

26. Oral treatment with a zinc complex of acetylsalicylic acid prevents diabetic cardiomyopathy in a rat model of type-2 diabetes - Activation of the Akt pathway

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Background Type 2 diabetics have an increased risk of cardiomyopathy and heart failure is a major cause of death among these patients. Growing evidence indicates that proinflammatory cytokines may induce the development of insulin resistance, and that anti-inflammatory medications may reverse this process. We investigated the effects of the oral administration of zinc and acetylsalicylic acid in the form of bis(aspirinato)zinc(II) complex Zn(ASA)₂, on different aspects of cardiac damage in Zucker diabetic fatty (ZDF) rats, an experimental model of type 2 diabetic cardiomyopathy.

Methods Nondiabetic control (ZL) and ZDF rats were pretreated orally with vehicle or Zn(ASA)₂ for 24 days. At the age of 29-30 weeks, both the electrical activities and the left ventricular (LV) functional parameters were assessed via electrocardiogram and conductance catheter system. Myocardial nitrotyrosine immunohistochemistry, TUNEL assay, and hematoxylin-eosin staining were performed. The protein expression of the PI3K/AKT pathway was quantified by Western blot.

Results Zn(ASA)₂ treatment significantly decreased plasma glucose concentration (39.6 ± 3.1 vs 50.4 ± 2.6 mM), while serum insulin levels were similar among the groups. Data from cardiac catheterization showed that Zn(ASA)₂ normalized the increased LV diastolic stiffness (end diastolic pressure volume relationship: 0.064 ± 0.008 vs 0.084 ± 0.014 mmHg/ μ l; end diastolic pressure: 6.5 ± 0.6 vs 7.9 ± 0.7 mmHg). Furthermore, ECG recordings demonstrated a restoration of prolonged corrected QT intervals (63 ± 3 vs 83 ± 4 ms, $p < 0.05$) with Zn(ASA)₂. Histological examination revealed an increase in the cardiomyocytes' transverse cross section area in ZDF compared to the ZL rats, which was significantly decreased after the Zn(ASA)₂ treatment. Additionally, a significant fibrotic remodelling was observed in ZDF compared to ZL rats, and Zn(ASA)₂-treated ZDF rats showed a similar collagen content as ZL animals. In diabetic hearts, Zn(ASA)₂ significantly decreased DNA fragmentation, nitro-oxidative stress, and up-regulated phosphorylated-Akt/Akt protein expression. Zn(ASA)₂ reduced cardiomyocyte death in a cellular model of oxidative stress.

Conclusions We demonstrated that treatment of type 2 diabetic rats with Zn(ASA)₂ reduced plasma glucose levels and prevented diabetic cardiomyopathy. The increased activation of the serine-threonine kinase Akt in the myocardium could, in part, help to explain the cardioprotective effects of Zn(ASA)₂.