PREVENTIVE EFFECT OF LITHIUM CHLORIDE ON THE DEVELOPMENT OF PREFERENCE FOR ETHANOL IN RATS

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Experiments on rats receiving a 5% solution of ethanol containing equivalent quantities of LiCl (experiment) or NaCl (control) as the sole source of fluid for 7 weeks showed that LiCl, producing a Li^+ concentration in the blood plasma of about 0.6 meq/liter, has a preventive action on the development of alcohol dependence. The study of the neurosecretory nuclei of the hypothalamus, pituitary, and adrenal cortex in the same animals showed definite correlation between the morphological and functional state of these formations, the degree of development of preference for alcohol, and the character of the action of LiCl on this process.

KEY WORDS: preference for ethanol; lithium; preventive effect.

The main factor hindering the successful treatment of alcoholism is recurrence [7]. It is this factor which is responsible for the urgent need to find therapeutic substances which can prevent the development of relapses. Considering that emotional affective disorders play an important role in the pathogenesis of chronic alcoholic poisoning [9] and that lithium salts are widely and successfully used for the preventive therapy of these disorders of varied genesis [1], in the writers' opinion there are good grounds for considering that lithium salts would be able to prevent the development of narcotic dependence in alcoholism. The investigation described below was carried out to test this hypothesis experimentally.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing initially 140-160 g, which received a 5% solution of ethanol as the sole source of fluid for 10 weeks. For 7 weeks, together with the ethanol solution the experimental animals received LiCl (7.5 meq/liter), whereas the control animals received NaCl with the equivalent quantity of cation. To confirm the specificity of the effect obtained, the experimental conditions were reversed for the next 3 weeks, i.e., while continuing to receive ethanol the rats of the experimental group were given NaCl instead of LiCl and the rats of the control group received LiCl instead of NaCl. Once a week the rats were placed in specially equipped experimental cages where they were given freedom of choice between a 5% solution of ethanol and water, after being deprived of fluid for the 12 h before the beginning of the measurements. The index of the degree of development of preference for ethanol was the coefficient of dependence, reflecting the ratio between absolute quantities of 5% ethanol solution and water (K = ethanol/water) consumed by each animal in the course of 3 h. During the period of maximal manifestation of the effect of LiCl (the 7th week of the experiment) the Li^+ concentration was determined in the blood plasma of the experimental rats by flame photometry [8]. To study the possible mechanism of action of lithium salts on the development of narcotic dependence in the rats, parallel with their preference for ethanol the dynamics of the state of the hypothalamus–pituitary–adrenal cortex system, which plays a leading role in adaptive reactions of the animal [6], was studied. For this purpose the experimental, control, and intact animals were decapitated at the stages of the experiments (3rd, 7th, and 10th weeks) characterized by the greatest changes in preference for ethanol. The brain and adrenals were fixed in Bouin's fluid and embedded in paraffin wax. Sections through the hypothalamus were stained with toluidine blue by Nissl's method and with paraldehyde–fuchsin by the Gomori–Gabe method, with counterstaining by Halmi's mixture, whereas the adrenals were stained with hematoxylin–eosin. The morphological and functional state of components of the hypothalamic–pituitary–adrenal cortex system was

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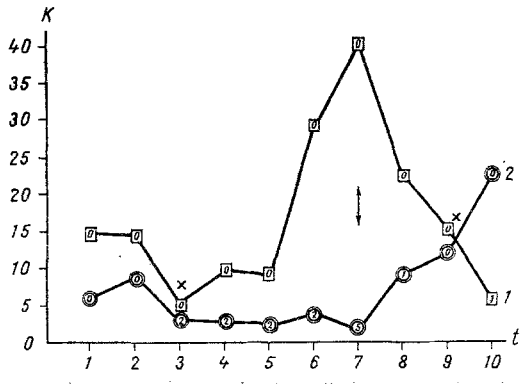

Fig. 1. Effect of LiCl (7.5 meq/liter) on development of preference of rats for ethanol (mean of 10-12 observations). Ordinate, coefficient of dependence; abscissa, times of observation (in weeks); 1, 2) control and experiment respectively; x) differences between control and experiment not significant ($P > 0.05$); arrow marks time of exchange of cations; numbers by curves denote number of rats with reversal of motivation at that time of observation.

assessed for the supraoptic (SON) and paraventricular (PVN) nuclei by counting the relative numbers of the different types of neurosecretory neurons [5] and by measuring the nuclei of these cells with the MOV-1 screw-adjusted ocular micrometer with calculation of their volume by the equation for an ellipsoid of rotation [2], and for the pituitary and adrenals on the basis of the dynamics of their weight and the volume of the cell nuclei in the different zones of the adrenal cortex.

