ACTION OF CONVULSANTS ON ANIMALS DIFFERING IN INDIVIDUAL RESISTANCE TO HYPOXIC HYPOXIA

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Individual differences in reactivity are attracting ever-increasing attention of research workers for it is only by taking them into account that scientifically based measures of control of adaptation to the action of various extremal factors can be developed [1, 2]. It has been shown [1, 3, 4, 10] that adaptation to hypoxia can be used to increase the resistance of the organism to various unfavorable influences, including to the action of convulsants [3, 8]. Considerable differences are known to exist in the individual resistance of man and animals both to hypoxia and to the action of various factors inducing epileptiform changes in brain activity [2, 5, 6].

The object of this investigation was to study correlation between resistance to hypoxia and resistance to the action of convulsants.

EXPERIMENTAL METHOD

Two series of experiments were carried out on male noninbred albino rats weighing 160-180 g. The animals were placed in a pressure chamber, in which the atmospheric pressure was lowered in the course of 60 sec to a level corresponding to an altitude of 11 km. The rats were kept at this "altitude" until the second terminal inspiration, after which normal atmospheric pressure was restored in the chamber. The time from the beginning of the "ascent" to the second terminal inspiration was counted as the survival time. From the 160 rats exposed to hypoxia, three groups of individuals distinguished by high, average, and low resistance were chosen by Berezovskii's method [5].

Each of the selected animals 3-6 days after the "ascent" in the pressure chamber was relaxed with succinylcholine and artificially ventilated. Under local procaine anesthesia craniotomy was performed and the dura removed above the somatosensory cortex. In the experiments of series I, to create an epileptiform focus a piece of filter paper soaked with a solution of the sodium salt of benzylpenicillin was applied to the cerebral cortex [9]. Cortical electrical activity was recorded before and after application by means of monopolar silver electrodes on the RM-45 polygraph (Japan).

In the experiments of series II strong acoustic stimulation and intraperitoneal injection of strychnine nitrate were used as convulsant factors. Of the 180 rats, three groups differing in resistance to hypoxia were selected on the basis of duration of survival at an "altitude" of 11 km. From 10 to 12 days after the "ascent" the rats were placed in turn in a special chamber in which they were exposed for 90 sec to the action of an acoustic stimulus (bell, 90 dB). Their behavioral responses were monitored visually. All these rats were given an injection of strychnine in a dose of 2.2 mg/kg 4 days after audiogenic stimulation. The time of onset and duration of the convulsions were recorded.

EXPERIMENTAL RESULTS

Analysis of the results of the experiments of series I (Table 1, Fig. 1) showed that resistance to hypoxia correlates with resistance to the convulsant action of penicillin: The less resistant an animal to high altitudes, the stronger the convulsant action of penicillin on it. In the group of animals with low resistance (n = 24) application of penicillin in a concentration of 12 mg/ml evoked characteristic epileptiform discharges (ED) in 19 rats; in

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TABLE 1. Action of Penicillin in a Concentration of 12 mg/ml on Rats Differing in Their Resistance to Hypoxia (M ± m; n = 24)

Group of animals	Time of appearance of ED after penicillin application, min	Number of animals in which penicillin application evoked	
		ED	ES
With low resistance	3±0,5	19	12
With average resistance	6,4±1,6	12	3
With high resistance	13,8±2,14	8	0
P	<0,05	<0,005	<0,001

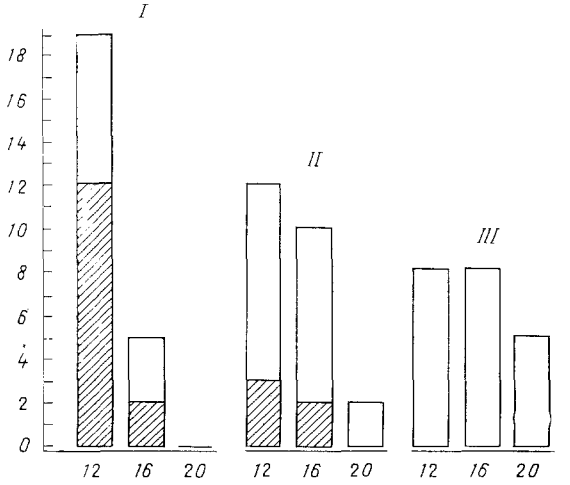

Fig. 1. Action of penicillin on animals differing in their resistance to hypoxic hypoxia. Abscissa, penicillin concentration (in mg/kg); ordinate, number of animals in which ED appeared (shaded parts denote number of rats in which both ER and ES were recorded). I) Animals with low resistance, II) with average resistance, III) with high resistance to hypoxia. Each group contained 24 rats.

12 of these animals, moreover, epileptiform seizures (ES) were recorded. In five rats of this group ED appeared only if the penicillin concentration was increased to 16 mg/ml, and two of them also developed ES. Meanwhile, in the group of highly resistant animals (n = 24) penicillin in a dose of 12 mg/ml evoked ED in only eight rats, in a dose of 26 mg/ml also in eight rats, and in a dose of 20 mg/ml, in five rats. In the remaining three animals penicillin, even in this concentration, evoked no ED. It is a particularly important fact that none of the animals of this group exhibited ES. Rats of the different groups also differed in the time of appearance of epileptiform activity after the beginning of penicillin application: In animals with low resistance it was 1-4 min, in those with average resistance 3-9 min, and in highly resistant animals 4-15 min (Fig. 2).

