Bay 60-2770 attenuates doxorubicin-induced cardiotoxicity by preventing mitochondrial membrane potential loss

Authors:
K H Lee¹, XX Zhao², H Cho¹, SR Lee¹, J S Woo¹, W Kim¹, ¹Kyunghlee University, Department of cardiovascular of internal medicine - Seoul - Korea Republic of, ²Kyung Hee Medical Center, Cardiovascular department - Seoul - Korea Republic of,

Topic(s):
Basic Science - Cardiac Diseases: Cardiomyopathies

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S82

Funding Acknowledgements:
Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education (NRF-2017R1C1B5075748).

Objectives: The highly effective anti-cancer agent doxorubicin (DOX) induces cardiotoxicity that involves increased oxidative stress, mitochondrial iron overload, DNA damage, necrosis and apoptosis. These effects are also associated with secondary tumorigenicity. Soluble guanylate cyclase (sGC) signaling is protective against cardiovascular disease and can chemosensitize cancer cells. The present study investigated the role of Bay 60-2770, an effective activator of oxidized and heme-free sGC, in alleviating DOX-induced cardiomyopathy (DOX-CM).

Methods: To quantify the protective effect of Bay 60-2770 on DOX-induced cardiac myocyte death and ROS generation, H9c2 cells were treated with 10 µM Bay 60-2770 for 24 h prior to DOX treatment (0.5-10 µM). Mitochondrial ROS and membrane potential were measured with MitoSOX RED and TMRE, respectively. To determine the role of Bay 60-2770 in DOX-CM, Bay 60-2770 was orally administered to 8-week-old male Sprague-Dawley rats 1 hour prior to every DOX treatment. LV dysfunction was then analyzed by echocardiography. The levels of autophagy-related proteins and mitochondrial iron-regulating proteins in the LV were analyzed. The % of autophagosomes in cardiac myocytes was examined by Cyto ID staining.

Results: Bay 60-2770 increased cell viability and reduced DOX-induced oxidative stress in H9c2 cells; these effects were mediated by PKG activation. Mitochondrial ROS and TMRE fluorescence were attenuated by Bay 60-2270 treatment in DOX-treated H9c2 cells. The ratio of Bax/Bcl-2 decreased after pre-treatment with Bay 60-2770, both in vivo and in vitro. Echocardiography demonstrated that pre-treatment with Bay 60-2770 significantly improved LV function. Moreover, Bay 60-2770 enhanced the protein expression of mitochondrial ferritin (MtFt) in heart tissue.

Conclusion: Bay 60-2770 reduces DOX-induced mitochondrial membrane potential loss and subsequent apoptosis. Moreover, improves cardiac function by upregulating MtFt and stimulating autophagy. These novel results highlight the therapeutic potential of Bay 60-2770 to prevent DOX-CM.