GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

# Pyrroloquinoline quinone rescues hippocampal neurons from glutamate-induced cell death through activation of Nrf2 and up-regulation of antioxidant genes

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Genet. Mol. Res. 11 (3): 2652-2664 (2012)
Received January 9, 2012
Accepted May 9, 2012
Published June 27, 2012
DOI http://dx.doi.org/10.4238/2012.June.27.3

**ABSTRACT.** Pyrroloquinoline quinone (PQQ) has been shown to protect primary cultured hippocampal neurons from glutamate-induced cell apoptosis by scavenging reactive oxygen species (ROS) and activating phosphatidylinositol-3-kinase (PI3K)/Akt signaling. We investigated the downstream pathways of PI3K/Akt involved in PQQ protection of glutamate-injured hippocampal neurons. Western blot analysis indicated that PQQ treatment following glutamate stimulation triggers phosphorylation of glycogen synthase kinase 3β, accompanied by maintenance of Akt activation. Immunostaining and quantitative RT-PCR revealed that PQQ treatment promotes nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2), and up-regulates mRNA expression of Nrf2 and the antioxidant enzyme genes, heme oxygenase-1 and glutamate cysteine ligase catalytic in glutamate-injured hippocampal neurons; this is a process dependent on the PI3K/Akt pathway, as evidenced by blocking experiments with PI3K inhibitors. In addition, increased ROS production and decreased glutathione

 

levels in glutamate-injured hippocampal neurons were found to be reduced by PQQ treatment. Collectively, our findings suggest that PQQ exerts neuroprotective activity, possibly through PI3K/Akt-dependent activation of Nrf2 and up-regulation of antioxidant genes. However, the ability of PQQ to scavenge ROS was not totally regulated by PI3K/Akt signaling; possibly it is governed by other mechanisms.

**Key words:** Pyrroloquinoline quinone; Reactive oxygen species; Nuclear factor erythroid 2-related factor 2; PI3K/Akt/GSK3β pathway; Glutamate

 