Protection of Inhibitory Circuit Dysfunction During Alzheimer's Disease Pathogenesis through Preservation of Retinoic Acid Signaling

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In the hippocampus, a balance between excitatory and inhibitory circuits is critical for normal learning and memory operations. In Alzheimer's disease (AD), amyloid precursor protein is metabolized into amyloid beta (Aβ), which form Aβ plaques that ultimately cause premature death. In the earliest stages of AD, performance during learning tasks is impaired, which is accompanied by hyperexcitability within the dentate gyrus (DG) and CA3 regions of the hippocampus. Excitability in DG-CA3 networks is modulated by diverse inhibitory parvalbumin (PV) and somatostatin (SOM)-positive circuits that provide somatic and dendritic synaptic inhibition, respectively. Despite the importance of these specific inhibitory circuits in normal DG/CA3 function, their roles during AD have yet to be determined. Moreover, some AD patients are deficient in vitamin A, which lowers retinoic acid (RA) levels and accelerates memory loss. In preclinical AD models, increasing RA levels can be protective against memory loss. Here, using new preclinical AD models that enable the study of these inhibitory circuits, we test the hypothesis that inhibitory circuits become dysfunctional in early stages of AD but are protected by RA intervention. Towards this end, we have generated novel triple transgenic (3Tg) $J20^{+/-}$ AD mouse models, which enable CRE-dependent expression of the red fluorescent protein tdTomato in PV or SOM circuits. In 3Tg mice, SOM:tdTomato expression revealed upregulation of SOM circuits, including a de-novo SOM circuit targeting DG principal cell dendrites. The appearance of this de-novo circuit coincides with memory deficits and was absent from sibling $J20^{-/-}$ controls. To determine RA effects on protection against AD-induced inhibitory circuit dysfunction, RA (20 mg/kg IP) or vehicle was administered (3x week for 8 weeks) to 3-month old 3Tg $J20^{+/-}$ or sibling $J20^{-/-}$ controls, followed by behavioral and subsequent histological/transcriptomic analyses. Consistent with previous studies in J20 mice, a modest hyperactivity phenotype was observed in 3Tg $J20^{+/-}$ relative to $J20^{-/-}$ mice in the Y-maze and Open Field Maze. In contrast, RA treatment normalized activity of $J20^{+/-}$ mice relative to $J20^{-/-}$ controls. Future experiments will determine the extent that RA-induced normalization of the $J20^{+/-}$ behavioral phenotype is accompanied by prevention of SOM and PV circuit dysfunction. Transcriptomic analyses will offer mechanistic insight into RA-induced epigenetic regulation of mRNA levels. In conclusion, this project increases knowledge of inhibitory circuit mechanisms during AD and reveal insights into mechanisms by which RA signaling is protective against AD pathogenesis.