BRAINSTEM MITOCHONDRIAL DYSFUNCTION AND NMDA RECEPTOR PATHWAY IN BREATHING ADAPTATION TO INTERMITTENT HYPOXIA

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The glutamatergic mechanism is an important element of respiratory rhythm generation in brainstem structures. Brain glutamate (Glu) content can be closely related to the intensity of ATP production by means of ATP influence on Glu decarboxylase (GAD) activity and a corresponding Glu transformation into γ-aminobutyric acid (GABA). It is known that deviations of mitochondrial (MT) energy metabolism (preferentially related to the complex I activity in the MT respiratory chain) are frequently manifested as non-specific reaction at early stages of pathological disorders, in hereditary anomalies, during aging and under acute hypoxia/ischemia episodes. We examined Glu NMDA pathways as one of the breathing regulation mechanism during adaptation to intermittent hypoxia treatment (IHT) in Wistar rats with experimental brainstem mitochondrial dysfunction (rotenone, 3 mg/kg, s.c.). The control rats (n=20) and rats with experimental brainstem mitochondrial dysfunction (EBMD, n=20) were subjected to IHT during 14 days (15 min hypoxia (12% O_2), 15 min room air breathing, 5 times per day). The MT energy metabolism in brainstem neurons was studied by Chance method with Clark electrode. Time-volume parameters of ventilation were estimated from diaphragmatic EMG activity (the amplitude of EMG which reflected V_T; frequency of EMG (*f*), and integrated EMG activity during 1-min intervals - minute diaphragmatic EMG output (MDO) as an index of minute ventilation). Diaphragmatic EMG was recorded under hypoxic loading (12% O_2) during 2.5 min intervals. The role of Glu in the mechanisms of breathing regulation was examined during the injection of a selective NMDA receptors blocker MK-801 (3 mg/kg, i.p.). Rotenone lowered respiration and ATP production at all metabolic states in brainstem neuronal MT, switching NAD oxidation to succinate-oxidative pathway. Adaptation to IHT in the EBMD animals significantly enhanced of MT energy metabolism in brainstem neurons and approached it to the control values. In the control rats, MK-801 reduced the peak MDO values ($p<0.05$) and made iit difficult to maintain MDO above the initial level at the last stage of the hypoxic respiratory response ($p<0.05$). At the same time, in this case, MK-801 reduced *f* of diaphragmatic EMG. The adaptation to IHT in the control rats was accompanied by more early reached MDO peak and a significant depression of V_T in hypoxic respiratory reaction under MK-801 injection. Accordingly, EBMD was characterized by a dramatically decreased MDO peak (2-fold, $p<0,.05$) and a paradoxical tendency to heighten MDO by 36% at the late stage of the hypoxic respiratory response to hypoxia. EBMD lead to a critical *f* depression at peak and in the late phase of response relatively to control ($p<0.05$). In the EBMD rats, MK-801 injection promoted a noticeable heightening in MDO, V_T, *f* of diaphragmatic EMG-activity in the last stage of the hypoxic respiratory response. IHT adaptation in the EBMD animals resulted in MDO and *f* components augmentation (by 20% and 34%, correspondingly) at the initial stage of hypoxic loading. After IHT, blockade of Glu NMDA receptors in the EMBD rats was characterized by *f* enhancement ($p<0.05$) and a tendency toward V_T rise in the last stage of the hypoxic respiratory response. Thus, a drop of brainstem MT energy production reduced the involvement of Glu NMDA pathways in the breathing regulation mechanism. This phenomenon could be based on the Glu decrease due to ATP insufficiency to Glu transformation into GABA in brainstem nuclei and subsequent paradoxical GABA effects on the hypoxic respiratory response during blockade of NMDA pathways. At the same time, there is adaptation to IHT accompanied by partial improvement of MT energy metabolism in brainstem structures and a shift in diaphragmatic EMG formation. The effect of IHT adaptation on diaphragmatic EMG could be related to Glu/GABA balance in the brainstem respiratory rhythm generator.