CYTOPROTECTIVE EFFECT OF KYNURENIC ACID INVOLVES THE MODULATION OF APOPTOTIC PATHWAYS AGAINST SIMULATED ISCHEMIA/REOXYGENATION INJURY OF CARDIAC CELLS

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Acute myocardial infarction (AMI) is a leading cause of disability and death worldwide, which is caused by multifactorial damage of cardiac cells. Until now, the only therapeutic approach to minimalize the cardiac injury is reperfusion therapy, which is necessary for survival. However, it might initiate further cardiac damage, therefore the analysis of molecules/processes, which potentially increase the tolerance of cardiac cells against ischemic injury have a great therapeutic potential in the field of experimental cardiology. In this study, we aimed to investigate the underlying mechanisms of the barely known and previously uncovered cytoprotective effect of kynurenic acid (KYNA) against simulated ischemia/reoxygenation (SI/R)-induced injury of H9c2 cardiac cells, focusing on apoptosis-related intracellular events. To investigate the anti-apoptotic effects of KYNA, H9c2 cardiac cells were subjected to 6 hours of simulated ischemia and 2 hours of reoxygenation (SI/R) in the presence or absence of 64 µM KYNA, and several markers of apoptosis (membrane blebbing, cell viability, cellular morphology, expression of apoptotic proteins) were assessed using light microscopy, confocal microscopy, western blots, immunocytochemistry and biochemical assays. According to our results, SI/R caused worsening of irreversible membrane blebbing and increased apoptosis related DNA damages (e.g. micronuclei formation, chromatin condensation, frequency of DNA double strand breaks), which outcomes were attenuated by administration of KYNA. The SI/R-induced increase of proapoptotic and decrease of antiapoptotic protein expressions were reverted by KYNA. In concordance with these findings, the activation of effector caspases (caspase-3, -7) increased upon SI/R, which effect was diminished by the applied KYNA treatment, suggesting potential anti-apoptotic processes mediated by KYNA. These data suggest that KYNA exerts its cytoprotective effect against SI/R-induced cardiac cell injury via modulation of apoptotic processes.

Keywords: kynurenines, tryptophan metabolite, programmed cell death, cellular damage, cardiomyocytes

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