Neuroprotective Activity of Angiotensin-Converting Enzyme Inhibitors in Cerebral Ischemia

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Captopril and enalapril improved rat survival after ischemia caused by bilateral occlusion of the common carotid arteries. The neuroprotective effect of the angiotensin-converting enzyme inhibitors was confirmed by histological examination.

Key Words: *angiotensin converting enzyme inhibitors; cerebral ischemia; neuroprotective effect; nuclear pyknosis; perivascular edema*

Captopril, enalapril, and other angiotensin-converting enzyme (ACE) inhibitors are widely used in cardiology, especially in the treatment of essential hypertension [1-4], which is often accompanied by ischemic disturbances of cerebral circulation. Therefore, neuroprotective activity of ACE inhibitors is a practically important problem.

MATERIALS AND METHODS

Cerebral ischemia was modeled by bilateral ligation of the common carotid arteries (CCA) in acute experiments on outbred rats (n=60, 200-250 g) anesthetized with ether. The neuroprotective effects of captopril and enalapril were evaluated by the postischemic survival rate and histological examination of brain tissue. The test drugs were injected intraperitoneally 50-60 min before or 30-40 min after ligation. An equal volume of saline was injected into control rats.

RESULTS

The postischemic survival in the control group was only 20-30%. The majority of animals died within 24 h postocclusion, while survivors gradually recovered and one week after ligation practically did not differ from intact animals.

Preliminary administration of Captopril in doses of 0.1, 1, and 5 mg/kg increased the survival rate to 57, 70, and 83%, respectively. No positive effect was obtained with higher doses. The neuroprotective effect was also observed after early postischemic administration of captopril (5 mg/kg, 20-30 min postocclusion), while the same dose administered in the late postischemic period (6 h postocclusion) had practically no effect (survival rate was 34%).

Preliminary injection of enalapril in doses 0.25, 1, and 5 mg/kg improved animal survival to 40-60%, while administration of this drug 20-30 min after ischemia had no effect on this parameter.

Brains for histological examination were isolated from rats sacrified under halothane anesthesia (to preserve blood filling of a microcirculatory bed), embedded in paraffin, and 3-5-μ slices were prepared. The slices were stained by the Nissl's method [5].

Histological examination of the brain tissue after cerebral ischemia in the control group revealed constricted arterial vessels with solitary erythrocytes and dilated plethoric venous vessels. Perivascular and pericellular edema was most pronounced in cortical areas. Single and grouped neurons with swollen bodies, signs of tigrolysis, perinuclear edema, and pyknosis were observed in the cerebral cortex. There also occurred proliferation of glial elements with signs of neurophagia (Fig. 1, *a*).

Similar, although less pronounced histological and hemodynamic changes were observed in rats treated with enalapril (1-5 mg/kg) (Fig. 1, *b*).

After preliminary administration of captopril (1-5 mg/kg) perivascular and pericellular edema occurred

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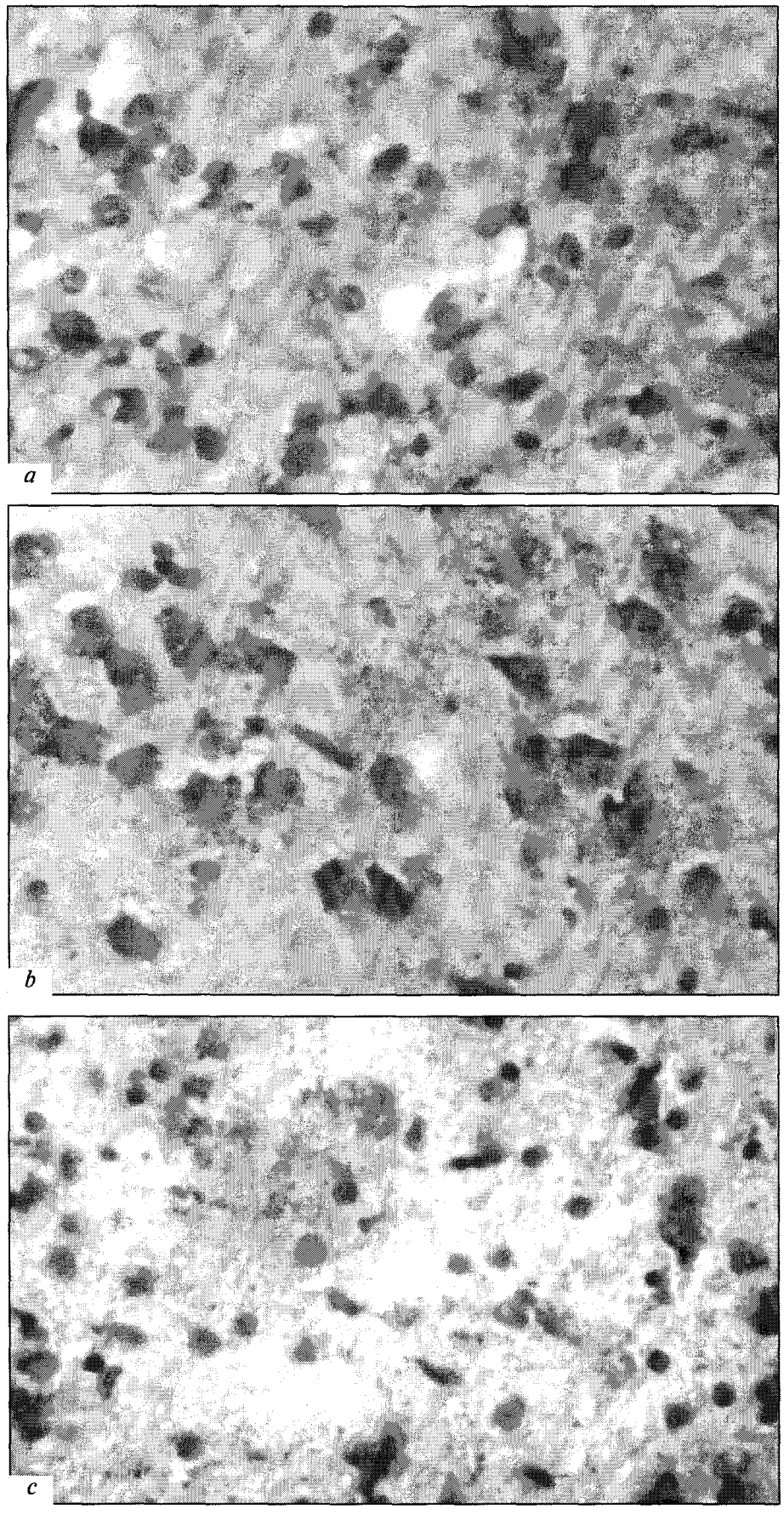

Fig. 1. Postischemic changes in the cerebral cortex in the control (*a*) and after pretreatment with enalapril (*b*) and captopril (*c*). Nissl staining, ×320.

predominantly in the cortical regions of the brain, where single neurons with hyperchromic nuclei and tigrolysis were found (Fig. 1, *c*).

Thus, ACE inhibitors, especially captopril demonstrated neuroprotective effect in cerebral ischemia, which agrees with published data [6] showing that apart from considerable increase in the survival rate, these drugs improve the neurological status of ischemic rats. Histological examination of brain tissue after experimental ischemia showed that captopril was superior to enalapril in the neuroprotective action. This was evidenced by the absence of dramatic histological changes such as nuclear pyknosis and perinuclear edema and by relative predominace of hemodynamic disturbances, which can be considered as compensatory and adaptive.

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