Results: No differences in synaptic number or expression of synaptic markers were found in the cortex of 5XFAD mice at 6 months of age compared with control littermates. nNOS dimerization was disrupted in the 5XFAD cortex, accompanied by an increase in ROS production. Furthermore, the levels of p25, a CDK5 activator, increased significantly and it colocalized with nNOS in the 5XFAD cortex.

Conclusion: Taken together, our results demonstrate that nNOS dimers are disrupted in the 5xFAD cortex with CDK5 activation, may be involved in the disruption of nNOS dimerization and the development of AD.

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Keywords: Alzheimer’s disease, neuronal nitric oxide synthase, dimerization, cyclin-dependent kinase 5, p25

PT581
Multiple accumulation of neurodegenerative disease-related proteins in familial granulin mutation brains
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Abstract
Granulin (GRN) mutations were identified in patients with familial frontotemporal lobar degeneration (FTLD) with ubiquitinopathy in 2006 studies. GRN transcript haploinsufficiency has been proposed as a disease mechanism that leads to the loss of functional progranulin (PGRN) protein. GRN mutations were first found in tau-negative FTLD patients, however, recent findings indicate that these mutations are associated with other neurodegenerative disorders with tau pathology, including Alzheimer’s disease and corticobasal degeneration. Moreover, PGRN reduction in tau transgenic mice is associated with increasing tau phosphorylation and accumulation.

To investigate the influence of a decline in PGRN protein on other forms of neurodegenerative-related protein accumulation, four human GRN mutation cases (age at death; 54, 55, 56 and 78 years old) were investigated by histochemical and biochemical analyses.

The results showed neuronal and glial tau accumulation in all cases analyzed. Massive neuronal tau staining revealed pretangle forms and glial tau in both astrocytes and oligodendrocytes. Furthermore, phosphorylated α-synuclein-positive structures were also found in oligodendrocytes and the neuropil. Immunoblot analysis of fresh frozen brain tissues revealed that tau protein was present in the sarcosyl-insoluble fraction, which was composed of three- and four-repeat tau isoforms, resembling Alzheimer’s disease.

Our data suggest that PGRN reduction might be the cause of neuroenoglial multiple proteinopathies, including TDP-43 proteinopathy, tauopathy and α-synucleinopathy, due to the accelerating accumulation of abnormal proteins.

PT582
Myristic Acid Hitchhiking on Sigma-1 Receptor to Fend Off Neurodegeneration
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Abstract
Neurodegenerative diseases are linked to tauopathy as a result of cyclin dependent kinase 5 (cdk5) binding to its p25 activator instead of its p35 activator and becoming over-activated. The overactive complex stimulates the hyperphosphorylation of tau proteins, leading to neurofibrillary tangles (NFTs) and stunting axon growth and development. It is known that the sigma-1 receptor (Sig-1R), an endoplasmic reticulum chaperone, is involved in axon growth by promoting neurite sprouting through nerve growth factor (NGF) and tropomyosin receptor kinase B (TrkB). It has also been previously demonstrated that a Sig-1R deficiency impairs the process of neurogenesis by causing a down-regulation of N-methyl-D-aspartate receptors (NMDArs). The study sought to understand the relationship between Sig-1R and tauopathy. It was discovered that the Sig-1R helps maintain proper tau phosphorylation and axon development by facilitating p35 myristoylation and promoting p35 turnover. Neurons that had the Sig-1R knocked down exhibited shortened axons and higher levels of phosphorylated tau proteins compared to control neurons. Here we discuss these recent findings on the role of Sig-1R in tauopathy and highlight the newly presented physiological consequences of the Sig-1R-lipid interaction, helping to understand the close relationship between lipids and neurodegeneration.