Some of the oxygen is evidently utilized for direct oxidation of metabolites contained in blood in the pulmonary capillaries. Possibly other mechanisms of the increase in $\dot{V}O_2PC$ also exist.

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# EFFECT OF PSYCHOTROPIC DRUGS ON ALCOHOL MOTIVATION IN NONINBRED ALBINO RATS


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UDC 616.89-008.441.13-092-02:615.214]-07

KEY WORDS: psychotropic drugs, alcohol motivation


Investigations into the behavior of rats with an inclination toward spontaneous consumption of ethanol have shown that one of the most characteristic features distinguishing them in the population is the weakness of their adaptive forms of behavior, as is shown, in particular, by their weak competitiveness in the struggle for biologically meaningful goals [5]. Ethanol normalizes the adaptive behavior of these animals [5], and this evidently is responsible for their use of ethanol. At the same time, it has been shown [4] that many psychopharmacological drugs, like ethanol, can normalize the adaptive behavior of these animals.

Accordingly, in the investigation described below, interaction between the effect of several drugs of different classes on the degree of inclination of animals to develop a depression-like state (DLS) in a conflict situation, which is one form of disadaptation, and their action on the formation of alcohol motivation was studied in noninbred male rats.

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(Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 101, No. 3, pp. 289-291, March, 1986. Original article submitted April 4, 1985.




0007-4888/86/0003-0284$12.50

TABLE 1. Effect of Drugs on TTI in HAR and LAR

| Experimental conditions | Dose, mg/kg | Effectiveness, % | |
|---|---|---|---|
| | | HAR | LAR |
| Control | — | 24,1 | 126,6 |
| Alcohol | 500 | 203,3* | 44,5* |
| Amitriptyline | 0,5 | 239,5* | 35,2** |
| | 2,5 | 376,0** | 89,8 |
| | 0,5 | 242,1* | 90,0 |
| | 10,0 | 446,6** | 132,2 |
| Phenazepam | 0,1 | 299,3* | 37,2* |
| | 1,0 | 244,0 | 120,1 |
| | 0,3 | 292,8* | 100,0 |
| | 6,0 | 366,9** | 102,2 |
| | 12,0 | 410,0** | 154,9 |
| Amphetamine | 1,0 | 9,4** | 9,2** |
| | 3,0 | 0** | 0** |

Legend. Effectiveness of action of the drug was estimated as the ratio of TTI recorded on the 2nd day to TTI recorded on the 1st day of the experiment. Here and in Table 2: *P < 0.05, **p < 0.01 compared with control

## EXPERIMENTAL METHOD

Experiments were carried out on 410 noninbred male albino rats weighing 200-250 g. In the experiments of series I the tendency of the animals to develop a DLS was estimated in a situation of unavoidable swimming, as described previously [2]. For this purpose the rats were placed for 600 sec in a plastic basin 32 cm in diameter and 50 cm high, with a water level of 20 cm (20°C). The total time of immobilization (TTI), when the rats swam passively in a slightly tilted forward vertical position, with their head just above the surface of the water, was recorded. According to data in the literature [8], the intensity of the DLS is directly proportional to TTI. Rats with high activity (HAR) with TTI of under 130 sec, and rats with low activity (LAR), with TTI of over 300 sec, were distinguished. The rats were then placed in a heated (32°C) cage for 30 min, and then returned to the animal house. The procedure was repeated after 24 h. The drugs (alcohol, amitriptyline, phenazepam, amphetamine) were injected intraperitoneally 30 min before the beginning of the experiments on the 2nd day of testing. Control animals received physiological saline in a dose of 1 µl/g body weight. In the experiments of series II, animals previously tested for the effect of drugs on the intensity of DLS, were kept for 20 days in individual cages measuring 40 × 12 × 15 cm, equipped with bowls of water and of 15% ethanol solution, and also a feeding bowl. The drugs were injected intraperitoneally into the rats twice a day for 10 days. in the same dose as was used during behavorial testing. The quantity of ethanol solution and water drunk by each rat was recorded daily both during administration of the drugs and for 10 days after their discontinuation.

In the experiments of series III the effect of the drugs on the formation of alcohol motivation was studied in rats which had not previously been tested for their inclination to develop DLS. These experiments were carried out in accordance with the same scheme as those of series II.

The results were subjected to statistical analysis with the use of Meddis' nonparametric test [7] and calculation of the significance of differences between mean values [6].

