PHYSIOLOGY

Individual Resistance of the Organism and Nerve Cell to Hypoxia

I. G. Vlasova and N. A. Agadzhanyan

UDC 615.217:615.272:612

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 118, № 11, pp. 454-457, November, 1994
Original article submitted January 25, 1994

The correlation between the pattern of a neuron's reaction to acute hypoxia and individual resistance to oxygen deficit is studied on rats *in vivo* as well as on surviving slices of their cerebellum *in vitro*. According to the survival time in a pressure chamber simulating an altitude of 11 km all the rats were divided into groups of high resistance, medium resistance, and low resistance to hypoxia. Survival time was 4.2 times longer in the high resistance group than in the low resistance group. In the cerebellar slices of high resistance animals 61.5% high-resistance neurons and 38.5% low-resistance neurons were recorded. On the other hand, in the high resistance animals the percentage of high-resistance neurons and low-resistance neurons was 31.2 and 68.8, respectively. The period of hypoxia development was 4.32 times longer in the high-resistance neurons as compared to low-resistance neurons. It is speculated that individual differences in the resistance to O_2 deficit are of a hereditary nature and manifest themselves not only on the level of the whole organism, but also in the individual nerve cell.

Key Words: *hypoxia; individual resistance; neurons*

It is known that during acute oxygen deficiency the first to be affected is the central nervous system, and hypoxia resistance, according to Palladini [10], is defined not by the vulnerability of liver cells but rather by the sensitivity of neurons. The selectivity of nerve cell damage in hypoxia was first described by C. and O. Vogt [13], who introduced the term "pathoclisis", attributing the individual susceptibility of neurons mostly to specific features of vascularization and possibly also of nervous tissue metabolism. Later the same conclusions were reached by other investigators [9,11,12,14]. A nonuniform pattern of response of neurons from different regions of the hippocampus to increasing hypoxia has been detected [8]. The existence of a correlation between the resistance of an individual organism as a whole and of an individual nerve cell to hypoxia remains an open question.

The goal of this work was to study the relationship between the response of individual neurons in surviving brain slices and of the organism as a whole to increasing hypoxia.

MATERIALS AND METHODS

The experiments were carried out on alert male white rats and their surviving cerebellar slices of 300-400 μ thickness. In order to determine the individual resistance to hypoxia the animals were "raised" in a pressure chamber to an altitude of 11 km at a rate of 150-200 m/sec. The resistance was estimated by the survival time (ST) at a given

Department of Normal Physiology, Russian People's Friendship University, Moscow

0007-4888/94/0011-1149$12.50

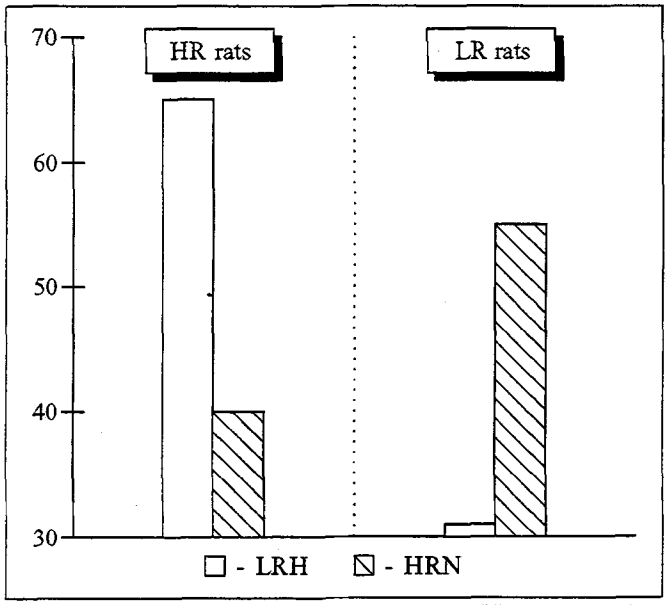

Fig. 1. Quantative distribution of HRN and LRN in cerebellar slices of HR and LR rats. Ordinate: percentage of HR and LR rats and of HRN and LRN.

