Antihypoxic Effects of Derivative on the EEG Power Spectra in Rats with Different Susceptibility to Oxygen Deficiency

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 124, No. 7, pp. 57-62, July, 1997
Original article submitted May 15, 1996

The succinate-containing hydroxypyridine derivative yancarb increases both the altitude tolerated by rats and their survival time at a high altitude, particularly in rats with low resistance to hypobaric hypoxia; it also prevents both phasic changes in the EEG characteristic of hypobaric hypoxia and hemispheric asymmetry and paroxysmal activity in the brain of highly resistant rats in the 5000-10,000 m range and in rats with low resistance in the 5000-11,000 m range. Antihypoxic effects of this substance are more pronounced in low-resistance rats and in the left hemisphere of both high- and low-resistant animals; in altitude range of 10,000-13,000 m these effects are weaker or absent.

Key Words: *cerebral cortex; Fourier EEG power spectra; hypobaric hypoxia; antihypoxants; succinate-containing hydrooxypyridine derivative*

Hypoxia inhibits the major NAD-dependent pathway of oxidation in the respiratory chain, particularly in the brain [1,2], which may impair the energy-synthesizing function of the cell. Under such conditions activation of alternative metabolic pathways providing energy for the respiration (for example, the succinate oxidase oxidation pathway), may be effective against hypoxia [1,2,6]. Verification of this possibility showed that succinate-containing compounds of the hydroxypyridine series (mexidol) increase the tolerance to acute hypobaric hypoxia [3,6]. Further investigations of the mechanisms of action of mexidol showed that its protective effects are due to activation of the succinate oxidase oxidation pathway and utilization of the succinate molecule as the energy substrate [3,6]. In this study we examined the effect of the hydroxypyridine derivative yancarb on survival of rats after acute hypobaric hypoxia and on the specific changes in EEG power spectra in the cerebral cortex.

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MATERIALS AND METHODS

Male random-bred rats (body weight 180-200 g) were used. They were divided into two groups according to the resistance to hypoxia: high and low (HR and LR, respectively) [5]. Electrodes were inserted and EEG recorded in unrestrained animals as described previously [4].

Control rats were placed in a flow altitude chamber, and EEG was recorded for 4 min before "elevation" (baseline EEG) and then at an altitude of 5000, 8000, 9000, 10,000, 11,000, 12,000, and 13,000 m. On each altitude the rats were left for 4 min (8 min at 11,000 m). Total period of elevation ranged from 25 to 35 min, depending on the time when agony began. At an altitude of 11,000 m, two 4-min EEGs were recorded. Experimental rats were injected with yancarb (40 mg/kg intraperitoneally) 20 min before elevation, and the EEG was recorded 15 min after the injection, after which EEG was recorded as in the control rats [4]. An additional EEG was recorded at 12,000 m in LR rats and at 13,000 m in HR rats because the hypoxia threshold was raised by yancarb.

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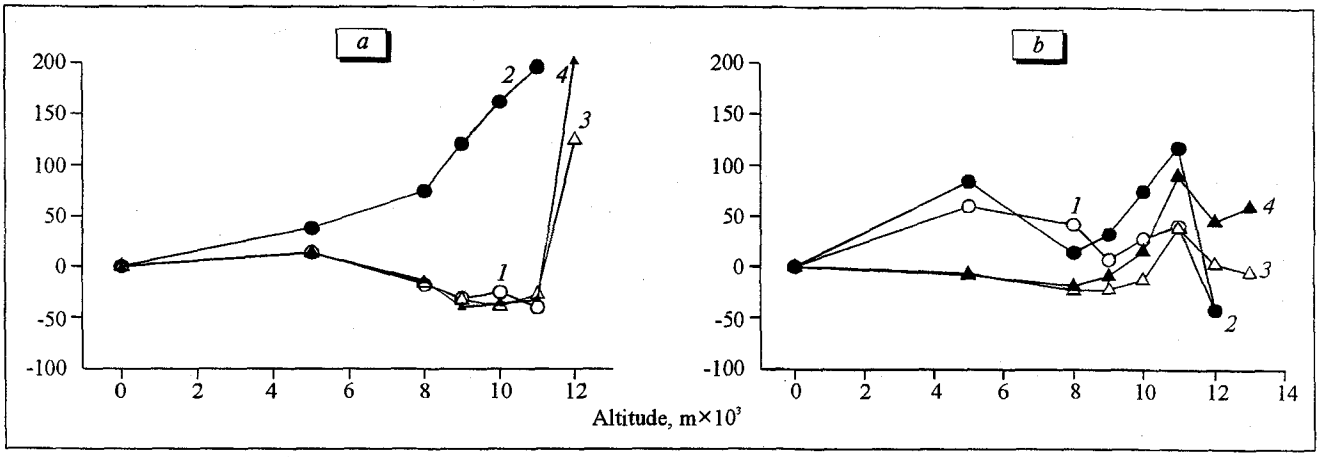

