Effect of Hypoxia of Increasing Severity on the Dynamics of Cerebral Cortex EEGs in Rats with Different Resistance to Acute Oxygen Deficiency

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EEGs recorded from the cerebral cortex of rats with high and low resistance to hypoxia during "elevation" in a pressure chamber differ in the dynamics of the EEG power spectra. EEGs of highly resistant rats show phasic changes in biopotentials correlating with the severity of hypoxia: primary increase in the absolute power of all frequency ranges is followed by normalization and a secondary increase with predominance of the slow-wave component, inhibition of the β_2 range and the emergence of interhemispheric differences, and terminal inhibition of the power of all frequency ranges. In rats with low resistance to hypoxia, phases of relative normalization of EEG spectra and their depression during terminal period are not observed, all changes being represented by a continuous increase in the power of the α and δ ranges with progressive inhibition of the β_2 range and then of the β_1 range. Interhemispheric asymmetry is significant throughout the period of power increase. A high amplitude burst activity is recorded in rats of both types starting from an altitude of 8000 or 9000 m. The pattern of EEG changes in rats exposed to hypoxia of growing severity consistently reproduces those observed in patients with ischemic stroke.

Key Words: *hypobaric hypoxia of increasing severity; dynamics of EEG power spectra; cerebral cortex; resistance to hypoxia, burst activity*

The electroencephalogram (EEG) objectively reflects the functional state of the brain in various diseases. Special experimental and clinical studies have led to the use of this method for detecting hypoxic and ischemic disorders of the central nervous system [1-6,11,13,15]. It was proved that bioelectrical modulations of brain activity are earlier and more sensitive indicators of the effects produced by oxygen insufficiency than ionic permeability, pH, levels of high-energy compounds, etc. [15]. The fact that hypoxia exerts different effects on brain metabolism in animals differing in the resistance to acute oxygen insufficiency [9] suggests that the dynamic response of EEG to oxygen deficiency is different in such animals. This suggestion was not confirmed experimentally. The only relevant evidence is that EEGs in animals differing in the susceptibility to acute hypoxia normalize in different manner [8]. Our objective was to study EEG dynamics in rats with high and low resistance to hypoxia during their "elevation" to the critical altitude in a pressure chamber.

MATERIALS AND METHODS

Random-bred white rats (body weight 180-200 g) with high and low resistance to acute hypoxia (HR and LR rats, respectively) determined in preliminary tests were used. Two weeks after the tests, nichrome

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TABLE 1. A Comparative Fourier Analysis of Cerebral Cortical EEGs Recorded Under Normobaric Conditions in Rats with Different Resistance to Hypoxia (*M±m*)

Type of rats	Cortex	Total spectral power, mV^2	Relative powers of frequency ranges, % of total power				
			δ	θ	α	β_1	β_2
HR	Left	770±287	23.4±1.8	32.7±3.3	9.0±0.5	14.5±1.4	14.6±2.8
	Right	739±262	24.8±1.7	33.9±2.7	9.2±0.4	13.9±1.1	12.0±2.3
LR	Left	572±87	20.0±1.2	33.5±3.4	8.6±0.4	14.9±1.4	17.6±2.9
	Right	757±186	22.0±2.1	38.4±3.4	9.6±0.7	12.9±1.5	11.5±2.2

electrodes for the recording of biopotentials were implanted into the cortex of right and left brain hemispheres of anesthetized rats in a stereotaxis apparatus [8]. Four or five days after the operation, the rats were placed in a flow-through pressure chamber where EEG was recorded in conscious and unrestrained rats during a 4-min period before "elevation" (baseline EEGs) and then (also for 4 min) at "altitudes" of 5000, 8000, 9000, 10,000, and 11,000 m. At the critical altitude of 11,000 m, the survival time (the time before the second agonal inspiration was noted) of LR rats was 3-4 min, whereas HR rats remained alive. These rats remained at that altitude for 10 min, and the EEG was recorded at the beginning and at the end of this period. Then they were elevated to an altitude of 12,000 m, which led to agony after 4-10 min. During the tests, the pressure chamber was shielded. The EEGs were recorded and processed in a computer using Alfa-MF software (Web Technology, Russia). The EEG records were processed using Fourier spectral analysis with determination of absolute total spectral powers for the EEG spectra and individual frequency ranges, amplitude and frequency of the dominant peak, and the relative powers of individual frequency ranges. Statistical significance was evaluated with the paired sign test.

