Mol Cell Biochem (2013) 382:47–58
DOI 10.1007/s11010-013-1717-4

Expression of angiotensin II and its receptors in activated microglia in experimentally induced cerebral ischemia in the adult rats

Chun-Yun Wu · Hao Zha · Qing-Qing Xia · Yun Yuan · Xiao-Yan Liang · Jing-Hui Li · Ze-Yun Guo · Juan-Juan Li

Received: 17 April 2013 / Accepted: 29 May 2013 / Published online: 11 June 2013

Abstract Expression of angiotensin II (Ang II) and its receptors (AT_1/AT_2) is undetected in the mature microglia in normal brain. We report here that the immunoexpression of Ang II and AT_1/AT_2 was altered in activated microglia notably at 1 week in rats subjected to middle cerebral artery occlusion (MCAO). Immunolabeled activated microglia were widely distributed in the infarcted cerebral tissue after MCAO. By enzyme immunoassay, Ang II protein expression levels of the ischemic tissues were decreased drastically at 12 h after ischemia, then rose rapidly at 3 days and 1 week after MCAO when compared with the control. On the other hand, AT_1 and AT_2 receptor mRNA and protein levels were up-regulated after MCAO, peaking at 12 h, but declined thereafter. Expression of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) mRNA and protein levels was concomitantly increased. Edaravone significantly suppressed Ang II and AT_1/AT_2 receptor expression as well as that of TNF-α and IL-1β suggesting that microglia-derived Ang II can act through an autocrine manner via its receptor that may be linked partly to the production of proinflammatory cytokines. We conclude that neuroinflammation in MCAO may be attenuated by Edaravone which acts through suppression of expression of Ang II and its receptors and proinflammatory cytokines in activated microglia.

Keywords Angiotensin II · Receptors · Activated microglia · Ischemia · Rats · Edaravone

Introduction

Angiotensin II (Ang II) is a peptide hormone which not only acts on the vasculature and heart, but also in the brain to mediate important neuroendocrine functions [1, 2]. Ang II exerts its effects on the central nervous system (CNS) primarily via the two G protein-coupled receptors, Ang II type 1 receptor (AT_1), and Ang II type 2 receptor (AT_2). The peptide Ang II, via AT_1 receptor, is one of the most important inflammation and oxidative stress inducers, and produces reactive oxygen species (ROS) by activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex [3].

Experimental evidence suggests an important role of Ang II and its receptors in hypoxic/ischemic brain injury. Ang II participates in the pathogenesis of ischemia via AT_1. The selective AT_1 receptor blocker improves the neurological outcome and reduces the infarct volume after experimental ischemia in the rat brain [4]. The cerebral AT_2 receptors are associated with neurite outgrowth and protection of brain tissue after focal cerebral ischemia [5]. Ang II could attenuate hypoxia-induced apoptosis in primary cortical neuronal cultures through activation of the AT_2 receptor [6]. The inflammatory response is mediated by the activated microglia which respond robustly to the neuronal damage [7]. However, the involvement of Ang II and its receptors in microglial activation and brain injuries (or inflammation) remains to be clarified.

C.-Y. Wu · H. Zha · Q.-Q. Xia · Y. Yuan · X.-Y. Liang · Z.-Y. Guo · J.-J. Li (✉)
Department of Histology and Embryology, Faculty of Basic Medical Sciences, Kunming Medical University, 1168 West Chunrong Road, Kunming 650500, People's Republic of China
e-mail: lijuanjuan527@163.com

J.-H. Li
Minimally Invasive Neurosurgery, First Affiliated Hospital of Kunming Medical University, 295 Xi Chang Road, Kunming 650032, People's Republic of China