

Synergy and mechanism of antioxidants N-Acetylcysteine and Allopurinol in combating diabetic cardiomyopathy and myocardial ischemic injury

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Abstract

Hyperglycemia-induced oxidative stress facilitates the development of diabetic cardiomyopathy (PMID: 22389139) and exacerbates myocardial ischemic reperfusion (MI/R) injury. Antioxidants N-acetylcysteine (NAC) and allopurinol (ALP) can synergistically reduce MI/R injury in streptozotocin (STZ)-induced diabetes (PLoS One. 2011;6:e23967), but the underlying mechanism is unclear. We postulated that NAC and ALP may attenuate MI/R injury primarily through phosphatidylinositol 3-kinase (PI3K)/Akt and Jak2/STAT3 mediated endothelial nitric oxide synthase (eNOS) activation in diabetes. Control (C) or STZ-induced diabetic (D) rats were untreated or treated with NAC (1.5g/kg/day) or ALP (100 mg/kg/day) or their combination for four weeks starting one week after STZ injection. NAC and ALP synergistically decreased myocardial infarct size in D rats subjected to 30 minutes of coronary artery occlusion and two hours of reperfusion, which was associated with restoration of myocardial phosphorylations of Akt, STAT3 and eNOS. Exposure of cultured rat cardiomyocytes to high glucose and 45 min hypoxia and 2 hours reoxygenation induced post-hypoxic cell death reflected as an increase of lactate dehydrogenase (LDH) leakage and reduced cell viability. NAC and ALP synergistically decreased post-hypoxic cell death that was associated with increased phosphorylations of Akt, STAT3 and eNOS. The PI3K inhibitor wortmannin and Jak2 inhibitor AG490, respectively attenuated NAC and ALP's protective effects in vivo and in vitro. We conclude that activation of both the PI3K/Akt and the Jak2/STAT3 signaling are major mechanisms by which NAC and ALP synergistically attenuated MI/R injury in diabetes.

Biography

Zhengyuan Xia had served as a cardiovascular anesthetist for more than 10 years in China before he completed his Ph.D study at the University of British Columbia (UBC), in Canada in 2004 and postdoctoral studies at UBC and University of Calgary in 2007. He is Assistant Professor and Honorary Associate Professor at the University of Hong Kong, and his major focus of research is cardiac protection during ischemia-reperfusion in diabetes. He has published more than 65 papers in reputed journals and serving as an editorial board member of Journal of Diabetes & Metabolism.