Hypertension-mediated enhancement of JNK activation in association with endoplasmic reticulum stress in rat model hippocampus with cerebral ischemia-reperfusion

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ABSTRACT. Acute brain ischemia can induce the activation of c-Jun N-terminal kinases (JNKs). Hypertension is a critical etiology for brain ischemia. We identified the effects of hypertension on the activation of JNK as well as its impact on SP600125, a JNK inhibitor, during endoplasmic reticulum stress (ERS) in the hippocampus using a rat model. Transient whole-brain ischemia was induced by 4-vessel occlusion (bilateral vertebral and bilateral common carotid arteries) in normal and spontaneous hypertensive rats. SP600125 (0.05 mg/kg, iv) was administered 30 min before ischemia. Morphological changes in hippocampal nerve cells were observed by cresyl violet staining. Phosphorylation of JNK, and expression levels of CHOP and GPR78,
markers for ERS, were detected by western blot at 1, 6, 24, and 48 h, and neurological outcomes were measured using an eight-arm radial maze 48 h after ischemia. Hypertension apparently aggravated impairment of memory function, decreased the density of surviving neurons, increased phosphorylation of JNK, and enhanced CHOP expression, but reduced GPR78 levels in hippocampal tissues following brain ischemia. SP600125 alleviated neurological dysfunction, improved neuron survival, decreased phosphorylation of JNK and levels of CHOP, but increased expression of GPR78 in rats with hypertension during cerebral ischemia by inhibition of ERS.

**Key words:** Hypertension; Ischemia/reperfusion; Endoplasmic reticulum stress; c-Jun N-terminal kinases; CAAT/enhanced I-binding protein