Abstract: P101

Inorganic nitrate restores cardiac ischemic tolerance in type 2 diabetic db/db mice and protects against ischemia-reperfusion injury via an effect mediated through red blood cells

Authors:
JN Yang¹, Y Tratsiakovich¹, A Mahdi¹, Z Zhou¹, JO Lundberg², J Pernow¹, ¹Karolinska Institute, Medicine - Stockholm - Sweden, ²Karolinska Institute, Department of Physiology and Pharmacology - Stockholm - Sweden,

On behalf: John Pernow

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Background: Inorganic nitrate, abundant in green leafy vegetables and beetroot, has been shown to exert beneficial cardiovascular effects including a reduction in blood pressure, and improve endothelial function and insulin sensitivity. These effects are thought to be mediated via sequential reduction of nitrate to nitrite and nitric oxide (NO). Previously we reported that hearts from type 2 diabetic db/db mice have impaired cardiac ischemic tolerance and that this effect involves reduced export of NO-like bioactivity from red blood cells (RBCs). It remains unknown whether nitrate supplementation may affect cardiac ischemic tolerance in diabetes through interference with RBC function.

Purpose: To test the hypothesis that dietary nitrate supplementation improves cardiac ischemic tolerance of hearts via an effect mediated through RBCs in type 2 diabetes.

Methods: Type 2 diabetic (db/db) and wild type (WT) mice on nitrate-free chow were treated with vehicle or nitrate (1 mM) in the drinking water for 4 weeks. Hearts were isolated and perfused using Langendorff technique. After 30 min stabilization, the hearts were subjected to 40 min global ischemia followed by 60 min reperfusion. In protocol 1, isolated hearts from db/db and WT mice given vehicle or nitrate were perfused with buffer. In protocol 2, only hearts from WT mice were used. Washed RBCs from WT or db/db mice treated with vehicle or nitrate were administered to WT hearts at the onset of ischemia. In both protocols post-ischemic recovery of cardiac function was evaluated by determination of left ventricular developed pressure (LVDP).

Results: Post-ischemic recovery of LVDP was impaired in hearts from db/db mice in comparison with hearts from WT mice in Protocol 1 (Fig. A). Dietary nitrate restored the ischemic tolerance of hearts from db/db mice but did not affect post-ischemic recovery of hearts from WT mice (Fig. A). In Protocol 2, administration of RBCs collected from vehicle-treated db/db mice significantly impaired post-ischemic recovery of hearts from WT mice (Fig. B). Notably, administration of RBCs from nitrate-treated db/db mice completely reversed the impairment of post-ischemic cardiac function induced by diabetic RBCs (Fig. B). Interestingly, post-ischemic cardiac function did not differ between hearts given RBCs from nitrate-treated db/db and WT mice (Fig. B).

Conclusion: Dietary nitrate restores cardiac ischemic tolerance in db/db mice and protects the heart against ischemia–reperfusion injury via an effect mediated through RBCs.
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Figure. Recovery of left ventricular developed pressure (LVDP) following global ischemia in isolated hearts from A) db/db and wild type (WT) mice treated with vehicle or nitrate and perfused with buffer and from B) untreated WT hearts given RBCs from WT or db/db mice treated with vehicle or nitrate. (n=4-7 in each group, *** p<0.001)