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BRAIN RESEARCH

Research Report

Amyloid beta deposition is related to decreased glucose transporter-1 levels and hippocampal atrophy in brains of aged APP/PS1 mice

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ABSTRACT

The amount of the glucose transporter type-1 (GLUT-1) is decreased in the hippocampus and cerebral cortex of AD patients. In this study we therefore wanted to investigate the causal relationship between β-amyloid (Aβ), GLUT-1 and hippocampal atrophy in the brains of young (8 months) and old (18 months) APP/PS1 mice. *Methods:* Aβ and GLUT-1 were visualized immunohistochemically. Aβ load, GLUT-1 amount, capillary density and GLUT-1 amount per capillary density were determined in cortical and hippocampal areas using computer-assisted analysis systems. Hippocampal atrophy was determined by calculating the width of the outer molecular layer of the dentate gyrus (DG). *Results:* In 18-month-old APP/PS1 mice we found a reduced GLUT-1 amount in the hippocampus but no differences in capillary density. The DG of these mice contained the highest level of Aβ in combination with hippocampal atrophy, and a reduced GLUT-1 amount per capillary density. At 8 months, no differences were observed. The highest Aβ deposition was found in the DG, although fourfold less compared to 18-month-old mice. *Conclusions:* We conclude that the GLUT-1 amount and capillary density in both wild type and transgenic mice decrease due to ageing. Further, a decreased amount of GLUT-1 is caused by decreased GLUT-1 amount/capillary density and not due to a reduced capillary density. We suggest that Aβ load in the hippocampus precedes the reduction of GLUT-1. A certain level of Aβ must be reached in the hippocampus, before it affects GLUT-1 amount/capillary density leading to further impairment of energy metabolism and hippocampal atrophy.

1. Introduction

Alzheimer's disease (AD) is a multifactorial neurodegenerative disease characterized by the presence of amyloid beta (Aβ) peptide containing plaques, and neurofibrillary tangles (NFT). Aβ accumulates in the brain either as neuritic plaques or as vascular deposits that cause cerebral amyloid angiopathy (CAA). Aβ is derived through the proteolytic cleavage of the

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amyloid precursor protein (APP) by β- and γ-secretases (see Selkoe and Schenk, 2003 for review). Aβ has been suggested to be a major contributor to the neurodegenerative processes in AD in which the entorhinal cortex, hippocampus and neocortex of AD patients are predominantly affected (Jack et al., 2004; Juottonen et al., 1999; Rombouts et al., 2000; Seab et al., 1988).

However, accumulated evidence suggests that vascular risk factors play an important role in AD. For example, AD and vascular dementia share the same risk factors (Breteler, 2000a,b), and pharmacotherapy improving cerebrovascular insufficiency decreases AD symptoms (de la Torre, 1997). There is also evidence showing that cerebral perfusion is decreased in AD patients (Farkas and Luiten, 2001). Cerebral blood flow diminishes with age (Kawamura et al., 1993; Reich and Rusinek, 1989); however, in AD, these perfusion/haemodynamic effects are even more pronounced and especially the parietal and temporal cortices are consistently shown to be affected (Farkas and Luiten, 2001).

Besides haemodynamic changes, various microvascular pathologies have been observed in AD patients, such as basement membrane thickening, pericyte degeneration, endothelial cell shape changes and luminal buckling (see de la Torre, 2002 for review). Furthermore, a decrease in vascular density is also frequently observed (Buee et al., 1997). Capillary degeneration in ageing rats can be induced by mild chronic cerebral hypoperfusion (De Jong et al., 1999), and this in turn may trigger cognitive and degenerative changes (de la Torre, 1994; Ni et al., 1994). These findings support the CATCH hypothesis of de la Torre (2000b), positing that advanced age, in combination with a vascular risk factor converges to create a critical attained threshold of cerebral hypoperfusion (CATCH). This further triggers brain microcirculatory disturbances and hypoperfusion. These changes may generate a chain of events

