STATE-DEPENDENT LEARNING INDUCED IN RATS BY ETHANOL AND ITS POSSIBLE PHARMACOLOGIC CORRECTION

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In the modern view state-dependent learning (in Russian, a "dissociated state") is abnormal behavior in which a skill or conditioned reflex is performed only after administration of a drug against the background of which it was formed [1, 13]. Ability to induce state-dependent learning (SDL) is known to be a feature of many psychotropic agents: tranquilizers [5, 10], opiates [6, 8, 14], barbiturates [5, 9, 12], and so on. SDL is widely used at the present time outside the USSR to evaluate the true narcogenic potential [8, 14] of psychoropic drugs. Ability to form SDL against the background of ethanol is particularly interesting, for in this case such a state can be regarded as equivalent to dependence on this substance [7, 11, 12].

The aim of this investigation was to study SDL formation induced by ethanol and to find ways of possible prevention and correction of the development of this syndrome.

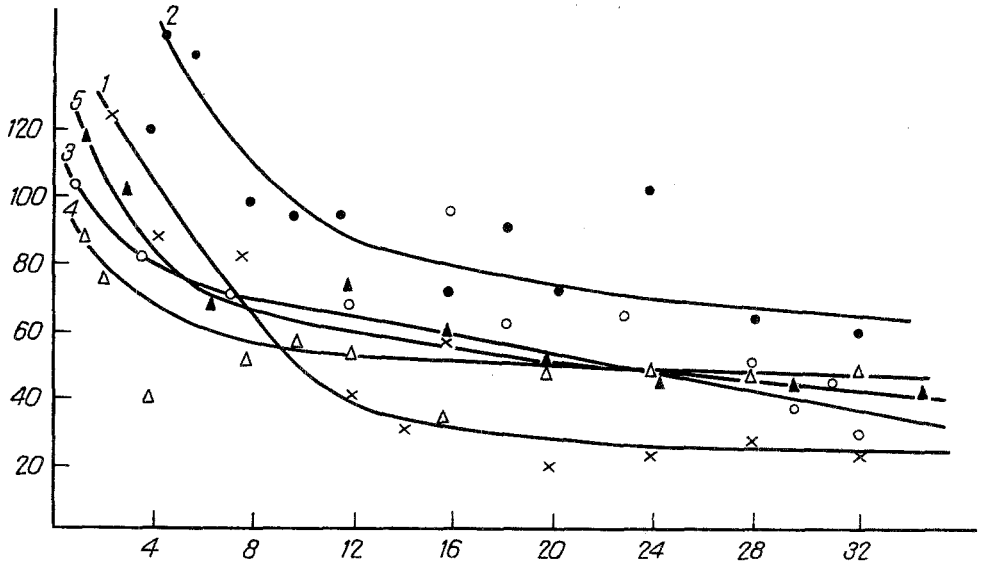

Fig. 1. Effect of pyracetam, lithium hydroxybutyrate, LN, and 3-HP conditioned labyrinthine reflex formation with positive reinforcement against the background of ethanol. Abscissa, time of injection of substance (in days); ordinate, average duration of reflex (in sec). Continuous lines show duration of reflex accompanied by daily injection of combination of drugs. 1) Ethanol; 2) ethanol + 3-HT; 3) ethanol + pyracetam; 4) ethanol + lithium hydroxybutyrate; 5) ethanol + LN.

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EXPERIMENTAL METHODS

Experiments were carried out on 80 noninbred male albino rats weighing 250-350 g in a T-maze by the method described previously [2]. To form SDL the animals were given the test drugs for their combinations daily and, against this background, a conditioned reflex (visiting a feeding bowl) was formed. To determine stabilization of SDL the duration of visiting the feeding bowl was recorded against the background of the drug and its replacement by physiological saline (in this case, 24 h after withdrawal). All the drugs tested were injected intraperitoneally in the following doses: lithium hydroxybutyrate 100 mg/kg 40 min before the experiment, pyracetam (α-pyrrolidone acetamide) 300 mg/kg 60 min before, 3-HP (a new 3-hydroxypyridine derivative) 100 mg/kg 40 min before, lithium nicotinate (LN) 100 mg/kg 40 min before, and ethanol (25% solution) 1.2 g/kg 10 min before the investigation began. Each dose of each drug was studied on 10 animals. Control animals received physiological saline.

EXPERIMENTAL RESULTS

Control rats trained daily in the maze formed a stable skill (visiting the feeding bowl) after a short latent period (under 5 sec) by the 22nd day of the experiment. Administration of ethanol (1.2 g/kg) under analogous conditions impaired stabilization of the reflex compared with the control at the final stages of conditioning.

Injection of lithium salts, pyracetam, and 3-HP throughout the period of conditioning did not significantly affect the rate of formation of the skill. For instance, on the 22nd day of conditioning the average time of performance of the reflex was 5.4 ± 1.2 sec in the control animals, 6.4 ± 1.6 sec after administration of 3-HP, 4.8 ± 1.9 sec after lithium hydroxybutyrate, 5.2 ± 1.2 sec arter pyracetam, and 5.6 ± 0.9 sec after LN.

