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NEURODEGENERATIVE DISEASE

Ever decreasing ripples

Expression of the ε4 isoform of apolipoprotein E (APOE4) is a major genetic risk factor for Alzheimer disease (AD). Here, Gillespie *et al.* show that expression of human *APOE4* in mouse hippocampal GABAergic interneurons results in changes in hippocampal network activity that are associated with learning and memory deficits.

Women carrying the *ε4* allele have a higher risk of developing AD than male carriers, and this sex bias can be modelled in mice in which the endogenous *Apoe* gene is replaced by knocking in the human *ε4* allele (*APOE4*-KI mice). By 6 months, female *APOE4*-KI mice show loss of GABAergic interneurons in the dentate gyrus (DG) and, by 16 months, these mice show memory deficits.

The authors compared field potential recordings from multichannel electrode arrays from the CA1, CA3 and DG regions of dorsal hippocampus in freely moving female *APOE4*-KI mice, with age-matched controls expressing the innocuous *ε3* allele. They focused their attention on sharp-wave ripples (SWRs), which are short bursts of high-frequency hippocampal oscillations that have been linked to memory consolidation and retrieval. The authors found that aged (12- to 18-month-old) *APOE4*-KI mice exhibited fewer SWRs than controls.

> “thoughout the hippocampal circuit, SWR-associated slow gamma power was much lower in aged *APOE4*-KI mice than in controls”

Furthermore, throughout the hippocampal circuit, SWR-associated slow gamma power was much lower in aged *APOE4*-KI mice than in controls. Slow gamma coherence between CA1, CA3 and DG hippocampal regions was not altered in *APOE4*-KI mice, suggesting that coordination between different hippocampal subregions was unaffected by the expression of *APOE4*, although the engagement of slow gamma oscillations during SWRs was impaired.

To investigate how these network activity changes might have a role in the cognitive impairments observed in aged *APOE4*-KI mice, the authors generated transgenic mice in which *APOE4* expression was prevented only in forebrain GABAergic interneurons (*APOE4*-KI/*Dlx*-Cre mice). Previous studies have shown that this genetic manipulation prevents degeneration of these interneurons and is sufficient to prevent the development of learning and memory deficits.

As with aged *APOE4*-KI mice, aged *APOE4*-KI/*Dlx*-Cre mice showed lower SWR frequency than controls. However, their SWR-associated slow gamma activity in CA1, CA3 and DG was restored to levels similar to in controls; slow gamma coherence was also similar to that in controls. Given that *APOE4*-KI/*Dlx*-Cre mice show no hilar GABAergic interneuron degeneration, these data suggest that slow gamma activity relies on these cells.

Electrophysiological recording in the hippocampus of 4- to 5-month-old *APOE4*-KI mice — before inhibitory cell loss and memory deficits are detectable — revealed that they have markedly fewer SWR events than controls, similar to aged *APOE4*-KI mice. By contrast, SWR-associated gamma power was only reduced in CA1 and this was attributable to a reduction in the proportion of SWRs with extremely high slow gamma power, suggesting an age-dependent progression of the slow gamma phenotype.

Together, these data indicate that the presence of the *ε4* allele results in a deficit in hippocampal SWR-associated slow gamma activity that becomes more extensive and more severe with age. This, together with the rescue of slow gamma activity and memory deficits by selective removal of APOE4 from a specific subpopulation of GABAergic interneurons suggests that APOE4 could contribute to cognitive impairment by affecting slow gamma activity.

Sian Lewis

ORIGINAL ARTICLE Gillespie, A. K. *et al.* Apolipoprotein E4 causes age-dependent disruption of slow gamma oscillations during hippocampal sharp-wave ripples. *Neuron* http://dx.doi.org/10.1016/j.neuron.2016.04.009 (2016)

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