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Autophagy impairment as a key feature for acetaminophen-induced ototoxicity

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Abstract

Macroautophagy/autophagy is a highly conserved self-digestion pathway that plays an important role in cytoprotection under stress conditions. Autophagy is involved in hepatotoxicity induced by acetaminophen (APAP) in experimental animals and in humans. APAP also causes ototoxicity. However, the role of autophagy in APAP-induced auditory hair cell damage is unclear. In the present study, we investigated autophagy mechanisms during APAP-induced cell death in a mouse auditory cell line (HEI-OC1) and mouse cochlear explant culture. We found that the expression of LC3-II protein and autophagic structures was increased in APAP-treated HEI-OC1 cells; however, the degradation of SQSTM1/p62 protein, the yellow puncta of mRFP-GFP-LC3 fluorescence, and the activity of lysosomal enzymes decreased in APAP-treated HEI-OC1 cells. The degradation of p62 protein and the expression of lysosomal enzymes also decreased in APAP-treated mouse cochlear explants. These data indicate that APAP treatment compromises autophagic degradation and causes lysosomal dysfunction. We suggest that lysosomal dysfunction may be directly responsible for APAP-induced autophagy impairment. Treatment with antioxidant *N*-acetylcysteine (NAC) partially alleviated APAP-induced autophagy impairment and apoptotic cell death, suggesting the involvement of oxidative stress in APAP-induced autophagy impairment. Inhibition of autophagy by knocking down of *Atg5* and *Atg7* aggravated APAP-induced ER and oxidative stress and increased apoptotic cell death. This study provides a better understanding of the mechanism responsible for APAP ototoxicity, which is important for future exploration of treatment strategies for the prevention of hearing loss caused by ototoxic medications.

Introduction

Acetaminophen (*N*-acetyl-p-aminophenol [APAP], also known as paracetamol) is widely used as a pain reliever and fever reducer. APAP is effective and safe at the therapeutic dosage. However, APAP overdose can cause severe hepatotoxicity in experimental animals and humans[1,2]. APAP-induced hepatotoxicity has been recognized for >50 years and its underlying mechanism is fairly well known. APAP is metabolized by a cytochrome P450 2E1 isozyme (CYP2E1) to a reactive intermediate, *N*-acetyl-p-benzoquinone imine (NAPQI). NAPQI causes the depletion of glutathione and the formation of APAP–cysteine adducts[3,4]. The APAP adducts lead to mitochondrial dysfunction and oxidative stress, which is a critical step in triggering hepatocyte necrosis and liver injury[5,6]. A previous study indicated that APAP adducts are removed through selective autophagy in primary mouse hepatocytes. The pharmacological induction of autophagy may be a novel and promising approach for treating APAP-induced liver injury[7].

Autophagy, meaning "self-eating" in Greek, is an important cellular degradation process that occurs in response to physiological or chemical stresses[8,9].

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