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Functional impact of cholinergic dysfunction on retrosplenial circuits in the 5xFAD mouse model of Alzheimer's disease

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Abstract

Background: The retrosplenial cortex (RSC) is critical for learning, memory and spatial navigation and is one of the first brain regions to show dysfunctional activity in the earliest stages of Alzheimer's disease. RSC receives dense cholinergic inputs from multiple basal forebrain regions. While decreased cholinergic tone is one of the hallmarks of the Alzheimer's disease, it is not known how this change impacts retrosplenial cells and circuits. In wild-type mice, cholinergic agonists induce persistent firing in limbic areas such as the entorhinal cortex and the prefrontal cortex. This persistent firing has been proposed as an important neuronal substrate for working memory and successful spatial navigation.

Method: Here, we investigated cholinergic-induced persistent firing in the retrosplenial cortex in the 5xFAD model of Alzheimer's disease. We combined pharmacological and whole-cell patch clamp techniques to characterize the response of retrosplenial cortex cells to carbachol (20 uM), a non-specific cholinergic agonist, in both wild type and 5xFAD mice aged P30-P75.

Result: In wild type animals, persistent firing in response to carbachol in deep layers of the retrosplenial cortex was commonly observed (66.6% of all cells tested). This persistent firing was blocked by atropine (10uM) indicating that it is dependent on muscarinic cholinergic receptors. Retrosplenial cells in 5xFAD animals rarely showed persistent firing (20%, $p<0.05$, binomial test comparing wild type vs 5xFAD).

Conclusion: Cholinergic hypofunction resulting from damage to basal forebrain neurons early in Alzheimer's disease has widely been linked to cognitive impairment. Our results point to a complementary mechanism impacting cholinergic control of cortical circuits: muscarinic receptor downregulation in the earliest stages of Alzheimer's disease. These changes prevent retrosplenial cortex cells of 5xFAD mice from responding to cholinergic activation with the kind of persistent firing that is important for working memory and spatial navigation, suggesting a mechanistic explanation for how cholinergic dysfunction leads to impaired spatial encoding by retrosplenial circuits.