Rescue of Neuronal Cell Death by ER-stress protein overexpression

2005 Fiscal Year Final Research Report Summary

Rescue of Neuronal Cell Death by ER-stress protein overexpression

Research Project

Project/Area Number

15200028

Research Category

Grant-in-Aid for Scientific Research (A)

Allocation Type

Single-year Grants

Section

一般

Research Field

Nerve anatomy/Neuropathology

Research Institution

Graduate School of Medical Science, Kanazawa University

Principal Investigator

OGAWA Satoshi Kanazawa University, Graduate School of Medical Science, Professor, 医学系研究科, 教授 (90283746)

Co-Investigator(Kenkyū-buntansha)

HORI Osamu Kanazawa University, Graduate School of Medical Science, Associate Professor, 医学系研究科, 助教授 (60303947)
KITAO Yasuko Kanazawa University, Graduate School of Medical Science, Assistant Professor, 医学系研究科, 助手 (00019613)

Project Period (FY)

2003 – 2005

Keywords

Astrocytes / Brain ischemia / ER-stress / Gene Therapy / Glutamic acid / Ischemic tolerance

Research Abstract

ORP150 is a novel stress protein localized in the endoplasmic reticulum (ER). To investigate the role of ORP150 in delayed neuronal cell death, we have examined its expression in the gerbil brain after the ischemic insult. The expression of ORP150 antigen, as well as its transcripts, was observed in the CA1 region after the occlusion of the common carotid artery, and this was enhanced by the preconditioning. In cultured neurons, exposure to either hypoxia or glutamate induced the expression of ORP150, and this was also observed by treating the culture with either thapsigargin or breferdin-A, indicating that both glutamate and hypoxia can cause stress in the ER (ER stress). Neurons became more vulnerable to these stresses following treatment of either cycloheximide or the infection with an adenovirus carrying ORP150 antisense structure, In contrast, the overexpression of ORP150 by adenovirus suppressed the neuronal cell death, and this was accompanied by the suppression of the Ca2+ elev

ation and proteolytic activity induced by glutamate. Further, overexpression of ORP150 in CA1 neurons by the adenovirus carrying ORP150-sense structure suppressed delayed neuronal cell death after ischemia. These date suggest a possible function of ORP150 as an intracellular apparatus, which participates in a protective response in ischemic tolerance.
Selective loss of dopaminergic neurons is the final common pathway in Parkinson's disease. We discuss the role of ER-stress in neuronal cell death in SNpc by introducing two models. Upregulation of Pael-Receptor in the substantia nigra pars (SNpc) of mice induces endoplasmic reticulum (ER) stress leading to a decrease in tyrosine hydroxylase and death of dopaminergic neurons. The role of ER stress in dopaminergic neuronal vulnerability was highlighted by their enhanced death in mice deficient in the ubiquitin-protein ligase Parkin and the ER chaperone ORP150, suggesting parkin dysfunction result in ER-stress mediated neuronal cell death. Conversely, transgenic rats overexpressing megsin (Tg meg), a newly identified serine protease inhibitor (serpin), demonstrated intraneuronal periodic-acid Schiff (PAS) positive inclusions, which distributed throughout the deeper layers of cerebral cortex, hippocampal CA1, and substantia nigrta. Enhanced ER stress was observed in dopamine neurons in SNpc, accompanied with loss of neuronal viability and motor coordination. In both subregions, PAS-positive inclusions were also positive with megsin. These data suggest that enhanced ER stress causes selective vulnerability in a set of neuronal populations.▲ Less

Research Products (19 results)

All | 2006 | 2005 | 2004 | 2003 | 2002 | Other

All | Journal Article | Book

[Journal Article] Deletion of SERP1/RAMP4, a component of the endoplasmic reticulum (ER) translocation sites, leads to ER stress. 2006

[Journal Article] The ER chaperone 150 kDa Oxygen Regulated Protein (ORP150) improves insulin resistance in Type 2 Diabetes Mellitus. 2005

[Journal Article] RP150/HSP12A regulates Purkinje cell survival : a role for endoplasmic reticulum stress in cerebellar development. 2004

[Journal Article] ORP150/HSP12A protects renal tubular epithelium from ischemia-induced cell death. 2004

[Journal Article] ORP150/HSP12A regulates Purkinje cell survival : a role for endoplasmic reticulum stress in cerebellar development. 2004

[Journal Article] Role of Herp in the endoplasmic reticulum (ER) stress response. 2004

[Journal Article] Prolonged ER Stress in Hypertrophic and Failing Heart Following Aortic Constriction : Possible Contribution of ER Stress to Cardiac Myocyte Apoptosis. 2004

[Journal Article] ORP150/HSP12A protects renal tubular epithelium from ischemia-induced cell death. 2004

[Journal Article] The expression of a novel stress protein '150-kDa oxygen regulated protein' in sudden infant death. 2003

[Journal Article] Accumulation of microglial cells expressing ELR motif-positive CXC chemokines and their receptors CXCR2 in monkey hippocanpus after ischemia-reperfusion. 2003

[Journal Article] Transmission of cell stress from endoplasmic reticulum to mitochondria : enhanced expression of Lon protease 2002

[Journal Article] Expression of 150-kd oxygen-regulated protein in the hippocampus suppresses delayed neuronal cell death. 2002

[Journal Article] Peg3/Pw1 Is Involved in p53-mediated Cell Death Pathway in Brain Ischemia/Hypoxia. 2002

[Journal Article] Transmission of cell stress from endoplasmic reticulum to mitochondria : expression of Lon protease. 2002

[Journal Article] Expression of ORP150 (150 kDa oxygen regulated protein) in the hippocampus suppresses delayed neuronal cell death. 2002

[Journal Article] Antitumor effect of reduction of 150-kDa oxygen-regulated protein expression on human prostate cancer cells. 2002

[Journal Article] Immunohistochemical detection of the 150-kDa oxygen-regulated protein in bladder cancer. 2002

[Journal Article] Deletion of SERP1/RAMP4, a component of the endoplasmic reticulum (ER) translocation sites, leads to ER stress.

[Book] 医学の歩み特集号:小胞体ストレス 2005

Published: 2007-12-12