Neurons and glial cells differentially metabolize internalized α-synuclein fibrils: Relevance to the propagation of α-synuclein pathology

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Abstract (250 words)
Parkinson's disease (PD) and other α-synucleinopathies are characterized by the α-synuclein (αS) aggregates that spread via the cell-to-cell transmission. We studied the contributions of various brain cells to the spreading of αS pathology by examining the metabolism of αS aggregates in neuronal and glial cells. In neurons, the full-length αS rapidly disappeared following αS PFF uptake but truncated αS accumulates with a half-life of days. Epitope mapping and fractionation studies indicate that internalized αS fibrils are truncated at the C-terminal region and remained insoluble in neurons. In contrast, microglia and astrocytes rapidly metabolized αS fibrils as the half-lives of αS fibrils in these glial cells were <6 hours. Differential uptake and processing of αS fibrils by neurons and glia was recapitulated in vivo where injection of fluorescently labeled αS fibrils initially accumulated in glial cells followed by rapid clearance while neurons stably accumulated αS fibrils at slower rate. Immunolocalization and subcellular fractionation studies show that internalized αS PFF is initially localized to endosomes followed by lysosomes. The lysosome is largely responsible for the degradation of internalized αS PFF as the inhibition of lysosomal function leads to the stabilization of αS in all cell types. Significantly, αS PFF causes lysosomal dysfunction in neurons. In summary, neurons are inefficient in metabolizing internalized αS aggregates, partially because αS aggregates cause lysosomal dysfunction, potentially generating aggregation-prone truncated αS. In contrast, glial cells may protect neurons from αS aggregates by rapidly clearing αS aggregates.
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