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Stimulation of autophagy is neuroprotective in a mouse model of human tauopathy

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The most common neurodegenerative diseases are characterized by the accumulation of misfolded proteins. Tauopathies, which include Alzheimer disease, progressive supranuclear palsy, corticobasal degeneration, Pick disease and cases of frontotemporal dementia and parkinsonism linked to chromosome 17, are characterized by the accumulation of hyperphosphorylated and filamentous MAPT/tau protein. The pathological mechanisms involved in MAPT protein accumulation are not well understood, but a possible impairment of protein degradation pathways has been suggested. We investigated the effects of autophagy stimulation on MAPT pathology in a model tauopathy, the human mutant P301S MAPT transgenic mouse line. In the brain of the trehalose-treated mutant mice, autophagy is activated and a reduced number of neurons containing MAPT inclusions, as well as a decreased amount of insoluble MAPT, are observed. The improvement of MAPT pathology is associated with increased nerve cell survival. Moreover, MAPT inclusions colocalize with SQSTM1/p62- and LC3-positive puncta, suggesting the colocalization of MAPT aggregates with autophagic vacuoles. Autophagy is not activated in the spinal cord of the human P301S MAPT transgenic mice and neuronal survival, as well as MAPT pathology, is unaffected. This study supports a role for autophagy stimulation in the degradation of MAPT aggregates and opens new perspectives for the investigation of autophagy as a pathological mechanism involved in neurodegenerative diseases.

Keywords: autophagy, neurodegenerative diseases, neuroprotection, protein aggregation, protein degradation, tau

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Tauopathies are a group of neurodegenerative diseases, which are characterized by the presence of inclusions made of filamentous hyperphosphorylated MAPT protein. Currently, the mechanisms involved in MAPT aggregation and degradation are not well understood. The accumulation of autophagic vacuoles has been described in Alzheimer disease and in a mouse model of tauopathy, suggesting a possible impairment of lysosomal degradation. Moreover, the neuroprotective role of autophagy activation has been demonstrated in various models of neurodegenerative diseases. However, the effects of autophagy stimulation in a model of pure tauopathy have not been reported.

In our study, trehalose, a mechanistic target of rapamycin (MTOR)-independent activator of autophagy, was administered to transgenic mice overexpressing human mutant P301S MAPT protein. Mice were treated with trehalose or sucrose in drinking water from weaning and were sacrificed at 20 weeks of age, when homozygous animals typically develop motor deficits. The treatment had no negative impact on the general health of the mice; we also failed to observe an improvement in the motor impairment of human P301S MAPT transgenic mice. Consistent with this, autophagy was not activated in the spinal cord, as assessed by the conversion of LC3-I into LC3-II. The failure of trehalose to activate autophagy was the likely cause of the persistence of insoluble MAPT in the spinal cord and the associated motor deficits in P301S MAPT mice.

In contrast, trehalose activated autophagy in the brain of human P301S MAPT transgenic mice, particularly in the pontine

nucleus of the brain stem and in layers I-III of the cerebral cortex. Autophagy stimulation induced a decrease in insoluble MAPT and in the number of neurons with MAPT inclusions. MAPT inclusions were co-stained with LC3- and SQSTM1-positive puncta, suggesting colocalization of MAPT aggregates and autophagosomes. Moreover, we observed an increase in the number of nerve cells in both the cerebral cortex and the pontine nucleus compared with P301S MAPT mice treated with sucrose, indicating improved neuronal survival in trehalose-treated animals.

Our results demonstrate that the in vivo stimulation of autophagy is neuroprotective, since it reduces the number of MAPT inclusions and improves nerve cell survival in cerebral cortex and brain stem. The mode of action of autophagy in the clearance of insoluble MAPT needs to be further investigated. In particular, the autophagic receptors involved in the clearance of MAPT remain to be identified. Our data indicate colocalization of SQSTM1 and MAPT inclusions, but we can at present not exclude a role for OPTN/optineurin, NBR1, CALCOCO2/NDP52, BNIP3L/NIX or WDFY3/ALFY in the degradation of insoluble MAPT. Although our study indicates that the stimulation of autophagy decreases the number of pathological MAPT inclusions, it is still unclear if autophagy impairment contributes to the development of pathology; further studies are needed to clarify this point and to identify autophagy components whose function may be impaired in human tauopathies. We also observed different effects of trehalose in spinal cord and brain, suggesting differential regulation of autophagy pathways. Altogether, our data indicate that autophagy stimulation and its tissue-specific regulation are attractive targets for the development of mechanism-based therapies of human neurodegenerative diseases.