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BRAIN RESEARCH

Research Report

Different dendrite and dendritic spine alterations in basal and apical arbors in mutant human amyloid precursor protein transgenic mice

Alán Alpár[a,*], *Uwe Ueberham*[b], *Martina K. Brückner*[b], *Gudrun Seeger*[b], *Thomas Arendt*[b], *Ulrich Gärtner*[b]

[a]*Department of Anatomy, Histology and Embryology, Semmelweis University Medical School, Tűzoltó u. 58, H-1450, Budapest, Hungary*
[b]*Department of Neuroanatomy, Paul Flechsig Institute for Brain Research, Universität Leipzig, D-04109 Leipzig, Germany*

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ABSTRACT

The extracellular deposition of amyloid-beta peptide (Aβ) in brain parenchyma is one of the characteristic features of Alzheimer's disease and is suggested to induce reactive and degenerative changes in neuronal cell bodies, axons and dendritic processes. In particular, within and in close proximity to amyloid plaques, distinctive morphological alterations have been observed, including changes in neurite trajectory and decreases in dendritic diameter and in spine density. Apart from these plaque-associated focal aberrations, little is known regarding modifications of the global dendritic morphology including the detailed and comparative quantitative analysis of apical and basal arbors. The objective of the present study was to investigate the effects of amyloid plaque deposition and elevated soluble Aβ on neuronal morphology in mutant human amyloid precursor protein (hAPP) transgenic mice (line Tg2576; [K. Hsiao, P. Chapman, S. Nilsen, C. Eckman, Y. Harigaya, S. Younkin, F. Yang, G. Cole, Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice, Science 274 (1996) 99–102]). Retrogradelly labeled callosal-projecting pyramidal cells in the primary somatosensory cortex were three-dimensionally analyzed. Although basal dendrites remained unaffected, analysis of apical trees revealed a number of unambiguous morphological changes. Thus, in TG2576 mice, the apical arbors were shortened in total length and less branched. Furthermore, the diameter of proximal dendritic segments was increased whereas that of distal segments was reduced. Analysis of spine numbers and distribution on basal and apical trees demonstrated a significant reduction in spine densities along the whole course of dendrites. The findings suggest that Aβ-related pathology induces morphological aberrations in basal and apical arbors to different degrees which are unrelated to direct plaque-associated changes.

* *Corresponding author*. Fax: +36 1 2155158.
E-mail address: dralpar@gmx.net (A. Alpár).

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1. Introduction

A characteristic hallmark of Alzheimer's disease (AD) brain is the accumulation of amyloid-beta (Aβ) peptides into insoluble extracellular plaques. The Aβ peptide arises from β- and γ-secretase processing of the amyloid precursor protein (APP) (reviewed in Turner et al., 2003). The generation of Aβ during normal metabolism suggests a physiological role in normal cell function (Haass et al., 1992). However, under certain conditions, Aβ may mediate neurotoxic effects as has been observed in vitro and in vivo (reviewed in Walsh et al., 2002; McKee et al., 1998). In particular, Aβ was found to disturb synaptic transmission by depressing or modifying glutamatergic and cholinergic activity (Dutar et al., 1994; Cullen et al., 1996; Kar et al., 1996; Kasa et al., 1997; Jhamandas et al., 2001; Pettit et al., 2001; Chen et al., 2002; Raymond et al., 2003). Furthermore, soluble Aβ has been shown to affect synaptic plasticity by inhibiting the induction of long-term potentiation (Wang et al., 2002; Raymond et al., 2003), to impair initial learning and to cause dose-dependant reductions in memory retentions (Flood et al., 1991). Aggregation of Aβ into fibrils and plaque deposition initiate fatal pathological processes which are suggested to lead to the disruption of neuronal connectivity, and do correlate with the severity of dementia (Cummings et al., 1996; Knowles et al., 1999; Tomidokoro et al., 2000).