## EXPERIMENTAL RESULTS

As the experiments showed, when the LAR were placed for a second time in a situation of unavoidable swimming, their TTI increased (Table 1), evidence of intensification of the DLS. Meanwhile in HAR, on the other hand, TTI was reduced, evidence of their adaptation to the experimental conditions.

Alcohol in a dose of 0.5 g/kg, administered to LAR before the second testing, completely normalized their behavior, and evidently reduced their tendency toward DLS formation. In HAR, alcohol in this same dose caused a marked disturbance of behavior and considerably increased TTI. The antidepressant amitriptyline, in doses of 0.5 and 2.5 mg/kg, and the tran-

TABLE 2. Effect of Drugs on Formation of Alcohol Motivation in HAR and LAR, and Also in Unselected Animals (USA) (M ± m)

| Experimental conditions | Dose, mg/kg | Group of animals | Mean daily ethanol consumption, % of control | | | |
|---|---|---|---|---|---|---|
| | | | 1st-5th days | 6th-10th days | 1st-5th days | 6th-10th days |
| Control | — | LAR | 42,0±4,9 | 54,0±6,5 | 57,6±0,7 | 53,9±6,9 |
| | | HAR | 9,7±2,3 | 10,2±1,4 | 7,6±6,5 | 6,9±5,1 |
| | | USA | 11,8±1,1 | 14,2±7,5 | 9,2±0,8 | 7,8±2,97 |
| Amitriptyline | 0,5 | LAR | 13,8** | 17,0** | 19,7* | 52,9 |
| | | HAR | 334,7** | 253,5** | 269,0** | 205,1** |
| | | USA | 58,7 | 103,1 | 154,2 | 359,2** |
| Phenazepam | 0,1 | LAR | 42,1* | 34,6* | 41,3* | 38,1* |
| | | HAR | 76,2 | 183,0* | 410,3* | 228,8* |
| | | USA | 72,6 | 122,4 | 120,3 | 226,3* |
| Amphetamine | 1,0 | LAR | 121,9 | 40,7* | 85,7 | 111,6 |
| | | HAR | 313,5** | 263,3* | 762,0** | 1243,5** |
| | | USA | 77,3 | 44,9 | 147,7 | 285,1 |

Legend. Values in control expressed in milliliters of 15% ethanol solution/kg body weight.

quilizer phenazepam, in a dose of 0.1 mg/kg, had the same effect both on LAR and on HAR. With an increase in the dose of these substances their positive effect decreased, and was replaced by a general depressant effect. The stimulator amphetamine led to a sharp reduction of TTI in both HAR and LAR (Table 1).

The action of these drugs (in doses effective in the previous series of experiments) on the formation of alcohol motivation was next investigated in LAR which, according to data obtained previously [2, 5], are "potential alcoholics," in HAR rejecting alcohol [2, 5], and in an unselected population of noninbred male albino rats. Amitriptyline and phenazepam largely prevented the formation of alcohol motivation in LAR but provoked the appearance of such motivation in HAR, which usually do not consume alcohol (Table 2). After withdrawal of the drugs their effect continued for 10 days and, in some cases (for example, when phenazepam was given to HAR), it had a tendency to increase. The results are in full agreement with clinical data on the high effectiveness of antidepressants and tranquilizers in a certain contingent of patients with chronic alcoholism [3]. In a study of the effect of these drugs on the formation of alcohol motivation in the unselected population, no statistically significant results were obtained, evidence of the necessity for preliminary selection of the animals for a differential search for specific pharmacologic agents to prevent the onset of a craving for alcohol (Table 2).

Amphetamine, which produces an undifferentiated fall of TTI in both HAR and LAR, and which evidently acts mainly on the motor components of this response, had only a transient effect on the formation of alcohol motivation in LAR. In HAR amphetamine greatly stimulated the appearance of an alcohol motivation, and this effect was particularly marked after withdrawal of the drug (Table 2).

These investigations thus indicate that antidepressants and tranquilizers can prevent virtually completely the appearance of addiction for alcohol in animals with weakness of adaptive forms of behavior. It must be recalled that in animals initially rejecting alcohol, chronic administration of such drugs, and also of stimulants of amphetamine type, facilitates the formation of experimental alcoholism. The results fully confirm the view expressed by the writers previously [1], that the search for drugs for the prevention and treatment of the early stages of alcoholism in preclinical experiments can be undertaken only on animals selected beforehand with respect to the degree of their tendency toward the formation of experimental alcoholism.

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