altitude expressed as the appearance of the second agony inhalation. The rats with an ST equal to 1-3 min were allocated to the low resistance (LR) group, those with an ST of at least 9 min to the high resistance (HR) group, and those with an ST of 4-8 min to the medium resistance (MR) group. As had been shown earlier by other authors, the groups differed not only in ST, but also in the pattern of metabolism and behavior [2-5,7]. Two weeks following the altitude treatment, the rats were sacrificed; from each rat 3 sagittal sections including the cerebellar cortex and nuclei were obtained and exposed to a 60-min adaptation in oxygenated (95% O_2 and 5% CO_2) and thermostable (32-33°C) perfusate (Earle solution, pH 7.4), after which the extracellular impulse activity (IA) of cerebellar neurons (Purkinje cells) was studied under conditions of normoxia and increasing hypoxia. Hypoxia was simulated by reducing pO_2 from 100% to 0% (substitution of nitrogen for carbogen). The content of oxygen during its increasing deficiency and reoxygenation was recorded by a polarograph and on a Corning type microanalyzer. In parallel with the change of oxygen regime, the following parameters were recorded: IA of Purkinje cells; time from the beginning of hypoxia to the total inhibition of IA; rate of recovery of the initial values during reoxygenation. The reliability of the results was evaluated using Student's *t* test.

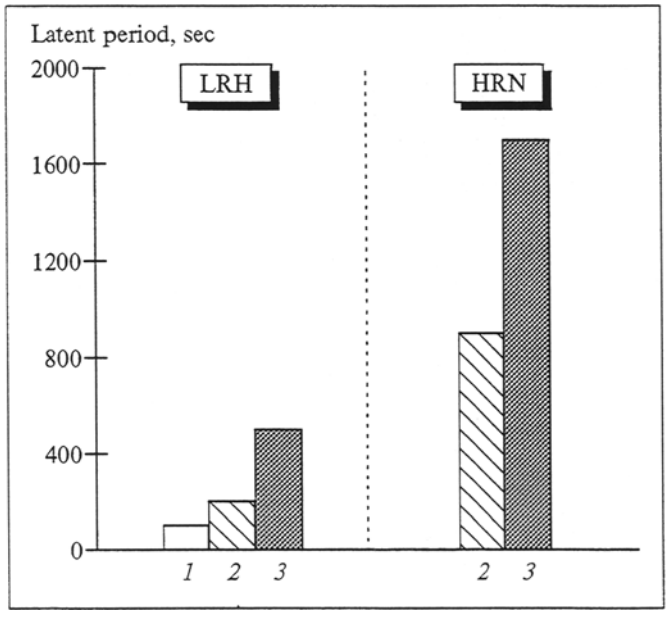

Fig. 2. Latent periods of phase transitions in IA of neurons in rat cerebellar slices under the influence of increased hypoxia. *1*) first inhibitory phase; *2*) activation phase; *3*) second inhibitory phase.

RESULTS

HR and LR rats were used in the experiments with surviving cerebellar slices. The ST of HR animals exceeded that of LR rats by a factor of 4.2 (Table 1).

Earlier in models of neuron culture *in vitro* and surviving slices we showed a phase type of response of neurons from different parts of the central nervous system to the decrease of pO_2, i.e., primary IA inhibition followed by hyperactivity and final total inhibition. In the course of reoxygenation the return of IA to the initial level is as a rule preceded by a phase of hyperactivity (activation overshoot) [6].

In the present experiments the period necessary for the development of the hypoxic state (i.e., from the initial level taken as 100% to total IA inhibition) proved to be different for the slices taken from HR and LR rats (Table 1). Neurons developing hypoxia more quickly were classified as low-resistance neurons (LRN), and those with prolonged hypoxia development as high-resistance neurons (HRN). A correlation is noted between the period of hypoxia development in HRN and LRN on the one hand and ST of HR and LR rats. In the case of HRN the development of the hypoxic state took 4.32 times longer than in LRN.

Both types of neurons were present in LR and in HR rats; however, in the LR animals the percentage of LRN exceeded that in the HR rats (68.8% and 31.2%, respectively), while in the cerebellar slices of HR rats the level of LRN was estimated as 38.5% and the level of HRN as 61.5% (Fig. 1).