Fig. 1. Dynamics of total power of Fourier EEG spectra at different altitudes in rats with low (*a*) and high (*b*) resistance to hypoxia. Ordinate: % of total power relative to baseline. *1*, *2*) left and right cortex in control rats; *3* and *4*) left and right cortex in yancarb-treated rats.

The effect of yancarb on the baseline EEG was evaluated in a separate series of experiments. To this end, EEG was recorded 15, 30, 60, 120, and 180 min after its injection (40 mg/kg intraperitoneally). Since yancarb produced similar effects on the EEG spectra in HR and LR rats, the baseline data for the two groups were pooled. The EEGs records were subjected to Fourier analysis, determining the total power of EEG spectra and of individual frequency ranges, the frequency of the dominant peak, and the relative power the various frequency ranges. Statistical significance of the data was evaluated by nonparametric paired sign test.

RESULTS

Yancarb raised the threshold of tolerated altitudes from 12,000 m to 13,000 m in HR rats (survival time 3-7 min) and from 11,000 m to 12,000 m in LR rats (survival time 10-20 min). In other words, yancarb rendered the rats more resistant to acute hypobaric hypoxia.

Under normobaric conditions yancarb had no effect on the total power or power spectra of the EEG during the first 15 min postinjection but slightly slowed down the oscillations of brain biopotentials, raised the total power of EEG spectra in the left hemisphere, shifted by 1.5-2 Hz to the left the frequency of the dominant peak, and increased the absolute power of δ and θ ranges in the left cerebral cortex 30-60 min postinjection without any significant changes in the right hemisphere (Table 1). The yancarb-induced changes in EEG developed for longer time compared with the time when the rats remained in the altitude chamber (25-35 min).

Under hypoxic conditions, the EEG dynamics in yancarb-treated HR and LR rats differed considerably from that in the control. In HR rats, no significant changes in the total power of EEG spectra were observed up to the altitude of 10,000 m, while substantial phasic changes, predominantly as a result of progressively increasing slow-wave oscillations [4], were noted in the EEGs of control rats at 5000 m and higher. Only at 11,000 m the total power of biopotential oscillations began to increase in experimental rats, along with the emergence of interhemispheric asymmetry. At 12,000 and 13,000 m, the total power decreased, but to a lesser extent than in the control group, without reaching the baseline (Fig. 1). In LR rats, no significant changes in the EEG spectra of both hemispheres were observed up to

TABLE 1. Spectral Analysis of Cerebral Cortex EEG Recorded in Yancarb-Treated Rats under Normobaric Conditions

Parameter	Left hemisphere	Right hemisphere
Relative power in ranges:		
δ	115.6±78*	35.2±68.8
θ	96.8±44.5*	35.8±58.8
α	38.7±93.2	25.5±65.1
β_1	25.6±73.2	6.2±36.4
β_2	14.3±27.7	-1.3±16.2
Total power	46.0±25.9	21.5±36.1
Absolute power in ranges:		
δ	21.0±23.5	7.5±24.3
θ	24.5±36.2	8.5±14.3
α	-16.0±16.1	-1.8±21.5
β_1	-18.7±24.8	-4.7±29.9
β_2	-16.3±32.2	-1.2±37.6
Frequency of dominant peak in EEG spectrum	-30.6±21.8*	-28.7±25.4*

Note. Values are the means expressed as % of baseline value taken as 100%. *$p<0.05$ compared with baseline.

