*	55±1,3*	67±1,1
Pycnomorphic neurons	4±0,4	6±0,2*	6±0,6	4±0,2	11±1,3*	6±1,1	4±0,6

*Differences significant compared with control ($P \leq 0.05$).

TABLE 2. Effect of Single Intraperitoneal Injection and Course of Injections of LiCl (200 mg/kg each) on RNA Content in Neurons of Neurosecretory Nuclei of Rat Hypothalamus (in conventional units, mean of 5-7 observations, M ± m)

Control	Time of investigation after injection of compound					
	Single injection (h)			Course of 6 injections (days)		
	3	24	72	1	7	30
	Supraoptic nucleus					
2,23±0,04	2,52±0,03*	2,60±0,03*	2,32±0,04	1,26±0,02*	2,54±0,05*	2,23±0,05
	Paraventricular nucleus					
2,26±0,03	2,45±0,03*	2,55±0,03*	2,33±0,04	1,29±0,04*	2,45±0,05*	2,28±0,05

*Differences significant compared with control ($P \leq 0.05$).

and by a high content of neurosecretion and RNA in their cytoplasm (Tables 1 and 2), was increased in the neurosecretory nuclei of the hypothalamus. Mobilization of neurohormones into the blood stream during this period of the experiment took place mainly from ME and was manifested as congestion of its capillaries and a decrease in the number of granules of neurosecretion in the terminal neurons.

The changes in HPNS 24 h after the beginning of the experiment continued to increase and substantial differences were found in the intensity of the response of its component structures. For instance, the number of neurons with an average content of neurosecretion in SON was increased more (by 70%) than in PVN (by 50%). Processes filled with neurosecretion appeared between the neurons. The response of structures of the neurohypophysis varied in intensity: In ME the content of neurosecretion fell slightly (by 7%), whereas in PLP it differed substantially (by 36%) from the control.

At the next time of observation (72 h) the morphological and functional state of all components of the HPNS, previously modified by the action of the compound, was restored and only in SON did the number of neurons with a high content of neurosecretion continue to be significantly increased.

Changes in HPNS of a different character were observed after a course of injections of LiCl into the rats. The number of actively secreting neurons in SON and PVN 24 h after the sixth injection of the compound (200 mg/kg each injection) was considerably reduced whereas the number of pycnomorphic cells was greatly increased (by 175-183%). In the morphological picture of the neurosecretory nuclei of the hypothalamus under these experimental conditions large cells with indistinct boundaries of their bodies and nuclei, whose cytoplasm was diffusely vacuolated and did not contain granules of neurosecretion, were predominant. Inhibition of synthesis of neurosecretion in SON and PVN was accompanied by a marked (by 77%) decrease in the RNA content in their neurons. The vascular plexus of the hypothalamus and pituitary was very abundant and its capillaries

were widely dilated. Fibers of the hypothalamo-hypophyseal tract were devoid of neurosecretion and appeared vacuolated. The content of neurosecretion in ME and PLP was sharply reduced: by 72% and 92% respectively.

Seven days after the end of the course of injections of LiCl into the rats active restoration of the neurosecretory process was observed and was particularly marked in SON, in which the number of neurons with a rich content of neurosecretion was 150% greater than in the control. The RNA content in the neurosecretory neurons also was considerably increased and was higher than the control. Numerous branching processes filled with neurosecretion reappeared between the neurons. The content of neurosecretion in ME and PLP was considerably increased and was close to the control level. The capillary network of the hypothalamus and pituitary remained moderately dilated and congested.

Thirty days after the end of the course of injections of the compound the morphological picture and indices of the functional state of the HPNS were similar to those of the control animals, except in SON, in which the number of neurons with a rich content of neurosecretion still remained increased.

The response of HPNS thus depends directly on the quantity of lithium administered and is characterized by activation of the synthesis and liberation of neurohormones following a single injection of LiCl or inhibition of hormone production in the neurosecretory nuclei of the hypothalamus and exhaustion of the reserves of neurosecretion in the structures of the neurohypophysis after a course of injections. These changes in hypothalamic neurosecretion were reversible; a phase of hypercompensation was observed, in the form of reactivation of synthesis of neurohormones on the seventh day after the end of the course of lithium injections. The differences in the intensity of the response of SON and PVN were due to their functional heterogeneity [9]. The changes found in the hypothalamic neurosecretion can be considered to play an important role in the pathogenesis of various neuroendocrine disturbances [10-12] arising as complications of the treatment of affective states by lithium salts.

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