Attenuation of endoplasmic reticulum stress using the chemical chaperone 4-phenylbutyric acid prevents cardiac fibrosis induced by isoproterenol

Ayala, Pedro

Montenegro, José

Vivar, Raúl

Letelier, Alan

Urroz, Pablo Aránguiz

Copaja, Miguel

Pivet, Deisy

Humeres, Claudio

Troncoso, Rodrigo

Vicencio, José Miguel

Lavandero, Sergio

Díaz-Araya, Guillermo

Increasing evidence indicates that endoplasmic reticulum (ER) stress is involved in various diseases. In the human heart, ischemia/reperfusion has been correlated to ER stress, and several markers of the unfolded protein response (UPR) participate during cardiac remodeling and fibrosis. Here, we used isoproterenol (ISO) injection as a model for in vivo cardiac fibrosis. ISO induced significant cardiomyocyte loss and collagen deposition in the damaged areas of the endocardium. These responses were accompanied by an increase in the protein levels of the luminal ER chaperones BIP and PDI, as well as an increase in the UPR effector CHOP. The use of the chemical chaperone 4-phenylbutyric acid (4-PBA) prevented the activation of the UPR, the increase in luminal chaperones and also, leads to decreased collagen deposition, cardiomyocyte loss into the damaged zones. Our results suggest that cardiac damage and fibrosis induced in vivo by the beta-adrenergic agonist ISO are tightly related to ER