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Testing of Matrix metalloproteinase inhibitors to prevent myocardial ischemia/reperfusion injury.

Introduction: It is well known that inhibition of matrix metalloproteinases (MMP) can reduce the ischemia/reperfusion (I/R) caused infarct size in rat heart. However, due to severe side effects. nonselective MMP inhibitors are not used in human therapy. Therefore aim of present study was to examine selective MMP-2 inhibitors.

Methods: 46 molecules with inhibitory effect on MMP-2 catalytic domain were measured in concentration of 1 μ M and 100 μ M on MMP-2 enzymes isolated from myocardium with gelatine zymography.

Out of the total 46 molecules 7 potential MMP-2 inhibitors were selected to test the viability on neonatal cardiomyocytes after simulated ischemia-reoxygenization system.

Three days old rat cardiac myocytes in vitro were subjected to 4 hour simulated ischemia (95% N₂, 5% CO₂+hipoxic solution) or normoxia (95% air, 5% CO₂+normoxic solution) followed by 2 hour reoxygenation (normoxia+medium). Cell viability was determined with calcein AM/propidium iodide fluorescent staining. MMP-2 inhibitors were administered in 4 different concentrations, and we used Ilomastat (0,5 μ M) as positive control.

Results: Out of the 46 MMP-2 inhibitor compounds 40 molecules inhibited the MMP-2 activity, 18 molecules have shown above 50% inhibition in concentration of 100 μ M and 4 of them have showed an inhibitory effect over 50% at concentration of 1 μ M also.

Out of the 7 molecules which were tested on cardiomyocytes 6 molecules increased cell viability after simulated I/R.

Conclusion: Based on the results seems the molecules are capable to inhibit MMP-2 and increase the cells survival after simulated I/R, therefore these molecules are may applicable in the treatment of I/R injury.

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