EFFICACY OF LITHIUM NICOTINATE IN THE TREATMENT OF EXPERIMENTAL ALCOHOLISM

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The aim of this investigation was to study the effect of lithium nicotinate [4] on the formation of an inclination for alcohol, the activity of the drug in the treatment of chronic alcohol dependence, and also the possibility of its use for the treatment of acute alcohol intoxication. An attempt was made to study the basic mechanisms of the antialcoholic action of this compound.

EXPERIMENTAL METHOD

Experiments were carried out by the techniques of antialcoholic screening of new preparations, developed by the Institute of Pharmacology, Academy of Medical Sciences of the USSR, on 2000 albino rats and 80 albino mice [2]. The biochemical parameters (content and relative proportions of oxidized and reduced forms of nicotinamide coenzymes, activity of alcohol dehydrogenase and catalase, intensity of lipid peroxidation) were investigated in the brain, liver, and kidneys of 30 albino rats before the beginning of alcoholization, in the 6th and 12th weeks of alcoholization, and at the end of a 14-day course of treatment with lithium nicotinate (sessional dose of the compound 10 mg/kg, intraperitoneally). Quantitative determination of NAD was carried out by the method in [8], the lipid peroxide level was judged from the content of malonic dialdehyde (MDA) [10], and alcohol dehydrogenase activity was studied by the method in [1] and catalase activity by the method in [5].

The EEG was recorded at the same times in the visual, sensomotor, and temporal regions of the cortex. Frequency-amplitude relations of the background EEG were analyzed after histographic processing by the method in [9].

EXPERIMENTAL RESULTS

Administration of lithium nicotinate to albino rats consuming alcohol for 10 days with free access to ethanol solution and water caused a significant decrease in the alcohol intake. The number of animals preferring alcohol was significantly reduced. One week after discontinuing the compound the experimental rats as before consumed less ethyl alcohol than the controls. The percentage of animals consuming not less than 2 ml ethanol daily did not rise under these circumstances.

Against the background of alcoholization for 3 months administration of lithium nicotinate for 2 weeks to animals consuming small quantities of ethyl alcohol reduced their ethanol consumption in the course of the 1st week by 16.3%, but during the 2nd week of administration of the drug by 59.9% ($P < 0.05$). In the group of animals consuming larger quantities of alcohol, similar results were obtained. The effect continued for 1 week after discontinuing administration of the lithium nicotinate.

The antialcoholic effect of the compound also was exhibited in rats which had consumed alcohol for 8 months. A statistically significant decrease in the ethyl alcohol consumption was observed during administration of lithium nicotinate (2 weeks) and for 1 week after discontinuing it. Control animals at the same times of investigation consumed an equal quantity of ethyl alcohol.

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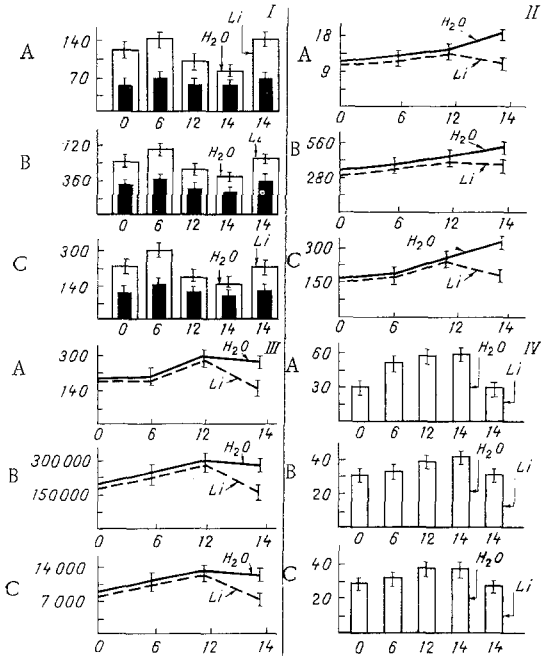

