Prolonged oxidative stress inhibits basal autophagy while inducing pro-autophagic signals in astroglial cells: role of quinone oxidoreductase 2 (QR2).

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Oxidative stress (OS) stimulates autophagy in different cellular systems, but it remains controversial if this rule can be generalized, especially in models of neurodegeneration. We have analyzed the effect of chronic OS induced by the parkinsonian toxin paraquat (PQ) on autophagy in astroglial cells and primary astrocytes, which represent the first cellular targets of neurotoxins in the brain. PQ (> 1 μM; > 6h) decreased the basal levels of LC3-II and LC3-positive vesicles, and its co-localization with lysosomal markers, both in the absence and presence of chloroquine. This was paralleled by increased number and size of p62 aggregates. Chronic, but not transient, exposure to 0.2-1.0 mM also decreased LC3 lipidation. Down-regulation of autophagy was also observed in astroglial cells chronically exposed to non-lethal concentrations of PQ. Surprisingly, PQ treatment led to inhibition of mTOR, activation of JNK and Erk and up-regulation of Beclin-1 expression, all signals that typically correlate with induction of autophagy. Reduction of OS by NMDPEF, a specific ubichinone oxidoreductase 2 (QR2/NQO2) inhibitor, but not by N-acetylcysteine, abrogated the inhibitory effect of PQ and restored basal autophagy. Activation of QR2 by menadione and genetic manipulation of QR2 expression confirmed the role of this enzyme in the inhibitory effect of PQ on autophagy. Thus, a prolonged OS inhibits LC3-lipidation and impairs autophagosome formation and autophagy flux, in spite of concomitant activation of several pro-autophagic signals. The fact that in astrocytes under chronic OS protective autophagy can be restored by inhibition of QR2 activity may be of clinical relevance for the treatment of OS-associated neurodegeneration.