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# The activation of autophagy protects neurons and astrocytes against bilirubin-induced cytotoxicity

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## HIGHLIGHTS:

1. Unconjugated bilirubin (UCB) at high concentration leads to neurotoxicity.
2. Autophagy activation protects neuronal cells from bilirubin cytotoxicity.
3. Autophagy activation by UCB involves mTOR/ER-stress/PKC/calcium signaling.

## Abstract

Unconjugated bilirubin (UCB) neurotoxicity involves oxidative stress, calcium signaling and ER-stress. The same insults can also induce autophagy, a process of “self-eating”, with both a pro-survival or a pro-apoptotic role. Our aim was to study the outcome of autophagy activation by UCB in the highly sensitive neuronal SH-SY5Y cells and in the resistant astrocytoma U87 cells. Upon treatment with a toxic dose of UCB, the conversion of LC3-I to LC3-II was detected in both cell lines. Inhibition of autophagy by E64d before UCB treatment increased SH-SY5Y cell mortality and made U87 cells sensitive to UCB. In SH-SY5Y autophagy related genes ATG8 (5 folds), ATG18 (5 folds), p62 (3 folds) and FAM129A (4.5 folds) were induced 8h after UCB treatment while DDIT4 upregulation (13 folds) started at 4h. mTORC1 inactivation by UCB was confirmed by phosphorylation of 4EBP1. UCB induced LC3-II conversion was completely prevented by pretreating cells with the calcium chelator BAPTA and reduced by 65% using the ER-stress inhibitor 4-PBA.

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