EXPERIMENTAL RESULTS

Development of a preference for ethanol was shown to develop irregularly in rats and LiCl had a marked effect on its formation. As Fig. 1 shows, after the first week of the experiment all the rats preferred the ethanol solution to water, but the degree of preference was much less in the animals receiving LiCl. In the 3rd week these differences were not statistically significant, mainly on account of a decrease in the ethanol consumption by the rats of the control group. Later the preference of these animals for ethanol began to increase again progressively, to reach a maximum by the 7th week. Consumption of the narcotic by rats of the experimental group, on the other hand, continued to decrease so that by the 7th week the previously developed motivation was reversed in 50% of the animals and they showed preference for water ($K < 1$). This effect of Li^+ was evidently specific, for replacement of the Li cation by Na (8th-10th week) resulted in the appropriate change in the attitude of the animals toward ethanol.

Under these experimental conditions significant changes also took place in the morphological and functional state of the hypothalamic–pituitary–adrenocortex system. As Table 1 shows, the states of SON and PVN showed marked changes in the course of the experiment, the character of which was determined both by the duration and by the conditions of the experiments. A marked increase in the number of highly active type 1a neurons in SON and PVN of both the experimental and control rats in the 3rd week of the experiment is evidence that activation of the neurosecretory process at that period did not correlate significantly with the action of LiCl. However, its effect was clearly manifested at the next period of observation (7th week). Whereas the high activity of the neurosecretory process recorded previously in the experimental rats still persisted at this period, the sharp increase in the number of relatively inactive (types 1c and 2) and pycnomorphic (type 3) neurons in SON and PVN of the control rats indicates that ethanol, if administered for a long time, causes marked inhibition of this function of the hypothalamus. These differences in the effect of ethanol and LiCl on the activity of SON and PVN likewise were evidently not accidental, for when Li cations were replaced by Na (8th-10th week) corresponding changes took place in their morphological and functional state. Comparison of some parameters of the morphology and function of the neurosecretory nuclei of the hypothalamus, the pituitary, and the adrenal cortex reveals the systemic character of the changes taking place in them, which was determined by the experimental conditions (Fig. 2). The only exception to the general rule was the varied response of cells of the zona glomerulosa of the adrenal cortex to these factors.

TABLE 1. Effect of Lithium Chloride (7.5 meq/liter) on Numbers of Different Types of Neurons in Neurosecretory Nuclei of Hypothalamus in Rats during Prolonged Consumption of Ethanol (mean of 5-6 observations, in %), M ± m

Type of neuron	Intact animals	Control animals			Experimental animals		
		time of investigation, weeks					
		3	7	10	3	7	10
				Supraoptic nucleus			
1a	52±3,0	81±3,0	17±2,6	76±3,6	71±3,2*	74±4,1*	18±3,0*
1b	27±2,6	8±1,7	37±3,0	11±2,4	19±1,5*	17±2,4*	41±2,4*
1c	13±1,5	2±0,4	26±2,6	1±0,2	2±0,6	1±0,2*	24±1,9*
2	3±0,8	1±0,2†	6±0,8	1±0,2	1±0,2	1±0,2*	7±1,3*
3	5±1,7	8±0,8†	14±0,6	11±1,7	7±1,3†	7±1,5*	10±2,8
				Paraventricular nucleus			
1a	28±2,8	64±3,2	7±1,7	58±2,8	59±2,1	47±3,0*	18±2,1*
1b	45±3,2	21±2,8	22±3,4	21±2,8	22±2,6	34±2,8*	39±3,0*
1c	17±2,8	8±1,9	41±2,5	10±1,3	11±1,1	8±1,3*	31±2,8*
2	6±1,3	2±0,6†	19±1,3	2±0,6	2±0,4	3±0,4*	2±0,4
3	4±0,8	5±1,3†	11±1,9	9±1,3	6±1,1†	8±1,5	10±1,9

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

†All indices except those indicated differ significantly compared with intact animals ($P \leq 0.05$).

