ALZHEIMER'S DISEASE

Alzheimer's disease resilience might lie within the thalamic nucleus reuniens

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Alzheimer's disease (AD) is one of the main neurodegenerative disorders in the dementia family of diseases. However, about one-third of the patients with AD-type neuropathology never meet the criteria for dementia, and the reason behind this resilience is unknown. Additionally, studies have shown that anomalies in low-arousal brain states, such as those occurring during sleep and anesthesia, correlate with a higher susceptibility to AD pathology and cognitive deficits. In *Nature Communications*, researchers show that for the APP/PS1 familial AD (fAD) mouse model, anesthesia negatively modulates brain activity, which can be reverted by deep brain stimulation of the thalamic nucleus reuniens (nRE), showing an important role of this brain region in AD.

The researchers performed electrophysiological, behavioral, and transcriptional measurements in wild-type and APP/PS1 mice to study the effect of anesthesia on brain activity and compare its effects on working memory between genotypes. They showed that, compared with wild-type mice, anesthesia induced an abnormal response in the hippocampus of fAD mice, showing a decline in working memory linked to the hyperexcitability of CA1, a group of hippocampal neurons related to cognition. Additionally, in fAD mice, postsynaptic potential recordings in the connection between the CA1 and the nRE showed an impairment in short-term synaptic plasticity associated with anesthesia. This impairment could be reversed by inhibiting the nRE-CA1 pathway by injecting tetrodotoxin, a sodium channel blocker, in the nRE, which suppressed CA1 hyperexcitability. Given that deep brain stimulation (DBS) is an important therapy in AD, the team tested how this intervention would modulate interictal epileptiform spikes (IESs), which are known for potentially interfering with working memory. Here, tonic DBS showed great potential to treat AD-related hyperexcitability in APP/PS1 mice by suppressing CA1 activity and preventing synaptic and memory dysfunctions. Finally, the researchers applied tonic DBS across time in non-anesthetized animals, starting before the onset of the disease, and saw that it effectively prevented age-dependent memory impairments in the AD mice.

A better understanding of AD resiliency could offer opportunities to develop more effective therapeutics. This study demonstrates the effect of nRE on CA1 hyperexcitability, manifesting through IESs, which ultimately might impair working memory in AD. More importantly, these findings show how tonic DBS can be potentially used as a preventive and therapeutic measure to counteract AD pathology.

Jorge Ferreira

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