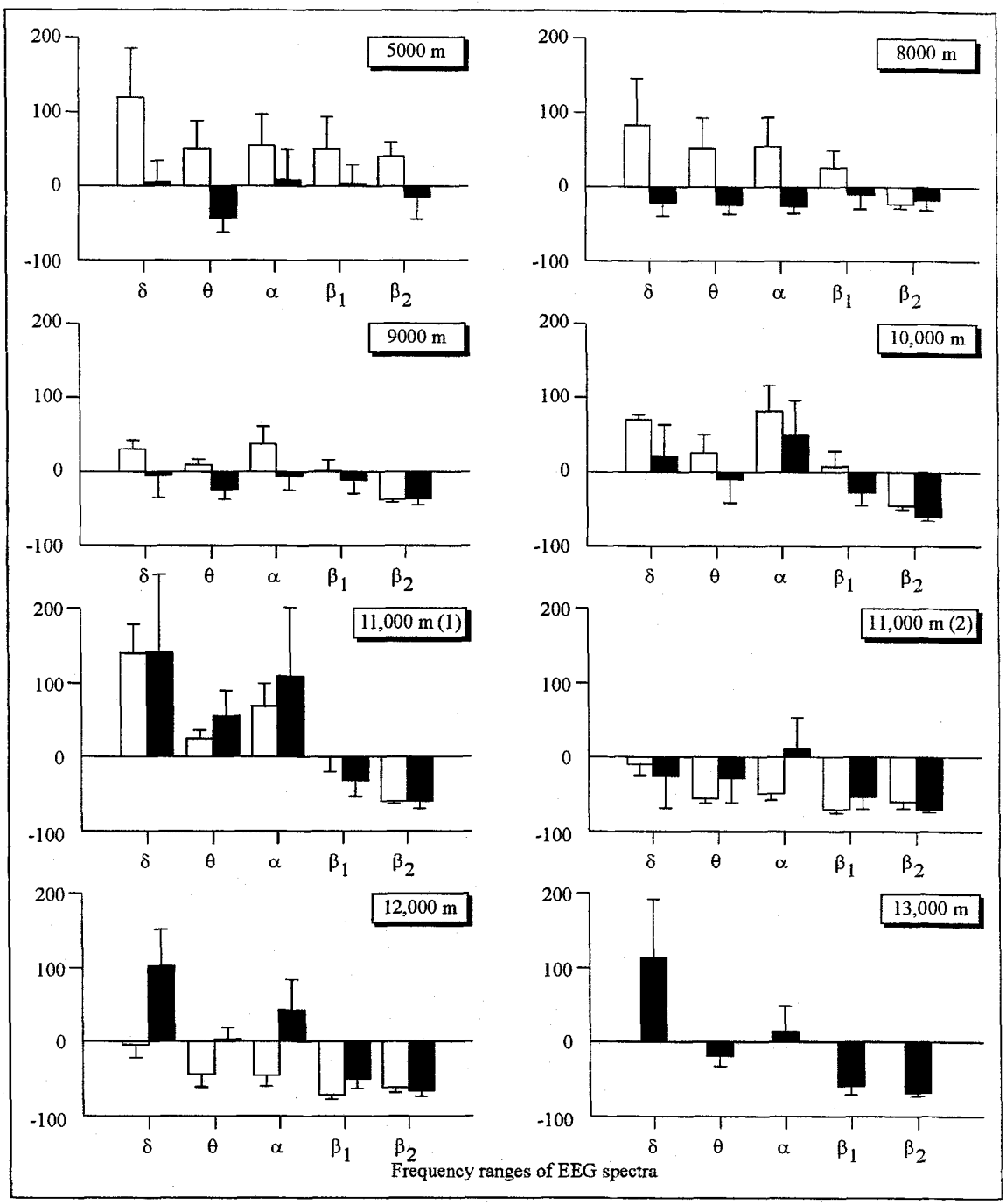

Fig. 2. Absolute power of EEG spectra in various frequency ranges at different altitudes in the left cortex of rats with high resistance to hypoxia. Here and in Fig. 3: ordinate: % of absolute power relative to baseline; white bars: control rats; black bars: yancarb-treated rats; (1) 1st-4th min EEG record; (2) 5th-8th min EEG record at 11,000 m.

11,000 m, although the total power tended to decrease below baseline. At these altitudes, in LR control rats the total power in the right hemisphere increased without any change in the left hemisphere [4]. In LR experimental but not control rats no changes in the level of interhemispheric asymmetry were observed at an altitude of 10,000 m and lower, while at higher altitudes the asymmetry increased considerably.

Yancarb also modified the power dynamics of EEG frequency spectra in various frequency ranges and their ratios under hypoxia. In the brain of HR rats at 5000 m, it considerably reduced the hypoxia-specific rise in the absolute power of all frequency ranges in both hemispheres (Fig. 2), and its protective effect was enhanced at 8000 m and persisted, though being less pronounced, at 9000 m. However,

