PLASMALOGENS IN THE BRAIN ARE REDUCED BY INFLAMMATORY SIGNALS, AGING AND CHRONIC STRESS LEADING TO GLIAL ACTIVATION IN MICE

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Neuroinflammation characterized by activation of glial cells is observed in various neurodegenerative diseases including Alzheimer's disease (AD). Although ether-type glycerophospholipids, plasmalogens (Pls), are reported to be reduced in the brain of AD patients, the mechanism of the reduction and the role of Pls in neuroinflammation have remained elusive. In the present paper, effects of inflammatory stimuli, ageing and stress on plasmalogens content and plasmalogens synthesizing enzyme, glycerone phosphate O-acyltransferase (GNPAT) expression were examined using mice as well as neuronal (N2A), microglial (MG6) and astrocyte cell lines. Knock down of the target genes was done by short hairpin RNA delivered by lentiviruses. Promoter region of *GNPAT* was cloned and chromatin immunoprecipitation (ChIP) assays were employed to study the precise transcriptional regulation.

LPS, Poly I:C and IL-1β significantly reduced the mRNA expression of *GNPAT* in the A1 and MG6 cells ($P<0.01$). Promoter study revealed that under the inflammatory signals, the NF-κB-induced c-Myc were recruited onto the *GNPAT* promoter to inhibit GNPAT expression. Systemic injection of LPS, aging and chronic stress (restraint stress) in mice also showed the activation of c-Myc and reduced the endogenous *GNPAT* in the brain. More interestingly, knock down of *GNPAT* in the cortex increased the activated phenotype of microglial cells and the expression of proinflammatory cytokines accompanied by NF-κB activation, suggesting further acceleration of neuroinflammation by the reduction of brain Pls. The similar mechanism of GNPAT reduction was found in the human cell lines, triple transgenic AD mice brain and the postmortem human AD brain tissues.

Our findings showed the neuroinflammation-induced down regulation of *GNPAT* transcription resulting in the reduction of Pls content in the brain. These findings may explain prolonged progression of AD and help us to explore preventive and therapeutic strategies to treat the neurodegenerative diseases like AD.