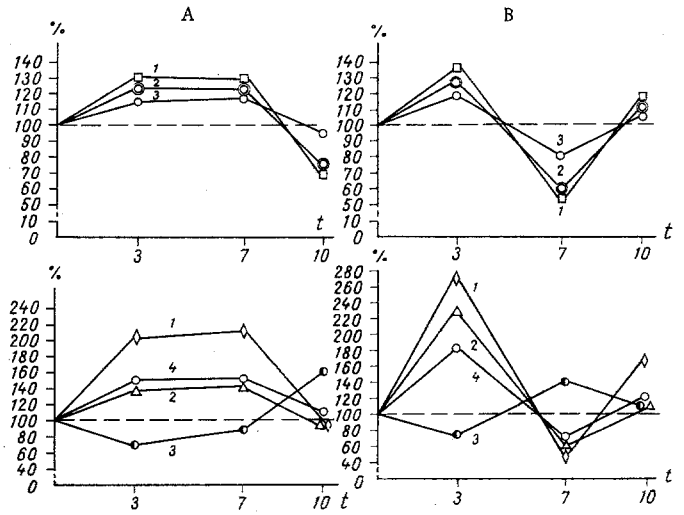

Fig. 2. Effect of LiCl on morphological and functional state of hypothalamic–pituitary–adrenal cortex system during prolonged consumption of ethanol (mean of five or six observations). Ordinate, values of test parameters relative to corresponding values in intact animals, taken as 100%; abscissa, times of observation (in weeks); A) experiment, B) control; top pair of graphs: 1, 2) volume of cell nuclei in supraoptic and paraventricular hypothalamic nuclei respectively (in μ^3), 3) weight of pituitary (in mg/100 g body weight); bottom pair of graphs: 1, 2, 3) volume of cell nuclei (in μ^3) of zona fasciculata, zona reticularis, and zona glomerulosa of adrenal cortex respectively, 4) weight of adrenals (in mg/100 g body weight).

Analysis of the results suggests definite correlation between the morphological and functional state of the hypothalamic–pituitary–adrenocortical system, the degree of development of preference for ethanol, and the character of the effect of LiCl on this process. The increase in the parameters reflecting the morphological and functional state of the above-mentioned system, reflecting activation of its function, was accompanied by a decrease in dependence on ethanol and, conversely, a reduction in these parameters was accompanied by an increase in preference for ethanol. The spontaneous decrease in preference for ethanol among rats of the control group in the 3rd week of the experiments is particularly interesting. The mechanism of this phenomenon can be imagined to be as follows. The preference for ethanol observed in the rats during the first days of the

experiment was not yet connected with the development of the neurochemical disturbances characteristic of this type of drug dependence, but was an expression of physiological motivation, determined by the high energy value of ethanol. The development of narcomania during prolonged ethanol consumption leads to threshold disturbances of metabolism at the molecular-cellular level of regulation, and attempts at their compensation at the level of the whole organism were evidently observed in the 3rd week of the experiment, in the form of activation of the function of the principal component of the nonspecific adaptation mechanism: the hypothalamic–pituitary–adrenocortical system. Later, inhibition of the hypothalamic neurosecretory centers by ethanol and the disturbance of the compensatory mechanisms operating with their participation were accompanied by a rapid increase in alcohol dependence.

Since the lithium concentration in the plasma of the experimental rats (0.6 ± 0.08 meq/liter) corresponds to the concentration usually used for the prevention of endogenous affective disturbances, this suggests that the preventive effect of LiCl under the conditions of clinical practice and in the present experiments has a similar mechanism. The psychotropic action of lithium salts is known to be associated with their depriming effect on energy metabolism [8]. This property of LiCl can evidently determine the relatively low level of ethanol consumption during the initial stage of their combined administration. Meanwhile, the subsequent decrease in ethanol consumption was possibly due to antagonism between ethanol and lithium as regards the activity of the hypothalamic centers of neuroendocrine regulation, mobilization of protective and adaptive potential of which delays the development of narcotic dependence. Differences in the response of the cells in different zones of the adrenal cortex during prolonged administration of ethanol agree with the results of clinical observations [4] and can evidently be explained by the autonomy of the central regulation of these structures [3]. This last fact, in turn, may point to the complex character of interaction between ethanol and lithium at the level of the regulatory systems of the brain.

It can accordingly be concluded from the results of these experiments that LiCl, in doses close to those used in clinical practice, has a preventive action on the development of preference for ethanol in rats. In the mechanism of this effect changes in the activity of the hypothalamic mechanisms of neuroendocrine regulation may play an important role.

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