RESULTS

HR and LR rats did not differ significantly in the baseline values of total EEG power and relative powers of individual ranges (Table 1). The θ rhythm predominated in the EEG power spectra, which agrees with previously reported data [2,4,14,14].

During stepwise elevation to the critical altitude, phasic changes in EEGs of HR rats differed from those in EEGs of LR rats. For HR rats, four distinct phases of change in the total EEG spectral power were identified (Fig. 1): 1) significant primary increase and a similar increase in both hemispheres at an altitude of 5000 m, 2) decrease at 8000 and 9000 m, which did not reach the baseline level, 3) secondary increase at 10,000 and 11,000 m, which was more pronounced in the right hemisphere, which indicated the appearance of interhemispheric asym-

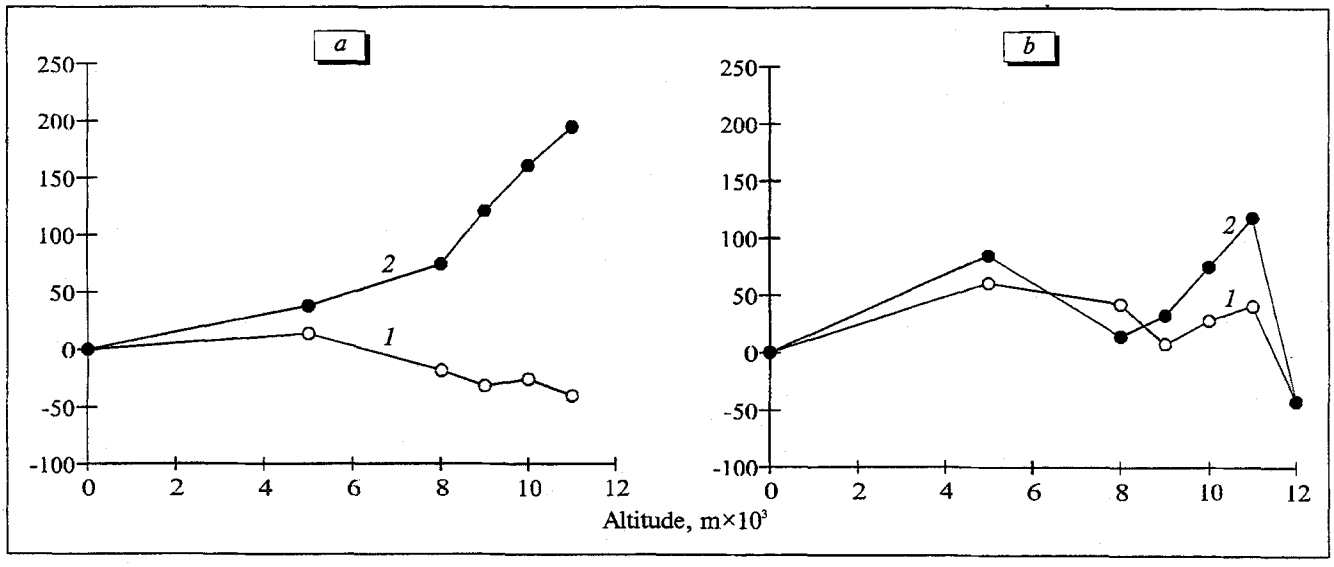

Fig. 1. Variations in the total EEG spectral power determined by Fourier analysis at different altitudes for the sensorimotor cortex of rats with low (*a*) and high (*b*) resistance to hypoxia. Ordinate: changes in the total power (% of the baseline value). *1*) left cortex; *2*) right cortex.

