Induction of thioredoxin and mitochondrial survival proteins mediates preconditioning-induced cardioprotection and neuroprotection.

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Abstract

Delayed cardio- and neuroprotection are observed following a preconditioning procedure evoked by a brief and nontoxic oxidative stress due to deprivation of oxygen, glucose, serum, trophic factors, and/or antioxidative enzymes. Preconditioning protection can be observed in vivo and is under clinical trials for preservation of cell viability following organ transplants of liver. Previous studies indicated that ischemic preconditioning increases the expression of heat-shock proteins (HSPs) and nitric oxide synthase (NOS). Our pilot studies indicate that the treatment of neuronal NOS inhibitor (7-nitroindazole) and 6Br-cGMP blocks and mimics, respectively, preconditioning protection in human neuroblastoma SH-SY5Y cells. This minireview focuses on nitric oxide-mediated cellular adaptation and the related cGMP/PKG signaling pathway in a compensatory mechanism underlying preconditioning-induced hormesis. Both preconditioning and 6Br-cGMP increase the induction of human thioredoxin (Trx) mRNA and protein for cytoprotection, which is largely prevented by transfection of cells with Trx antisense but not sense oligonucleotides. Cytosolic Trx1 and mitochondrial Trx2 suppress free radical formation, lipid peroxidation, oxidative stress, and mitochondria-dependent apoptosis; knock out/down of either Trx1 or Trx2 is detrimental to cell survival. Other recent findings indicate that a transgenic increase of Trx in mice increases tolerance against oxidative nigral injury caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Trx1 can be translocated into nucleus and phosphoactivated CREB for a delayed induction of mitochondrial anti-apoptotic Bcl-2 and antioxidative MnSOD that is known to increase vitality and survival of cells in the brain and the heart. In conclusion, preconditioning adaptation or a brief oxidative stress induces a delayed nitric oxide-mediated compensatory mechanism for cell survival and vitality in the central nervous system and the cardiovascular system. Preconditioning-induced adaptive tolerance may be signaling through a cGMP-dependent induction of cytosolic redox protein Trx1 and subsequently mitochondrial proteins such as Bcl-2, MnSOD, and perhaps Trx2 or

HSP70.