CARDIOPROTECTIVE ACTIVITY OF SIDENAFIL IN RATS WITH CHRONIC NITRIC OXIDE SYNTHASE INHIBITION

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Phosphodiesterase-5 (PDE-5) inhibitors are beneficial in pulmonary hypertension and congestive heart failure, two conditions associated with coronary heart disease and ischemia. PDE-5 inhibition with sildenafil attenuates cardiomyocyte apoptosis in a chronic model of doxorubicin cardiotoxicity, and reduces the hypertrophic response to isoproterenol in the rat heart, reducing myocardial leakage of creatine kinase and troponin T.
This study investigated whether sildenafil counteracts the cardiovascular alterations induced by N^{ω}-nitro-L-arginine methyl ester (L-NAME) in *ex vivo* heart preparations from L-NAME-treated rats subjected to ischemia-reperfusion.
Sildenafil was given orally at doses of 0.37, 0.75 or 1.5 mg kg^{-1}day for four weeks, either alone or with L-NAME (35-40 mg kg^{-1} day in the drinking water). Systolic blood pressure and urinary parameters (6-keto-prostaglandin $F_{1\alpha}$, thromboxane B_2, 8-isoprostane-prostaglandin $F_{2\alpha}$ and nitrite/nitrate) were measured in conscious rats. Isolated hearts were subjected to low-flow ischemia-reperfusion, and myocardial levels of cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) were determined. Endothelial vascular dysfunction was examined in aortic rings.
Sildenafil dose-dependently prevented systolic blood pressure rising in L-NAME-treated rats (from 129 ± 8 to 183 ± 6 mmHg; $P < 0.001$). This was associated with normalization of urinary 8-isoprostane-prostaglandin $F_{2\alpha}$ and other biochemical parameters. Post-ischemic ventricular dysfunction was worse in preparations from L-NAME-treated rats than controls. Sildenafil dose-dependently reduced this effect, and creatine kinase and lactate dehydrogenase release were lower too. cGMP and cAMP levels, both low in myocardial tissue from L-NAME-treated rats (-69%, $P < 0.01$ and -57%, $P < 0.05$ *vs* controls) were restored by sildenafil. In norepinephrine-precontracted aortic rings from L-NAME-treated rats acetylcholine lost its vasorelaxant effect, and sildenafil restored it.
This study indicates that in a rat model of chronic nitric oxide deprivation, where hypertension and aggravation of post-ischemic ventricular dysfunction are associated with loss of vascular endothelium-relaxant function, sildenafil provided significant cardiovascular protection, primarily by maintaining tissue cGMP levels.