**Commentary**                                                    **Open Access**

# Commentary: Protective Effects of Isorhamnetin on N2a Cell Against Endoplasmic Reticulum Stress-induced Injury Is Mediated by PKCε

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## Article Info

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## ABSTRACT

Neuronal apoptosis is an important pathophysiological factor of Alzheimer's disease (AD). Inhibition of endoplasmic reticulum stress (ERS)-induced neuronal apoptosis is an effective strategy to deal with AD. In this commentary, we summarize the relationship between AD and ERS injury-induced neuronal apoptosis, and highlight the protective effects and mechanism of isorhamnetin (Iso) against ERS-induced injury in N2a cells. Moreover, this commentary discusses the recent findings in the role of Iso in other diseases.

Alzheimer's disease (AD) is a chronic neurodegenerative disease, and the fourth leading cause of death, behind heart disease, cancer and stroke[1]. The clinical manifestations of AD include deteriorating cognitive function and memory, a decline in functioning in daily life activities, anda variety of neuropsychiatric symptoms and behavioral disorders[2,3]. The risk of AD gradually increases with age. There are more than 30 million AD patient living in the world today[4,5].

The etiology and pathogenesis of AD is not clear. AD is characterized by the accumulation of misfolded β-amyloid proteins caused by various genetic and environmental factors. These Aβ-plaques are associated with several pathological changes including the aggregation of misfolded proteins, formation of tissue precipitation, intracellular calcium disturbance, DNA fragmentation and lipid peroxidation. Together, these factors induce neuronal apoptosis and necrosis[6]. Thus, inhibiting neuron apoptosis is an effective way to prevent AD.

The endoplasmic reticulum (ER) is theprincipal organelle for protein synthesis, protein folding and maintenance of calcium homeostasis[7]. Numerous stimuli, such as hypoxia and oxidative stress, can perturb calcium balance, and promote accumulation of unfolded and misfolded proteins in the ER lumen. This is known as endoplasmic reticulum stress (ERS)[8]. ERS is one of the key drivers of apoptosis. ERS induces apoptosis, through activation of the ASK and p38 MAPK signal pathway, trigger the kinase function of IRE1[9-11]. Additionally, p38MAPK is reported to promote phosphorylation and activation of pro-apoptotic protein Bax[12,13].

Recent studies suggest that AD pathology is associated with ERS[14]. ERS generates a toxic environment in neurons, which in turn activates endoplasmic reticulum pathways that ultimately cause apoptosis[15]. Thus, inhibition of ERS injury may be an effective strategy to prevent AD.

Our study "Protective Effects of Isorhamnetin on N2a Cell Against Endoplasmic Reticulum Stress-induced Injury Is Mediated by PKCε" suggests that Isorhamnetin (Iso) serves as a neuroprotective against ERS-induced apoptosis.

Iso has been reported to inhibit anoxia/reoxygenation-induced apoptosis by STAT1. In our study, we identify the protective effect and molecular mechanism of Iso inhibition of ERS-induced apoptosis in N2a cells. During ERS, GRP78 is released in the lumen and IRE1α and ATF6 are activated, resulting in up-regulation of ERS marker geneGRP78.Thus, we used GRP78protein levels to estimate ERS injury and determine optimal concentration and pretreatment time for Iso.

ERS also results in $Ca^{2+}$release from the ER into the cytosol, which induces ROS burst, and eventually neuronal apoptosis[16-18]. herefore, we evaluated the cytosol $Ca^{2+}$ concentration, ROS levels and apoptosis to illustrate the protective effects of Iso on ERS injury. We have found that Isoeffectivelyinhibits ERS-induced GRP78 up-regulation, cytosol $Ca^{2+}$ overload, ROS burstand apoptosis.

Previous studies have shown that protein kinase C epsilon (PKCε)can inhibit apoptosis by regulating ROS production and $Ca^{2+}$homeostasis. Quercetin also inhibits ROS generation and apoptosis by activating the PKCε signal pathway. Therefore, we hypothesized that Iso, as a metabolite of quercetin, can attenuate ERS-induced ROS burst and $Ca^{2+}$ overload through the PKCε signal pathway. To test our hypothesis, we applied a PKCε specific inhibitor, εV1-2, to to approve our hypothesize. As expected, we found that εV1-2 reversed the protective effect of Iso on ERS injury in N2a cells. This study was the first to demonstrate that Iso can elicit protective effects against ERS injury in N2a cells and that these effects are mediated, at least in part, via the PKCε pathway.

Iso, one of the flavonoids, has gained considerable attention due to its wide range of biological and pharmacological properties. It has been reported that Iso is efficacious in protecting hepatocytes against oxidative stress by activating Nrf2 and inhibiting ROS production by up-regulating antioxidant protein HO-1 and GCL expression[19]. Iso has anti-inflammatory effects through HO-1activity, which was mediated by the Nrf2/PPAR-γ pathway[19-21]. Iso can also activate the NF-κB signaling pathway to inhibit inflammation and cell proliferation. Additionally, Iso has been shown to inhibit various types of cancer. Ramachandran[22] found that Iso inhibited the migratory/invasive properties of gastric cancer cells through modulation of the PPAR-γ activation pathway. Jaramillo[23] found that Isoinhibtied colon cancer cells growth by interrupting cell cycle progression. Iso is also found to promote lung cancer cell apoptosis through mitochondria-dependent caspase activation in vitro and vivo[24]. Moreover,

Iso can mediate Akt and mitogen-activated protein kinase signal pathways to inhibit cell proliferation and induce apoptosis in breast cancer[25].

In summary, the therapeutic significance and chemopreventive capabilities of Iso in inflammation, AD and cancer warrant further study. These findings also support further investigation of the pharmacological and molecular mechanisms of other flavonoids on ERS-induced neuron apoptosis.

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