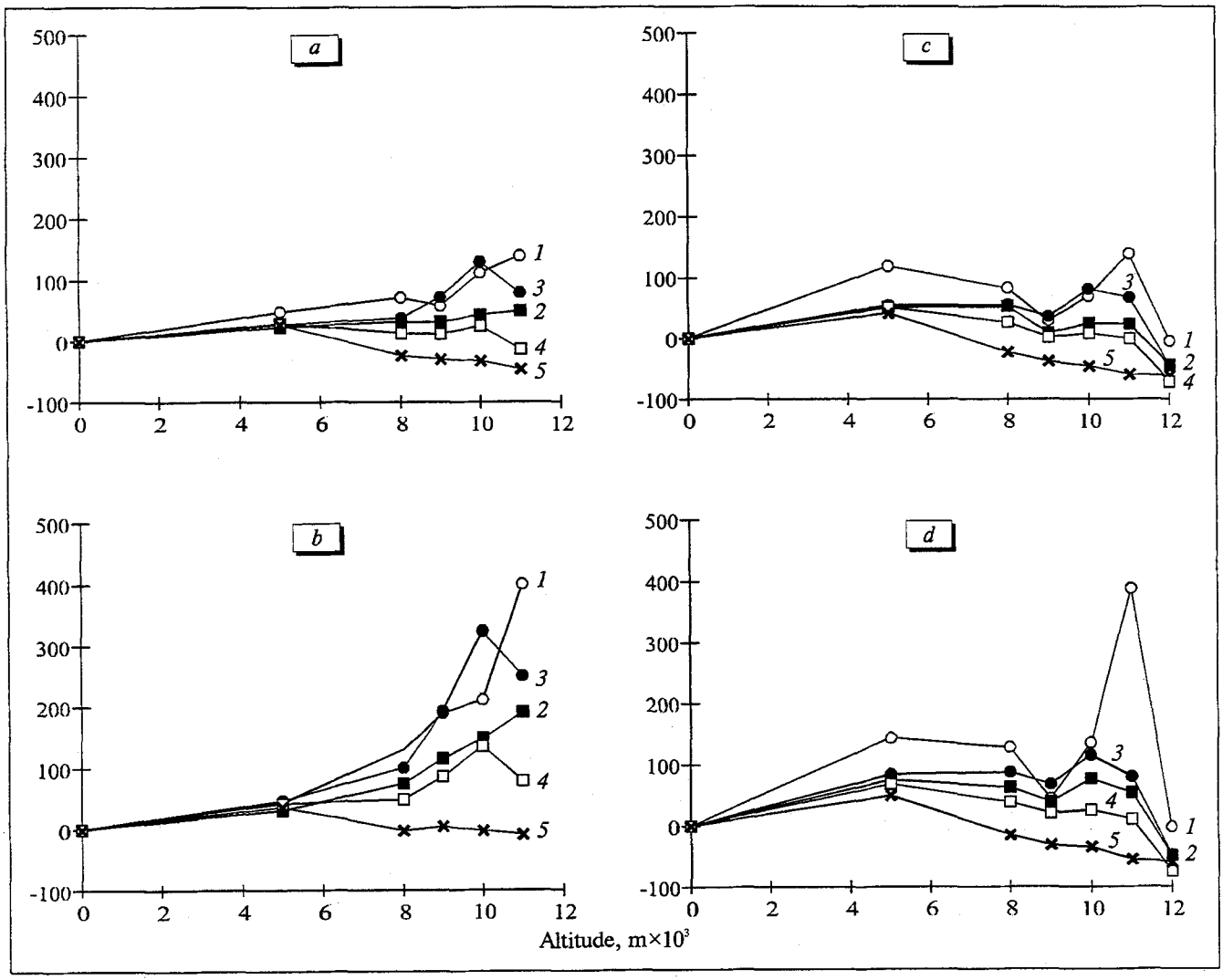

Fig. 2. Variations in the absolute spectral powers of individual ranges of cerebral cortical EEGs at different altitudes in rats with high (HR) and low resistance (LR) to hypoxia. Ordinate: changes in the absolute power of ranges (% of the baseline value). Left cortex (*a*) and right cortex (*b*) of LR rats; left cortex (*c*) and right cortex (*d*) of HR rats. Here and in Fig. 3: *1*, *2*, *3*, *4*, and *5* are delta, theta, alpha, $beta_1$, and $beta_2$ ranges of the EEG spectrum, respectively.

metry, and 4) sharp decrease at an altitude 12,000 m preceding the death of the rats. In contrast, phasic changes in the total power of EEG spectra were not observed in LR rats. The total EEG spectral power in this group continuously increased in the right hemisphere and slightly changed in the left hemisphere. Thus, in LR rats interhemispheric asymmetry appeared at an altitude of 5000 m and progressively increased until the terminal stage.

