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Oxidative Stress Related Alteration of Mitochondrial Dynamics in Cellular Models

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Abstract : Introduction: Oxidative stress induces an imbalance in mitochondrial fusion and fission processes, finally leading to cell death. The two antioxidant molecules, BGP-15 and L2286 have beneficial effects on mitochondrial functions and on cellular oxidative stress response. In this work, we studied the effects of these compounds on the processes of mitochondrial quality control. Methods: We used H9c2 cardiomyoblast and isolated neonatal rat cardiomyocytes (NRCM) for the experiments. The concentration of stressors and antioxidants was beforehand determined with MTT test. We applied 1-Methyl-3-nitro-1-nitrosoguanidine (MNNG) in 125 µM, 400 µM and 800 µM concentrations for 4 and 8 hours on H9c2 cells. H_2O_2 was applied in 150 µM and 300 µM concentration for 0.5 and 4 hours on both models. L2286 was administered in 10 µM, while BGP-15 in 50 µM doses. Cellular levels of the key proteins playing role in mitochondrial dynamics were measured in Western blot samples. For the analysis of mitochondrial network dynamics, we applied electron microscopy and immunocytochemistry. Results: Due to MNNG treatment the level of fusion proteins (OPA1, MFN2) decreased, while the level of fission protein DRP1 elevated markedly. The levels of fusion proteins OPA1 and MNF2 increased in the L2286 and BGP-15 treated groups. During the 8 hour treatment period, the level of DRP1 also increased in the treated cells ($p < 0.05$). In the H_2O_2 stressed cells, administration of L2286 increased the level of OPA1 in both H9c2 and NRCM models. MFN2 levels in isolated neonatal rat cardiomyocytes raised considerably due to BGP-15 treatment ($p < 0.05$). L2286 administration decreased the DRP1 level in H9c2 cells ($p < 0.05$). We observed that the H_2O_2-induced mitochondrial fragmentation could be decreased by L2286 treatment. Conclusion: Our results indicated that the PARP-inhibitor L2286 has beneficial effect on mitochondrial dynamics during oxidative stress scenario, and also in the case of directly induced DNA damage. We could make the similar conclusions in case of BGP-15 administration, which, via reducing ROS accumulation, propagates fusion processes, this way aids preserving cellular viability.
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