The Alzheimer disease-causing SwAPP mutation increases the vulnerability of hippocampal neurons in mice

Mohajeri,M.H.[1], Saini,K.[1], Wollmer,M.A.[1], Schulz,J.G.[3], Wolfer,D.P.[2], Lipp, H.P.[2], Nitsch, R.M.[1]

[1]Psychiatry Research, [2]Anatomy, [3]Virology, University of Zurich, Zurich, Switzerland

To determine whether Alzheimer's disease (AD)-causing APP mutations affect the vulnerability of neurons, we used pilocarpine-induced seizures in 7 week-old mice expressing the Swedish APP (SwAPP) mutation. In SwAPP mice, twice as many neurons degenerated in the hippocampal CA1 and CA3 regions, as compared to wild-type littermates with identical seizures. Without seizures, the SwAPP mutation caused no neuronal loss. Therefore, the mutation alone was not toxic, but it may increase the vulnerability of neurons to environmental stresses. Importantly, the SwAPP mice had no amyloid plaques at this age, indicating that the increased vulnerability occurred long before the onset of amyloid plaque formation. These data suggest that increased brain levels of soluble A-beta are associated with higher vulnerability of neurons in vivo. Our data therefore support the concepts of early diagnosis of AD, along with early A-beta-lowering treatments.
Genetic background had a strong effect on the magnitude of seizure-induced damage to hippocampal neurons, with FVB being most susceptible to damage, and C57/BL6 most resistant, consistent with the possibility of differentially expressed neuroprotective factors in CNS, and clearly indicating the importance of tightly controlled genetic background in studies of neuronal vulnerability in mice. The seizure-induced damage was functionally relevant because the performance of lesioned mice in Morris water maze worsened significantly with the increasing severity of the lesions, and paralleled neuronal loss in hippocampal CA1 and CA3 regions.

Supported by: NCCR on Neural Plasticity and Repair, SNF