Sex-dependent Alteration of Cytochrome P450 Expression by Acute Doxorubicin Cardiotoxicity

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Background: There is inconclusive evidence about the role of sex as a risk factor of doxorubicin (DOX)-induced cardiotoxicity. Recent experimental studies have shown that adult female rodents are protected against DOX-induced cardiotoxicity. However, the mechanisms of this sexual dimorphism are not fully elucidated. We have previously demonstrated that DOX-induced cardiotoxicity alters the expression of several cytochrome P450 (CYP) enzymes in the hearts of male rats. Nevertheless, the sex-dependent effect of DOX on the expression of CYP enzymes is still not known. Therefore, in the present study, we determined the effect of acute DOX cardiotoxicity on the expression of *CYP* genes in the hearts of both male and female mice.

Methods: Acute DOX cardiotoxicity was induced by a single intra-peritoneal injection of 20 mg/kg DOX in male and female adult C57Bl/6 mice. Control and DOX-treated mice were euthanized one day after DOX or saline injection. Thereafter, the hearts were harvested, weighed, and snap frozen in liquid nitrogen. Total RNA was extracted from the frozen tissues, and expression of natriuretic peptides, inflammatory markers, and *CYP* genes was measured by real-time PCR.

Results: In both male and female animals, acute DOX cardiotoxicity reduced the heart weight to tibial length ratio, inhibited b-type natriuretic peptide and *Cyp1a1* gene expression, and induced *Cyp2j9* and *Cyp4a10* gene expression as compared to saline-treated mice. In a sex-dependent manner, tumor necrosis factor alpha gene expression was inhibited; cyclooxygenase-2 and *Cyp1b1* gene expression was induced in the hearts of DOX-treated male mice as compared to saline-treated male mice, but not in DOX-treated females. On the other hand, the expression of *Cyp2c29*, *Cyp2c44*, and *Cyp2e1* genes was induced in the hearts of female DOX-treated mice as compared to saline-treated female mice, but not in DOX-treated males.

Conclusions: The alteration of cardiac *CYP* expression by acute DOX toxicity is sex-dependent. Since cardiac CYP enzymes metabolize several endogenous compounds to biologically active metabolites, sex-dependent alteration of CYP enzymes may play a role in the sexual dimorphism of DOX-induced cardiotoxicity.