DOUBLE- IMMUNE CHALLENGE WITH THE TOLL-LIKE RECEPTOR 3 AGONIST POLYI:C INDUCES AD-LIKE NEUROPATHOLOGY IN AGED MICE

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Introduction: Postmortem brain studies consistently reveal strong inflammatory reactions in the vicinity of beta-amyloid (Aβ) plaques and neuronal lesions. However, despite the growing number of studies linking neurotoxic inflammatory responses to Alzheimer’s disease (AD) pathogenesis, little information is available on early inflammatory processes which might possess stronger disease-inducing and -modifying potential than Aβ plaque-associated inflammatory responses. We have recently shown that a prenatal immune challenge using the Toll-like receptor-3 agonist and viral mimic PolyI:C (polyriboinosinic acid-polyribocytidilic acid) causes morphological abnormalities indicative of premature aging in wild-type mice. However, neither widespread amyloidosis nor any overt Tau pathology was evident.

Aim: We tested whether a second immune challenge during adulthood would be sufficient to trigger the development of AD-like neuropathology in aged wild-type mice.

Methods: We employed two cohorts of mice that were exposed to PolyI:C (5 µg/mg, i.v.) or 0.9% NaCl at gestation day 17. At 8 or 15 months, they were challenged with a second viral-like infection using PolyI:C or NaCl as control. Neuropathological changes, including densities of Aβ- and Reelin-positive plaques, phosphorylation levels of Tau, and glia activation were analyzed immunohisto- and biochemically 3 months post-treatment.

Results: We found a widespread fibrillary Aβ plaque deposition in the hippocampal formation and neocortex of PolyI:C/PolyI:C-challenged mice compared to controls. Levels of phosphorylated Tau and activated glia cells were also significantly enhanced after a double-immune challenge.

Conclusion: These results show that a combined pre- and postnatal viral-like infection can precipitate the development and progression of AD-like neuropathology in aged wild-type animals.