α-Synuclein Aggregate Preparations Induce Neurodegeneration and Cognitive Decline: A Novel Model for Parkinson’s Disease

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Aggregates of α-Synuclein Proteins

- α-synuclein pathology is clearly linked to Parkinson’s disease (PD) and related dementia
- PD drug discovery needs translational in vitro and in vivo models that are recapitulating sporadic disease onset
- Here, we report novel models based on neurodegeneration induction by minute amounts of highly reproducible α-synuclein oligomer (αSO) or fibrillar (αSF) preparations
- αSO and αSF induce dose and time-dependent neurodegeneration in primary mouse neurons and iPSC cell-derived human neuronal cultures
- Neurodegeneration is more pronounced for αSO than αSF and stronger on striatal neurons than hippocampal neurons
- αSO/F-induced neurodegeneration is dose dependently attenuated by brain-derived neurotrophic factor, providing a possible control for assays
- A single striatal intra-striatal injection of αSO or αSF induce cognitive decline in the NOR assay. Deficits start at day 90 for αSF, and after day 15 and up to the maximum investigated time period (3 months) for αSO, indicating neurodegeneration in the perirhinal cortex. However, up to three month, no deficit is detected in the pre-frontal cortex based Y-maze assay.
- αSF induces clear and progressing α-synuclein pathology after day 15, whereas αSO does not induce α-synuclein pathology within three month

A Single αSF Injection into the Striatum induced spreading in Mice

15 weeks old male C57BL/6 mice were injected intra-striatal at day 0 with mouse α-synuclein fibrils

Top figures: ‘Spreading’ of α-synuclein aggregates is shown for the ipsilateral side after 60 days for striatum, substantia nigra, frontal cortex and hippocampus

Spreading was already seen 11 days after a single αSF injection into the striatum and extended continuously until the maximal investigated period of 90 days

αSF injection into the striatum or hippocampus did not result in any ‘spreading’ until the maximal investigated period of 90 days

Bottom figures: ‘Spreading’ of α-synuclein aggregates is shown for the contralateral side after 60 days for striatum, substantia nigra, frontal cortex and hippocampus

Whereas ‘spreading’ into to contralateral frontal cortex was strong, almost not transfer to the contralateral side was obtained for the striatum and the substantia nigra

Spreading into the hippocampus was very sparse, similarly in both, the ipsilateral and contralateral side

α-Synuclein-Aggregate Induced Cognitive Deficit in the Novel Object Recognition Assay

BDNF Dose-Dependently Rescues αSO-Induced Neurodegeneration

- Primary mouse striatal neurons were grown in 48-well plates, in triplicates
- At day 10, increasing concentrations of BDNF were added to the medium
- Neurons were challenged for 72h with αSO
- Read-out: MTT assay

BDNF and αS-Antibodies Prevent αSO-Induced Neurodegeneration

- Primary mouse striatal neurons were grown in 48-well plates
- At day 10, medium is supplemented with vehicle (left group) or αS (right group)
- Different dilutions of α-synuclein antibodies were used to treat neurons
- A clear dose dependent rescue of the antibodies was observed

αSO and αSF Induce Different Immune Response in Mouse Astrocytes

- Mouse primary cortical astrocytes are cultured in 6 well plates
- Treatment by 10 μM α-synuclein aggregates (conc. based on monomer) starts at DIV 6 and are harvested at the indicated times
- Treatments are performed in triplicates
- Read-out: ELISA assays in conditioned medium

A Novel Model for Parkinson’s Disease

- Read-out: ELISA assays in conditioned medium
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Bottom figures: ‘Spreading’ of α-synuclein aggregates is shown for the contralateral side after 60 days for striatum, substantia nigra, frontal cortex and hippocampus

Whereas ‘spreading’ into to contralateral frontal cortex was strong, almost not transfer to the contralateral side was obtained for the striatum and the substantia nigra

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