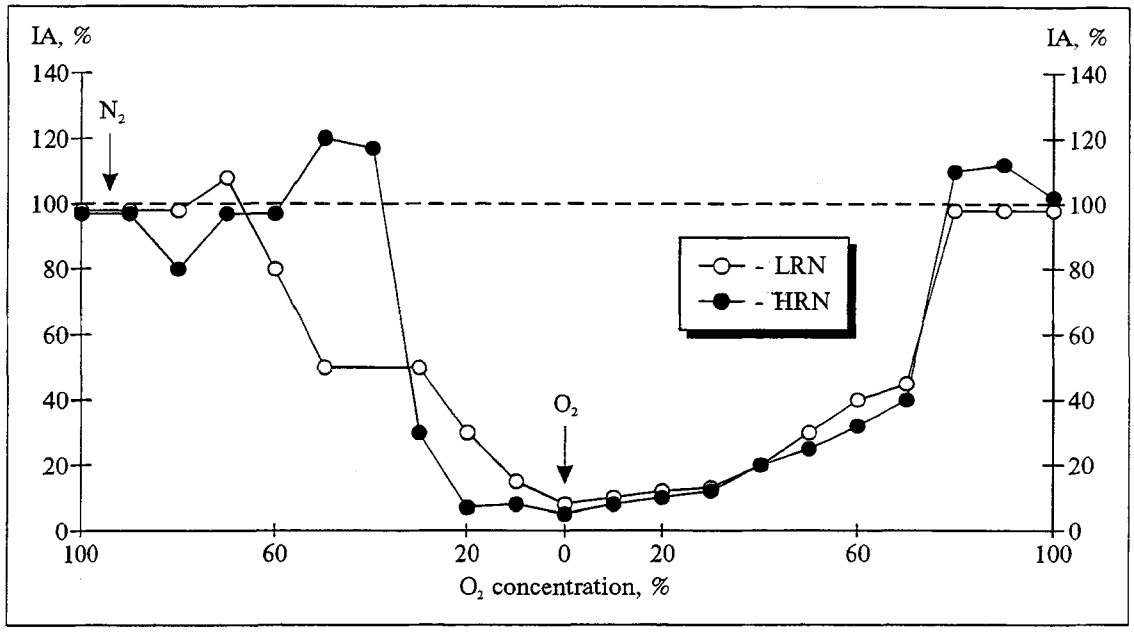

Fig. 3. Phase changes of IA in HRN and LRN in rat cerebellar slice induced by increasing hypoxia and during reoxygenation. Dotted line represents initial IA.

It is worth mentioning that LRN and HRN exhibit opposite types of reaction to the pO_2 decrease in the medium. LRN are characterized by a considerable reactivity expressed in the appearance of the first inhibition phase with a 20-25% IA decrease as soon as 130.0±3.68 sec (Fig. 2) after the start of hypoxia treatment, at pO_2 equal to 70-80% (78.8±1.69%) (Fig. 3), and a distinct activation phase with a latent period of 296.0±8.79 sec at pO_2 in the range of 40-60% (58.0±3.21%) with a 15-25% increase in spike frequency as compared to the initial level. The activation phase was followed by a second inhibitory (terminal) phase with a latent period of 621.66±6.84 sec and a 50% fall of IA (O_2 concentration at that time 36.3±0.65%). Total IA blocking took place at a relatively zero O_2 concentration in the perfusate.

Unlike LRN, HRN as a rule lacked the first inhibitory phase; an activation phase was not always recorded and it was weakly expressed, with a latent period of 1086.6±38.14 sec at a O_2 concentration within 80-70% (76.4±1.52%), and was followed by a gradual decrease in the frequency of IA. Then a plateau of IA (50% of the initial value) was observed within the 60-30% range of O_2 concentration. Only when pO_2 fell below 30%, did an inhibition (though less steep than in the case of LRN) of IA occur with a latent period of 1949.0±93.4 sec.

The reoxygenation-associated restoration period for LRN was shorter - 732.0±4.6 sec at pO_2 92.0±5.96%, than for HRN - 1006.6±77.19 sec at pO_2 94.12±3.02%, and was associated with activation overshoot at pO2 within 80-90%. As a result of oxygenation, the IA was restored to the initial level in 28% of LRN and 70% of HRN.

