observed fall of CF is not directly connected with the toxic effect of ethanol and acetaldehyde on the vessels.

The existence of positive correlation between the blood ethanol concentration of the rate 2 h after routine injection of ethanol and the rate of outflow of CPK from the heart indicates that ethanol, at the height of its concentration, has a damaging action on cardiomyocytes and on their sarcolemma. It also follows from the results of this investigation that the severity of the cardiac disturbances in rats with high and low tolerance to ethanol was identical, whereas acetonemia, a manifestation of alcohol-induced ketosis, has no direct toxic action on the heart.

The results shed light on the causes of lack of success in the simulation of alcohol cardiomyopathy by the use of semivoluntary methods of alcoholization of animals [7-9]. In such cases acetaldehyde does not accumulate and the highest blood ethanol concentrations do not exceed 2 g/liter [1, 4].

The leading factors in heart damage during forced alcoholization of rats are thus the accumulation of acetaldehyde in the body and the presence of periodically occurring high blood ethanol concentrations.

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ABOLITION OF DISTURBANCES OF ELECTRICAL STABILITY OF THE HEART IN POSTINFARCTION CARDIOSCLEROSIS BY A FACTOR INDUCING GABA ACCUMULATION IN THE BRAIN

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KEY WORDS: sodium valproate, postinfarction cardiosclerosis, fibrillation of the heart

Recent investigations have shown that adaptation to short-term stress not only limits many kinds of stress-induced damage [5], but also prevents arrhythmia and fibrillation of the heart associated with acute ischemia, myocardial infarction, and disturbance of the electrical stability of the heart in postinfarction cardiosclerosis [4]. Studies of the protective effect of adaptation have shown that it is based on activation of the stress-limiting system of the body and, in particular, of the GABA-ergic system, which is manifested as marked accumulation of GABA in the brain. In complete agreement with this it has been shown that injection of a chemical factor, inducing GABA accumulation in the brain, namely sodium

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valproate, an inhibitor of GABA transferase, itself prevents arrhythmia and fibrillation of the heart, without any adaptation, during acute ischemia and reperfusion of the myocardium [6]. Meanwhile the problem of whether sodium valproate can be used to abolish disturbances of the electrical stability of the heart in postinfarction cardiosclerosis, when stress and ischemia are both absent, remains unsolved.

The aim of this investigation was to study this problem by examining the effect of sodium valproate on the electrical thresholds of fibrillation of the heart in animals with postinfarction cardiosclerosis.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 300-350 g. Postinfarction cardiosclerosis was produced by ligation of the left coronary artery by Selye's method [12]; two months later all the animals undergoing this operation were found to have a single connective-tissue scar in the myocardium of the left ventricle, and the volume of scar tissue amounted to 25% of the weight of the myocardium of the ventricles [7]. Electrical stability of the heart was studied in acute experiments under pentobarbital anesthesia (50 mg/kg) in four groups of animals: 1) control; 2) postinfarction cardiosclerosis; 3) injection of sodium valproate; 4) postinfarction cardiosclerosis + injection of sodium valproate. Two parameters were determined: the electrical threshold of fibrillation of the heart and its ectopic activity in response to vagus nerve stimulation. For this purpose the cervical portion of the right vagus nerve was isolated initially, and 10 min after division of the nerve its peripheral end was stimulated by pulses (duration 2 msec, delay 5 msec, frequency 200 Hz) applied through platinum electrodes from ÉSL-2 stimulator. When this method was used the control animals developed vagus bradycardia, whereas animals with postinfarction cardiosclerosis developed multiple extrasystoles against a background of vagus bradycardia (Fig. 1). The electrical thresholds of ventricular fibrillation was later determined by means of an SEN-3201 stimulator ("Nihon Kohden," Japan), triggered by the ECG wave, and the heart was stimulated by single premature square pulses 10 msec in duration through a coaxial electrode, inserted into the myocardium of the wall of the right ventricle (Fig. 2). The ECG was recorded continuously throughout the experiment. Sodium valproate was injected in a dose of 200 mg/kg 90 min before the acute experiments, intraperitoneally. Incidentally, the choice of dose of the drug was determined by its pharmacodynamics and pharmacokinetics, which are such that about 88% of the sodium valproate is bound by blood proteins and its concentration in the brain is 1/4-1/5 of its plasma level [9]. Studies of the ratio of the plasma valproate concentration and its therapeutic effects in man [10] and animals [14], moreover, have shown that optimal sessional doses lie between 200 and 400 mg/kg. Finally, injection of the drug in a dose of 200 mg/kg causes a marked rise of the brain concentration of GABA, correlating with the anticonvulsant action of valproate [11].

EXPERIMENTAL RESULTS

The data given in Table 1 illustrate quantitatively the main result of the experiment and they show that postinfarction cardiosclerosis is accompanied by lowering of the threshold of fibrillation of the heart by two-thirds and by an enormous increase of ectopic activity, i.e., multiple extrasystoles against the background of vagus bradycardia. Under the influence of sodium valproate the fibrillation threshold was returned to a subnormal level and the number of extrasystoles was reduced tenfold. Thus this synthetic activator of a stress-limiting system, a GABA reservoir, completely reproduces the effect of adaptations and has an antiarrhythmic action.

