conclusion that, during stress, catecholamines are evidently important for the formation of a definite rhythm of concerted production of cytokines, which is responsible for enhanced growth of early hemopoietic precursors [11]. On the other hand, the active metabolism of adrenergic antagonists [3] is evidence that it is precisely at the early stages of development of the immobilization-induced stress response that the interaction between the sympathetic nervous system and the cells of HIM plays an important role in the enhanced production of cytokines.

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Adaptation to Periodic Hypoxia Restricts Subdural Hemorrhage during Audiogenic Epileptic Seizures in Rats

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Adaptation to periodic hypoxia in a pressure chamber exhibits various protective effects in experiment and clinical practice [5,6]. In particular, it raises the rat's resistance to audiogenic epileptic seizures and reduces the severity of seizures [1,5]. Until recently, however, it was unclear how preadaptation to hypoxia under the conditions used for treating patients (for example, those with bronchial asthma and neuropsychic diseases) [6] affects the severity of the subdural hemorrhage usually observed in the brain during audiogenic epilepsy in Krushinskii-Molodkina (KM) rats [1]. The importance of this topic stems from the fact that adaptation to periodic hypoxia has not yet been used in the management of epilepsy in clinical practice.

The objective of the present study was to assess the effect of preadaptation to prolonged periodic hypoxia under clinically approved conditions

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TABLE 1. Protective Effect of Adaptation to Periodic Hypoxia against Audiogenic Epilepsy and Subdural Hemorrhage

Group (number of animals)	Latency of convulsive fit, sec	Incidence of subdural hemorrhage, %	Mean area of subdural hemorrhage, mm^2	Cortisole content in plasma, nmol/liter
Audiogenic epilepsy ($n=7$)	5.0±0.7	86±14	48.6±21.9	41.5±1.7
Audiogenic epilepsy in rats adapted to periodic hypoxia ($n=10$)	10.1±1.8	40±16*	5.6±2.0**	19.2±1.7**

Note. One and two asterisks indicate reliability of differences: $p<0.05$ and $p<0.01$, respectively.

on the severity of seizures and of subdural hemorrhage in KM rats during the development of audiogenic epilepsy in response to a strong auditory stimulus.

MATERIALS AND METHODS

The studies were performed on 17 KM rats with a genetic predisposition to audiogenic epilepsy. Seven animals were used as controls; ten rats were adapted to hypoxia during one month, 6 h daily, in a pressure chamber with rarefied air (corresponding to a 5000-m altitude). After the completion of the session of adaptation to periodic hypoxia the experimental and control rats were exposed to a strong auditory stimulus as described previously [2]. Over the first 1.5 min of auditory stimulation the latency and severity of the convulsive fit were determined. During further auditory stimulation, intracranial hemorrhages developed in the KM rats, and these were morphologically verified.

Immediately after the completion of auditory stimulation the animals were quickly decapitated; blood was collected in cooled tubes for subsequent determination of the cortisol level by radioimmunoassay using Russian-manufactured kits. The brain was fixed in 10% formalin, and the incidence and severity of subdural hemorrhage, the area of which was calculated on microphotographs with the aid of a Pericol 1000 system (France), were assessed.

RESULTS

The data presented in Table 1 attest to the protective effect of preadaptation to periodic hypoxia. The latency of the convulsive fit increased in adapted animals twofold, this being evidence of a reduced excitability of the CNS. A noteworthy fact is that alterations in the latency of epileptiform activity were not previously observed either for adaptation under Alpine conditions or for a 2-week adaptation in a pressure chamber at a 5000-m altitude [1].

Concomitantly with the increased latency, the blood concentration of the stress marker hormone cortisol dropped sharply in adapted animals: at the maximum development of audiogenic epilepsy this value constituted 19.2±1.7 nmol/liter in adapted animals vs. 41.5±1.7 nmol/liter in the controls ($p<0.05$).

The incidence of subdural hemorrhage was 2.2 times lower in the rats adapted to hypoxia than in nonadapted animals. Whereas an extensive confluent hemorrhage was observed in 43% of cases in the control group, this was entirely absent in the adapted rats. The mean area of subdural hemorrhage in the rats adapted to hypoxia was 8.6 times smaller than in the control (Table 1).

Thus, adaptation to periodic hypoxia reduced the incidence and area of subdural hemorrhage.

The data obtained indicate that the regime of adaptation to periodic hypoxia which was employed by us proved to be optimal: in contrast to the earlier used regimes [1], it prolonged the latency, reduced the stress response during the development of audiogenic epilepsy, and, what is especially important, reduced manyfold the incidence and area of subdural hemorrhage after seizure development. In consideration of the latter fact, two possible causes of the protective effect of preadaptation to periodic hypoxia must be taken into account.

Activation of the major stress-limiting systems (GABA-ergic, opioid-ergic, antioxidant, and prostaglandin systems) in the organism has been proven for adaptation to hypoxia [12]. Accordingly, a pronounced antistress effect of this adaptation and its ability to restrict the increase of the blood content of catecholamines and corticosteroids during immobilization and emotional-pain stress have been established [7]. An important fact is that activation and metabolites of the said systems are able to reduce seizures caused by diverse factors [3, 9]. Such a consistency, in our view, is not incidental, and provides a basis for speculation that the antistress effect of adaptation to hypoxia is, at the same time, an anticonvulsive effect.

Adaptation to hypoxia induces the growth of blood vessels in vital organs, above all in the heart and brain [5, 11]. The genetic mechanism of this adaptive phenomenon has been explored by W. Shapper et al. [13]. For an assessment of our find-

ings it is important that, along with the vessel growth during adaptation to hypoxia, a reduction of their muscle tone is observed [4, 8], as well as a reduction of the response of the resistive vessels to vasoconstrictors and an enhancement of the response to vasodilators [4]. This may limit the rise of pressure in the brain vessels and decrease the likelyhood of rupture of the venous walls, damage to which plays a decisive role in the development of subdural hemorrhage for audiogenic epilepsy in KM rats [1,10]. This factor, as well as the possible growth of the venous bed and structural changes in the vein walls, appear to determine the adaptive protection of the brain against subdural hemorrhage during the development of audiogenic epilepsy.

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Animal Resistance to Sublethal Hypoxia May Be Raised More by Adaptation to Stress than by Adaptation to Hypoxia

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Adaptation to moderate hypoxia is thought to raise human and animal resistance to sublethal hypoxia [5], and this has been used in the training of mountain climbers and pilots [2]. In addition to this direct protective effect of adaptation, there is a possibility of increasing resistance to hypoxia due to cross-protective effects of adaptation to other factors. For instance, adaptation of animals to repeated stress lowers 6.5-fold the mortality for the

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