The next stage of the investigations was to study the effect of pyracetam, lithium hydroxybutyrate, LN, and 3-HP on conditional reflex formation against the background of ethanol. Combined treatment was given from the 1st day of the investigations. The experiments showed that lithium salts and pyracetam facilitated reflex formation against the background of ethanol in the initial stages. In the later stages of conditioning, however, a statistically significant impairment of stabilization of the skill was observed in groups receiving combined treatment. This effect was manifested most clearly in the case of 3-HP which, in addition, did not facilitate the initial stages of conditioning (Fig. 1). The drugs tested thus prevented the formation and stabilization of the conditioned reflex connection formed against the background of ethanol.

The aim of the next stage of the investigation was to study two problems: the possibility of preventing the development of SDL by simultaneous administration of drugs with ethanol and the possibility of abolishing already established dependence on alcohol by means of drugs. To study the first problem a series of experiments was carried out in which the drugs were given in combination with ethanol throughout the period of formation of SDL; in the second case the drugs were given to animals with SDL already formed against the background of ethanol. It was found that SDL developed in rats receiving ethanol daily on the 28th day. In animals receiving pyracetam, 3-HP, and lithium salts for 1 month, SDL was not observed. Similar data were obtained previously for lithium carbonate and pyracetam [13].

The use of various drugs simultaneously with ethanol showed that they can significantly modify SDL formation. Injection of physiological saline instead of the combination of ethanol + lithium hydroxybutyrate did not disturb the skill as was observed in animals receiving ethanol alone. Similar effects were produced by pyracetam, 3-HP, and LN. For instance, whereas with ethanol alone the degree of dissociation on the 28th day of administration was 4, with combined administration of ethanol and pyracetam it was 1.5. The greatest effect so far as preventing of dissociation is concerned was given by lithium hydroxybutyrate (Table 1).

In experiments to study the possibility of abolishing already established SDL in rats receiving 25% ethanol solution for 30 days, a combination of ethanol with the test drugs was given. The degree of dissociation after combined administration was significantly lower than when ethanol alone was replaced by physiological saline.

Conditioning against the background of ethanol thus leads to the rapid development of an abnormal dissociated state (SDL), evidence of the appearance of drug dependence on this substance. The study of the possible means of correction of this state showed that this property is shared by pyracetam, lithium salts, and the antioxidant 3-HP. It can be postulated that the mechanism of action of lithium salts on the effects of ethanol is connected with their

TABLE 1. LDS Formation against the Background of Ethanol and Its Combinations with Pyracetam, Lithium Hydroxybutyrate, LN, and 3-HP on the 28th Day of Injection of the Drugs (M ± m)

Experimental conditions	Mean latent period of reflex, sec	Degree of dissociation
Control	97±7,0060	
Ethanol (total group)	24±1,6205	4,04
Control	41±1,9153	
Ethanol (animals with good learning powers)	5±0,4766	8,20
Control	153±7,0537	
Ethanol (animals with poor learning powers)	43±2,7855	3,56
Control	61±5,7567	
Ethanol + pyracetam	41±5,6238	1,49
Control	122±10,3064	
Ethanol + 3-HP	67±4,5754	1,82
Control	49±6,6724	
Ethanol + lithium hydroxybutyrate	38±3,1456	1,29
Control	52±5,2256	
Ethanol + LN	39±5,6748	1,34

Legend. Degree of dissociation calculated as ratio between the values for injection of physiological saline and injection of drug.

normothymic effect, and also with their ability to depress activity of the dopaminergic system, leading to weakening of alcohol motivation [4]. Considering the antioxidative active of 3-HP, its ability to change the phospholipid composition and physicochemical properties of the membrane, and also its ability to inhibit lipid peroxidation [3], it can be tentatively suggested that membranotropic mechanisms are involved in the mechanism of the antialcoholic effect of this drug.

LITERATURE CITED

1. A. A. Azarashvili, Investigation of Mechanisms of Memory by Means of Physiologically Active Compounds [in Russian], Moscow (1981).
2. T. L. Garibova, K. E. Voronin, and G. M. Rudenko, Byull. Éksp. Biol. Med., No. 11, 570 (1984).
3. L. D. Smirnov and K. M. Dyumaev, Khim.-farm. Zh., No. 4, 412 (1982).
4. A. N. Yavorskii, New Data on the Pharmocology and Clinical Use of Lithium Salts [in Russian], Moscow (1984), pp. 34-41.
5. F. C. Colpaert, L. K. C. Desmedt, and P. A. J. Janssen, Eur. J. Pharmacol., 37, 113 (1976).
6. F. C. Colpaert, C. J. E. Niemegurs, P. A. J. Janssen, et al., Eur. J. Pharmacol., 47, 115 (1978).
7. W. M. Cox. Physiol. Psychol., 9, 276 (1981).
8. V. F. Gellert and S. G. Holtzman, J. Pharmacol. Exp. Ther., 211, 596 (1979).
9. E. C. Krimmer and H. Barry, Fed. Proc., 39, 402 (1980).
10. H. Lal, G. T. Shearman, S. Fielding, et al., Neuropharmacology, 19, 785 (1980).
11. D. A. Overton, The Biology of Alcoholism, ed, by B. Kissin and H. Begleiter, Vol. 2, New York (1972), pp. 193-217.
12. D. A. Overton, Psychopharmacology, 53, 195 (1977).
13. D. A. Overton, Psychopharmacology, 76, 385 (1982).
14. M. D. B. Swedberg and T. U. C. Järbe, Drug Discrimination: Applications in CNS Pharmacology, ed. by F. C. Colpaert and J. L. Slangen, Amsterdam (1982), pp. 147-164.