44504 - PROPOFOL REDUCES HYDROGEN PEROXIDE INDUCED CARDIAC AND ENDOTHELIAL CELL APOPTOSIS: ROLE OF AKT SURVIVAL SIGNALING PATHWAY

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INTRODUCTION: Endothelial nitric oxide (NO) produced by eNOS (endothelial nitric oxide synthase) is capable of inhibiting apoptosis and is regarded as a cell survival factor 1. The phosphatidylinositol 3-kinase (PI3K)/Akt cell survival pathway is able to regulate its expression and activation 2. We tested the hypothesis that propofol modulates Akt activated endothelial nitric oxide synthase expression to confer protection in endothelial cells and cardiomyocytes exposed to oxidative stress.

METHODS: Cultured human umbilical vein endothelial cells (ATCC, CRL1730) and Rat H9c2 cardiac myoblasts (ATCC, CRL1446) were used in an experimental model where hydrogen peroxide (H₂O₂) was used as the stimulus of oxidative stress. Study groups included 1) control, 2) cultured cells incubated with H₂O₂ (100 μ M for endothelial cells and 400 μ M for cardiac myoblasts) alone, 3) cells incubated with propofol (50 μ M) alone, or 4) cells pretreated with propofol 50 μ M for thirty minutes then co-incubated with H₂O₂. Cell viability was assessed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cell apoptosis was evaluated by Hoechst 33258 staining. Activity of caspase-3 was determined by the colorimetric CaspACE™ Assay System (Promega, USA). Expressions of total Akt, phospho-Akt and endothelial nitric oxide synthase (eNOS) were detected by Western blotting.

RESULTS: H₂O₂ decreased cell viability, induced cell apoptosis and increased caspase-3 activity in both endothelial cells and cardiomyocytes. H₂O₂ did not cause significant change in eNOS expression. Propofol significantly protected cells from H₂O₂-induced cell damage and apoptosis. Propofol significantly decreased caspase-3 activity, increased eNOS expression, but did not change phospho-Akt expression in endothelial cells. Propofol significantly decreased caspase-3 activity and enhanced phospho-Akt expression in cardiomyocytes compared to H₂O₂ stimulated cells.

CONCLUSIONS: The phenolic antioxidative and caspase-3 related antiapoptotic effects of propofol indicate its pleiotropic nature, acting differently on endothelial cells and cardiomyocytes via Akt-independent vs Akt-dependent pathways, respectively. We provide possible mechanistic support for the use of propofol as a preemptive cardioprotectant for cardiac surgery, where elevated oxidant stress may preexist (eg. diabetes).

Reference

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