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Antioxidant N-acetylcysteine improves cardiac diastolic function in diabetic rats by attenuating PKCβ$_2$ activation and improving caveolae function and eNOS signaling

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Objective: Hyperglycemia induced oxidative stress is implicated in the development diabetic cardiomyopathy, which is also associated with excessive activation of protein kinase C (PKC) β$_2$, caveolae dysfunction and impairedendothelial nitric oxide (NO) synthase (eNOS)/NO signaling. We tested the hypothesis antioxidant N-acetylcysteine (NAC)could attenuate myocardial dysfunction in diabetic rats by suppressing hyperglycemia induced oxidative damage in the myocardium subsequent to inhibition of myocardial PKCβ$_2$ activation and caveolae dysfunction and rescuing eNOS/NO signaling.

Methods: Controlor streptozotocin (STZ)-induced diabetic rats were either untreated or treated with N-acetylcysteine (NAC, 1.5 g/kg/day) or the PKCβ inhibitor LY333531 (LY, 1 mg/kg/day) by oral gavage for four weeks.

Results: Diabetes decreased heart rate (HR) and the ratio of peak velocity of early and late diastolic filling (E/A) and increased left ventricular isovolumic relaxation time (IVRT), as well as the ratio of heart weight to body weight, all of which except HR were attenuated by NAC or LY.Levels of 15-F2t-isoprostane, superoxide anion (O_2^-) and nitrotyrosine production were increased, whereas NOlevels were decreased in diabetes. Diabetes induced increase of O_2^- levels was blocked by the nitric oxide synthase (NOS) inhibitor L-NAME, indicating "NOS uncoupling". In addition, diabetes elevated cardiac levels of p-PKCβ$_2$, Caveolin-1 and inducible NOS expression, anddecreased levels of caveolin-3, p-Akt (Ser 473) and p-eNOS(Ser 1177) expression in diabetic heart. All these alterations were attenuated or reversed by NAC or LY. **Conclusions:**Antioxidant NAC treatment improves cardiac diastolic dysfunction by attenuating PKCβ$_2$activation, caveolae dysfunction and eNOSsignaling.

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