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BRAIN RESEARCH

Research Report

α7 nicotinic acetylcholine receptor expression by vascular smooth muscle cells facilitates the deposition of Aβ peptides and promotes cerebrovascular amyloid angiopathy

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ABSTRACT

Deposition of beta-amyloid (Aβ) peptides in the walls of brain blood vessels, cerebral amyloid angiopathy (CAA), is common in patients with Alzheimer's disease (AD). Previous studies have demonstrated Aβ peptide deposition among vascular smooth muscle cells (VSMCs), but the source of the Aβ and basis for its selective deposition in VSMCs are unknown. In the present study, we examined the deposition patterns of Aβ peptides, Aβ40 and Aβ42, within the cerebrovasculature of AD and control patients using single- and double-label immunohistochemistry. Aβ40 and Aβ42 were abundant in VSMCs, especially in leptomeningeal arteries and their initial cortical branches; in later-stage AD brains this pattern extended into the microvasculature. Aβ peptide deposition was linked to loss of VSMC viability. Perivascular leak clouds of Aβ-positive material were associated primarily with arterioles. By contrast, control brains possessed far fewer Aβ42- and Aβ40-immunopositive blood vessels, with perivascular leak clouds of Aβ-immunopositive material rarely observed. We also demonstrate that VSMCs in brain blood vessels express the α7 nicotinic acetylcholine receptor (α7nAChR), which has high binding affinity for Aβ peptides, especially Aβ42. These results suggest that the blood and blood–brain barrier permeability provide a major source of the Aβ peptides that gradually deposit in brain VSMCs, and the presence and abundance of the α7nAChR on VSMCs may facilitate the selective accumulation of Aβ peptides in these cells.

1. Introduction

An abundance of pathological and experimental evidence lends strong support to the notion that aging-associated changes in the macro- and microvasculature of the brain play a critical role in the initiation and progression of a number of neurodegenerative diseases including Alzheimer's disease (AD) (Bailey et al., 2004; Buee et al., 1997; de la Torre

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and Hachinski, 1997; de la Torre, 2004; Esiri et al., 1997; Farkas and Luiten, 2001; Jellinger, 2002; Pluta et al., 1996; Zlokovic, 2005, 2008). The pathology of these changes goes beyond those generally attributed to "normal aging", including thinning of the walls of microvessels, microaneurysms, looping and twisting of vessels, separation of the tunica intima from the tunica media (producing the so-called "double-barreling" effect) and perivascular leakage of plasma components (Buee et al., 1994; Delacourte et al., 1987; Kalaria and Hedera, 1995; Miyakawa and Kuramoto, 1989; Ravens, 1978; Revesz et al., 2002, 2003; Vinters, 1987; Vonsattel et al., 1991). All can result in impaired blood flow regulation as well as disruption of the structural and functional integrity of the blood–brain barrier (BBB), thus allowing an influx of plasma components into the brain tissue which can disrupt brain homeostasis. Risk factors for these vascular changes, particularly in the context of AD, include aging, hypertension, diabetes, the ApoE4 allele, atherosclerosis and ischemia (Akomolafe et al., 2006; Breteler, 2000; Hofman et al., 1997; van Oijen et al., 2007; Pluta, 2007; Whitmer et al., 2005).

Cerebral amyloid angiopathy (CAA) is a common vascular pathology marked by deposition of beta-amyloid (Aβ) peptides in the walls of brain blood vessels. CAA is most commonly observed and prominent in leptomeningeal arteries, but also often extends into the microvasculature of the cerebral cortex (Ghiso and Frangione, 2001; Vinters et al., 1994; Zlokovic et al., 1993). It occurs sporadically in aged individuals, is common in patients with vascular cognitive impairment and AD, and is thought to be universally present in Down Syndrome patients with AD (Attems, 2005; Attems et al., 2005; Rensink et al., 2003). For reasons unknown, amyloid deposits tend to be localized to vascular smooth muscle cells (VSMCs) in the tunica media of leptomeningeal and cerebrocortical arteries and arterioles (Davis-Salinas and Van Nostrand, 1995; Frackowiak et al., 1994, 2004; Jellinger, 2002). Loss of VSMCs eventually eliminates any local regulation of blood flow and dramatically increases risk of hemorrhage (Breteler, 2000; Davis-Salinas and Van Nostrand, 1995; Domnitz et al., 2005; Frackowiak et al., 1994, 2004; Herzig et al., 2004; Jellinger, 2002; Miao et al., 2005; Winkler et al., 2001; Zlokovic, 2005).

