

# Protective effect of lipoic acid against oxidative stress is mediated by Keap1/Nrf2-dependent heme oxygenase-1 induction in the RGC-5 cell line

Koriyama Y, Nakayama Y, Matsugo S, Kato S.

Department of Molecular Neurobiology, Graduate School of Medicine. Electronic address: koriyama@med.kanazawa-u.ac.jp.

Oxidative stress plays a key role in neurodegeneration of CNS neurons such as Alzheimer disease, Parkinson's disease and glaucoma. R- $\alpha$ -lipoic acid (R-LA) has been shown to have a neuroprotective effect through its antioxidant activity. However, the mechanism underlying its neuroprotection is totally unknown in retinal neurons.

In this study, we show that R-LA has a dramatic neuroprotective effect against oxidative stress-induced death of the retinal neuronal RGC-5 cell line. We observed that R-LA induces the expression of heme oxygenase-1 (HO-1) by promoting the translocation of NF-E2-related factor 2 (Nrf2) to the nucleus. We examined the mechanism underlying HO-1 induction by R-LA by focusing on downstream signaling pathways. We found that R-LA activates Akt, and HO-1 induction by R-LA (involving Nrf2 translocation to the nucleus) was suppressed by phosphoinositide 3-kinase (PI3K) inhibitors.

In addition, R-LA produced reactive oxygen species (ROS), including hydrogen peroxide. Pretreatment with a ROS scavenger or a NADPH oxidase inhibitor suppressed R-LA-induced Nrf2 translocation to the nucleus and HO-1 induction. These results suggest that ROS production triggered by R-LA might modify Kelch-like ECH-associated protein (Keap1), which in turn induces HO-1 expression through the PI3K signaling pathway. Furthermore, R-LA significantly attenuated cell death and accumulation of 4-hydroxy-2-nonenal (4HNE) in the retina induced by optic nerve injury in vivo through an HO-1 activity-dependent mechanism.

These data demonstrate for the first time that R-LA exerts a neuroprotective effect against oxidative stress in retinal neurons in vitro and in vivo by inducing HO-1 through Keap1/Nrf2 signaling.

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