a-Synuclein Accelerates Mitochondria-Dependent Axonal Degeneration in a Mouse Model of MPAN: Axonal Enlargement Without Dopaminergic Neuron Loss

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Many neurodegenerative diseases involve progressive neuronal dysfunction associated with mitochondrial impairment, protein aggregation, and axonal pathology, leading to detrimental motor and cognitive decline. Mitochondrial membrane protein–associated neurodegeneration (MPAN) is a rare disorder caused by loss-of-function mutations in the C19orf12 gene and shares pathological features with Parkinson's disease, including a-synuclein accumulation and dopaminergic cell degeneration. However, it remains unclear whether a-synuclein aggregation initiates early degeneration or accumulates as a consequence of mitochondrial damage. To investigate this relationship, a C19orf12 knockout mouse model (PAN) was used to compare age-dependent axonal degeneration with a-synuclein exposure. Dopaminergic axon terminal structure in the striatum of wildtype (WT) and PAN mice was analyzed at 7–9 and 18 months using anti-tyrosine hydroxylase immunostaining. In a separate cohort (7–9 months), mice injected with pre-formed a-synuclein fibrils (PFFs) unilaterally injected into the striatum, with the contralateral hemisphere serving as an internal control, were examined. Axonal area in the striatum and dopaminergic neuron counts in the substantia nigra were quantified. Normal aging increased axon size in PAN mice, with greater enlargement at 18 months (p˜0.0004) compared to 9 months (p˜0.0539). PFF injection further increased axon size in PAN mice relative to non-injected controls (p˜0.0218), while WT mice were unaffected. Despite structural change, dopaminergic neurons survived after injection (p˜0.1203). These results suggest that a-synuclein accelerates existing mitochondrial and age-dependent axonal pathology in MPAN rather than initiating degeneration, providing insight into early mechanisms

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