Inhibition of central angiotensin-converting enzyme with enalapril protects the brain from ischemia/reperfusion injury in normotensive rat

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ABSTRACT

Background and the Purpose of the study: Central Angiotensin Converting Enzyme (ACE) has an important role on cerebral microcirculation and metabolism. However, its role in terms of protecting the brain from ischemic/reperfusion (I/R) injury are debatable. This study evaluated the role of ACE, using enalapril as ACE inhibitor, in protection of the brain from I/R injury during transient focal cerebral ischemia (TFCI) in normotensive rat.

Method: Male Sprague Dawley rats (280-320g) randomly assigned to control ischemic and enalapril pre-treated ischemic groups. Enalapril was injected intraperitoneally 1 h before middle cerebral artery occlusion (MCAO) at the dose of 0.03 or 0.1 mg/kg. Cerebral ischemia was induced by 60 min MCAO followed by 24 hrs reperfusion. After evaluation of neurological deficit scores (NDS) the animal was sacrificed for assessment of cerebral infarction and edema.

Results: TFCI induced cerebral infarctions (283±18 mm3), brain edema (4.1±0.4%) and swelling (9.8±1.5%) with NDS of 3.11±0.36. Non-hypotensive dose of enalapril (0.03 mg/kg) improved NDS (1.37±0.26), reduced cerebral infarction (45%), brain edema (54%) and swelling of the lesioned hemispheres (34%) significantly. However, hypotensive dose of enalapril (0.1mg/kg) could improve neurological activity (1.67±0.31) and failed to reduce cerebral infarction (276±39mm3) and swelling (10.4±1.4%).

Conclusion: In the rat model of transient focal cerebral ischemia, inhibition of angiotensin converting enzyme with non-hypotensive doses of enalapril has the benefit of improving neurological activity, reducing cerebral infarction, brain swelling and edema of acute ischemic stroke. Therefore, it is reasonable to conclude that central renin-angiotensin system may participate in ischemic/reperfusion injury of the cerebral cortex.

Keywords: Cerebral ischemia, Lesion volume, Edema, ACE inhibition, Enalapril

INTRODUCTION

The critical role of renin–angiotensin system (RAS) in cardiovascular and fluid hemostasis is well established and some evidences exist about the role of angiotensin-converting enzyme (ACE) activity and angiotensin II in ischemic neuronal injury (1). It is suggested that inhibition of the RAS might be effective not only in reducing the incidence of stroke but also attenuating neuronal injury after stroke (2). Recent clinical studies revealed that ACE inhibitors, which are used as anti-hypertensive drugs, reduce the risk and the severity of secondary attacks of the stroke (3). Long term treatment with ACE inhibitors has shown to prevent the occurrence of stroke in spontaneously hypertensive or salt loaded-Dahl salt-sensitive rats (4, 5). Moreover, ACE inhibitors are reported to improve neurological recovery from cerebral ischemia/reperfusion (I/R) injury and reduce the mortality rate in spontaneously hypertensive rats (6). Pathological remodeling of cerebral vessels that occur during chronic hypertension is reported to interfere with the outcome of ACE inhibition and other neuroprotective agents (5). Therefore, this study was designed to induce cerebral I/R injury in normotensive rats to alleviate the interaction of hypertension in protective action of ACE inhibitors. Experimental-induced transient focal cerebral ischemia is widely used to examine the functional impairments resemble to those that have been observed in human stroke (7). Previously the beneficial effects of non-hypotensive dose of enalapril, an ACE inhibitor, in improving neurological activity and reducing cerebral infarction volume in normotensive rats exposed to 60 min middle cerebral artery occlusion (MCAO) was reported (8). Brain edema is a destructive phenomenon that worsens cerebral I/R

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