Role of the redox protein thioredoxin in cytoprotective mechanism evoked by (-)-deprenyl.

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Abstract

Through the inhibition of monoamine oxidase type B (MAO-B), (-)-deprenyl (selegiline) prevents the conversion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to the toxic metabolite 1-methyl-4-phenylpyridinium ion (MPP+) and also prevents the neurotoxicity in the dopaminergic neurons in animal models. Cumulative observations suggest that selegiline may also protect against MPP+-induced neurotoxicity, possibly through the induction of pro-survival genes. We have observed that thioredoxin (Trx) mediates the induction of mitochondrial manganese superoxide dismutase (MnSOD) and Bcl-2 during preconditioning-induced hormesis. We therefore investigated whether the redox protein Trx plays any role in the neuroprotective mechanism of selegiline against MPP+-induced cytotoxicity in human SH-SY5Y neuroblastoma cells and also in primary neuronal cultures of mouse midbrain dopaminergic neurons. After confirming that selegiline protects against MPP+-induced cytotoxicity, we observed further that selegiline, at 1 microM or less, induced Trx for protection against oxidative injury caused by MPP+. The induction of Trx was blocked by protein kinase A (PKA) inhibitor and mediated by a PKA-sensitive phospho-activation of mitogen-activated protein (MAP) kinase Erk1/2 and the transcription factor c-Myc. Selegiline-induced Trx and associated neuroprotection were concomitantly blocked by the antisense against Trx mRNA, but not the sense or antisense mutant phosphothionate oligonucleotides, not only in human SH-SY5Y cells but also in mouse primary neuronal culture of midbrain dopaminergic neurons. Furthermore, the redox cycling of Trx may mediate the protective action of selegiline because the inhibition of Trx reductase by 1-chloro-2,4-dinitrobenzene ameliorated the effect of selegiline. Trx (1 microM) consistently increased the expression of mitochondrial proteins MnSOD and Bcl-2, supporting cell survival (Andoh et al., 2002). In conclusion, without modifying MAO-B activity, selegiline augments the gene induction of Trx, leading to elevated expression of antioxidative MnSOD and antiapoptotic Bcl-2 proteins for protecting against MPP+-induced neurotoxicity.