Pravastatin attenuates carboplatin-induced cardiotoxicity via inhibition of oxidative stress associated apoptosis

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摘要

Abstract

The objective of this study was to evaluate the cardiac toxicity induced by carboplatin, a second generation platinum-containing anti-cancer drug, and to test whether pravastatin can reduce this cardio-toxicity. In the present study, infusion of carboplatin (100 mg/kg) to mice resulted in decreased survival rates and abnormal cardiac histology, concomitant with increased cardiac apoptosis. In addition, treatment of cultured rat cardiomyocytes with carboplatin (100 μM for 48 h) caused marked apoptosis and increased caspase-3, -9, and cytochrome C, but decreased BCL-XL protein expression, and this was inhibited by reactive oxygen species (ROS) scavenger n-acetylcysteine. Furthermore, pretreatment of cardiomyocytes with pravastatin (20 μM) before carboplatin exposure significantly attenuated apoptosis and decreased caspase-3, -9, cytochrome C activity. Lastly, mice pre-treated with pravastatin before carboplatin treatment showed improved survival rate and cardiac function, with reduced cardiomyocyte apoptosis via activating Akt and restoring normal mitochondrial HAX-1 in heart tissue. In summary, our results show that carboplatin can induce cardiotoxicity in vivo and in cultured cells via a mitochondrial pathway related to ROS production, whereas pravastatin administration can reduce such oxidative stress thus prevented cardiac apoptosis. Therefore, pravastatin can be used as a cytoprotective agent prior to carboplatin chemotherapy.