Mol Cell Biochem (2014) 385:125–132
DOI 10.1007/s11010-013-1821-5

The AKT/mTOR pathway mediates neuronal protective effects of erythropoietin in sepsis

Guo-Bin Wang · Yun-Lan Ni · Xin-Ping Zhou · Wei-Fang Zhang

Received: 17 June 2013 / Accepted: 13 September 2013 / Published online: 22 September 2013

Abstract Sepsis is one of the most common causes of mortality in intensive care units. Although sepsis-associated encephalopathy (SAE) is reported to be a leading manifestation of sepsis, its pathogenesis remains to be elucidated. In this study, we investigated whether exogenous recombinant human erythropoietin (rhEPO) could protect brain from neuronal apoptosis in the model of SAE. We showed that application of rhEPO enhanced Bcl-2, decreased Bad in lipopolysaccharide treated neuronal cultures, and improved neuronal apoptosis in hippocampus of cecal ligation and peroration rats. We also found that rhEPO increased the expression of phosphorylated AKT, and the antiapoptotic role of rhEPO could be abolished by phosphoinositide 3-kinase (PI3K)/AKT inhibitor LY294002 or SH-5. In addition, systemic sepsis inhibited the hippocampal-phosphorylated mammalian target of rapamycin (mTOR) and p70S6K (downstream substrates of PKB/AKT signaling), which were restored by administration of exogenous rhEPO. Moreover, treatment with mTOR-signaling inhibitor rapamycin or transfection of mTOR siRNA reversed the neuronal protective effects of rhEPO. Finally, exogenous rhEPO rescued the emotional and spatial cognitive defects without any influence on locomotive activity. These results illustrated that exogenous rhEPO improves brain dysfunction by reducing neuronal apoptosis, and AKT/mTOR signaling is likely to be involved in this process. Application of rhEPO may serve as a potential therapy for the treatment of SAE.

G.-B. Wang · Y.-L. Ni · X.-P. Zhou · W.-F. Zhang (✉)
Department of Surgical Intensive Care Unit, The First Affiliated Hospital, Medical College, Zhejiang University, Qingchun Road 79, Hangzhou 310003, People's Republic of China
e-mail: zhangweifang8@gmail.com

Keywords Sepsis · Apoptosis · rhEPO · AKT/mTOR signaling · Cognitive dysfunction · Hippocampus

Abbreviations

CLP	Cecal ligation and peroration
LPS	Lipopolysaccharide
mTOR	Mammalian target of rapamycin
MWM	Morris water maze
rhEPO	Recombinant human erythropoietin
SAE	Sepsis-associated encephalopathy
TUNEL	Terminal deoxynucleotidyl transferase-mediated dUTP nick-end-labeling

Background

Sepsis and its consequences are the most common causes of death in intensive care units. Sepsis-associated encephalopathy (SAE), which manifests itself with symptoms such as irritability, confusion, stupor, and even outright coma, is a common complication of systemic sepsis [1]. Patients with SAE have a higher mortality rate compared to those without brain involvement, likely reflecting the severity of disease and the direct adverse effects of central nervous system (CNS) [2]. Recent study has demonstrated that cecal ligation and peroration (CLP) rats manifest dysfunctions in the creatine kinase activities and mitochondrial respiratory chain [3]. In addition, the uncoupling of oxidative phosphorylation in mitochondria also takes place in the brain of septic mice [4]. These evidences illustrated that cell apoptosis and mitochondrial dysfunction within the CNS may be involved in the SAE pathogenesis. Moreover, a recent investigation indicated that sepsis is associated with long-term neurological disorder in animal models [5].