Phasic changes in EEG in response to hypoxia of increasing severity with predominating excitatory rhythms at the initial stage of elevation (5000 m), slow-wave activity at a higher altitude (8000 m), and progressive inhibition of electric activity and its complete disappearance in the terminal period (11,000-12,000 m) were demonstrated previously [1,5,7,11,12]; however, individual differences were not considered.

Different patterns of dynamics of the total EEG spectral power in HR and LR rats are determined by specific changes in the powers of various ranges and by the ratios between these powers. Thus, at an altitude of 5000 m, the primary increase in the total EEG power in HR and LR rats resulted from the increases in the absolute powers of the fast-wave and slow-wave ranges, but particularly of the δ range, which became dominant, its amplitude increasing by 46-80% (Fig. 2). Changes in the absolute powers of individual EEG spectral ranges in LR rats were significantly smaller than in HR rats, although the direction of changes was the same. The hypoxic hyperactivation of baseline pulse activity described in a number of studies [1,5,7,9,11,13,15] probably reflects the excitation of cortical neurons, which can be reproduced by hypoxia modeling in isolated nerve

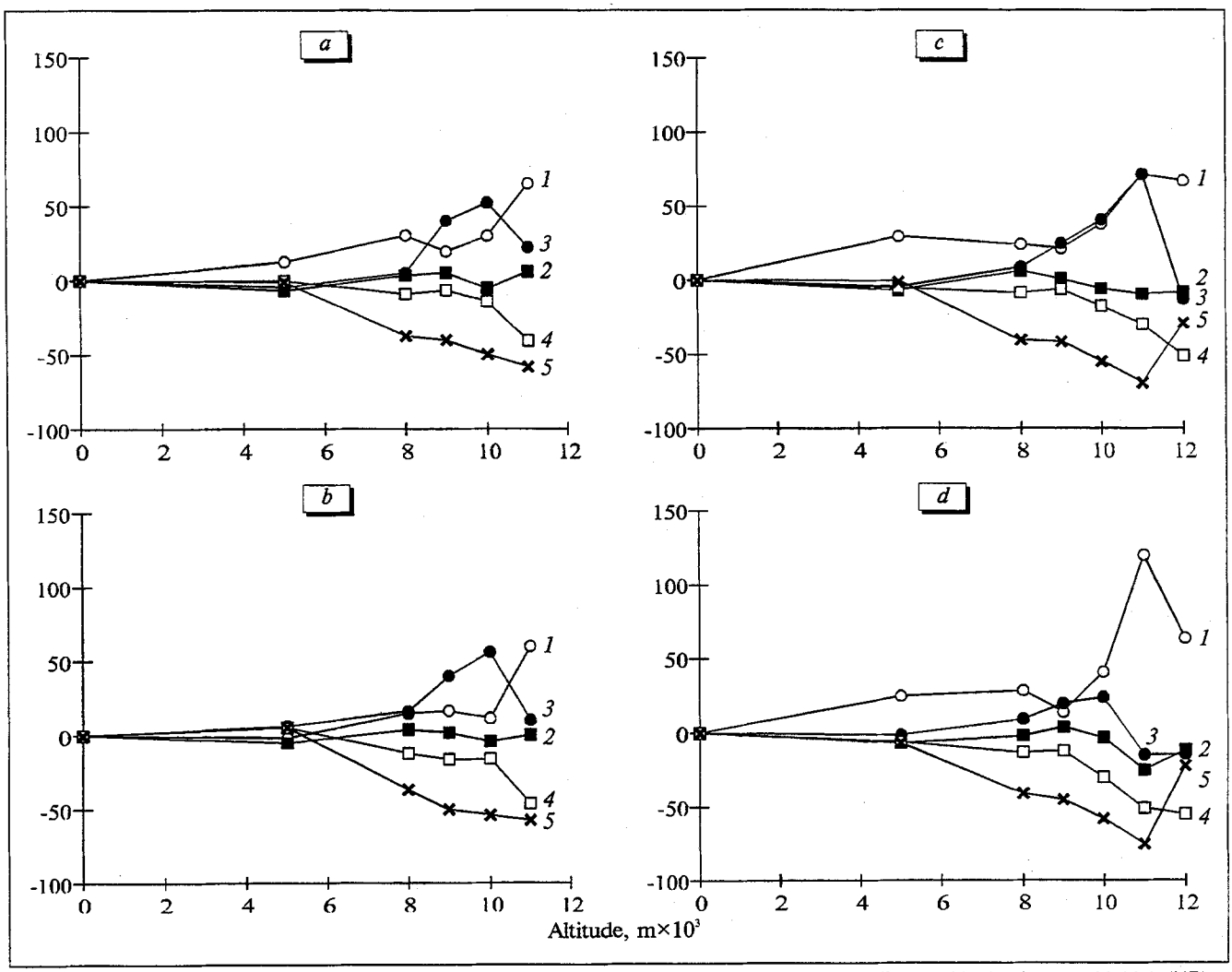

Fig. 3. Variations in the relative spectral powers of individual ranges of cerebral cortical EEGs at different altitudes in rats with high (HR) and low resistance (LR) to hypoxia. Ordinate: changes in relative powers of the ranges (% of the baseline value). Left cortex (*a*) and right cortex (*b*) of LR rats; left cortex (*c*) and right cortex (*d*) of HR rats.

cells and correlates with intensification of their oxidative metabolism [9,10]. Activation of the β range, particularly of its fast component (β_2), at the initial stage of hypoxia is considered as a consequence of compensatory activation of the reticular formation [3]. Hypoxia of greater severity caused a decrease in the absolute power of all frequency ranges in HR rats, the maximum decrease being observed at an altitude of 9000 m. Meanwhile, all parameters remained above the baseline level with the exception of the β_2 range whose activity amounted only to 35% of the baseline value. During this period, the relative power of the θ range remained virtually unchanged, while the δ and α ranges predominated (Fig. 3). Marked inhibition of fast β waves after their short-term compensatory activation was demonstrated for hemispheric ischemic stroke [3]. The secondary increase in the total EEG power in HR rats (the maximum being reached at 11,000 m) reflected a strong activation of the δ and α ranges coinciding with relatively small changes in the θ and β_1 ranges and continuing marked inhibition of the β_2 range amounting to 60-70% during this period (Figs. 2 and 3). The interhemispheric asymmetry noted when the total EEG power was analyzed was then associated with a significant dominance of the right hemisphere in terms of all parameters. Finally, the reduced total EEG spectral power in the cerebral cortex of HR rats during the terminal period (at 12,000 m) correlated with the inhibition of absolute powers of all ranges. The greatest relative changes were observed in the fast-wave ranges and the smallest changes in the long-wave ranges. Thus, at this altitude the EEGs were represented almost exclusively by slow waves (0.5-2 Hz) (Fig. 2).

A reduction in the power of the EEG spectrum with predominance of the slow-wave (δ) component indicates substantial ischemic disorders in the brain

[3,6,14,17]. This agrees with the observation that deterioration of the condition of patients with hemispheric ischemic stroke is associated with decreased electrical activity of the brain and increased power of the δ range (0-4 Hz) which usually correlates with brain edema [3].

In contrast to HR rats, in LR rats the initial excitatory phase was followed by an increase in the absolute powers of the EEG spectral ranges (except the β_2 range). Changes in the right hemisphere were more pronounced (3- to 4-fold) than in the left hemisphere (Fig. 2). In general, the patterns of the EEG spectra in both groups of rats were characterized by an increase in the proportion of slow waves and a decrease in that of fast waves, particularly at an altitude of 11,000 m. The α range and hypersynchronous slow-wave δ rhythm whose high activity persisted until the terminal state predominated. No depression of the EEG was observed at the terminal stage. The response to hypoxia in the cortex of LR rats developed predominantly in the right hemisphere. This determined the pronounced interhemispheric asymmetry at all altitudes which was particularly strong in the period preceding the terminal stage.

