EFFECT OF ADAPTATION TO HYPOXIA ON RESISTANCE OF RATS TO THE EPILEPTOGENIC ACTION OF PENICILLIN

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Correlation exists between resistance to hypoxia and to the action of epileptogenic agents: The higher the resistance of a given individual to hypoxia, the higher its resistance to the action of various factors inducing seizures also [2]. Adaptation to hypoxia has been shown to increase the resistance of the organism to various unfavorable influences, including to the action of epileptogenic factors [1, 3, 7-9].

The aim of this investigation was to study the possibility of increasing the resistance to seizures of rats with low resistance to hypoxia by pressure chamber adaptation.

EXPERIMENTAL METHOD

Experiments were carried out on 180 noninbred male albino rats weighing 160-180 g. The rats 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 11,000 m. The animals were kept at this "altitude" until the beginning of agonal respiration, after which normal pressure was restored in the pressure chamber. The time from the beginning of "ascent" to the second terminal inspiration was considered to be the survival time. By the method described previously [2, 4], 48 animals of low resistance were selected from 180 rats subjected to acute hypoxia, and these were divided into two groups with 24 rats in each group.

Animals of the first group were adapted to hypoxia for 30 days by keeping them in a pressure chamber at an "altitude" of 5000 m for 8 h daily. This "altitude" was reached in stages, starting with 1000 m, and extending over 4 days. Animals of group 2 (control) were kept in the pressure chamber also for 8 h daily, but they were not exposed to hypoxia. The rest of the day, all the animals were kept under standard animal house conditions.

After the completion of true and false training animals of both groups were tested for resistance to the epileptogenic action of penicillin. The rats were immobilized with succinylcholine and artificially ventilated. Under local procaine anesthesia part of the cranial bone and dura mater above the somatosensory cortex were removed. To create an epileptic focus, a piece of filter paper soaked with a solution of the sodium salt of benzylpenicillin, in concentrations of 12,000, 16,000, and 20,000 IU/ml was applied to this area of the cerebral cortex. Electrical activity in this region of the sensomotor cortex (the electrocorticogram — ECoG) was recorded by means of monopolar silver ball electrodes (diameter of ball 0.5 mm) on an RM-45 polygraph (Japan). The results were subjected to statistical analysis by Student's t test and the chi-square test.

EXPERIMENTAL RESULTS

Application of penicillin led to the appearance of epileptic activity (EA): against the background of the spontaneous ECoG, high-amplitude spike discharges (epileptic discharges — ER), with an amplitude initially of 200-300 μV appeared 3-10 min after application, 10-15 sec later their amplitude had increased to 1-2 mV (Fig. 1), and thereafter it remained unchanged until the end of the experiment. The duration of these ED was 100-160 msec. The subsequent course of development of the epileptic process differed in different animals. In the rats which could be regarded as most resistant to the epileptogenic action of penicillin, ED were recorded for 2-3 h (Fig. 1: 1, 2), after which they were generated steadily less frequently

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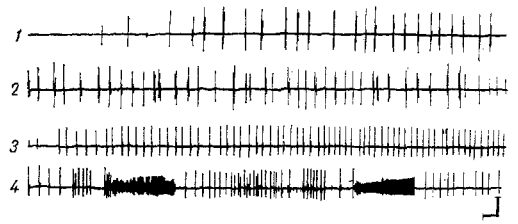

Fig. 1

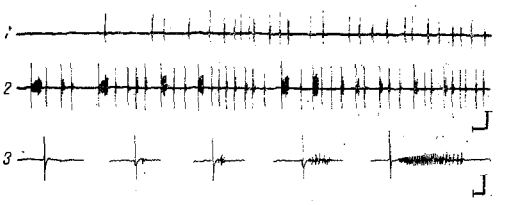

Fig. 2

Fig. 1. Example of development of EA in sensomotor cortex of 2 rats differing in resistance to epileptogenic action of penicillin. 1, 3) 5 min, 2, 4) 60 min after application of penicillin. Only ED were recorded in a highly resistant rat (1, 2), whereas both ED and EF developed in a rat with low resistance. Calibration: 1 mV, 10 sec.

