Inhibition of endoplasmic reticulum stress and mitochondrial oxidative stress limits the development of abdominal aortic aneurysm and cardiac hypertrophy

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Abstract

Background and purpose: Persistent endoplasmic reticulum (ER) stress and its deleterious crosstalk with mitochondria trigger oxidative stress, mitochondrial dysfunction and inflammation contributing to the pathophysiology of a myriad of cardiovascular diseases linked with hypertension such as abdominal aortic aneurysm (AAA) and cardiac hypertrophy. The purpose of this work was to determine whether inhibition of ER and mitochondrial stress is effective preventing aneurysm development and cardiac hypertrophy in angiotensin II (AngII)-infused apolipoprotein-E-deficient (ApoE-/-) mice. Experimental approach and results: The expression of ER stress markers (Hspa5, Atf4, Atf6, Chop and Ern1) was up-regulated in aneurysmal abdominal aortas from AngII-infused ApoE-/-mice. The treatment with ER stress inhibitors improved survival, decreased systolic blood pressure, limited the incidence and severity of AAA and reduced the AngII-induced increase of aortic diameter evaluated by ultrasonography. These beneficial effects were mimicked by the mitochondria-targeted tetrapeptide SS31. The disorganisation of elastin and collagen fibres, the increased expression of metalloproteinases and pro-inflammatory markers and the infiltration of immune cells induced by AngII in the abdominal aorta were effectively reduced by both, ER inhibitors and SS31. Additionally, treatment with SS31 prevented the alteration of mitochondrial dysfunction and reduced ER stress markers expression and plasmatic ROS levels. Mechanistically, CHOP deficiency in ApoE-/-mice reduced the blood pressure and the incidence of AAA. Interestingly, both pharmacological interventions and CHOP deficiency attenuated AngII-induced cardiac hypertrophic remodelling and improved systolic and diastolic function. Conclusions: Our data evidence that inhibition of ER and mitochondrial stress limits abdominal aortic aneurysm formation, increases survival and ameliorates hypertensive cardiac hypertrophy.

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