CORRECTIVE ACTION OF ANTIOXIDANT IN RATS WITH CHRONIC EMOTIONAL-PAINFUL STRESS

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KEY WORDS: chronic emotional-painful stress; reactivity of the autonomic nervous system; cytochrome oxidase; antioxidants.

It was shown previously that chronic emotional-painful stress (EPS) leads to the development of a neurosis-like state in rats, characterized by disturbances of control of autonomic processes (including the system of cardiovascular regulation) and of behavior (conditioned-reflex activity). It has been suggested that cerebral hypoxia, an invariable result of many pathological processes, constitutes an essential link in the pathogenesis of neurosis [1]. The writers have shown that chronic EPS induces activation of brain cytochrome oxidase (CCO), and this effect was interpreted as compensatory, reflecting increased efficiency of oxygen utilization in circulatory cerebral hypoxia [4]. Data showing activation of lipid peroxidation (LPO) in the brain in various forms of oxygen insufficiency have recently been obtained [9, 11]. It is also known that nonenzymic free-radical oxidation is an invariable stage in the pathogenetic mechanisms of stress injury [6].

This paper describes the study of the effect of a synthetic antioxidant (AO) — compound F-801 [2] — on behavior, autonomic characteristics, and brain energy metabolism in chronic EPS, with a view to studying the possibility of pharmacologic correction of disturbances induced by experimental neurosis-producing procedures.

EXPERIMENTAL METHOD

Experiments were carried out on 32 noninbred male albino rats weighing 200-220 g. A state of chronic EPS was created by the combined action of white noise followed by electrodermal stimulation [4] daily for 4 days. The AO was injected intraperitoneally in a dose of 40 mg/kg on 0.5 ml of physiological saline before every EPS session. The animals were divided into four groups: 1) control, 2) rats receiving EPS, 3) control rats receiving AO, 4) rats receiving AO while exposed to EPS.

Before the beginning of exposure to stress (preliminary testing) and after its end, the animals' behavior was evaluated in an "open field" (horizontal and vertical motor activity, number of groomings, defecations, and visits to the center of the field during 5 min of observation), and the blood pressure (BP) and heart rate (HR) were recorded during function testing (with hypokinesia for 2 h).

The animals' general condition was determined by calculating the relative weight of the internal organs (adrenals, spleen, thymus, and heart). Brain energy metabolism was evaluated in relation to CCO activity [10]. For this purpose, the cortex and hippocampus were isolated from the brain which had been cooled for 1 min. After weighing, the tissue was homogenized in two volumes of medium and CCO activity was determined in a system with ascorbate (3 mM), tetramethyl-para-phenylenediamine (TMPD) (1-400 μM), and amytal (1.6 mM) to inhibit respiration. The results were subjected to statistical analysis by the Wilcoxon and Wilcoxon—Mann—Whitney method [3].

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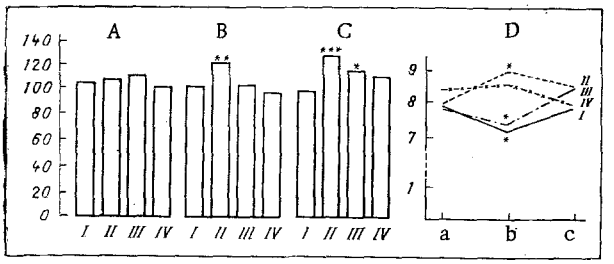

Fig. 1. Reactivity of autonomic nervous system during hypokinesia. A, B, C) Changes in BP (in mm Hg); D) changes in HR (number of beats/sec). A (a) background; B (b) 1 h of hypokinesia; C (c) 2 h of hypokinesia. *P = 0.05, **P = 0.005, ***P = 0.001. B, C) Significance of differences compared with group 1; D) significance of differences compared with background for each group. Here and in Figs. 2 and 3: I-IV) groups of animals.

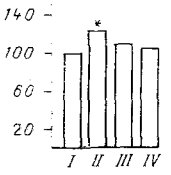

Fig. 2

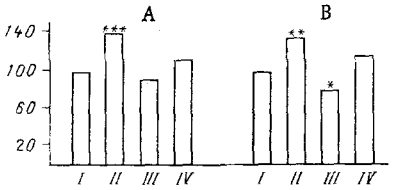

Fig. 3

Fig. 2. Relative weight of heart (in % of control). *P = 0.001 compared with group 1.

