Astrocyte calcium signaling can protect against neuroinflammation induced by α-synuclein oligomers

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It is now realized that Parkinson´s Disease (PD) pathology extends beyond the substantia nigra affecting both central and peripheral nervous systems and exhibits a variety of non-motor symptoms often preceding motor features. Neuroinflammation induced by activated microglia and astrocytes is thought to underlie these manifestations. Aggregated α-synuclein has been strongly associated with neuroinflammation; however, we still lack critical information about the structural identity of the α-synuclein conformers that activate microglia and/or astrocytes and the molecular pathways involved. To address this important gap, we have used primary microglia and quiescent astrocytes, post-mortem brain tissue from PD patients and A53T α-synuclein transgenic mice that recapitulate, in the absence of cell death, key features of PD-related inflammatory responses, i.e. increased levels of pro-inflammatory cytokines and complement proteins. We found that these mice exhibit significant elevations in endogenous antibodies indicating an active immune reaction that positively correlated with the levels of SDS-resistant oligomeric but not monomeric α-synuclein. Detailed 3D reconstruction analysis of individual cells revealed altered microglia and astrocyte number and retraction of astrocyte processes. Using RNAseq and secretomic analyses combined with cell type-specific immunofluorescence intensity, we mapped the signaling pathways that are stimulated in microglia and astrocytes in the presence of α-synuclein oligomers. Our results indicate that astrocyte activation promotes the upregulation of T-type Ca^{2+} channels on astrocytes that mediate the secretion of IGFBPL1, an IGF-1 binding protein of neuroprotective potential. Our work supports a causative link between neuron-produced α-synuclein oligomers and sustained neuroinflammation *in vivo* and proposes that the induction of astrocytic calcium signaling can act as a cell type-specific compensatory mechanism against α-synuclein-induced neuroinflammation by promoting IGF-1 signaling.

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