EFFECT OF ADENOSINE AND β-ENDORPHIN ON CONTRACTIONS OF THE VAS DEFERENS OF RATS DIFFERING IN PREDISPOSITION TO ETHANOL

R. Yu. Yukhananov and A. I. Maiskii

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Marked differences in the level of ethanol consumption and in predisposition toward the development of experimental alcoholism are clearly observable both in a population of noninbred albino rats and in animals of inbred and selectively bred lines [1, 4]. Animals distinguished by a higher level of voluntary ethanol consumption under conditions of free choice between a solution of alcohol and water have been shown to have initially higher tolerance to the effects of ethanol: narcotic [9], analgesic, hypothermic, etc. [5, 7]. There are two possible explanations of this group of phenomena: differences in effects are due either to an unequal rate of ethanol metabolism or differences in function of the nervous system.

Animals differing in their predisposition to ethanol consumption differ in their sensitivity not only to ethyl alcohol. Differences in their responses to adrenergic, cholinergic, and enkephalinergic substances have been discovered [10]. There is evidence that adenosine also depresses to different degrees the motor activity of animals differing in their predisposition to ethanol consumption [6].

The aim of this investigation was to examine the possible role of the nervous system in the realization of the different sensitivity to ethanol of animals with different durations of exposure to ethanol narcosis. To rule out any possible effect of the metabolic systems of the animal, experiments were carried out on the vas deferens, isolated from rats differing in the duration of their exposure to ethanol.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 250-280 g, kept on a standard animal house diet and with natural daylight and darkness. The duration of ethanol narcosis was determined by the method described previously [1]. The vas deferens was incubated in Krebs' solution, ventilated with carbogen, at 37°C. Contractions of the smooth muscles were recorded under isometric conditions. Two platinum electrodes were used for electrical stimulation; the frequency of stimulation was 0.1 Hz, the amplitude 60 V, and the pulse duration 1 msec. To study the sensitivity of the vas deferens to ethanol, adenosine, and β-endorphin, a procedure of recording described by the writers previously [3] was used. To determine the concentration of the substance reducing the amplitude of contractions by 50% (ID_{50}), and Hill's coefficient, log-logit transformation of the dependence of inhibition of contraction on concentration of substance in the cuvette was used. The significance of differences was estimated by Student's method.

EXPERIMENTAL RESULTS

Ethanol, added to the incubation medium in a concentration of 80 mM inhibited contractions of the isolated vas deferens by 20%. Inhibition of contractions by 50% took place

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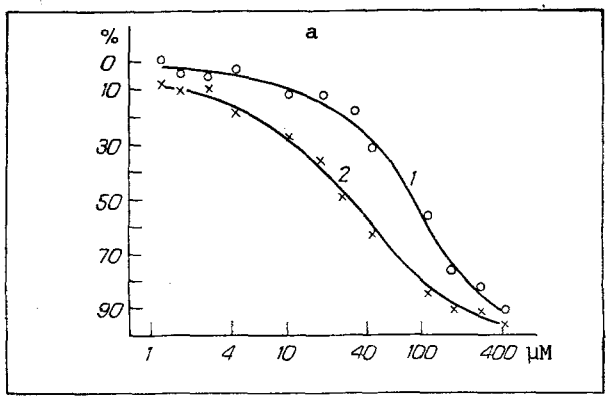
TABLE 1. Inhibition of Contractions of Vas Deferens of Rats Differing in Duration of Ethanol Narcosis (M + m; n = 4)

Substance	SS rats		LS rats	
	ID_{50}	Hill's coefficient	ID_{50}	Hill's coefficient
Adenosine, μM	36,4±3,3*	0,7±0,1	62,3±9,2	0,8±0,1
β-Endorphin, nM	46,5±11,3*	1,0±0,1	219,5±43,2	0,9±0,1
Ethanol, mM	209,1±23,4	1,1±0,1	204,7±39,3	1,3±0,3

