Mol Cell Biochem (2014) 385:179–190
DOI 10.1007/s11010-013-1826-0

Peroxisome proliferator-activated receptor-α activation protects against endoplasmic reticulum stress-induced HepG2 cell apoptosis

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Received: 29 June 2013 / Accepted: 13 September 2013 / Published online: 26 September 2013

Abstract Live ischemia–reperfusion injury is associated with endoplasmic reticulum (ER) stress-induced apoptosis. Activation of peroxisome proliferator-activated receptor-α (PPARα) may inhibit hepatocyte apoptosis induced by oxidative stress and protect against liver injury. This study aimed to investigate the effects of PPARα activation, through a specific agonist, on ER stress-induced apoptosis in human liver hepatocellular carcinoma (HepG2) cells. HepG2 cells were challenged with H_2O_2 and treated with WY14643, a selective PPARα agonist, in the presence or absence of the PPARα antagonist of MK886. Cell viable assay (MTT) and immunostaining were used to evaluate cell viability. The level of apoptotic cell death was quantified through Annexin V/PI staining. Alanine aminotransferase, asparatate aminotransferase, and malondialdehyde levels were measured to determine the presence of cellular injury and oxidative stress. RT-PCR and Western blot analysis were used to detect mRNA and protein expression of PPARα, BiP, and CHOP. Immunofluorescence was utilized to determine the intracellular localization of CHOP. H_2O_2 and MK886 both reduced the viability of HepG2 cells, increased oxidative stress and apoptosis, up-regulated the BiP and CHOP expression, and induced CHOP translocation from the cytoplasm to the nucleus. Compared with cells treated with H_2O_2 alone, pre-administration of WY14643 increased cell viability, attenuated apoptosis, improved cell function, down-regulated BiP and CHOP expression and inhibited CHOP translocation. The effects of WY14643 were completely abolished using the MK886 antagonist. PPARα activation protects against H_2O_2-induced HepG2 cell apoptosis. The underlying mechanisms may be associated with its activation to suppress excessive ER stress.

Keywords PPARα · Oxidative stress · Endoplasmic reticulum stress · Hepatocyte · Apoptosis

Introduction

Liver ischemia–reperfusion (LIR) injury often occurs in a number of clinical settings, such as liver resection surgery, liver transplantation, and hemorrhagic shock, and results in hepatic cell damage and death [1]. Previous studies have demonstrated that endoplasmic reticulum (ER) stress is an initiator of apoptosis during LIR injury [2–4]. LIR injury is associated with Ca^{2+} escape from the ER to the cytosol and this process in turn triggers the production of reactive oxygen species (ROS), leading to oxidative stress and producing a number of unfolded proteins that accumulate in the ER [5, 6]. To cope with the increase in unfolded proteins, mammalian cells generate a specific adaptive response called the unfolded protein response (UPR) [4, 7, 8]. Upon activation of the UPR, the chaperone BiP (GRP78) binds to misfolded proteins thereby activating proximal UPR transducer proteins, such as PKR-like ER-

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