ALZHEIMER DISEASE

Prostaglandin E₂ signalling is implicated in inflammation early in the Alzheimer disease course

Prostaglandin E₂ (PGE₂) signalling via the E-prostanoid 3 (EP3) receptor could be a key component of a toxic inflammatory response that contributes to the development of Alzheimer disease (AD), a new study reported in *Annals of Neurology* indicates. The researchers, led by Katrin Andreasson at Stanford University School of Medicine, CA, USA, suggest that their findings could assist the discovery of novel preventive strategies for AD.

Early clues that prostaglandins might be involved in AD pathogenesis came from epidemiological observations in normal ageing cohorts who were taking NSAIDs—drugs that block activity of the COX-1 and COX-2 enzymes, which catalyse the first committed step of prostaglandin synthesis. “In the mid-1990s, an association was noticed between patients with osteoarthritis who took NSAIDs and a significant reduction in prevalence of AD, suggesting that taking NSAIDs prevented or delayed the onset of AD,” explains Andreasson.

The EP3 receptor is one of a family of four PGE₂ receptors (EP1–4), and its sister molecule EP2 has already been implicated in inflammation in various neurodegenerative conditions. Andreasson and colleagues found that EP3 was upregulated in brain tissue taken at postmortem from patients with mild cognitive impairment or AD, suggesting that this receptor might have a similar role.

To test this hypothesis, the researchers turned their attention to mouse models of neuroinflammation and AD. In the APPSwe-PS1ΔE9 (APPS) transgenic mouse, a model of familial AD, EP3 expression was found to increase in the hippocampus around the time of onset of inflammation.

The team went on to investigate whether the EP3 receptor was involved in a neuroinflammatory response to amyloid-β (Aβ) peptides *in vivo*. “We found that injection of Aβ₄₂ into the cerebral ventricles of wild-type mice resulted in a robust proinflammatory response associated

Amyloid plaque stained with the anti-amyloid-β antibody 6E10 (green), as well as antibodies against Iba1 (red; stains microglia) and CD68 (white; stains activated microglia), illustrating the microglial inflammatory response in the APPS mouse model. Image courtesy of K. Andreasson.

with oxidative damage in the form of lipid peroxidation,” says Andreasson. “However, in EP3-deficient (EP3^{-/-}) mice this inflammatory response was almost completely blocked, indicating a critical function of EP3 signalling in transducing the Aβ peptide inflammatory response.”

In the APPS mouse, memory deficits usually manifest at around 10 months of age, so Andreasson and colleagues examined 8-month-old animals to attempt to capture the preclinical phase of AD. Deletion of EP3 in these mice led to a marked decrease in levels of both inflammatory proteins and Aβ in the brain. “Interestingly, deletion of only one allele of EP3 was enough to reverse pathology, indicating that partial inhibition of EP3 may be sufficient to exert a beneficial anti-inflammatory, anti-amyloid effect,” says Andreasson.

The researchers believe that further study of prostaglandin signalling in animal models of AD could help them to

illuminate the cellular and molecular events that underlie the preclinical phase of this condition, and to identify possible targets for preventive therapies. “Since AD is really a disease of ageing, if one could simply shift the curve of disease onset to the right by just 5 years, there would be a significant reduction in AD prevalence,” concludes Andreasson. “Preventive strategies, if they can be identified, could be extremely important in stemming the looming AD pandemic that is predicted with the ageing of the post-World War II generation.”

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Original article Shi, J. *et al.* Inflammatory prostaglandin E₂ signalling in a mouse model of Alzheimer's disease. *Ann. Neurol.* doi:10.1002/ana.23677

Further reading Szekely, C. A. *et al.* Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review. *Neuroepidemiology* 23, 159–169 (2004) | Andreasson, K. Emerging roles of PGE₂ receptors in models of neurological disease. *Prostaglandins Other Lipid Mediat.* 91, 104–112 (2010)