In addition to the dynamics of brain rhythms described in HR and LR rats elevated to the critical altitude, the EEGs showed changes that can characterized as "burst activity." In some rats, paroxysmal rhythmic activity was observed at 5000 m, being more frequent at higher altitudes (over 8000 m). Each burst lasted 2-7 sec, and the total proportion of paroxysmal activity in a 4-min EEG record varied from 10% to 50%, depending on the altitude. Three types of high-amplitude discharges were identified: delta, theta, and alpha frequency ranges with amplitudes of 250 to 600 μV (for the employed method of EEG recording their amplitudes in the cortex usually range from 50 to 100 μV) (Fig. 4). The high-amplitude α rhythm with a frequency of 10 Hz was observed predominantly at altitudes of 9000-11,000 m, being more pronounced in LR rats compared with HR rats, where it was 2- to 3-fold shorter. By contrast, paroxysmal activity of the θ range was higher in HR rats; it occurred at 8000-11,000 m, being particularly pronounced at 10,000 m: its proportion in the total EEG spectrum was about 60%. In LR rats, this activity was significant only at 9000 m (10%). Finally, a slow-wave high-amplitude activity was recorded at 8000 m and at all higher altitudes, although up to 10,000 m inclusive it amounted only to 0.5-0.8% in the EEGs of LR rats and to 0-0.4% in those of HR rats. Starting from 11,000 m, its proportion in the total EEG spectrum increased to 15% in LR rats and to 49% in HR rats, with inhibition of the fast-wave burst activity and θ-range activity. At 12,000 m, the δ rhythm with fre-

