Linking neuroinflammation and neurodegeneration in an α-synuclein seeding/spreading mouse model of Parkinson's disease

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Previous research has shown that injecting fibrillar alpha-synuclein (α-syn) into the striatum of mice induces pathology resembling Parkinson's disease (PD), particularly the formation of Lewy body (LB)-like structures and significant degeneration of the nigrostriatal pathway. This study investigated whether introducing oligomeric forms of exogenous mouse α-syn into the striatum would lead to the development of LB-like inclusions and related neurodegeneration.
In this experiment, C57BL/6 mice received bilateral intrastriatal injections of recombinant oligomerized α-syn and were euthanized at 30, 60, or 180 days post-injection. The injections caused the accumulation of phosphorylated α-syn within neurons, forming diffuse Lewy neurites (LN) and LB-like inclusions. These inclusions were identified in brain regions connected to the striatum, with the highest concentrations in the motor cortex and amygdala. Biochemical analysis revealed a significant increase in insoluble α-syn aggregates in the striatum and midbrain of the injected mice compared to controls. These aggregates consisted of monomers and higher molecular weight species, suggesting the presence of multimers or ubiquitinated α-syn in urea/SDS-soluble fractions. During the spread of α-syn, glial cells exhibited various activation states, contributing to an inflammatory response. A marked increase in cytokine release was observed in both the striatum and midbrain as early as 3 hours post-injection, although this effect was no longer detectable at later time points. However, α-syn oligomers promoted the activation of astrocytes and microglia in the striatum at 180 days post-injection, as indicated by the morphological changes. Although bilateral reductions in dopaminergic neurons in the substantia nigra at 180 days were observed, they did not result in significant motor impairments in behavioral tests such as the open-field, rotarod, or pole test. However, a significant and progressive decline in muscle strength was detected. The novel object recognition (NOR) test revealed that mice 180 days post-injection spent significantly less time exploring novel objects than controls, suggesting additional cognitive impairments.
In summary, these findings suggest that α-syn oligomers can trigger the pathological conversion of endogenous α-syn, leading to progressive neurodegenerative changes that model α-synucleinopathy in mice.

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