BMC Neuroscience

Poster presentation

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Alpha-Synuclein aggregate formation in oligodendroglia OLN-t40 cells stably transfected with alpha-Synuclein

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from Annual Meeting of the Study Group Neurochemistry. International Conference of the Gesellschaft für Biochemie und Molekularbiologie 2006 (GBM 2006): Molecular pathways in health and disease of the nervous system
Witten, Germany. 28–30 September 2006

Published: 23 March 2007

BMC Neuroscience 2007, **8**(Suppl 1):P13 doi:10.1186/1471-2202-8-S1-P13

Alpha-Synuclein (alpha-syn) is the major building block of cytoplasmic inclusions in neurodegenerative disorders named synucleinopathies, such as Parkinson's Disease and multiple system atrophy (MSA). In MSA glial cytoplasmic inclusions (GCIs) originating in oligodendrocytes are prominent. During disease progression a shift in alpha-syn solubility is observable, and oxidative modification of alpha-syn has been linked to neurodegeneration and fibril formation. Furthermore, an overlap of pathological features of patients with tauopathies, e.g. frontotemporal dementias including Pick's disease and progressive supranuclear palsy, has been reported, and it has been argued that alpha-syn aggregation can induce the fibrillization of tau.

To investigate the possible involvement of oxidative stress in alpha-syn aggregate formation, we have engineered OLN-t40 cells, a cell line with oligodendroglial characteristics stably expressing the longest human isoform of the microtubule associated protein Tau, to express wild type alpha-syn or the A53T alpha-syn mutation. alpha-Syn expression in both cell lines caused the appearance of small punctuated alpha-syn aggregates, which did not stain with thioflavine S, and were negative for tau and heat shock proteins (HSPs). These aggregates were more abundant in cells expressing the A53T alpha-syn mutation and therefore OLN-t40-A53T cells were used in the following studies.

Oxidative stress, exerted by hydrogen peroxide, led to an enlargement of the cytoplasmic protein inclusions, and to the recruitment of Tau and HSP90, HSP70 and alphaB-crystallin to the inclusions. However, oxidative stress did not cause an increase in alpha-syn in the detergent insoluble fraction, possibly indicating that alpha-syn did not further accumulate and was of prefibrillary nature, and still degradable by the proteasomal system. To test this, cells were treated with hydrogen peroxide first and then with the proteasomal inhibitor MG-132. The results show that oxidative stress followed by proteasomal inhibition leads to a decrease in alpha-syn solubility and to the occurence of larger thioflavine S-positive inclusions, which was not seen either after oxidative stress or proteasomal inhibition alone.

In summary, oxidative modification in combination with proteasomal impairment, contributes to alterations in the solubility of alpha-syn, and leads to the formation of inclusions resembling GCIs. HSPs were upregulated and together with tau recruited to the GCIs, possibly further contributing to the formation of degenerative inclusions.