Calcineurin/NFAT Signaling in Activated Astrocytes Drives Network Hyperexcitability in Aβ-Bearing Mice

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Hyperexcitable neuronal networks are mechanistically linked to the pathologic and clinical features of Alzheimer's disease (AD). Astrocytes are a primary defense against hyperexcitability, but their functional phenotype during AD is poorly understood. Here, we found that activated astrocytes in the 5xFAD mouse model were strongly associated with proteolysis of the protein phosphatase calcineurin (CN) and the elevated expression of the CN-dependent transcription factor nuclear factor of activated T cells 4 (NFAT4). Intrahippocampal injections of adeno-associated virus vectors containing the astrocyte-specific promoter Gfa2 and the NFAT inhibitory peptide VIVIT reduced signs of glutamate-mediated hyperexcitability in 5xFAD mice, measured in vivo with microelectrode arrays and ex vivo brain slices, using whole-cell voltage clamp. VIVIT treatment in 5xFAD mice led to increased expression of the astrocytic glutamate transporter GLT-1 and to attenuated changes in dendrite morphology, synaptic strength, and NMDAR-dependent responses. The results reveal astrocytic CN/NFAT4 as a key pathologic mechanism for driving glutamate dysregulation and neuronal hyperactivity during AD.