**Biometal dyshomeostasis is intensively involved in the pathogenesis of neurodegeneration related to Alzheimer’s disease (AD). The underlying mechanisms are not completely elucidated. Microglia plays essential roles in the proteolytic clearance of amyloid beta (Abeta), the most important pathogenic molecule for AD. In this study, we tested the hypothesis that Cu(II) inhibits microglial Abeta clearance through disrupting autophagy-mediated lysosomal degradation of this peptide.**

**Methods:** LC3-II protein was detected with Western blot analysis. Autophagic flux was detected through RFP-GFP-tandem fluorescent tagged LC3 (tf-LC3) transfection. Lysosomal acidification was examined with LysoTracker Red immunosorbent assay (ELISA). Results: At subneurotoxic doses, Cu(II) increased LC3-II protein levels, accompanied with increased protein levels of p62, a selective autophagic substrate. Inhibition of lysosomal degradation with bafilomycin A1 pretreatment abrogated the Cu(II)-induced elevation in LC3-II protein level. Moreover, Cu(II) led to a marked increase in the number of yellow LC3 dots with a marginal elevation in red-only dots in RFP-GFP-tandem fluorescent LC3 (tf-LC3) transfected microglia, implying an impairment in autophagic flux. Cu(II) treatment also reduced lysosomal acidification, as demonstrated by the decreased LysoTracker Red fluorescence. Lysosomal number and volume were also decreased after Cu(II) exposure. In addition, Cu(II) decreased expression of transcription factor EB (TFEB) and its target genes. Importantly, Cu(II) disrupted phagocytic uptake of oligomeric Abeta1-42 and lysosomal Abeta1-42 degradation in microglial cells. These effects were partially rescued by the mammalian target of rapamycin kinase complex 1 (mTORC1) inhibitor PP242, which activates TFEB signaling and lysosome biogenesis. Conclusions: Collectively, our results suggest that non-neurotoxic Cu(II) caused impaired autophagic flux and lysosomal function (acidification and biogenesis) in microglia, and thus reduced autophagy-mediated Abeta clearance. This may represent a novel mechanism for Cu(II)-induced neurodegeneration in AD.

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