Reactive astrocytes augment hippocampal inhibitory tone via GABA transporter-3/4 to facilitate synaptic balance in Alzheimer's disease

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Abstract

Background and Purpose: Cognitive decline is a major symptom in Alzheimer's disease (AD), which is closely associated with synaptic excitatory-inhibitory imbalance. Here, we investigated whether astrocytic mechanisms involving the astrocyte-specific GABA transporter 3/4 (GAT3/4) play a role in altering the synaptic balance in AD and whether these mechanisms correlate with presynaptic cannabinoid type-1 receptors (CB1-Rs). **Experimental approach:** Using the APPNL-F/NL-F knock-in mouse model of AD, aged-matched to wild-type mice, we performed in vitro electrophysiological whole-cell recordings combined with immunohistochemistry in the CA1 and dentate gyrus (DG) regions of the hippocampus. Comparative neuroanatomy experiments were also performed in post-mortem brain tissue from human AD patients, age-matched to healthy controls. **Results:** We observed a higher expression of GABA content and GAT3/4 co-localised with reactive astrocytes, which enhanced tonic inhibition in the CA1, and DG of APPNL-F/NL-F mice compared to the age-matched wild-type animals. Blocking GAT3/4 - associated tonic inhibition in APPNL-F/NL-F mice resulted in an enhanced frequency of synaptic excitation, suggesting a presynaptic mechanism. These data also correlated with an up-regulation of CB1-Rs in astrocytes and cholecystokinin (CCK)-containing interneurons, which also enhanced tonic inhibition in the AD model, but did not affect GAT3/4 -associated tonic inhibition. The neuroanatomical results were mirrored in post-mortem tissue of AD patients. **Conclusions:** Our data suggest that reactive astrocytes lead to augmented tonic inhibition in the hippocampus, which probably plays an important presynaptic compensatory role in attempting to restore AD-associated neuronal hyperactivity. Therefore, reducing tonic inhibition through GAT3/4 may not be a good therapeutic strategy for AD.

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Supplementary Figure 1