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Apolipoprotein E polymorphism and dendritic shape in hippocampal interneurons

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Abstract

The apolipoprotein E genetic polymorphism exerts a well described influence on Alzheimer's disease (AD) risk, although the pathogenetic mechanism is still not clear. Increasing evidence points to a diminished neuroplasticity in apolipoprotein E ε4-allele carriers. But, alternatively or additionally, developmental differences in dendritic geometry may be associated with the polymorphism. We morphometrically examined the dendritic ramification of CA1 Parvalbumin-positive GABAergic hippocampal neurons ($n = 571$) in matched pairs of aged non-demented individuals with different apolipoprotein E genotype. We chose Parvalbumin-positive interneurons since they lack potentially confounding AD-like cytoskeletal changes. To minimize the risk of transneuronal dendritic changes due to significant deafferentation we focused on non-demented individuals. In this chosen paradigm, neither the disease-associated apolipoprotein E ε4-allele nor the apolipoprotein E ε2-allele had a significant impact on dendritic shape when compared to the most common allelic variant apolipoprotein E ε3/3. At least with respect to the studied cell type, the data suggest that the apolipoprotein E polymorphism does not modulate the original formation of dendrites in vivo, contrary to conclusions drawn from in vitro studies on neurite outgrowth.
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Keywords: Alzheimer's disease; Apolipoprotein E (apoE); Dendritic plasticity; Hippocampus; Parvalbumin

1. Introduction

Apolipoprotein E (APOE; gene, apoE; protein) is the major lipid transporter in the brain [46] where most other apolipoproteins are absent [23,39]. In humans, the three alleles APOE ε2, ε3, and ε4 code for three isoforms apoE2, apoE3 and apoE4. The APOE ε4 allele represents a well described genetic risk-factor for Alzheimer's disease (AD) [14,40] and lowers the clinical and neuropathological age of onset by 10–20 years [13,36] when compared to the most common APOE ε3 allele. APOE ε2 carriers develop AD later [36] expressing the tangle-dominant form [5]. Though we do not understand apoE's role in AD pathogenesis, a plasticity-related hypothesis has emerged [37,38]. The APOE ε4 allele is associated with a poor outcome after brain injury [26]. Dendritic remodeling occurs in AD and correlates with the numeric tangle-density [17]. The dendritic remodeling is likely transcellularly induced by deafferentation [35]. Subsequently to an entorhinal cortex lesion, sprouting is impaired in APOE ε4-transgenic mice [47]. The degree of mossy fibre sprouting seems to be halved [43–45]. In the human hippocampus, apoE levels are increased in APOE ε3/3 individuals showing first AD-related neurofibrillary changes in the entorhinal cortex and decreased in later stages of the disease. These presumably plasticity-related increases in hippocampal apoE are much less pronounced in APOE ε4 allele carriers [21]. Cultured neurons and immortalized neuronal cells showed an inhibited neurite (out)growth and differentiation response in the presence of apoE4 [15,24,30,31]. This effect depends on cell type, source and state of apoE [43]. A reduction in dendritic length was found in unlesioned apoE4-transgenic in older but not in younger mice when compared to wildtype or APOE3-transgenic animals [25].

These findings suggest that APOE ε4-carriers may develop AD earlier in life because of a lower plastic capacity

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to cope with age-related challenges. Alternatively, developmental differences in dendritic tree complexity may be associated with individual alleles.

Previous studies found regressive (in AD) or progressive dendritic changes (in non-demented cases with early AD-related histopathology) [2]. In AD cases, Ji et al. [25] reported a lower spine density in the dentate gyrus in APOE ε4 allele carriers than in APOE ε3/3 individuals. So far, there is only one study concerning the APOE genetic polymorphism on dendritic arborisation [3]. This study reported a decreased dendritic remodeling in AD cases carrying one or two APOE ε4 alleles. All AD-groups, however, had been compared to a group of non-demented individuals lacking an APOE ε4 allele. The possibility therefore remains that APOE ε4 allele carriers may have had a less differentiated dendritic tree before AD-related neuropathological changes became evident. Furthermore, projection neurons are well known to form paired helical filaments, the major constituent of neurofibrillary tangles. These filaments (in form of neuropil threads) are first seen in the most apical proportions of the dendrites [7].

