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Vardenafil limits infarction at reperfusion in isolated rat hearts dependent on guanylyl cyclase and PKG

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The type 5 phosphodiesterase inhibitor vardenafil (VAR) reduces myocardial infarct size following ischemia/ reperfusion injury when applied prior to ischemia or at reperfusion in models of in situ hearts. Little is known about the underlying protective signaling. Here, we test whether VAR is protective in a cell model of calcium stress as well as in isolated rat hearts. HL-1 cardiomyocytes were loaded with tetramethylrhodamine ethyl ester (TMRE, 100 nM) which causes cells to fluoresce proportional to their mitochondrial membrane potential (Ψm). A reduction of fluorescence serves as an indicator of collapse of Ψm, and, presumably to permeability transition pore (mPTP) formation. Cells were subjected to the calcium ionophore calcimycin (CAL) (100 μM) which causes mPTP formation due to calcium overload. Fluorescence intensity was measured after 80 minutes of calcium stress with FACS technique. Treatment with CAL reduced the mean cell fluorescence (903 ± 28 arbitrary units (a.u.), vs. 548 ± 29 a.u. in untreated cells, $p < 0.001$) while VAR (1 nM) could protect the cells (698 ± 40 a.u., $p < 0.001$). This protection could be blocked by either the guanylyl cyclase (GC) inhibitor ODQ (20 μM) (519 ± 41 a.u.) or the protein kinase G blocker KT5823 (1 μM) (513 ± 22 a.u.), while inhibition of NO-synthase with L-NAME had no effect. To further support the results, isolated rat hearts were subjected to 30 min regional ischemia followed by 120 min reperfusion. As expected, VAR (10 nM) at 5 min prior to reperfusion reduced infarct size as percentage of the ischemic zone from 46.6 ± 2.1% in control hearts to 26.2 ± 2.7% ($p < 0.001$). This protective effect could be blocked with co-administration of ODQ (43.9 ± 2.2%), while L-NAME was not effective, confirming a role for GC but not for NOS in VAR's protection. Taken together, these results further support the hypothesis that PDE-5 inhibitors induce protective effects in the ischemic heart in addition to their well known clinical effects in the treatment of erectile dysfunction in men.