Legend. *$p < 0.05$: significant differences between values for SS and LS



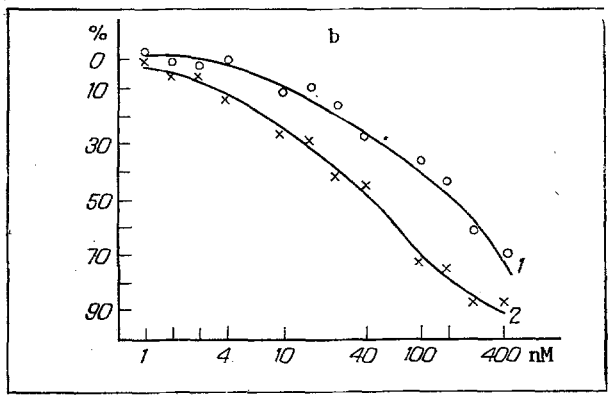


Fig. 1. Inhibition of contractions of rat vas deferens by adenosine (a) and β-endorphin (b). 1) LS animals; 2) SS animals. Ordinate, degree of inhibition of contractions; abscissa, concentration of substance.

when the concentration of alcohol in the medium was raised to 204-209 mM, the action of ethanol on the vas deferens isolated from short-sleeping (SS) and long-sleeping (LS) animals being identical (Table 10). The inhibitory effect of ethanol in these experiments was evidently connected with its nonspecific effect on synaptic membranes, as a result of which the release of neurotransmitter was inhibited, and also with its direct action on smooth-muscle cells. Unlike ethanol, adenosine acts through purigenic receptors, located, it is considered, on the presynaptic membrane [8]. Inhibition of contractions of the vas deferens by adenosine was completely blocked by theophylline in a concentration of 25 μM. These experiments showed that ID_{50} for adenosine is only half as high on the vas deferens isolated from SS rats as from LS rats (Table 1). An increase in the adenosine concentration in the incubation medium almost completely inhibited contractions of the vas in both groups of animals (Fig. 1a).

More significant differences in the sensitivity of the nerve-muscle preparations from animals of the two groups were found in relation to β-endorphin, for which specific ε-receptors

exist on the rat vas deferens. ID_{50} for SS rats was found to be 4 times lower than for LS rats (Table 1). Since naloxone in a concentration of 100 nM completely blocks the action of β-endorphin, it can be postulated that its effect in the present experiments was mediated through specific opiate receptors. The maximal effect of β-endorphin on contractions of the vas deferens did not differ significantly in the groups of animals studied (Fig. 1b).

Discovery of the difference between the action of adenosine and β-endorphin on the isolated rat vas deferens can be explained by differences in the sensitivity of the peripheral nervous system of SS and LS animals, and it is independent of metabolic factors. The fact that in these experiments ethanol equally inhibited contractions of the vas deferens of SS and LS animals suggests that differences in the effects of ethanol are not associated with unequal sensitivity of the peripheral nervous system, although the possibility cannot be ruled out that ethanol may differ in its effect on the peripheral and central nervous system; the ethanol concentration in the present experiments, moreover, exceeded realistic values for the whole organism. This may be connected either with lower sensitivity of the isolated organ to the action of alcohol or with the fact that in the whole organism a number of ethanol are mediated by its metabolic products, which can interact with specific receptors in the nervous system.

We showed previously that the endogenous enkephalinergic system may participate in the realization of the effects of ethanol [2]. As the available data show, the concentration of opioid peptides is depressed in SS animals, and this can be compensated by increased sensitivity of the opiate receptors. We know that the anxiolytic action of adenosine and its analogues is realized through adenosine receptors [11]. Very probably more marked activation of purinergic receptors takes place in SS rats under the influence of alcohol or its metabolites, for these animals have an initially higher sensitivity of their adenosine receptors.

It can thus be concluded that short-sleep animals, which utilize more ethanol under conditions of free choice, possess initially higher sensitivity of their purinergic and enkephalinergic systems, activation of which is responsible for the pharmacologic effect in the form of sedation and euphoria.

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