Cholinergic Surveillance over Hippocampal RNA Metabolism and Alzheimer's-Like Pathology

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Abstract:

The relationship between long-term cholinergic dysfunction and risk of developing dementia is poorly understood. Here we used mice with deletion of the vesicular acetylcholine transporter (VACHT) in the forebrain to model cholinergic abnormalities observed in dementia. Whole-genome RNA sequencing of hippocampal samples revealed that cholinergic failure causes changes in RNA metabolism. Remarkably, key transcripts related to Alzheimer’s disease are affected. BACE1, for instance, shows abnormal splicing caused by decreased expression of the splicing regulator hnRNPA2/B1. Resulting BACE1 overexpression leads to increased APP processing and accumulation of soluble Abeta1-42. This is accompanied by age-related increases in GSK3 activation, tau hyperphosphorylation, caspase-3 activation, decreased synaptic markers, increased neuronal death, and deteriorating cognition. Pharmacological inhibition of GSK3 hyperactivation reversed deficits in synaptic markers and tau hyperphosphorylation induced by cholinergic dysfunction, indicating a key role for GSK3 in some of these pathological changes. Interestingly, in human brains there was a high correlation between decreased levels of VACHT and hnRNPA2/B1 levels with increased tau hyperphosphorylation. These results suggest that changes in RNA processing caused by cholinergic loss can facilitate Alzheimer’s-like pathology in mice, providing a mechanism by which decreased cholinergic tone may increase risk of dementia.

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