Manganese superoxide dismutase and inducible nitric oxide synthase modify early oxidative events in acute Adriamycin-induced mitochondrial toxicity

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Abstract

In the present study, we used genetically engineered B6C3 mice [mice overexpressing manganese superoxide dismutase (TgM\textsuperscript{+/+}), mice in which inducible nitric oxide synthase had been inactivated (iNOSKO\textsuperscript{−/−}), and crosses of these two genotypes] to study the role of manganese superoxide dismutase (MnSOD) and inducible nitric oxide synthase (iNOS) in the development of acute Adriamycin-induced cardiotoxicity. Both nontransgenic and genetically engineered mice were treated with 20 mg/kg Adriamycin and cardiac left ventricular tissues studied at 0, 3, 6, and 24 hours. Ultrastructural damage and levels of 4-hydroxy-2-nonenal (4HNE) protein adducts and 3-nitrotyrosine (3NT) were determined in cardiomyocytes using immunogold ultrastructural techniques. Our previous results showed that Adriamycin caused mitochondrial injury without significant nuclear or cytoplasmic damage at early time points. Interestingly, overexpression of MnSOD protected against acute mitochondrial injury, whereas deficiency in iNOS potentiated mitochondrial injury in comparison with levels of injury present in cardiomyocyte mitochondria of nontransgenic mice. In TgM\textsuperscript{+/+} mice, there was a significant inverse correlation between mitochondrial injury and 4HNE/3NT levels at all time points analyzed, suggesting that reactive oxygen species/reactive nitrogen species damage products directly regulated acute Adriamycin-induced mitochondrial injury in these mice. The present studies are the first to directly quantify the effects of MnSOD and iNOS on mitochondrial injury during acute Adriamycin-induced cardiotoxicity and show extensive and specific patterns of posttranslational modifications of mitochondrial proteins following Adriamycin treatment.

Keywords: Adriamycin, 4-hydroxy-2-nonenal protein adducts, 3-nitrotyrosine, reactive oxygen species, reactive nitrogen species, manganese superoxide dismutase, inducible nitric oxide synthase, mitochondrial injury

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