Vitamin A (VA) signaling disruptions are observed in Alzheimer’s disease (AD). Deficiency of retinoid acid (RA), a VA metabolite, may contribute to hippocampal dentate gyrus (DG) hyperactivity seen in the amnesic mild cognitive impairment stage of AD and alter excitation/inhibition (E/I) balance. Intact inhibitory somatostatin (SOM) and parvalbumin (PV) circuits normally maintain E/I balance. Inhibitory SOM and PV circuits contribute to DG network hyperactivity, and lead to behavioral abnormalities. Impaired RA signaling may alter excitation/inhibition (E/I) balance, suggesting RA deficiency may alter behavioral abnormalities. There is a need to investigate risk factors, such as diet that can allow for low-cost prophylactic modifications and could save billions of dollars.

It is estimated that 5 million Americans live with AD and total estimated cost of care per person is $250, 170. The Mediterranean diet, known for pairing vegetables and oils, mitigates AD risk, potentially enhancing bioavailability of vitamin A (VA). Low or high serum VA levels correlate with accelerated or delayed AD onset, respectively.

Hyperactivity in the human hippocampal dentate gyrus (DG) is observed in amnesic mild cognitive impairment stage of AD. During hyperactivity, synthesis of VA metabolite, retinoid acid (RA), may be impaired, suggesting RA deficiency may alter excitation/inhibition (E/I) balance and contribute to DG network hyperactivity, and lead to behavioral abnormalities. Intact inhibitory somatostatin (SOM) and parvalbumin (PV) circuits normally maintain E/I balance.

Objective: Investigate impact of RA signaling on DG SOM circuitry during AD pathogenesis.

Methods: Mouse models were treated with RA (RT) or vehicle (VT) and subjected to behavioral testing in the Y-maze and Open Field Maze (OFM). Brains were then harvested for histological and transcriptomic analyses. Behavioral testing revealed VT AD mice traveled a greater distance than WT AD mice (t(5)=5.00, p=0.009). WT AD and VT mice did not vary in overall distance traveled (t(16)=0.00, p=0.727), suggesting phenotype normalcy. Histological analysis revealed SOM+ and PV-tdTomato (tdT) expression in the DG inner molecular layer (IML) of WT (J20-) and AD mice. SOM+tdT expression was absent in the DG IML of 5/6 male RT AD mice, consistent with a rescue of phenotype. However, SOM+tdT expression in the DG IML of 3/3 female RT AD mice persisted, indicating sex differences in RA signaling. Transcriptomic pairwise comparison of VT WT and AD to VT WT and AD showed partial normalization of differentially expressed genes, particularly within the Synaptopodin Signaling pathway. RA appears to have protective effects against AD pathogenesis among males. The sex differences observed warrant further investigation involving a larger sample size of mice per group matched by age and sex.

Results: Experimental design

Table: Days 1, 2, 3, 4, 1, 2, 3, 4, 1, 2, 3, 4

- Vehicle (0 mg/kg IP in corn oil)
- Retinoic Acid (20 mg/kg IP in corn oil)

Hyperactivity was observed in both the Y-maze and Open Field Maze (OFM) in vehicle-treated AD mice (red) relative to WT mice (blue). An 8-week treatment with RA normalized behavior in both tasks.

Y-maze: Consistent with the hyperactivity phenotype of AD mice, VT AD mice traveled a greater distance compared to WT mice (U=500; p=0.009). In contrast, RT AD and WT mice did not vary in overall distance traveled, indicating normalization of phenotype (U=16.000, p=0.727).

Open Field Maze (OFM): VT AD mice traveled a greater distance compared to WT mice (mean difference = 2.27 cm) while, in contrast, RT AD and RT WT mice did not vary in overall distance traveled (mean difference = 127 ± 262 cm, p=0.031).

Histological analysis revealed SOM+tdT circuitry by RA treatment.

Sex-specific prevention of DG SOM:tdT circuitry by RA treatment

Molecular pathways are normalized by RA treatment

Conclusions

1. Retinoic acid rescues the hyperactivity phenotype of AD mice.
2. Increased tdTomato expression in SOM-CRE+/tdTomato+/- J20- mice suggests SOM circuits are affected differently by PV circuits during AD pathogenesis.
3. RA appears to have a protective effect in the AD pathogenesis of males.
4. The Synaptopodin Signaling pathway may be involved in the mechanism by which retinoid acid rescues the behavioral hyperactivity phenotype of AD mice.

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