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ACTION OF ALCOHOL ON RATS WITH CHRONIC EMOTIONAL-PAINFUL STRESS

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KEY WORDS: alcohol; stress; lipid peroxidation.

Data obtained recently have shown that a neurosis-like state arising in experimental animals as a result of chronic emotional-painful stress (EPS) is accompanied by the creation of hypoxic conditions in the brain [1, 5]. Chronic alcohol consumption by experimental animals is known to lead to morphological change in the brain [3] and to long-term disturbances of higher nervous activity [4] and also of neurotransmitter systems [9]. Meanwhile the antistress action of alcohol in experimental animals has been described [11, 14].

The aim of this investigation was to study the effect of chronic alcohol consumption on reactivity of the autonomic nervous system and on oxidative processes in the rat brain.

EXPERIMENTAL METHOD

Experiments were carried out on 30 noninbred male albino rats weighing 200-250 g. The state of chronic EPS was created by combined exposure to "white noise" and subsequent electrodermal stimulation coupled with flashes of light on a stochastic schedule [5] daily for 4 weeks. The animals were divided into four groups: 1) control (intact rats), 2) animals exposed to EPS, 3) animals receiving a 20% solution of ethanol after water deprivation, 4) animals subjected to EPS and consuming ethanol. The rats were given alcohol from the first day of EPS. Under these conditions the rats of group 3 consumed 2-2.5 g/kg alcohol per head (calculated as 100% ethanol) daily, whereas animals of group 4 received 30-40% more.

Before the beginning of exposure to stress and alcohol consumption, and after the end of these procedures, the animals' behavior was assessed in an open field test and the autonomic parameters were studied during functional loading by hypokinesia (the animals were kept in special tubes, restricting their movements, for 2 h). The heart rate (HR) was recorded by means of a piezoelectric crystal. The blood pressure (BP) was determined by the appearance of pulsed waves after constriction of the base of the tail with a cuff.

To determine the stage of stress, according to Selye's system, the relative weight of the internal organs (adrenals, spleen, thymus, heart, and brown fat) was calculated. The level of brain energy metabolism was

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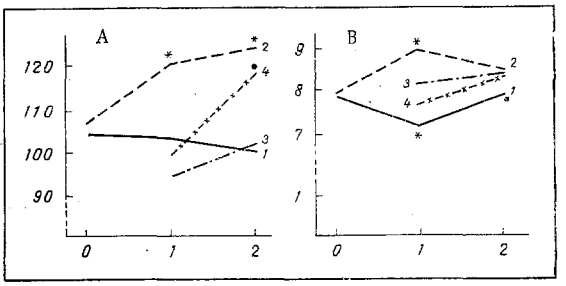

Fig. 1. Reactivity of autonomic nervous system during hypokinesia. Abscissa, duration of hypokinesia (in h); ordinate, A) BP (in mm Hg), B) HR (beats/sec). 1-4) Groups of animals. *P < 0.05 compared with background, **the same compared with 1 h of hypokinesia.

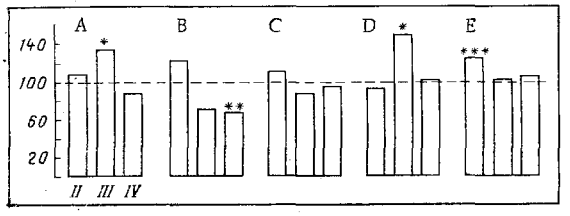

Fig. 2. Relative weight of organs. Ordinate, weight of organ (in % of control). A) Spleen, B) thymus, C) adrenals, D) brown fat, E) heart. *P < 0.05, **P < 0.005, ***P < 0.001 compared with control. Remainder of legend the same as in Fig. 1.

assessed by measuring cytochrome oxidase (CCO) activity [5]. For this purpose, the cortex and hippocampus were isolated from brain cooled for 1 min, the tissue was homogenized in 2 volumes of medium, and CCO activity was determined in a system with ascorbate (3 mM), tetramethyl-p-phenylenediamine (TMPD, 1-400 μM), and with inhibition of respiration by amobarbital (1.6 mM). The results were subjected to statistical analysis by the Wilcoxon and Wilcoxon–Mann–Whitney tests.

