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The Role of ATP-Sensitive Potassium Channels and Nitric Oxide in the Protective Effect of Preconditioning of the Brain

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Objective. The role of ATP-dependent potassium (K^+_{ATP}) channels in the neuroprotective effect of ischemic (IPre) and pharmacological (PPre) preconditioning and changes in blood levels of nitric oxide (NO) metabolites were studied in conditions of cerebral ischemia. **Materials and methods.** Ischemic stroke (IS) was modeled in male rats (n = 86) by electrocoagulation of a branch of the middle cerebral artery (MCA). The nonselective K^+_{ATP} channel blocker glibenclamide and the K^+_{ATP} channel activator diazoxide were used. IPre and PPre were performed one day before MCA occlusion. Blood concentrations of NO, nitrates (NO_3^-) and nitrites (NO_2^-) were determined in experimental animals at 5, 24, and 72 h after MCA occlusion. Results. IPre decreased the lesion zone by 37% ($p < 0.05$), while prior administration of glibenclamide countered the action of IPre. The protective effect of PPre was analogous to that of IPre. Decreases in blood levels of oxygenated R-conformers of hemoglobin-bound NO (Hb-NO) were seen 5 h after MCA occlusion, with an inversely proportional increase in the concentration of nonoxygenated T-conformers; there were also increases in NO_3^- and NO_2^- concentrations. NO_3^- and NO_2^- levels showed normalization by one day after MCA occlusion, along with changes in the concentrations of Hb-NO complexes – R-conformers dominated, while the blood level of T-conformers reached a minimum. Furthermore, by 24 h there was a correlation between blockade of K^+_{ATP} channels and decreases in serum NO_3^- and NO_2^- levels ($p < 0.03$). **Conclusions.** The neuroprotective effect of preconditioning was due to activation of K^+_{ATP} channels. Analysis of blood levels of NO metabolites in rats with IS showed that Hb-NO complexes in the R-conformation stored and carried NO to the tissues, releasing NO on occurrence of the R → T transition in ischemic conditions.

Keywords: cerebral ischemia, ischemic tolerance, neuroprotection, preconditioning phenomenon, ATP-dependent potassium channels, nitric oxide, hemoglobin, spectrophotometry, electron paramagnetic resonance.

The resistance of the brain to deficient blood supply can increase in response to brief episodes of ischemia-reperfusion or hypoxia [1], transient hypothermia [2], or other moderate stressors able to activate endogenous defense mechanisms and increase tissue resistance to subsequent severe ischemia [3–5]. This phenomenon is termed preconditioning. Activation of adenosine triphosphate-dependent potassium (K^+_{ATP}) channels is regarded as the main component of responses in models of preconditioning [3]. Decreases in ATP levels during ischemia lead to opening of K^+_{ATP} channels in the plasma membrane; the role of these channels is to restore low concentrations of Na^+ and Ca^{2+} ions in the cytosol and prevent depolarization. Activation of K^+_{ATP} channels in the inner mitochondrial membrane is associated with protecting mitochondria against Ca^{2+} ion overload [6]. The leading role in the development of preconditioning is played by the mitochondrial pool [7].

The role of nitric oxide (NO) in the development of ischemic cell damage is just as important. The nature of the action of NO depends on the intensity and location of its

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