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Chronic Exercise Reduces Fibrosis and Hypertrophy but not Oxidative Stress in Diabetic Cardiomyopathy

Diabetic cardiomyopathy refers to the cardiac manifestations observed in the heart as a result of altered glucose homeostasis that is reflected as fibrosis, cellular hypertrophy, increased sources of oxidative stress, such as the NADPH oxidases (NOX), apoptosis, and finally systolic and diastolic dysfunction (1). Exercise is known to exert salutary effects on cardiovascular function, mainly through the increase in the expression of nitric oxide synthase, particularly eNOS (2).

Aims: We tested the hypothesis that chronic exercise could reverse the cardiac maladaptations and oxidative stress that are produced by diabetes.

Methods. Diabetes was induced in rats by a single dose of alloxan (200/mg kg, i.p). Diabetic rats were randomly assigned to a sedentary group (n=5) or submitted to a program of exercise on a motor-driven treadmill (80% of maximal aerobic capacity) 5 days/week, for 4 weeks (n=5). Another group of normoglycemic rats was used as control (n=7). Cardiac fibrosis was evaluated by Sirius red staining, hypertrophy was estimated measuring the perimeter and area of cardiac myocytes in haematoxylin & eosin stained sections. The levels of NOX and NOS enzymes were evaluated by real-time PCR and Western Blotting. Cardiac levels of tetrahydrobiopterin were analyzed by HPLC (3).

Results. Chronic exercise reduced cardiac fibrosis (4.43 ± 0.9 % control, 8.68 ± 0.7 % diabetic and 5.72 ± 0.7 % diabetic + exercise, ($p<0.05$, ANOVA). Cellular hypertrophy was also reduced in diabetic rats by exercise: myocyte perimeter 297 ± 17 μm^2 in control group, 446 ± 26 diabetic group and 363 ± 14 diabetic + exercise; myocyte perimeter: 73 ± 7 µm in control group, 89.5 ± 4.3 diabetic group, 78.7 ± 2.7 diabetic + exercise, $p<0.05$.

Biochemically, exercise increased the levels of the NADPH oxidases NOX2 and NOX4 mRNA levels ($p<0.05$, ANOVA).

Neither diabetes nor exercise induced changes in the levels of cardiac eNOS ($p=0.4139$). On the contrary, diabetes increased the level of uncoupled eNOS, evaluated as the ratio of eNOS dimer/monomer: 1.3 ± 0.36 in control group, 0.38 ± 0.04 diabetic group and 0.26 ± diabetic + exercise, $p<0.05$. Furthermore, exercise was unable to restore the intracardiac levels of tetrahydrobiopterin, an essential cofactor for NOS activity, that were reduced in diabetic rats: 2.69 ± 1.3 nmol/L in control group, 0.31 ± 0.04 diabetic group and 0, 36 ± 0.06 in diabetic + exercise, $p<0.05$.

Conclusions. These results suggest that chronic exercise was able to reverse cardiac remodelling in the diabetic heart, but was unable to restore the nitroso-redox imbalance imposed by oxidative stress. This later could by restored by pharmacological manipulations.

(1) Huynh K *et al.* (2014). *Pharmacology & Therapeutics* **142**: 375–415

(2) Calvert J and Lefer D.(2013*). Physiology* **28**: 216–224

(3) Alp N et al. (2003). *J. Clin. Invest.* **112**: 725–735