EXPERIMENTS RESULTS

Assessment of the animals' behavior in the open field test revealed no difference between the groups after 4 weeks of alcoholization and EPS. The reduction with age in horizontal motor activity, observed in all groups and reflecting the degree of orientation-investigative behavior of the animals, and the increase in their emotionality (based on the number of defecations), observed in all groups, are familiar facts [10]. The dynamics of reactivity of the autonomic nervous system during functional loading is illustrated in Fig. 1. Values of BP and HR could not be measured in the animals consuming alcohol before the beginning of hypokinesia (groups 3 and 4), for the weak pulse waves observed with low values of BP could not be detected by the piezoelectric crystal. No significant fluctuations of BP in response to loading were found in the control group. In the animals of group 2 hypokinesia caused a rise of BP, i.e., the condition known as transient hypertension, induced by chronic EPS and exhibited during functional loading, developed. In rats subjected to EPS against the background of alcohol consumption (group 4) BP was higher than in the control (group 1), but only after 2 h of hypokinesia, i.e., alcohol partly prevented the development of hypertension. In the animals of group 2 hypokinesia also induced quickening of the heart rate (Fig. 1B), whereas in the control animals, HR fell a little during loading. The heart rate in alcoholized rats was intermediate in value and was the same as that in the rats of group 1.

Investigation of the internal organs of the animals revealed no gastric ulcers. The weight of the adrenals in groups 2-4 (Fig. 2) did not differ significantly from the control. EPS led to a significant increase in weight of the heart muscle, which was not observed in alcoholized animals subjected to EPS. Hypertrophy of the heart in the rats of group 2 was evidently the result of transient hypertension [7], observed in these animals during

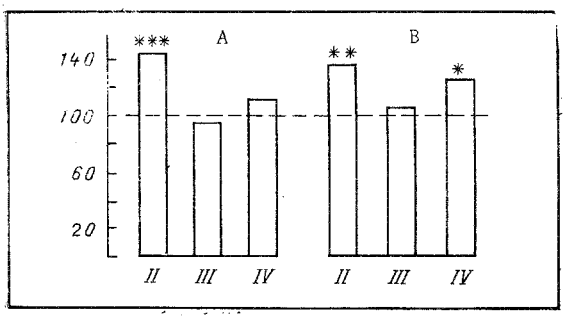

Fig. 3. CCO activity in neocortex (A) and hippocampus (B). Ordinate, CCO activity (in % of control). Remainder of legend as to Fig. 2.

functional loading. The absence of hypertrophy of the heart muscle in the rats of group 4 is in agreement with data given in [14], when an increase in weight of the heart was found during chronic (2 weeks) audiogenic stress, but no such effect was observed during chronic ethanol consumption. Involution of the thymus observed in rats consuming alcohol (Fig. 2B) may be connected with immunodeficiency of the T lymphocyte component observed during chronic alcohol consumption [8]. In the rats of group 3 an increase in weight of the brown fat was found: this evidently reflects stimulation of lipogenesis by ethanol, and also shifts in noradrenalin metabolism arising during alcohol consumption [9].

CCO activity was raised in the cortex and hippocampus of the rats of group 2 (Fig. 3). This effect, discovered in the writers' previous investigation [5], is regarded as compensatory, reflecting the increase in activity of oxygen utilization in circulatory hypoxia of the brain, due to chronic EPS [1]. Alcohol consumption by the rats completely abolished the EPS-induced activation of CCO in the cerebral cortex. CCO activity in the hippocampus of rats consuming alcohol and subjected to EPS was higher than in the control animals, but lower than in animals subjected to EPS and not consuming ethanol. Alcohol consumption thus completely prevented the EPS-induced increase in CCO activity in the cortex, and partly prevented it in the hippocampus. The results are evidence of the antistress action of alcohol.