To understand this result it is essential to realize that in these experiments disturbances of the electrical stability of the heart were caused not by stress and acute ischemia, but by the presence in the heart of a postinfarction scar, which did not disappear or decrease in size under the influence of a single injection of sodium valproate. It can accordingly be postulated that besides other well-known local factors [15], an important role in the onset of disturbances of electrical stability of the heart in postinfarction cardiosclerosis may be played by increased excitability of the nerve centers of the brain, under the influence of modified impulsation from the heart, which is known to make an important contribution to the pathogenesis of cardiac arrhythmia and fibrillation [13]. Consequently, sodium valproate could act at both the central level and the cardiac level. In this case abolition of disturbances of electrical stability by means of the GABA reservoir could be explained, first, by limitation of excitability of the nerve centers of the brain and inhibition of the central

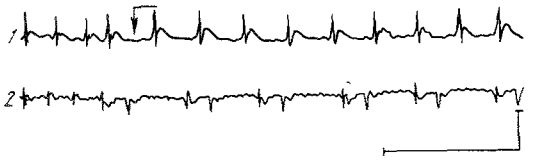

Fig. 1

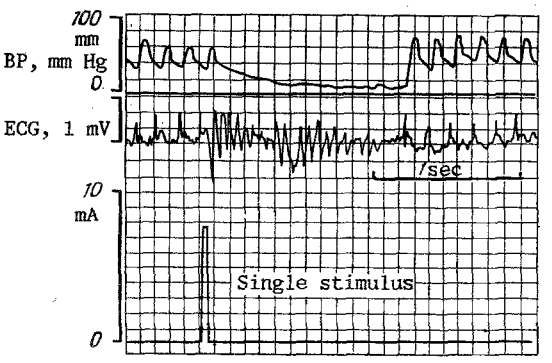

Fig. 2

Fig. 1. Method of determination of ectopic activity of the heart during vagus nerve stimulation. 1) Control; 2) postinfarction cardiosclerosis. Arrow indicates vagus nerve stimulation. Calibration: 1 mV, 1 sec.

Fig. 2. Method of determination of electrical thresholds of fibrillation of the heart.

TABLE 1. Abolition of Disturbances of Electrical Stability of the Heart in Postinfarction Cardiosclerosis with the Aid of Sodium Valproate (M ± m)

Experimental conditions		Heart rate beats/min	Ventricular fibrillation threshold, mA	Number of extrasystoles superposed on vagus bradycardia
Control	(11)	389±11	6,8±0,7	19
Postinfarction cardiosclerosis	(11)	380±13	2,3±0,3	401
Injection of sodium valproate	(11)	379±8	6,4±0,7	0
Postinfarction cardiosclerosis + injection of sodium valproate	(11)	390±12	5,3±0,7	40

Legend. Number of experiments given in parentheses.

component of the pathogenesis of arrhythmias. This hypothesis is in agreement with data showing that persistent arrhythmias can be induced without any damage to the heart by blocking GABA receptors of the anterior amygdaloid nucleus by microinjection of penicillin into it; later such arrhythmias can be abolished by electrical coagulation of this structure [1]. Second, sodium valproate could act at the cardiac level, for all components of the system responsible for GABA biosynthesis likewise are present in the heart [3] and during stress, moreover, activation of GABA in the heart has been demonstrated [3]. In addition, in separate experiments on isolated rat hearts it was shown that injection of sodium valproate directly into the perfusion fluid has a marked antiarrhythmic action in acute ischemia [8].

In the context of the facts described above, the most important conclusion is that disturbances of electrical stability of the heart in postinfarction cardiosclerosis, as well as its predisposition to the development of arrhythmia, which is well known in this state, are abolished just as effectively by sodium valproate as cardiac arrhythmias accompanying acute ischemia. Since sodium valproate is a relatively nontoxic anticonvulsant, widely used in the treatment of epilepsy [2], but not in clinical cardiology, these data provide important evidence for the use of this and other activators of the GABA system as antiarrhythmic agents.

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EFFECT OF HIGHLY DISPERSED COPPER POWDER ON SUPEROXIDE DISMUTASE AND GLUTATHIONE PEROXIDASE ACTIVITY IN EXPERIMENTAL MYOCARDIAL INFARCTION

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An important role of active forms of oxygen in ischemic tissue damage has been postulated [7]. The discovery of proteolytic conversion of xanthine dehydrogenase into the oxidase form, accompanied by accumulation of hypoxanthine, the substrate of xanthine oxidase, in the course of ATP catabolism [7], which must inevitably be accompanied by increased generation of the superoxide anion-radical – $O_2^{\cdot-}$ – is experimental confirmation of this hypothesis. Our own [3] and other data [2] testify to the importance of reduction of enzymic utilization of $O_2^{\cdot-}$ on account of inhibition of superoxide dismutase (SOD) activity in the ischemic cardiomyocytes. Meanwhile an increase in the concentration of hydroxyl radicals ($OH^{\cdot}$ [5]) in perfusion fluid of the ischemic myocardium has been found with the aid of spin traps, and addition of SOD to a cardioplegic solution leads to effective protection of the myocardium in coronary occlusion [8].

The active center of cytosol SOD contains copper, which is responsible for the catalytic activity of the enzyme; it has been shown, moreover, that in animals with copper deficiency in the tissues, SOD activity is sharply depressed [13]. Copper deficiency in the body also leads to myocardial damage [6, 14] and to disturbance of lipid metabolism during the development of pathology of the cardiovascular system [12]. It is logical to suggest on the basis of the facts described above that administration of copper preparations in myocardial ischemia and infarction may have a beneficial action on the course of the pathological process.

The writers showed previously that administration of highly dispersed powders (HDP) of metals has great advantages over the corresponding salts because of their much lower toxicity and their more prolonged action [4]. Accordingly, in the investigation described below the effect of HDP of copper was investigated on the activity of antioxidative enzymes (SOD) and glutathione peroxidase (GP) in the ischemic myocardium and on survival of animals after coronary occlusion.

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