

# Effects of the aldose-reductase inhibitor 5(6)-(benzo[d]thiazol-2-ylmethoxy)benzofuroxane on long cardiac QT interval induced by perfusion of isolated heart with a high glucose concentration

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Diabetes is a multifactorial pathology characterized by hyperglycemic conditions that cause detrimental effects on various organs (Tsujimoto et al., 2014), including the prolongation of the cardiac QT interval. Long cardiac QT interval is partly sensitive to antioxidant drugs acting on the levels of nitric oxide (NO) bioavailability and accumulation of reactive oxygen species (Ceriello et al., 2002; Di Filippo et al., 2002). Sartini et al., (2012) recently discovered a series of new benzofuroxane derivatives which may modulate hyperglycemia-induced modifications through the inhibition of aldose reductase (ALR2), the spontaneous release of NO and the excellent hydroxyl radical scavenging activity. The aim of our work was to investigate the effects of the most active benzofuroxane derivative, the 5(6)-(benzo[d]thiazol-2-ylmethoxy)benzofuroxane (BF-5m) at doses of 0.01-0.05-0.1  $\mu$ M, on the prolongation of cardiac QT interval and the increase of coronary perfusion pressure (CPP) induced by high concentration of glucose (33.3 mM concentration) in isolated perfused rat hearts (Di Filippo et al., 2002). The results obtained showed that BF-5m dose dependently diminished the QT interval of 10%, 32% and 41%, respectively for the dose of 0.01-0.05-0.1  $\mu$ M. Similarly, the CPP was reduced of 20% by BF-5m 0.05  $\mu$ M and of 32% by BF-5m 0.1  $\mu$ M. Since we hypothesized that these cardioprotective effects could have been related to an eventual modulation of sirtuin-1 (SIRT1) pathway, a NAD<sup>+</sup>-dependent protein deacetylase with an important role in glucose concentration (Chakrabarti et al., 2003), biochemical analysis were performed on heart homogenates in order to assess the SIRT1 expression. These were increased by the addition of BF-5m at sub maximal dose (0.05  $\mu$ M) to the high glucose Krebs with a significance of  $p < 0.01$ . BF-5m treatment also increased the expression levels of Mn-SOD and FOXO-1, two targets of SIRT-1. Functionally, pretreatment of the rats with EX527 (10 mg/kg/day i.p.), an inhibitor of SIRT1 activity (Solomon et al., 2006), decreased the BF-5m cardio-protection. Overall, these results suggest that the new benzofuroxane derivative BF-5m supply cardio-protection from high glucose induced cardiac electrical instability through the increase of SIRT1 protein and activity into the heart tissue.

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