Fig. 1. Changes in concentrations of nicotinamide coenzymes (I), activity of alcohol dehydrogenase (II) and catalase (III), and malonic dialdehyde level (IV) during alcoholization and treatment with lithium nicotinate. A) Brain, B) liver, C) kidneys. I) Abscissa, periods of alcoholization (in weeks). Ordinate, concentration of nicotinamide coenzymes (in μg/g tissue). Unshaded columns — NAD + NADP; black columns — NADH + NADPH. II) Abscissa, periods of alcoholization (in weeks). Ordinate, alcohol dehydrogenase activity, in μmole/g/h. III) Abscissa, times of alcoholization (in weeks). Ordinate, catalase activity (catalase units). IV) Abscissa, times of alcoholization (in weeks). Ordinate, malonic dialdehyde concentration (in μmoles/g tissue).

The possibility of using lithium nicotinate for the treatment of acute alcohol intoxication was studied in an acute experiment. Administration of the compound shortened the time spent by the animals in the side position: 89 ± 28 min in the experiment and 113 ± 29 min in the control ($P < 0.02$) in mice and 75 ± 31 and 92 ± 29 min respectively ($P < 0.05$) in rats. Lithium nicotinate had a definite effect also on survival of albino rats and mice in a state of acute alcoholic intoxication. This was shown by a decrease in the percentage mortality among mice (experiment 15 ± 6.6%, control 55 ± 7.9%, $P < 0.01$) and albino rats (25 ± 6.8% and 55 ± 8.1% respectively, $P < 0.01$).

Besides a marked decrease in alcohol consumption, under the influence of lithium nicotinate definite changes in spontaneous brain electrical activity also were observed in animals consuming alcohol for 3 and 8 months, as shown by synchronization of cortical potentials, an increase in the amplitude of all rhythms, and an increase in frequencies predominantly of the Δ and θ bands. Slow high-amplitude bursts of spindles also were found.

Administration of lithium nicotinate caused an increase in the total content of oxidized and reduced forms of nictotinamide coenzymes in the brain, liver, and kidneys (Fig. 1).

The greatest increase in the level of oxidized forms of NAD + NADP (by 33.2%), incidentally, was observed in the brain of the experimental animals (results of biochemical tests are given only for the group of "heavy drinking" albino rats; the results obtained in the group of "abstemious" animals are not statistically significant, although showing the same tendency). Ethanol metabolism was substantially altered. In the liver, kidneys, and brain alcohol dehydrogenase activity was restored to normal. In the organs mentioned, catalase activity fell and also returned close to normal. Administration of the compound lowered the MDA level in the liver and brain.

Experiments on albino rats and mice thus clearly demonstrated the antialcoholic activity of lithium nicotinate. The compound can delay the formation of a liking for alcohol. If given when a "mental" or "physical" alcoholic motivation is already established, the compound also has a depriming effect. In acute experimental alcoholic poisoning the compound weakens the symptoms of intoxication.

The detoxicating effect of lithium nicotinate in the treatment of acute alcoholic poisoning is evidently due to the presence of nicotinic acid, which is widely used in the treatment of acute alcoholic intoxication. Meanwhile lithium, like sodium, is a carrier of alkaline valencies, and is particularly valuable in the control of metabolic acidosis, a characteristic feature of acute alcoholic poisoning.

Since a decisive role is ascribed to a decrease in the concentration of oxidized forms of nicotinamide coenzymes in the process of formation of dependence on alcohol [3, 7], the normalization of this parameter under the influence of lithium nicotinate is evidently a key stage in the understanding of its depriming effect. The reduction in activity of ethanol-oxidizing enzymes under the influence of the compound is particularly interesting. It is well known that the degree of alcoholic euphoria is definitely dependent on the rate of oxidation of ethanol. According to Ezrielev [3], the appearance of drugs inhibiting and modifying alcohol metabolism has laid the foundations of a new line of treatment of alcoholism. Finally, the fall in the brain and liver MDA levels of the alcoholized animals is evidence that lithium nicotinate can regulate free-radical lipid oxidation by preventing lipid peroxidation.

The positive effect of lithium nicotinate is also confirmed by the study of the EEG spectrum, for increased synchronization of the EEG is linked with depression of alcohol motivation [6].

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