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BRAINSTEM MITOCHONDRIAL ENERGY PRODUCTION AND GLUTAMATE NMDA RECEPTOR PATHWAYS IN BREATHING REGULATION DURING HYPOXIA

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Glutamate (Glu) is considered the main excitatory neurotransmitter in the formation of respiratory activity in the central pattern generator under both normoxic and hypoxic conditions. At the same time, Glu level is closely related to the intensity of ATP production in the brain by means of the ATP influence on Glu decarboxylase activity (GAD) and the correspondent transformation of Glu into GABA. Deviations of mitochondrial (MT) energy metabolism (preferentially related to the activity of complex I in the MT respiratory chain) are frequently manifested as a non-specific reaction in early stages of any pathological disorders, in specific hereditary anomalies, in aging, and under acute hypoxic/ischemic episodes. We studied the relationship between the brainstem MT energy production and Glu NMDA receptor pathways in the mechanisms of breathing regulation during hypoxic episodes in Wistar rats; control animals (6 months, n=10) and animals with experimental brainstem MT dysfunction (EBMD) (6 months, n=10). Processes of the MT energy metabolism in brainstem neurons were evaluated by a Chance method with a Clark electrode. The time-volume parameters of ventilation were estimated from the integrated diaphragmatic EMG-activity during 1-min intervals - minute diaphragmatic EMG output (MDO) as an index of minute ventilation. Diaphragmatic EMG activity was recorded under hypoxic loading (12% ?2) during 2.5 min intervals. The role of Glu in the mechanisms of breathing regulation was examined during the injection a selective NMDA receptors blocker MK-801 (3 mg/kg, i.p.). EBMD was provoked by rotenone (3 mg/kg), a specific inhibitor of the complex I in the MT respiratory chain. Rotenone infusion was accompanied by a significant drop in tissue respiration and ATP production in all metabolic states (V3, V4, V3/V4, ?TP/? under the oxidation of glutamate+malate and succinate+rotenone, ?<0.05) in the brainstem neurons. Accordingly, EBMD was characterized by dramatically decreased MDO peaik (2-fold, $p<0.05$) and by paradoxical tendency to heightened MDO (36%) at a late stage of the respiratory response to hypoxia. EBMD lead to critical depression of breathing frequency (by 42% at peak, 44% at a late phase of the response relatively to control, $p<0.05$) and by less affected amplitude of diaphragmatic EMG-activity. During EBMD, blockade of Glu NMDA receptors provoked a paradoxical rise in MDO at a late stage of the response to hypoxia (21%). Accordingly, in EBMD animals blockade of Glu NMDA receptors did not appreciably affect frequency of diaphragmatic EMG activity. At the same time, in the EMBD rats, blockade of Glu NMDA pathways was accompanied by a noticeable impairment of the amplitude component of diaphragmatic EMG activity at a late stage of the response to hypoxia. In this case amplitude was heightened relatively to the analogous control without EMBD ($p<0.05$). Thus, a gradual decline of the brainstem MT energy production reduced the involvement of Glu NMDA pathways in the mechanisms of breathing regulation. This

phenomenon can be explained by a drop of Glu level, ATP insufficiency for Glu transformation into GABA, or by subsequent paradoxical GABA effects on the hypoxic respiratory response during blockade of central NMDA pathways.