Roles of thioredoxin in nitric oxide-dependent preconditioning-induced tolerance against MPTP neurotoxin.

闕壯卿
Chiueh CC;Andoh T;Chock PB

Abstract

Hormesis, a stress tolerance, can be induced by ischemic preconditioning stress. In addition to preconditioning, it may be induced by other means, such as gas anesthetics. Preconditioning mechanisms, which may be mediated by reprogramming survival genes and proteins, are obscure. A known neurotoxicant, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), causes less neurotoxicity in the mice that are preconditioned. Pharmacological evidences suggest that the signaling pathway of NO-cGMP-PKG (protein kinase G) may mediate preconditioning phenomenon. We developed a human SH-SY5Y cell model for investigating ()NO-mediated signaling pathway, gene regulation, and protein expression following a sublethal preconditioning stress caused by a brief 2-h serum deprivation. Preconditioned human SH-SY5Y cells are more resistant against severe oxidative stress and apoptosis caused by lethal serum deprivation and 1-mehtyl-4-phenylpyridinium (MPP(+)). Both sublethal and lethal oxidative stress caused by serum withdrawal increased neuronal nitric oxide synthase (nNOS/NOS1) expression and ()NO levels to a similar extent. In addition to free radical scavengers, inhibition of nNOS, guanylyl cyclase, and PKG blocks hormesis induced by preconditioning. S-nitrosothiols and 6-Br-cGMP produce a cytoprotection mimicking the action of preconditioning tolerance. There are two distinct cGMP-mediated survival pathways: (i) the up-regulation of a redox protein thioredoxin (Trx) for elevating mitochondrial levels of antioxidant protein Mn superoxide dismutase (MnSOD) and antiapoptotic protein Bcl-2, and (ii) the activation of mitochondrial ATP-sensitive potassium channels [K(ATP)]. Preconditioning induction of Trx increased tolerance against MPP(+), which was blocked by Trx mRNA antisense oligonucleotide and Trx reductase inhibitor. It is concluded that Trx plays a pivotal role in ()NO-dependent preconditioning hormesis against MPTP/MPP(+).