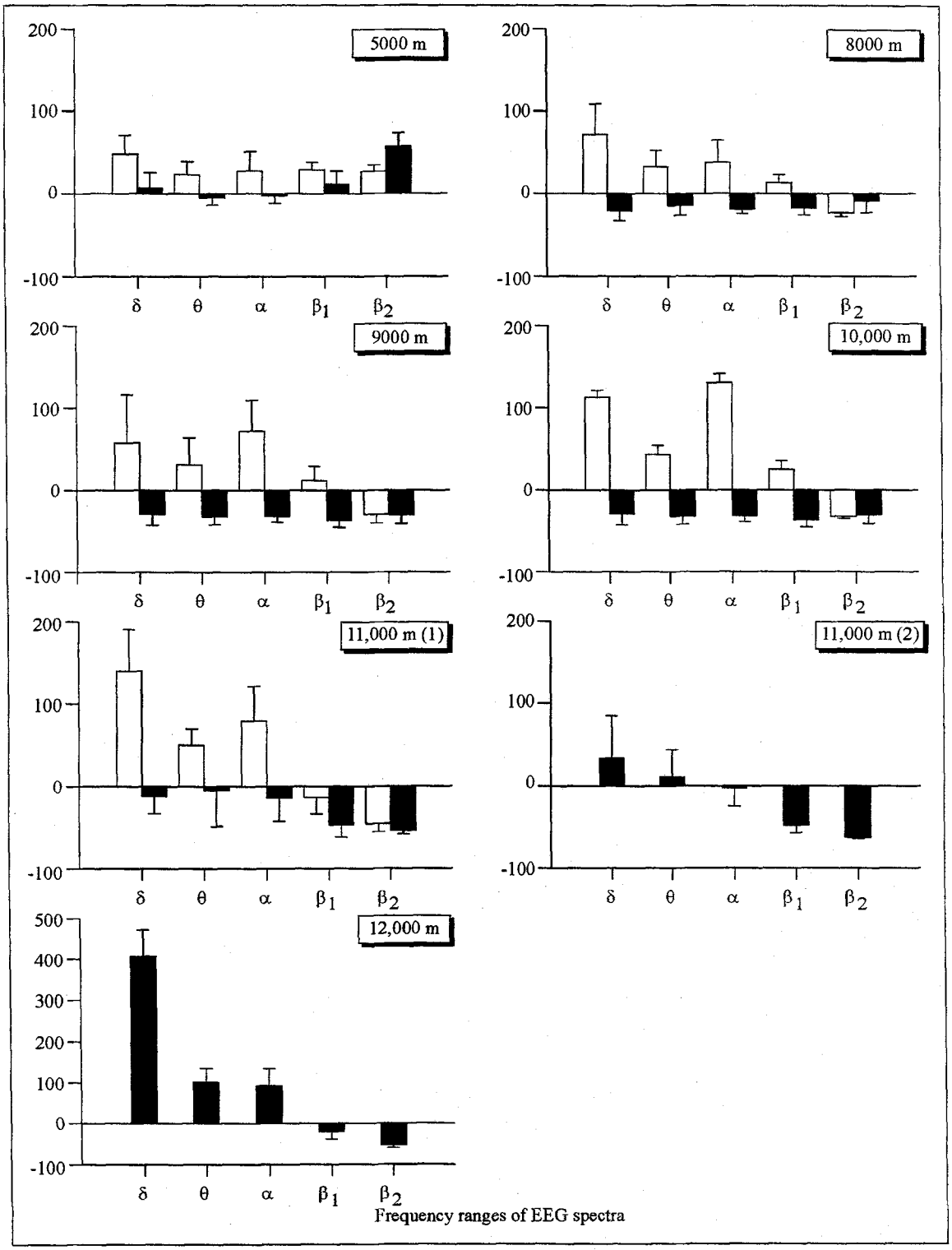

Fig. 3. Absolute power of EEG spectra in various frequency ranges at different altitudes in the left cortex of rats with low resistance to hypoxia.

yancarb had no effect on the dynamics of most frequency ranges in the cerebral cortex of HR rats at 10,000 m and higher and failed to limit the development of depression at 11,000 m if the rats remained at this altitude more than 4 min, nor did it limit the subsequent increase in the absolute and relative EEG spectral power at 12,000 and 13,000 m or the reduction in the power of β_1 and β_2 ranges at these altitudes (Fig. 2).

In LR rats, yancarb also prevented activation of all frequency ranges at 5000 m, with the exception of β_2 whose absolute and relative powers at this

altitude were 55% and 36%, respectively, than in LR controls (Fig. 3). The effect of yancarb in the left hemisphere was more pronounced than in the right, being stronger at the altitudes of 8000-10,000 m, where the pattern of EEG spectra was virtually the same as under normobaric conditions, by contrast to LR controls in which progressive increase in the power in the δ and α ranges with corresponding decrease in the β_2 range was observed [4]. In experimental LR rats, but not in LR controls, no terminal increase of absolute power in the δ, θ, and α ranges was observed at 11,000 m, although, like in LR controls, the fast-wave activity in the spectra was inhibited. The terminal phase in the EEGs of yancarb-treated LR rats (12,000 m) was characterized by a dramatic (400-700%) rise in the absolute power of δ waves and a 120-150% increase in the proportion of slow waves; the relative power of fast oscillations decreased by 80%.

Previously, we showed that the EEG spectrum dynamics characteristic of progressive hypoxia involves the emergence of a high amplitude, burst-like activity at 8000 m and higher [4]. In the present study, yancarb shifted the threshold for hypersynchronized activity of the δ range from 8000 to 9000 m and that for high amplitude activity in the α range from 9000 to 10,000 m, but had no effect on the paroxysmal activity in the θ range, which appeared at 8000 m, as in the control rats. Yancarb also reduced by 50% the total duration of such activity in all ranges.

Our data show that yancarb not only increases the resistance to acute hypoxia, but also prevents the development of phasic changes [4] in EEG power spectra recorded from the cerebral cortex in the altitudes range 5000-10,000 m in HR rats and 5000-11,000 m in LR rats, exerts antihypoxic effects both in HR and LR rats, although more pronounced and occurring in wider range in LR rats. The method used in this study to record EEG in unrestrained animals at different "altitudes" can be used for selecting antihypoxic agents capable of correcting brain dysfunction in acute hypoxia or ischemia.

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