Strychnine differed in its action on animals which differed in resistance to hypoxia (Table 2). The strongest convulsant effect after injection of strychnine was observed in the group of animals with low resistance. In this group the largest number of epileptiform attacks was observed, they were longer in duration, and they were tolerated less well by the animals than in the other groups (seven rats died during a convulsion), and they appeared after a shorter latent period. Highly resistant animals were found to be more resistant to the convulsant action of strychnine than rats of the other two groups.

Investigations into the action of audiogenic stimulation of animals differing in resistance to hypoxia revealed no significant difference in their resistance to this convulsant factor.

TABLE 2. Effect of Injection of Strychnine and of Audiogenic Stimulation on Rats Differing in Their Resistance to Hypoxia (M ± m; n = 26)

Group of animals	Number of animals in which strychnine injection caused		Duration of strychnine convulsions, sec	Number of animals in which audiogenic stimulation evoked	
	ES	death		hyperkinesia	ES
With low resistance	17	7	77,0±3,8	5	5
With average resistance	9	6	57,0±4,1	5	4
With high resistance	3	0	28,0±3,6	4	3
P	<0,05	<0,02	<0,01	>0,05	>0,05

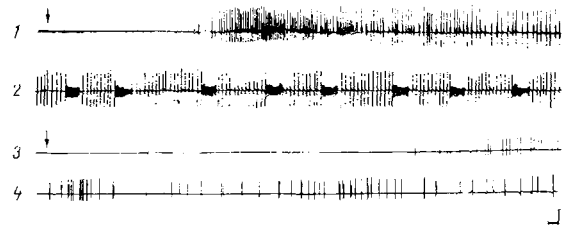

Fig. 2. Epileptiform changes on ECoG of rats with low and high resistance after application of penicillin. 1) ECoG of rat with low resistance, during application; 2) fragment of ECoG recorded 1 h after application; 3) ECoG of highly resistant rat during application; 4) fragment of ECoG recorded 1 h after application. Arrows indicate beginning of application. Time marker 10 sec. Calibration 500 μV.

The results thus indicate that resistance to convulsions correlates with resistance to oxygen deficiency. Animals with high resistance to hypoxia are also highly resistant to the convulsant action of penicillin and strychnine. These results agree with experiments in which electrical stimulation was used as the convulsant agent [3]. Those investigations showed that the total duration of the seizure and also the duration of its tonic and clonic phases were significantly shortened in rats highly resistant to hypoxia. The fact that acoustic stimulation did not lead to the discovery of differences in its action on the animals was evidently explicable on the grounds that different brain structures participate in the development of audiogenic convulsions and of convulsions evoked by penicillin and strychnine [7]. The results of the present experiments demonstrate definite differences in the activity of the CNS of animals differing in their individual sensitivity to hypoxia.

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PREVENTION OF DISTURBANCES OF ELASTICITY AND THE CONTRACTILE FUNCTION OF THE NONISCHEMIC PART OF THE HEART IN EXPERIMENTAL INFARCTION WITH THE ANTIOXIDANT IONOL

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Activation of lipid peroxidation (LPO) has been shown to develop in heart muscle of the ischemic and nonischemic portions of the heart in experimental infarction [4] and also after emotional-painful stress [5] and marked disturbances of elasticity and contractility of the myocardium arise [1, 3]. It has been suggested that activation of LPO in the nonischemic parts of the heart in infarction may play a role in injury to the sarcolemma and sarcoplasmic reticulum of the cardiomyocytes, with a resulting disturbance of Ca^{++} transport and depression of the elasticity of the myocardium and of its contractile function [1, 3]. Since the contractility of the residual parts of the myocardium largely predetermines the work of the heart and the fate of the patient with an infarct, it is important to study ways of preventing disturbances of the contractile function of the nonischemic parts of the myocardium by means of LPO inhibitors, namely antioxidants.

The object of this investigation was to study the effect of preliminary administration of of the powerful synthetic antioxidant ionol on the contractile function of a region of the heart known to be nonischemic (the right atrium) in experimental infarction of the left ventricle.

EXPERIMENTAL METHOD

Experiments were carried out on female Wistar rats weighing 180-220 g. Experimental infarction was produced by ligation of the descending branch of the left coronary artery by Selye's method [9]. The animals were decapitated 24 h after ligation of the artery. The area of the infarct (in mm^2) was more than 60% of the total area of the left ventricle on the outer surface and about 45% on the inner surface. Animals subjected to thoracotomy but without occlusion of the coronary artery, and also intact animals served as the controls. Since there were no differences in the contractile function of the right atrium in the animals of these two series, the ionol used to protect the nonischemic myocardium was injected into control intact animals and into intact animals in which a myocardial infarction was subsequently formed. Ionol (2,6-di-tert-butyl-4-methylphenol) was injected in a dose of 50 mg/kg daily for 3 days before creation of the infarct and again 2 h after the operation. The compound was injected in the same dose and at the same time intervals into the control animals.

The atria were removed for study of their contractile function immediately after decapitation of the animals and placed in a constant-temperature bath with oxygenated Krebs–Henseleit solution (95% O_2 + 5% CO_2, 34°C, pH 7.4) so that the base of the atrium was fixed and the auricle was attached to a "Physiograph DMR-4B myograph, recording isometric contractions (from Narco Bio-Systems, USA). The atrium contracted spontaneously for 40-50 min, after which it was gradually stretched to a length at which it developed maximal tension during isometric

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