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Role of salubrinal in protecting cardiomyocytes from doxorubicin-induced apoptosis

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ABSTRACT. We determined whether salubrinal can protect cardiomyocytes from doxorubicin-induced apoptosis and explored the related mechanisms to provide experimental evidence for exploring novel drug candidates to decrease cardiac toxicity. Neonatal rat cardiomyocytes were isolated, cultured *in vitro*, and pretreated with salubrinal (10, 20, or 40 μM) to observe their response to doxorubicin-induced cell apoptosis. Lactate dehydrogenase assay, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling staining, and flow cytometry were used to assess the extent of cardiomyocyte apoptosis. Fluorescent probes conjugated with 2',7'-dichlorofluorescein diacetate and a chemiluminescence assay were used to detect the production of reactive oxygen species. Western blotting was employed to quantify expression levels of cleaved caspase-3, cytosolic cytochrome c, and B-cell lymphoma-extra large (Bcl-xL). The mechanisms of salubrinal-related functions were also explored. Salubrinal effectively inhibited doxorubicin-induced reactive oxygen species production and

nicotinamide adenine dinucleotide phosphate oxidase activation, decreased the levels of cleaved caspase-3 and cytosol cytochrome c, and increased Bcl-xL expression, thereby protecting cardiomyocytes from doxorubicin-induced apoptosis. Furthermore, salubrinal was found to protect cardiomyocytes by decreasing the dephosphorylation of eukaryotic translation initiation factor 2α (eIF2α). Salubrinal can protect cardiomyocytes from doxorubicin-induced apoptosis through its effects on eIF2α. It possibly ameliorates cardiac toxicity and can be used in clinical practice.

Key words: Salubrinal; Doxorubicin; Cardiac toxicity; Cell apoptosis; eIF2α

