

Disrupted calcium dynamics in reactive astrocytes occur with endfeet-arteriole decoupling in an amyloid mouse model of Alzheimer's disease

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While cerebrovascular dysfunction and reactive astrocytosis are extensively characterized hallmarks of Alzheimer's disease (AD) and related dementias, the dynamic relationship between reactive astrocytes and cerebral vessels remains poorly understood. Here, we used jGCaMP8f and two photon microscopy to investigate calcium signaling in multiple astrocyte subcompartments, concurrent with changes in cerebral arteriole activity, in fully awake eight-month-old male and female 5xFAD mice, a model for AD-like pathology, and wild-type (WT) littermates. In the absence of movement, spontaneous calcium transients in barrel cortex occurred more frequently in astrocyte somata, processes, and perivascular regions of 5xFAD mice. However, evoked arteriole dilations (in response to air puff stimulation of contralateral whiskers) and concurrent calcium transients across astrocyte compartments were reduced in 5xFAD mice relative to WT. Synchronous activity within multi-cell astrocyte networks was also impaired in the 5xFAD group. Using a custom application to assess functional coupling between astrocyte endfeet and immediately adjacent arteriole segments, we detected deficits in calcium response probability in 5xFAD mice. Moreover, endfeet calcium transients following arteriole dilations exhibited a slower onset, reduced amplitude, and lacked relative proportionality to vasomotive activity compared to WT. The results reveal nuanced alterations in 5xFAD reactive astrocytes highlighted by impaired signaling fidelity between astrocyte endfeet and cerebral arterioles. The results have important implications for the mechanistic underpinnings of brain hypometabolism and the disruption of neurophysiological communication found in AD and other neurodegenerative conditions.

Sponsored By: grant from NIH P01AG078116 and RF1AG027297

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