The addition of the aldose reductase inhibitor benzofuroxane derivative BF-5m to prolonged moderate exercise training enhances the protection of the rat heart from diabetic damage

M. Donniacuo[1], B. Rinaldi[1], B. Ferraro[1], C. La Motta[2], M.C. Trotta[1], L. Sodano[1], R. Maisto[1], S. Sartini[2], S. Cosconati[3], C. Rossi[4], F. Ferraraccio[5], M. D'Amico[1], C. Di Filippo[1]

[1]Dept. of Experimental Medicine, Section of Pharmacology 'L. Donatelli', Second University of Naples, Naples, Italy
[2]Dept. of Pharmacy, University of Pisa, Italy
[3]DiSTABiF, Second University of Naples, Italy
[4]Dept. of Clinical and Experimental Medicine and Surgery 'Magrassi, Lanzara', Second University of Naples, Naples, Italy
[5]Dept. of Clinical, Public and Preventive Medicine, Second University of Naples, Naples, Italy

The prevalence of diabetes mellitus has been growing with its related complications, such as cardiovascular disease, nephropathy and neuropathy. Clinical and experimental data suggest that these intracardiac abnormalities are also negatively affected by systemic neurohumoral and cytokine imbalances (Selvin et al., 2010). Exercise training has been recognized as a non pharmacological tool to prevent the pathological consequences of diabetes (Campos et al., 2012). However, exercise training alone may not be sufficient to exert beneficial effects on the cardiovascular system because of the long-term multifactorial etiology of diabetic complications. In this study we have investigated whether the association of a new antioxidant, NO-releasing and selective aldose reductase 2 inhibitor, benzofuroxane derivative BF-5m (Sartini et al., 2012) and prolonged moderate exercise training could give better outcomes and preserve the diabetes-induced cardiac damage. 20 Sprague-Dawley (SD) rats were treated with a single intraperitoneal injection of streptozotocin (STZ; 65 mg/kg). Development of diabetes was confirmed 7 days after injection of STZ measuring the plasma glucose levels. Rats with plasma glucose levels above 200 mg/dl or higher were included in the study. SD rats were allocated into two main experimental group: sedentary and trained by walking at a speed of 10 min/day on a treadmill for 2 weeks. From week 3, training consisted of running of 30 m/min, 45 min/day, 5 days/week, for 6 weeks. To evaluate the cardiac function before, during and at the end of the study a non-invasive transthoracic M-Mode echocardiography was performed. Western blot analyses were performed on the heart to assess SERCA2 as marker of heart function, and MnSOD as marker of oxidative stress, and an ELISA assay was performed to assess plasma insulin levels. Pericapillary fibrosis and interstitial mesenchymal cells have been evaluated following staining with anti-vimentin antibody.
Our results demonstrated in trained rats a significant increase of the heart rate ($p<0.05$) with a significant increase of EF compared with sedentary ones. As expected, high levels of blood glucose led long QT interval (e.g. 185±19 milliseconds) in sedentary rats. This value was decreased up to 22% after a moderate prolonged exercise training. SERCA2 and MnSOD protein expressions were significantly higher in trained rats compared to the sedentary ones ($p<0.05$). Immunohistochemical data showed in sedentary rats a clear evidence of a damaged structure with no few signs of well tissue organization. Exercise training reduced the perivascular fibrosis compared to sedentary ones. Treatment of sedentary rats with BF-5m significantly increased the LVEF compared to the untreated sedentary ones. In trained rats, the addition of BF-5m increased these parameters up to 38% respect to sedentary untreated rats, and up to 16% respect to the trained untreated rats. The addition of BF-5m to physical activity significantly increases the plasma insulin (e.g. 133%, $p<0.05$). Consequently, the plasma glucose levels were significantly decreased by 12% ($p<0.05$). SERCA2 and MnSOD protein expressions were significantly increased after the association of a prolonged exercise training and BF-5m with values twice and fourfold higher respectively compared to the sedentary treated rats ($p <0.01$). Interestingly, in trained rats treated with BF-5m, there is a marked reduction of perivascular and interstitial fibrosis and a constant presence of interstitial fibrocytes. In conclusion, this new compound, especially if combined with exercise training, may be a powerful new tool in the fight against diabetes mellitus and its damage.

References

Selvin E et al. (2010) N Engl J Med. 362:800-11
Campos et al. (2012) PLoS One. 7:e52764
Sartini et al. (2012) J Med Chem. 55:10523-3