Parvalbumin-positive neurons do not form tangles or neuropil threads and their dendrites become reduced only very late in AD after massive deafferentation [35]. In non-demented individuals, including those meeting the Braak-criteria for AD-related paired helical filaments of stages I–III, these neurons probably will not show a remodeling of their dendritic arborisation due to AD-related neuropathological changes. The Parvalbumin-staining fills the whole dendritic tree of a given neuron and highlights Golgi-like single cells with specificity for GABAergic neurons [28]. Thus, these neurons are particularly suited to study dendritic arborisation under the influence of the APOE genetic polymorphism.

From the cell culture data [15,24,30,31] one might suppose a basic difference in the dendritic shape of human neurons depending on the APOE genotype (development-related hypothesis). In this study, we tried to minimize a potential influence of AD-related intrinsic cytoskeletal alterations and significant deafferentation-induced dendritic remodeling. We hypothesized that the shape of the dendritic tree in the selected cell population should be essentially identical if the APOE genetic polymorphism exerts its influence on dendrite growth only after plastic challenge (plasticity-related hypothesis) but different if there was already a general developmental impact of the APOE genotype (development-related hypothesis).

2. Material and methods

2.1. Brain samples

A total of 28 carefully selected non-demented cases were studied comprising 571 Parvalbumin-positive neurons under morphometric consideration. Cases were obtained from routine autopsies carried out at the neuropathological department of the Charité (Berlin) during 1999–2003. Cases with a clinical history of neurological or psychiatrical diseases were excluded from the study.

2.2. Histopathological examination and APOE genotyping

The brains were cut into hemispheres and the left one was sliced. Some slabs were snap-frozen after dissection and stored at −80 °C until further use. The hippocampal formation from the right hemisphere was dissected free en bloc. Tissue blocks were fixed either in 4% paraformaldehyde or in an immunofixative (see below) and after routine histological examinations only those cases were selected for further analysis which were free of neuropathological findings other than those characteristic of incipient AD. Blocks from the uncus comprising the transentorhinal/entorhinal cortex, the hippocampus and adjacent temporal cortex and from the occipital cortex were taken from the left hemisphere, cut into 1 cm thick slabs, and embedded in polyethylene glycol. From these blocks 100 μm thick sections were cut and used for Braak-staging [9] using the Gallyas stain [19] for tau-pathology and Campbell–Switzer for Aβ-peptide detection [12]. Both techniques have previously been shown to be as sensitive as immunocytochemical detection approaches [10,32,41,42]. In order to control for a possible influence of AD-related neuropathology, all cases were staged according to the Braak classification [9]. The staging considered the distribution of neurofibrillary tangles (NFT). Briefly, six stages can be distinguished: Braak 0 = no AD-related neuropatholgical changes; stages I/II = 'transentorhinal/entorhinal' stages, with alteration of the transentorhinal or transentorhinal and entorhinal layer pre-α; stages III/IV = 'limbic stages', with additional affection of additional (deeper) entorhinal cortex layers and hippocampal sector CA1 and subiculum; and stages V/VI = 'isocortical stages', showing tangles in isocortical association areas and later even in primary cortical fields. The amyloid deposition can be classified into three stages (A–C): A = initial amyloid deposits in the isocortex; B = amyloid deposits in all isocortical association areas and mild involvement of the hippocampal formation; C = densely packed amyloid deposits in all isocortical areas and involvement of the hippocampal formation.

APOE genotyping was performed as described [33] using the primer pairs F4 and F6 described by Emi et al. [16].

2.3. Immunocytochemistry

In order to reduce confounding effects, we then matched appropriate cases with respect to APOE genotype, Braak stage (for tau-pathology and if possible also for Aβ deposition), age and gender [20]. Five pairs consisted of APOE ε3/3 and APOE ε2/3 or APOE ε2/2 spanning an age range from 65 to 75 years and nine of APOE ε3/3 and APOE ε4/3 or APOE ε4/2 individuals within an age range of 65–84 (Table 1). Unfortunately, the availability of APOE ε4

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