In addition to the large scale of studies focusing upon physiological and behavioral changes caused by increased soluble Aβ levels and Aβ amyloidosis (reviewed by Turner et al., 2003), morphological alterations of neurons have been addressed as well. In AD, several morphological aberrations have been observed including progressive neuritic dystrophy, ectopic sprouting and increased curvature of dendritic processes (Scheibel and Tomiyasu, 1978; Larner, 1995; Irizarry et al., 1997; Knowles et al., 1999). However, there is only little evidence about the pathogenetic factors causing changes in neuronal morphology. At least some of these changes may be due to local effects of Aβ concentration and deposition. Thus, in the close vicinity of plaques, the dendritic density is reduced (Knowles et al., 1998). Neuronal processes crossing Aβ deposits exhibit a radially changed morphology whereas segments inside are characterized by a reduced diameter and a loss of spines (Knowles et al., 1999; Le et al., 2001; Tsai et al., 2004). Moreover, amyloid deposition has been suggested to cause even neurite breakage and disruption of neuronal connections (Tsai et al., 2004).

Apart from thorough studies on focal dendritic aberrations in the microenvironment of Aβ depositions, only limited data have been presented addressing effects of elevated Aβ levels and amyloidosis on more global parameters of dendritic morphology. Therefore, the objective of the present study was to characterize alterations of apical and basal dendritic arbors of neocortical pyramidal cells in transgenic mice that developed Aβ-related pathology. We took advantage of TG2576 mice that overexpress human APP with the Swedish mutation resulting in high levels of amyloidogenic Aβ and the development of abundant cortical amyloid plaques reminiscent of AD pathology (Hsiao et al., 1996). For the assessment of morphological effects, callosal-projecting pyramidal neurons were analyzed: a population known to be most severely affected in AD (Hampel et al., 1998).

2. Results

Injection of BDA into the corpus callosum revealed a large number of retrogradely traced pyramidal neurons with Golgi-like staining in layers II, III and Vb within S1 cortex of both hemispheres (Fig. 1) that allowed ideal conditions for true 3D reconstruction of neuronal morphology (Fig. 2). However, only layer II/III neurons of the side opposite to the injection were included in the study. In Tg2576 mice, in addition to neurons,

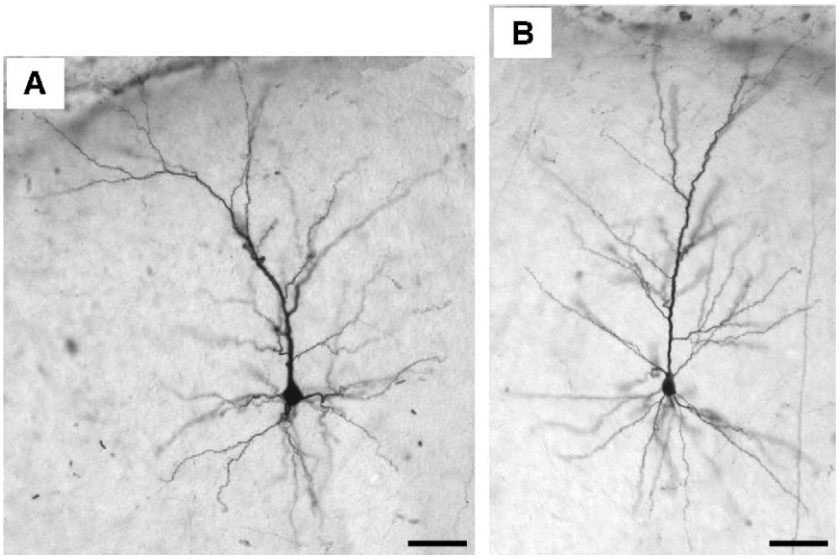

Fig. 1 – Representative retrogradely labeled commissural neurons in layers II/III of the primary somatosensory cortex of transgenic (A) and wild-type (B) mice. Principal cells have thicker but shorter apical dendritic shaft in transgenic animals than in wild-types. Scale bars: 30 μm.