Mol Cell Biochem (2013) 383:149–159
DOI 10.1007/s11010-013-1763-y

Neuroprotective effect of 2-(4-methoxyphenyl)ethyl-2-acetamido-2-deoxy-β-D-pyranoside against sodium nitroprusside-induced neurotoxicity in HT22 cells

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Received: 25 April 2013 / Accepted: 10 July 2013 / Published online: 20 July 2013

Abstract 2-(4-Methoxyphenyl) ethyl-2-acetamido-2-deoxy-β-D-pyranoside (GlcNAc-Sal), the salidroside analog was synthesized and shown to inhibit hypoglycemia and serum limitation induced apoptosis in PC12 cells. This study investigated the protective effects of GlcNAc-Sal on sodium nitroprusside (SNP)-induced cytotoxicity in HT22 cells. Cell viability tests and Hoechst 33342 staining comfirmed that GlcNAc-Sal pretreatment attenuated SNP-stimulated apoptotic cell death in HT22 cells in a concentration-dependent manner. The measurements of reactive oxygen species (ROS), nitric oxide (NO) production and apoptosis-related gene and protein expression suggest that the protection of GlcNAc-Sal, shown in this study, might be mediated by inhibiting intracellular ROS and NO production, and regulating apoptosis-related gene and protein expression during SNP stimulation. Perhaps, this study might contribute to the development of GlcNAc-Sal as an agent for preventing and/or treating a variety of NO-induced brain diseases.

Keywords 2-(4-Methoxyphenyl)ethyl-2-acetamido-2-deoxy-β-D-pyranoside · SNP · Apoptosis · HT22 cells

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Introduction

Oxidative stress has roles in various pathological conditions, including cardiovascular disease, cancer, neurological disorders, diabetes, and aging [1]. One component of oxidative stress, nitric oxide, is a highly reactive and cell-damaging free radical classified as both a reactive oxygen species (ROS) and nitrogen species (RNS). Nitric oxide, synthesized from arginine by three isoforms of nitric oxide synthase (NOS) [2], causes an increase in peroxynitrite [3, 4], which mediates most of the neurotoxic actions of NO. NO also inhibits the mitochondrial respiratory chain and eventually leads to irreversible cellular damage [5, 6]. Many studies have shown that inducible nitric oxide synthase (iNOS) mRNA, protein, and enzymatic activity are upregulated in the brain after transient or permanent brain ischemia in rodents [7–9]. Increases in NO can therefore cause apoptosis by affecting the cell death machinery in various cells [10–13].

Apoptosis, also known as programmed cell death, is a biological process with a crucial role in normal development and tissue homeostasis [14]. Apoptosis involves chromatin condensation and fragmentation, phosphatidylserine exposure, cellular disassembly, and intracellular fragmentation without rupturing the plasma membrane. Several genes have been shown to have a role in the regulation of apoptosis. Apoptosis is especially relevant and important for the progression of neurodegenerative disorders.

Salidroside is the main active ingredient from the root of *Rhodiola rosea* L. and has been used as an adaptogen in traditional Tibetan medicine. Apart from its roles against inflammation [15] and apoptosis [16, 17], salidroside has been shown to exert potent anti-oxidative effects in various cell types and disease models [18–23]. Both natural and