It has recently been established that exposure to stress causes activation of lipid peroxidation (LPO) in many organs and tissues of animals [6]. Data on the effect of chronic alcoholization on LPO processes in the body are contradictory. Some investigators have observed an increase in LPO in the tissues of animals after injection of ethanol [13]. However, other investigations have shown that ascorbate-dependent LPO is considerably depressed in the liver microsomes of animals with chronic alcoholic intoxication [2], and that superoxide dismutase activity is considerably increased [12]. It has also been shown that administration of ethanol increases the concentration of the natural antioxidant, ascorbic acid, in the tissues and urine [15]. Data in the literature indicate that LPO processes are inhibited under the influence of chronic alcohol consumption. This suggests that the antistress action of alcohol observed in experimental animals by the present writers and others [11, 14] is connected with partial normalization of LPO when intensified on account of stress.

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PHARMACOLOGIC CORRECTION OF DISTURBANCES OF CARDIAC CONTRACTILITY IN STRESS

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KEY WORDS: stress; cardiac contractility; glycogen; drugs.

Previous investigations have shown that emotional stress (ES) causes marked excitation of the adrenergic and pituitary-adrenal systems [3], followed by activation of lipid peroxidation (LPO) and disturbance of oxidation and phosphorylation in the mitochondria of the heart [5], by structural changes in the myocardium [11], and also by depression of cardiac contractility [4]. It has also been shown that excessive excitation of the adrenergic and pituitary-adrenal systems [6, 7, 12] and disturbances of the metabolism and structure of the heart [10] can be prevented by the use of drugs acting selectively on different components of the pathogenesis of stress injury to the heart.

In this investigation the effect of certain metabolites of natural antistressor systems of the body and membrane protectors on cardiac contractility and also on the glycogen content in the myocardium was studied in animals during stress, for this problem has not been studied adequately.

EXPERIMENTAL METHOD

Experiments were carried out on 144 male albino rats weighing 190-230 g. ES was produced in the form of an anxiety neurosis by the method described previously [6, 7]. The animals were divided into six groups: 1) control, 2) animals subjected to ES; groups 3, 4, 5, and 6 of animals received sodium hydroxybutyrate (GHBA), prolactin, propranolol, and ionol respectively. GHBA was injected in a dose of 100 mg/kg intraperitoneally 30 min before ES and 3 h after the beginning of exposure to stress, prolactin was injected in a dose of 2.5 units/100 g subcutaneously 60 min before ES, propranolol in a dose of 5 mg/kg subcutaneously 30 min before ES, and ionol in a dose of 120 mg/kg intraperitoneally once a day for 3 days before ES.

The contractile function of the heart was studied under conditions of relative rest and during isometric contraction (compression of the aorta for 30 sec) with respect to the following parameters: the developed pressure (P_d), velocity of contraction (V_c) and relaxation (V_r), and the intensity of functioning of structures (IFS), calculated as the product of heart rate and developed pressure, divided by the weight of the left ventricle. The investiations were conducted under pentobarbital anesthesia (8 mg/100 g) with an open chest and under artificial respiration. The pressure in the left ventricle was measured by means of a VI6-6TN electromanometer and recorded photographically on the N-105 oscilloscope [1]. The glycogen content in the heart muscle of the rats was determined by the method in [15]. Contractility of the heart was studied and the glycogen concentration measured 45 h after the end of exposure to stress, at the time of maximal changes in metabolism, structure, and function of the heart [5].

EXPERIMENTAL RESULTS

ES evoked marked depression of cardiac contractility (Tables 1 and 2). Whereas in a state of relative rest the parameters characterizing cardiac contractility were depressed by 15-20%, after compression of the

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