Sound Deprivation Exacerbates Region-Specific Amyloid Pathology and Cognitive Impairment in a Mouse Model of Alzheimer's Disease

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Hearing loss is a major modifiable risk factor for Alzheimer's disease (AD), but the underlying mechanisms linking auditory dysfunction to AD pathology remain poorly understood. Here, we investigated whether sound deprivation impacts amyloid-beta (Aβ) accumulation and cognitive decline using the 5xFAD mouse model of AD. Conductive hearing loss was induced by bilateral earplug insertion from 2 to 4 months of age in wild-type (WT) and 5xFAD mice of both sexes. Auditory function was assessed by auditory brainstem response (ABR) test shortly after earplug removal. ABR thresholds were elevated in both WT and 5xFAD mice, confirming effectively reduced auditory sensitivity during 2-month earplug period. While WT mice exhibited no detectable changes in Aβ pathology following sound deprivation as expected, 5xFAD mice showed significantly increased Aβ accumulation in subcortical auditory brainstem regions, including the inferior colliculus and trapezoid body, following prolonged sound deprivation. To determine the reversibility of these effects, mice underwent a 2-month recovery period post-earplug removal. Although hearing thresholds fully recovered in WT and 5xFAD mice, Aβ accumulation in auditory brainstem regions continued to progress in 5xFAD mice. Behavioral testing further revealed impaired recognition memory in sound-deprived 5xFAD mice, despite no changes in hippocampal Aβ pathology. These findings suggest that auditory brainstem pathology may independently contribute to cognitive deficits. Overall, our results demonstrate that reduced auditory input accelerates AD-like pathology specifically within the auditory pathway and contributes to cognitive impairment, highlighting a potential mechanistic link between hearing loss and AD progression.

Sponsored By: NIH R01 DC018797, Alzheimer's Association 23AARG-1026470

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