Fig. 2. EA in focus in rat sensitive to epileptogenic action of penicillin. 1) 5 min, 2) 40 min after application of penicillin; 3) separate fragments of the previous trace. Calibration: 1, 2) 1 mV, 10 sec; 3) 1 mV, 1 sec.

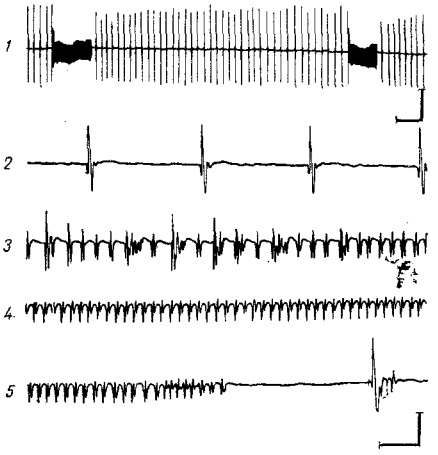

Fig. 3. Structure of ED developing during EF (3, 4, 5) and during interictal period (2). 1) fragment of ECoG recorded 50 min after application of penicillin; 2-5) successive fragments of ECoG recorded during development of EF (55 min after application of penicillin). Calibration: 1) 1 mV, 10 sec; 2-5) 1 mV, 1 sec.

and disappeared. In the less resistant rats ED increased in frequency 20-30 min after application, and each was followed by an after-discharge, which gradually increased in amplitude and duration (Fig. 2) and could become converted into an epileptic fit (EF). In animals with the greatest predisposition to epilepsy, EF occurred 15-20 min after penicillin application, leaving out the after-discharge stage (Fig. 1: 3, 4). During EF, discharges resembling a spike-wave complex in structure, appeared and their frequency increased during development of the fit (Fig. 3). After EF, interictal ED were recorded on the ECoG (Fig. 3:1), and this alternation of EF and ED was observed for 40-90 min. Thus the resistance of the individual to seizures could be judged on the basis of the epileptiform changes on the ECoG.

The results of the experiments to study the effect of application of various concentration of penicillin on the ECoG of animals adapted to hypoxia and of control animals are given in Table 1. The results are evidence that adaptation to hypoxia increases the resistance of animals with initial low resistance to the epileptogenic action of penicillin, as reflected in an increase in the latent period of onset of ED from 3 ± 0.5 min (control) to 6.8 ± 1.7 min in the adapted animal ($P \pm 0.05$) and a less frequency appearance of ED and EF. In the case of application of penicillin (12,000 IU/ml) ED occurred in 18 control animals but only in 11 adapted animals ($P < 0.05$). When penicillin was applied in this concentration EF occurred in 10 unadapted rats but in only 2 adapted animals ($P < 0.01$).

TABLE 1. Epileptogenic Action of Penicillin on Adapted Control Rats

Group of animals	Penicillin concentration, IU/ml	Latent period of onset of ED, min	Number of animals in which penicillin induced	
			ED	ED and EF
Control	12 000	3±0,5	18	10
	16 000		4	2
	20 000		—	—
Adaptation	12 000	6,8±1,7	11	2
	16 000		10	2
	20 000		3	—

To induce the same degree of EA in the cortex in rats adapted to hypoxia, higher concentrations of penicillin were required than in the control. The development of EA in the cerebral cortex of rats adapted to hypoxia, after application of penicillin, was more difficult both at the stage of formation of the epileptic focus (the period of appearance of ED) and at the stage of marked seizure activity (period of EF generation).

Preliminary adaptation to moderate hypoxia of animals with low resistance thus increases their resistance not only to hypoxia, but also to the epileptogenic action of penicillin, Incidentally, comparison of the results of the present investigation with those obtained previously [2] shows that adaptation for 30 days in a pressure chamber increases the resistance to seizures of animals with low resistance to hypoxia, up to the level of animals with average, but not high resistance. On the basis of views that the development of EA in the brain is prevented by tonic activity of structures of the antiepileptic system [6], it can be postulated that adaptation to hypoxia evoked tonic activation of this system, as a result of which the resistance of the rats to the epileptogenic action of penicillin was enhanced: The latent period of appearance of EA increased after application of penicillin, but the number of animals in which penicillin induced EA decreased.

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