

A PRENATAL IMMUNE CHALLENGE PROVIDES A KEY IMPETUS FOR WILD-TYPE MICE TO UNDERGO ACCELERATED AGING AND DEVELOP AD-LIKE NEUROPATHOLOGY

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The key hallmarks of Alzheimer's Disease (AD) include proteinaceous aggregates in the form of amyloid plaques and neurofibrillary tangles, neuroinflammation and neurodegeneration. Several studies focus on inflammation in AD-like disease-states, but little is known about earlier, potentially disease-triggering inflammatory reactions.

We have recently shown that prenatal exposure to the viral mimic PolyI:C (polyriboinosinic acid:polyribocytidilic acid) results in significant loss of Reelin-producing neurons and morphological abnormalities indicative of premature aging.

Here, we investigated the effects of a prenatal infection on aging and AD-like neuropathology.

The wild-type mice were studied at three different age points, i.e., 6, 9 and 15 months.

We found highly significant changes in the PolyI:C versus control group with respect to AD-like neuropathology. For instance, using immunohistochemical and immunoelectron studies, we found larger and more numerous amyloid-like plaques compared to controls. There were also distinct fibrillary structures reminiscent of A β within Reelin-positive granular deposits. Biochemical analyses showed concomitantly higher levels of A β 40 and A β 42 peptides, and significant elevations in levels of inflammatory cytokines including interleukin-1 α and 1 β . We also observed significant alterations in Reelin processing, and increases in Tau phosphorylation in plaque-rich brain areas. These changes followed a similar temporal pattern as seen in AD pathology.

Our findings suggest that a prenatal infection induces long-term alterations in inflammatory modulators, which may have abnormal effects on Reelin expression and processing, later favouring amyloidogenic APP processing and Tau hyperphosphorylation. In all, these results are indicative that an *in utero* infection may represent an important driving force of AD-related neurodegenerative processes.