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N-Acetylcysteine Enhances Cardiac HO-1 Protein Expression and Antioxidant Capacity in Diabetic Rats

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Introduction: The antioxidant N-acetylcysteine (NAC) restores volatile anesthetic isoflurane-induced preconditioning against myocardial infarction in hyperglycemia (1). However, the mechanism whereby NAC restores isoflurane preconditioning cardioprotection is unclear. Elevated heme oxygenase-1 (HO-1) leads to improved postischaemic cardiac function in type 1 diabetes (2), and enhancement of cardiac antioxidant capacity facilitates postischemic myocardial functional recovery (3). Therefore, we hypothesized that NAC may increase cardiac antioxidant capacity by enhancing HO-1 expression in diabetes.

Methods: Control or streptozotozin-induced type 1 diabetic rats were either untreated (C, D) or treated with NAC (1.5g/kg/day, D+NAC) delivered by oral gavage for four weeks. Myocardial tissue protein contents of HO-1 and Cu/Zn Superoxide dismutase (Cu/Zn SOD) were determined using Western blotting. Myocardial total SOD and catalase enzyme activities as well as levels of 15-F2t-isoprostane, a specific marker of oxidative stress, were determined using an enzymatic immunoassay. The total antioxidant activity of myocardial tissue was determined using a colorimetic assay. Data were analyzed using two-way analysis of variance with Bonferroni corrections.

Results: Myocardial 15-F2t-isoprostane (IsoP) was increased in the diabetic myocardium and this was accompanied by compensatory increases in HO-1 (1.5-fold in D vs. C, $P<0.05$) and Cu/Zn SOD ([start_en]223C;2-fold in D vs. C, $P<0.01$) protein expressions and an increase in myocardial total antioxidant activity ([start_en]223C;1.6-fold in D vs. C, $P<0.01$). The total SOD and catalase activities were also increased in D rats ($P<0.05$ vs. C). NAC treatment prevented the compensatory increases of Cu/Zn SOD protein expression and increases in SOD and catalase activities ($P>0.05$, D-NAC vs. C; $P<0.05$, D-NAC vs. D) but led to a further increase in myocardial HO-1 protein expression ([start_en]223C;2-fold in D vs. C, $P<0.05$) that was coincident with a further increase in myocardial total antioxidant activity ([start_en]223C;2.1-fold in D vs. C, $P<0.05$).

Conclusions: N-acetylcysteine treatment preferably enhances HO-1 protein expression in the diabetic myocardium, leading to increased endogenous myocardial antioxidant capacity. This may represent a mechanism by which N-acetylcysteine restores the isoflurane-induced preconditioning leading to cardioprotection in hyperglycemia.

References:

1. Kehl F, et al. Anesthesiology. 2003 ;98(6):1384-90.

2. Shen WL. et al. Clin Exp Pharmacol Physiol. 2008 Jul;35(7):820-6

3. Xia Z. et al. Can J Physiol Pharmacol. 2003;81(1):14-21.

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