PHARMACOLOGICAL MODULATION OF CARDIAC QT INTERVAL PROLONGATION THROUGH ALR2 SELECTIVE INHIBITION

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Prolongation of cardiac QT interval is one of the most dangerous consequence of hyperglycemia [1] and is partly sensitive to antioxidant drugs acting on the nitric oxide bioavailability, glycosylated products, accumulation of reactive oxygen species and impairment of ionic pumps [2, 3]. Here we show that the selective inhibition of the endogenous aldose reductase 2 (ALR2) activity, involved in the oxidative damage in the heart following diabetes [4], by the newly synthetized benzofuroxane derivative 5(6)-(benzo[d]thiazol-2-ylmethoxy)benzofuroxane (BF-5m) (0.01 – 0.05 – 0.1 μM), dose-dependently results in cardioprotection from the electrical instability. This cardioprotection is exerted by reduction of the long cardiac QT interval and the decrease of the coronary perfusion pressure (CPP) in isolated rat heart perfused with high glucose (33 μM). BF-5m also promotes increase of the expression and activity of endogenous antioxidant pathways and free radical scavengers such as SIRT1 and MnSOD into the heart following exposure to high glucose. This result is also confirmed by the increase in the expression of the Forkhead transcription factor 1 (FOXO-1), a direct downstream product of SIRT1 activity involved in gluconeogenesis, glycogenolysis, and adipogenesis [5]. To confirm these results, the expression of the potassium channel KNCE1 involved in QT prolongation, of the sarcoplasmic reticulum calcium uptake pump SERCA and of SIRT1 has been analyzed in H9C2 cardiomyocytes, cultured in high glucose (33 μM) and pretreated with BF-5m (0.01 – 0.025 – 0.5 μM). Also the expression levels of mir-1, down-regulating KCNE1, and of mir-25, down-regulating SERCA, have been analyzed.

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