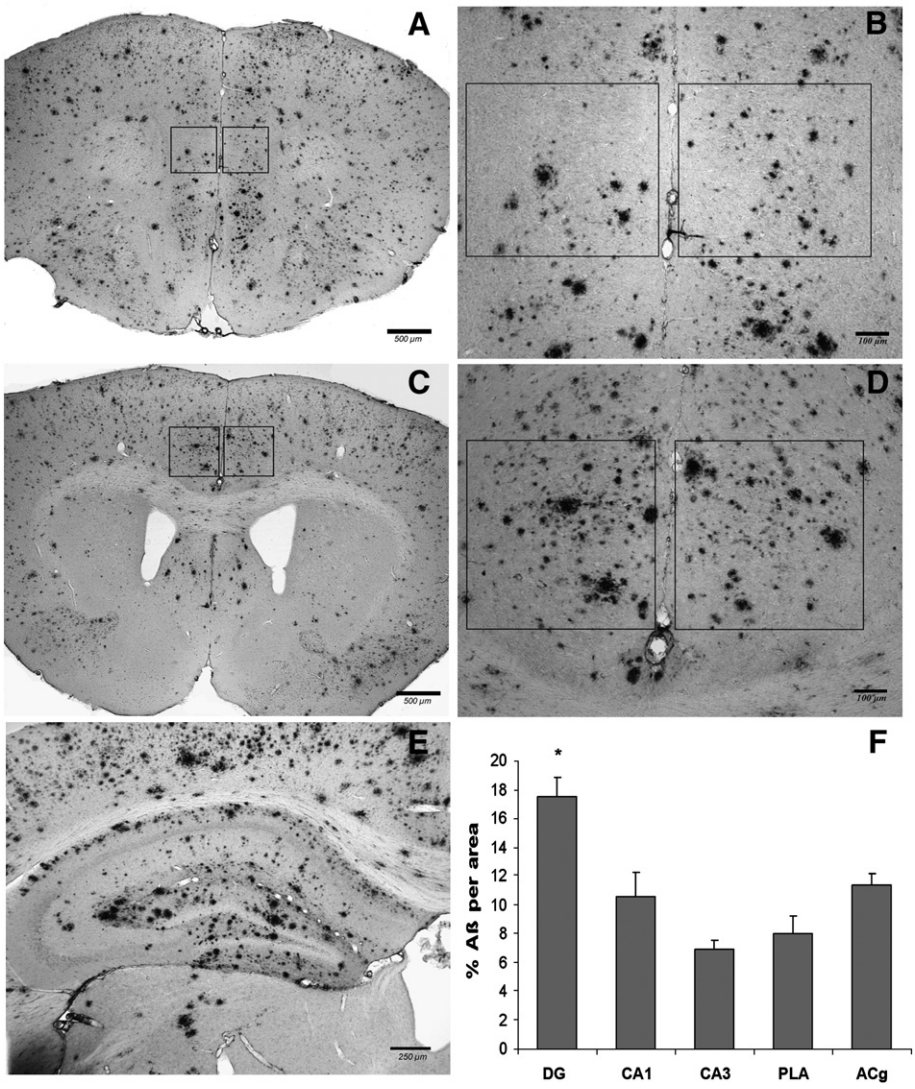

Fig. 1 – Amyloid beta (Aβ) deposition in the brains of 18-month-old APP/PS1 mice. Representative examples of the amyloid load in prelimbic area (PLA; A = 2.5× and B = 10×), anterior cingulated gyrus (ACg; C = 2.5× and D = 10×) and hippocampus (E = 5×) stained with WO-2 antibody (mouse anti-human $A\beta_{4-10}$). (F) Dentate gyrus (DG) exposes the highest amount of Aβ compared to all other areas. Values represent mean ± SEM. *$p < 0.05$.