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Cerebral glucose transport and blood-brain barrier morphology are altered in function of apolipoprotein E genotype in mice

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The blood-brain barrier (BBB) is a dynamic and biological barrier, which physically separates the blood from the central nervous system (CNS). Several studies suggest that changes in the BBB occur in Alzheimer's disease (AD). Among the three common isoforms of apolipoprotein E (ApoE, alleles ε2, ε3 or ε4), the expression of the ε4 allele is a major genetic risk factor for AD. We hypothesized that ε4 allele exerts a pathogenic role by affecting the functional and morphological properties of the BBB. Using the quantitative in situ brain perfusion technique, we first found lower (13.0 - 17.0%) brain transport coefficient (Clup) of [3H]-diazepam in APOE4 mice at 4 and 12 months, compared to APOE2 and APOE3 mice, reflecting a decrease of cerebral vascularization. Accordingly, results from immunofluorescence experiments revealed reduced cerebral vessel density (26 and 38%) and thinner basement membrane (30 and 35%) in 12-month-old APOE4 mice compared to APOE2 and APOE3 mice, suggesting vascular atrophy. In addition, APOE4 mice displayed a 29% reduction of [3H]-D-glucose transport through the BBB compared to APOE2 mice without significant changes in the expression of its transporter GLUT1 in brain capillaries. However, an increase of 41.3% of RAGE was found in brain capillaries of 12-month-old APOE4 mice compared to APOE2 without significant changes of LRP1. In conclusion, profound divergences were observed between APOE genotypes at the cerebrovascular interface. Further investigations are needed to determine whether these allele-specific BBB anomalies contribute to the development of AD.

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