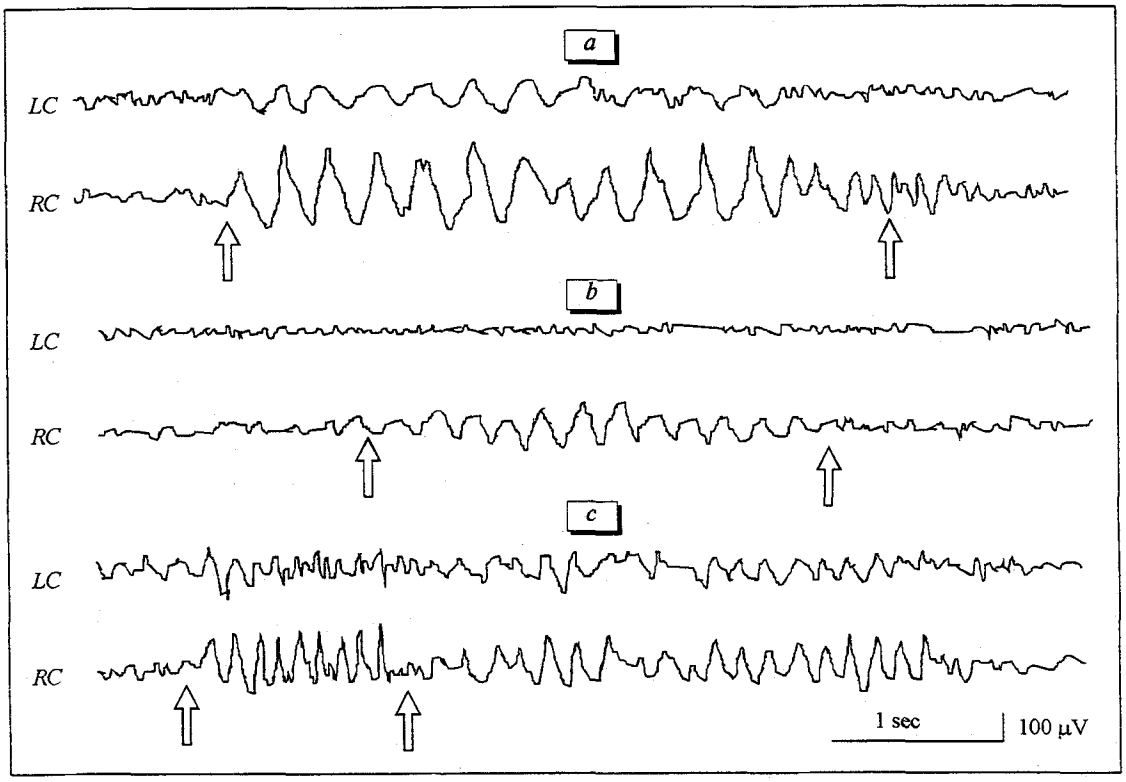

Fig. 4. Types of high-amplitude burst activity emerging in the sensorimotor cortex of rats at different altitudes. Activities in the δ (*a*), θ (*b*), and α rhythm (*c*). Left (*LC*) and right cortex (*RC*). Arrows indicate the emergence and disappearance of burst activity.

quencies of 1.6 to 2 Hz and amplitudes of 300 to 500 μV predominated in some HR rats and preceded the depression of bioelectrical activity. There is evidence that the emergence of burst activity in the range of δ rhythms and instability of power spectrum reflect the possible development of the mesencephalic stage of secondary brain stem syndrome [3].

Our results indicate that analysis of EEG power spectra in rats exposed to hypoxia of increasing severity is a highly informative method of detecting phasic disturbances of brain function characteristic of hypoxia and can be used for predicting individual resistance of animals to oxygen deficiency. The hypoxia-induced changes in EEG are more pronounced in the right hemisphere and in HR rats.

REFERENCES

1. N. A. Agadzhanyan, L. G. Voronin, and P. G. Goroyan, *Zh. Vyssh. Nervn. Deyat.*, **1**, 42 (1969).
2. I. V. Gannushkina, A. L. Antelava, and M. V. Baranchikova, *Byull. Eksp. Biol. Med.*, **118**, No. 10, 360-363 (1994).
3. E. I. Gusev, *Pat. Fiziol.*, No. 4, 44-51 (1992).
4. V. I. Gusel'nikov, *Electrophysiology of the Brain* [in Russian], Moscow (1976).
5. S. B. Daniyarov and E. M. Vilenskaya, *Zh. Vyssh. Nervn. Deyat.*, No. 2, 337-343 (1969).
6. E. A. Zhirmunskaya, *Vestn. Akad. Med. Nauk SSSR*, No. 5, 27-30 (1966).
7. E. A. Kovalenko, in: *Oxygen Regimen in the Body and Its Regulation* [in Russian], Kiev (1966), pp. 167-168.
8. S. V. Krapivin, V. E. Romanova, *et al.*, *Fiziol. Zh.*, **77**, No. 7, 11-19 (1991).
9. L. D. Luk'yanova, in: *Pharmacological Correction of Hypoxic States* [in Russian], Moscow (1989), pp. 5-8.
10. L. D. Luk'yanova and I. G. Vlasova, *Byull. Eksp. Biol. Med.*, **108**, No. 9, 266-272 (1989).
11. V. B. Malkin, in: *Oxygen Deficiency* [in Russian], Kiev (1963), pp. 563-570.
12. V. A. Negovskii, *Pathophysiology and Therapy of Agonies and Clinical Death* [in Russian], Moscow (1954).
13. O. M. Parfenova and M. N. Livanov, *Byull. Eksp. Biol. Med.*, **19**, No. 3, 36-42 (1945).
14. M. B. Plotnikova, O. E. Vaizova, and N. I. Suslov, *Byull. Eksp. Biol. Med.*, **118**, No. 12, 565-571 (1994).
15. M. O. Samoilov, D. G. Semenov, *et al.*, *Fiziol. Zh.*, **80**, No. 11, 37-43 (1994).
16. G. N. Chernobaeva and L. D. Luk'yanova, in: *Pharmacological Correction of Hypoxic States* [in Russian], Moscow (1989), pp. 17-21.
17. B. Cohen, E. Bravo-Fernandez, and A. J. Sances, *Electroencephalogr. Clin. Neurophysiol.*, **41**, No. 4, 376-402 (1976).