Thioredoxin-1 suppresses MPP+/MPTP neurotoxicity through enhancing autophagy

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Autophagy is a lysosomal degradative process used to recycle obsolete cellular constituents and eliminate damaged organelles and misfolded protein. Autophagy is associated with the pathogenesis of Parkinson's Disease (PD). Thioredoxin-1 (Trx-1) is a redox regulating protein and plays an important role in PD. However, the relationship between autophagy and Trx-1 in PD has not been reported. Cell and mouse models of PD were used to examine the relationship of autophagy and Trx-1. We showed that the expression of microtubule-associated protein light chain 3 (LC3-II), an auto-phagosome membrane marker was induced by 1-methyl-4-phenylpyridinium ion (MPP+)/1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in PC12 cells and mice. Rapamycin autophagy inducer decreased toxicity by MPP+ in contrast to chloroquine autophagy inhibitor which increased toxicity by MPP+. These results suggest that autophagy plays a protecting role against MPP+ neurotoxicity. The over-expression of Trx-1 in PC12 cells and mice reversed LC3-II expression by MPP+/MPTP. Importantly, Forkhead box O3A (FOXO3A) expression was decreased by MPP+/MPTP in PC12 cells and Substantia Nigra pars compacta (SNpc) of mice. The decrease of FOXO3A was enhanced by down-regulation of Trx-1 and reversed by Trx-1 over-expression in mice. These results suggest that Trx-1 suppresses MPP+/MPTP neurotoxicity by enhancing FOXO3A/autophagy pathway. Our present study indicates FOXO3A may be a new potential target for treatment of PD.

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