The source of the Aβ peptides that deposit within brain blood vessels and mechanisms that drive its selective deposition in VSMCs remain to be elucidated (Attems et al., 2005; Farkas and Luiten, 2001). One widely believed scenario, referred to as the "Drainage Hypothesis", suggests that Aβ peptides are produced primarily within neurons and, after being secreted into the interstitial space, make their way into the perivascular space of local vessels and enter the circulation (Weller et al., 1998). Reports that cerebrovascular Aβ is first observed in the abluminal basement membrane of blood vessels, the site farthest away from the lumen, support this possibility (Yamaguchi et al., 1992). Another hypothesis suggests that the blood is main source of the Aβ peptides that deposit in VSMCs, implying that Aβ peptides gain access

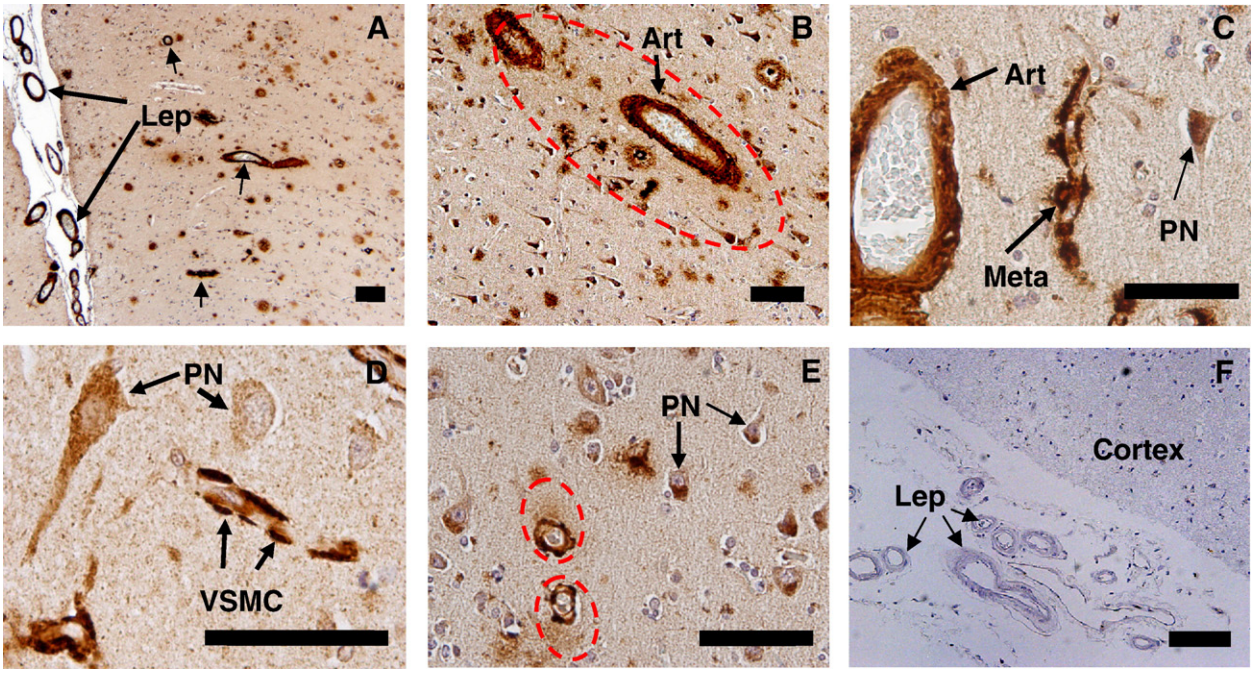

Fig. 1 – Aβ42 accumulation in VSMCs and perivascular Aβ42-immunopositive leak clouds in the cerebral cortex of AD brains. (A) Leptomeningeal arteries (Lep) on the cortical surface and their branches (black arrows) entering the brain parenchyma exhibit intense Aβ42 immunostaining (dark brown). Art, arterioles. (B) Many arterioles are surrounded by a diffuse cloud of Aβ42-immunopositive material (red dashed line). (C and D) Aβ42 deposition in VSMCs of a medium-sized arteriole (Art) and adjacent meta-arteriole (Meta) reflect the distribution and orientation of VSMCs. In meta-arterioles the punctate pattern of Aβ42 immunostaining is generated by VSMCs oriented longitudinally within the vessel wall. PN, pyramidal neuron. (E) Cross-section of arteriolar VSMCs laden with Aβ42 with surrounding cloud of extravasated Aβ42 (red dashed line). (F) AD brain section reacted with detection antibody only demonstrating lack of staining. (Scale bars = 200 μm). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)