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THE EFFECT OF PRO-INFLAMMATORY CYTOKINE IL-1β ON THE CENTRAL AND PERIPHERAL RESPIRATORY CONTROL MECHANISMS ON THE BACKGROUND OF SEVERE HYPOXIA

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ВЛИЯНИЕ ПРОВОСПАЛИТЕЛЬНОГО ЦИТОКИНА ИЛ-1β НА ЦЕНТРАЛЬНЫЕ И ПЕРИФЕРИЧЕСКИЕ МЕХАНИЗМЫ РЕГУЛЯЦИИ ДЫХАНИЯ НА ФОНЕ ТЯЖЕЛОЙ ГИПОКСИИ

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Pro-inflammatory cytokine IL-1β, as inflammatory mediators participate in neuroimmune interactions in the central nervous system. It's assumed that IL-1β affect the central and peripheral breathing control in acute hypoxia that occurs simultaneously with systemic inflammation. The purpose of this study was to evaluate the influence IL-1β on respiratory responses following progressive hypoxia and ability to survive after hypoxic apnea. We studied the influence of IL-1β (10 μg/kg) on respiration and the ability to survive acute hypoxic challenge in anesthetized Wistar rats. The response of tidal volume, breathing rate, minute lung ventilation, oxygen saturation, during acute hypoxia was examined using pneumotachography methods. Increasing hypoxia was created by rebreathing method. The results indicated that during progressive acute hypoxia animals given IL-1β were unable to sustain breathing efforts for as long as control rats. Following hypoxic apnea IL-1β decrease the ability to autoresuscitate compared with control groups. Thus IL-1β reduces the tolerance of animals to acute hypoxia and the ability to spontaneously autoresuscitate after apnea. We assume that that IL-1β inhibit inspiratory neurons and decrease the sensitivity of the carotid chemoreceptors to hypoxic stimulation.

Keywords: pro-inflammatory cytokines; breathing control; acute hypoxia.

Провоспалительный цитокин IL-1β в качестве медиатора воспаления участвует в нейроиммунных взаимодействиях в центральной нервной системе. Предполагается, что IL-1β влияет на центральные и периферические механизмы регуляции дыхания при острой гипоксии, возникающей одновременно с системным воспалением. Целью исследования явилось изучение влияния IL-1β на респираторные реакции в условиях прогрессирующей гипоксии и способность к спонтанному восстановлению дыхания после гипоксического апноэ. На наркотизированных крысах линии Wistar изучали влияние IL-1β (10 мг/кг) на реакции респираторной системы в условиях прогрессивно нарастающей гипоксии и выживаемость после гипоксического апноэ. Методом пневмотахографии регистрировали дыхательный объем, частоту дыхания, минутную вентиляцию легких, насыщение артериальной крови кислородом. Нарастающую гипоксию воспроизводили методом возвратного дыхания. Результаты показали, что IL-1β уменьшает устойчивость респираторной системы к прогрессирующей острой гипоксии и возможность спонтанного возобновления дыхания после апноэ в постгипоксическом периоде. Предполагается, что снижение устойчивости организма к прогрессивно нарастающей гипоксии происходит в результате депрессивного влияния IL-1β на активность инспираторных нейронов дыхательного центра и чувствительность каротидных хеморецепторов к гипоксической стимуляции.

Ключевые слова: провоспалительные цитокины; регуляция дыхания; острая гипоксия.

Introduction. It is known that pro-inflammatory cytokines such as interleukin-1β (IL-1β), as inflammatory mediators participate in neuroimmune interactions in the central nervous system [1]. The expression of cytokines and their receptors was found in the respiratory center, on the carotid body's glomus cells — structures that carry out central and peripheral mechanisms of breathing control. In the development of pathological conditions an important role belongs to IL-1β, which is produced in the acute phase of the immune response in response to infection and inflammation. IL-1β has been shown to be the main mediator between the inflammation and hypoxemia leading to decrease the functional reserves of the respiratory system and developing a terminal state, often leading to death [2]. It is assumed that proinflammatory cytokines can affect the central and peripheral mechanisms of regulation of respiration in acute hypoxia. The aim of this study was to evaluate the influence IL-1β on respiratory responses following progressive hypoxia and ability to survive after hypoxic apnea.

Material and methods. We studied the influence of IL-1β (10 μg/kg) on respiration and the ability to survive acute hypoxic challenge in anesthetized Wistar rats. The response of tidal volume (VT), breathing rate (BR), minute lung

ventilation (MLV), oxygen saturation (SpO_2), esophageal pressure (Pes), the appearance time of apnea (ATA), inspired oxygen concentration (F_IO_2) during acute hypoxia was examined. Increasing hypoxia was created by rebreathing method.

Results and discussion. In control rats at acute hypoxia VT exceeded the normoxic values by $237 \pm 31\%$ ($p < 0{,}05$), Pes by $620 \pm 57\%$ ($p < 0{,}001$). BR_and MLV decreased by 92% ($p < 0.001$) and $70 \pm 13\%$ ($p < 0.001$), respectively. In rats with IL-1β VT was $322 \pm 37\%$ ($p < 0.05$), Pes and MLV increased by $264 \pm 28\%$ ($p < 0.05$) and by $151 \pm 21\%$ ($p < 0.05$). BR decreased by $40 \pm 7\%$ ($p < 0.05$) as compared with the normoxia. In control rats, apnea occurred when F_IO_2 decreased to 4–3%, in experimental rats to 8–7%. The duration of apnea in the control group was 44.2 ± 3 seconds, in rats with IL-1β — 31.2 ± 4 seconds. Spontaneous respiration recovery in the post-hypoxic period was observed only in 50% of experimental animals, whereas in control rats survival was 100%. The results show that the effect of IL-1β to a greater extent affected the neurons of the dorsal respiratory group, causing a more significant increase in the VT and Pes in animals of the experimental group, rather than BR. A large degree of mortality in the experimental group could be associated with the depressive effect of IL-1β on the central mechanisms of respiratory regulation, which form inspiratory effort. An earlier onset of apnea with a lesser degree of hypoxia in experimental rats could be a consequence of the effect of IL-1β on the chemoreflex (peripheral) mechanisms of breathing control, causing a decrease in the sensitivity of the carotid chemoreceptors to hypoxic stimulation.

Conclusion. Thus, hypercytokinemia reduces the tolerance of anesthetized animals to acute hypoxia and the ability to spontaneously autoresuscitation after apnea. It is assumed that the basis of the mechanisms of reducing the resistance to acute hypoxia is peripheral and central mechanisms of respiratory control.

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