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