Fig. 3. CCO activity (in %) in neocortex (A) and in hippocampus (B). *P = 0.05, **P = 0.005, ***P = 0.001 compared with group 1.

EXPERIMENTAL RESULTS

In all groups a significant (P = 0.01) decrease in horizontal activity in the "open field" after the end of exposure to stress was found compared with preliminary testing, in agreement with data in the literature, according to which the emotionality of animals rises with age and their motor activity diminishes [8]. According to all parameters recorded in the "open field" test there was no signficant difference between the groups. This is evidence that neither chronic EPS nor injection of the above-mentioned dose of AO caused any change in the inborn type of behavior in an "open field."

Reactivity of the autonomic nervous system was judged by changes in BP and HR during fraction testing. Animals of group 2, in which transient hypertension induced by chronic EPS appeared in response to the test load, were most sensitive to hypokinesia. BP in the rats of this group after 1 and 2 h of hypokinesia was above the background level, and also higher than in the control (Fig. 1). Fluctuations of HR also were most marked in the rats of group 2 (Fig. 1). Transient hypertension was not observed in animals of groups 3 and 4. The higher BP in the rats of group 3 after 2 h of hypokinesia compared with the control can be explained by the higher background values of BP in these animals.

On investigation of the internal organs no gastric ulcers were found, and the weight of the adrenals, thymus, and spleen did not differ from the control, i.e., the state of the animals exposed to stress can be assessed as Selye's phase of resistance [7]. However, the weight of the heart muscle of the animals of group 2 was greater (P = 0.001, Fig. 2). The phenomenon of compensatory hypertrophy of the heart, developing in diseases of the cardiovascular system, is known and is regarded as a variant of adaptation of heart muscle to increased loads [5]. In this case hypertrophy of the heart was caused by transient hypertension, appearing in the animals of group 2 during hypokinesia. EPS against the background of AO did not cause the development of hypertension or an increase in weight of the heart.

EPS caused an increase in CCO activity by 40% in the cortex and by 35% in the hippocampus (Fig. 3). AO did not affect CCO activity in the cortex but reduced it by 20% in the hippocampus. Injection of AO during EPS prevented the increase in CCO activity in the cortex and hippocampus. Activity of the enzyme in the rats of group 4 was significantly lower than in those of group 2 and did not differ from the control.

AO thus abolishes autonomic disturbances induced by EPS by normalizing BP values during function testing, preventing hypertrophy of the heart and also normalizing CCO activity in parts of the brain when increased in experimental neurosis. The results suggest that the molecular mechanism of the pathogenesis of neurosis is based on activation of LPO.

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CORRELATION BETWEEN CARDIAC ARRHYTHMIAS IN ACUTE MYOCARDIAL ISCHEMIA AND ACTIVITY OF CERTAIN STRUCTURES OF THE LIMBIC AND NORADRENERGIC SYSTEMS

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Negative emotional overstrain can give rise to a disturbance of the cardiac rhythm [2, 6-12]. It has been shown [5] that hyperactivation of a structure of the limbic system, namely the anterior amygdaloid nucleus, by the creation of a generator of pathologically enhanced excitation in it [4], can lead to disturbance of the cardiac rhythm.

In this investigation changes in electrical activity (EA) in the limbic structures of the brain after ligation of the coronary artery were studied and the effect of coagulation of these structures are changes in cardiac activity in acute myocardial ischemia (MI) was determined. Considering connections between adrenergic and limbic structures [14, 16-18], the role of the locus coeruleus (LC) in these processes also was investigated.

EXPERIMENTAL METHOD

Experiments were carried out on 90 noninbred male rats weighing 160-200 g under pentobarbital anesthesia (40 mg/kg). After preliminary immobilization (succinylcholine 0.2 mg/kg) and artificial ventilation, total bilateral electrical coagulation of the caudal and rostral regions of the hippocampus, the ventromedial and posterior hypothalamus, amygdala, and LC was carried out in accordance with stereotaxic atlases [13, 15] on the animals of group 1 (42 experiments, seven animals in each series). A current of 5 mA was passed for 15-20 sec for coagulation. Immediately after coagulation high ligation of the anterior left

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