Effect of Hypobaric Hypoxia on the Development of Long-Term Posttetanic Potentiation in Slices of Rat Olfactory Cortex: Correction with Hypoxic Preconditioning

Ya. E. Lyubimov, E. I. Tyulkova, and M. O. Samoilov

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We studied the effect of *in vivo* hypobaric hypoxia on the development (after 3 h) of *in vitro* long-term posttetanic potentiation in Wistar rats. Severe hypoxia suppressed induction of posttetanic potentiation in slices of the olfactory cortex. Preconditioning exposure (moderate hypobaric hypoxia) prevented inhibition of posttetanic potentiation induced by severe hypoxia.

Key Words: *preconditioning; hypobaric hypoxia; posttetanic potentiation; olfactory cortex*

Neurobiological studies over the last decade revealed and deciphered the phenomenon of ischemic/hypoxic tolerance of the brain [7,8], *i.e.* improvement of neuronal resistance after moderate hypoxia/ischemia exposures (preconditioning) [4].

The protective effects of pre-exposure to moderate hypoxia are usually evaluated by morphological criteria of neuronal survival in various brain areas (*e.g.*, hippocampus) after exposure to severe hypoxia/ischemia. Our previous studies showed that severe hypobaric hypoxia induces massive death of neurons (apoptosis) in sensory structures of rat brain (CA1-CA4 fields of the hippocampus, piriform cortex, and neocortex). This effect was diminished after preconditioning [3,9].

The effect of severe hypoxia on functional activity of neurons in the archicortex and neocortex of preconditioned and non-preconditioned animals remains unknown.

Bioelectric activity is one of the main criteria of functional activity of neurons. This characteristic reflects the mechanisms of various forms of synaptic plasticity, including long-term potentiation of synaptic transmission. Long-term posttetanic potentiation (LTPP) of synaptic transmission is extensively used as a model of nonassociative learning at the synaptic level. The amplitude and slope of the excitatory postsynaptic potential (EPSP) in neurons remain high for a long time (tens of minutes) after short-term (several seconds) high-frequency (100 Hz) stimulation of afferent fibers. Here we studied the effect of harmful or protective hypobaric hypoxic exposure (HE) on LTPP induction in neurons of rat olfactory cortex.

MATERIALS AND METHODS

Experiments were performed on male Wistar rats weighing 180-200 g. Two series were performed. The animals were exposed to different regimens of HE before electrophysiological studies. In series I (severe HE) pressure in a flow altitude chamber decreased to 180 mm Hg, which corresponded to a height of 11,000 m (3-h exposure). In series II (moderate hypoxic preconditioning) the animals were repeatedly (3 times with 24-h intervals) elevated to a height of 5000 m. Pressure in an altitude chamber was 360 mm Hg (2-h exposure). Severe

I. P. Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg. ***Address for correspondence:*** anoxia@pavlov.infran.ru. M. O. Samoilov

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hypoxia was presented 24 h after the last preconditioning exposure. In control animals, the induction of LTPP was studied without hypobaric exposure.

Tangential slices (400-500 μ) from the olfactory cortex of rats exposed to hypoxia in an altitude chamber were placed in an incubation medium containing 132.0 mM NaCl, 4.5 mM KCl, 1.2 mM Na_2HPO_4, 1.3 mM $MgSO_4$, 2.3 mM $CaCl_2$, 2.5 mM $NaHCO_3$, 7.5 mM HEPES, and 10 mM glucose (pH 7.35-7.40). The medium was saturated with oxygen. The temperature was maintained at 36°C. The lateral olfactory tract was stimulated with single rectangular pulses (0.07 msec, 1-5 V) delivered through platinum bipolar electrodes of an ESU-1 stimulator. Focal potentials in slices were recorded using glass microelectrodes filled with 1 M NaCl (7-10 MΩ). The reference electrode was placed in a chamber. Focal potentials were amplified and transmitted to a computer. The signals were recorded and processed with special software. The amplitude of EPSP was measured from the isoline to the peak.

Potentiation (tetanic stimulation) was induced by 500 pulses: 5 trains of 100 pulses each, 1 sec duration, 1 sec interval, 100 Hz frequency, 90% of maximum intensity. Focal potentials in response to single test pulses were recorded before and after tetanic stimulation. Potentiation treatment (induction of posttetanic potentiation) was performed 3 h after severe HE.

The results were analyzed by Student—Fisher *t* test ($p<0.05$).

RESULTS

Potentiation stimulation was followed by the development of long-term potentiation in control animals. EPSP amplitude increased to 125% of the basal level after 20-min potentiation and remained unchanged over 40-50 min. EPSP amplitude progressively decreased in the follow-up period and reached the basal level by the 75th minute of posttetanic potentiation (Fig. 1, *1*).

Severe HE *in vivo* (series I) impaired induction of potentiation. Tetanic stimulation 3 h after severe HE did not increase EPSP amplitude in all 7 slices (Fig. 1, *2*).

Moderate hypoxic preconditioning (series II) abolished the effect of severe HE on potentiation. No significant differences were revealed between posttetanic potentiation in series II and control series. The induction of potentiation did not differ in series II and control animals (Fig. 1, *3*). Our results are consistent with published data that hypoxic preconditioning has a protective effect [4,5].

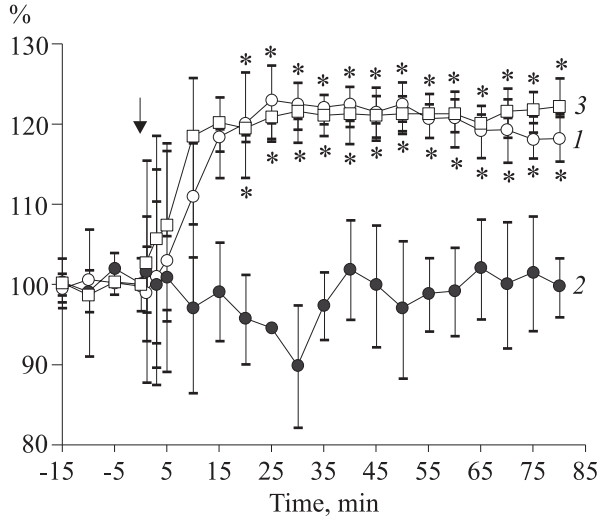

Fig. 1. Effect of severe hypobaric hypoxia on LTPP in preconditioned and non-preconditioned animals. Posttetanic potentiation in control animals (*n*=7, *1*); the absence of posttetanic potentiation in non-preconditioned animals after severe hypoxia (*n*=7, *2*); posttetanic potentiation in preconditioned animals after severe hypoxia (*n*=5, *3*). Arrow: tetanic stimulation. **p*<0.05 compared to animals exposed to severe hypoxia (*2*).

We found that learning and skill performance in non-preconditioned rats were impaired in the early period after severe HE. These abnormalities were less significant in preconditioned animals [1, 9]. Moreover, hypobaric hypoxic preconditioning improves neuronal survival after severe HE [3,9] and contributes to the tolerance of neurons to severe anoxia in brain slices [2,6].

Our results indicate that moderate hypobaric hypoxic preconditioning abolishes impairment of LTPP induction, an elementary form of learning at the cellular level, under conditions of severe hypoxia.

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