Comparative analysis revealed a significant reactivity of LRN exceeding that of HRN and demonstrated in a prominent phase type of LRN reaction to the oxygen deficiency. The low hypoxia resistance of LRN was also shown in the shorter latent periods of the development of all hypoxia phases and the comparatively high levels of O_2 at which total IA inhibition occurred. The distinctive features of HRN were the lack of primary inhibition of IA, low reactivity, less pronounced activation phase, the ability to retain the 50% level of IA for a long time despite the increasing hypoxia,

TABLE 1. Time of Development of Hypoxic State in Rats and Neurons with Different Resistance to Oxygen Deficiency ($M \pm m$)

Type of rat	ST, sec	Type of neurons	Time of development of hypoxic state in cerebellar neuron (till total IA blocking), sec
LR	130.62±0.81	LRN	380.0±21.01
HR	549.6±3.21	HRN	2510.0±144.08

Note. All differences are reliable ($p<0.01$)

and total inhibition attained at a lower pO_2 as compared to LRN. All these features are evidence of the significant adaptive capacities of HRN as compared to LRN, as well as of the different metabolic pathways involved in their realization. This hypothesis has found confirmation in the morphological studies of other authors [1], who observed a predominance of "dark" neurons in the sensorimotor cortex of HR as compared to LR rats, the presence of which is an index of compensatory processes in hypoxia-resistant animals.

An interesting analogy is noted between the behavior of LR rats and LRN reactions during acute oxygen deficieny. During the "lifting" LR animals demonstrated extreme anxiety, they were characterized by intensive locomotor activity, frequent seizures, and high reactivity, which was also intrinsic to the LRN. On the other hand, the HR animals showed no inappropriate movements, and an economy of reactions was observed, as is the situation with HRN, which did not exhibit sharp alterations of electric activity despite the increasing hypoxia. All the above-mentioned properties enable HR animals and their nerve cells to promptly activate the emergency mechanisms of adaptation to a given extreme factor.

Thus, individual differences in the response to hypoxia are of a hereditary nature, and are realized primarily at the level of the genome of the individual nerve cell, whose metabolism determines the functioning of organs, systems, and the organism as a whole under conditions of oxygen deficiency.

REFERENCES

1. E. I. Baranova, *Mechanisms of Adaptation of the Physiological Functions of the Organism* [in Russian], Tomsk (1985), p. 78.
2. V. A. Berezovskii, K. A. Boiko, *et al., Hypoxia and Individual Peculiarities of Reactivity* [in Russian], Kiev (1978).
3. V. A. Berezovskii, T. V. Serebrovskaya, and A. A. Ivashkevich, *Kosm. Biol.*, **21**, № 1, 34 (1987).
4. O. A. Boiko, L. A. Kurbakov, and T. P. Gridina. *Current Topics in Modern Physiology* [in Russian], Kiev (1986), p. 151.
5. L. D. Luk'yanova, *Physiological Problems of Adaptation* [in Russian], Tallin-Tartu (1984), p. 128.
6. L. D. Luk'yanova, and I. G. Vlasova, *Byull. Eksp. Biol. Med.*, **108**, № 9, 266 (1989).
7. N. A. Patkina, V. V. Zagustina, and B. G. Bershadskii, *Zh. Vyssh. Nervn. Deyat.*, **31**, № 6, 1224 (1981).
8. K. Kawasaki, S. F. Traynels, and R. Dingledine, J. Neurophysiol., **63**, № 3, 385 (1990).
9. T. Kirino, A. Tamura, and K. Sano, *Prog. Brain Res.*, **63**, 39 (1985).
10. G. Palladini, A. Conforti, and L. Medolago-Albani, *Brain Res.*, **10**, № 1, 45 (1976).
11. W. A. Pulsinelli, *Prog. Brain Res.*, **63**, 29 (1985).
12. R. Suzuki, T. Yamaguchi, and Y. Inava, *Ibid.*, p. 59
13. C. Vogt and O. Vogt, *J. Psychol. Neurol.*, **47**, 237 (1937).
14. T. Wieloch and B. K. Siesjo, *Prog. Brain Res.*, **63**, 69 (1985).