

Inhibition of PDE2 Reduces Progression of Traumatic Brain Injury-Induced Memory Deficits

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ABSTRACT

Traumatic brain injury (TBI) exacerbates cognitive deficits in the development of Alzheimer's disease (AD) and related dementia (ADRD). Early features of pathology in susceptible neurons of patients with TBI-related AD/ADRD include mitochondrial dysfunction and synaptic damage, yet the intricate molecular mechanisms remain elusive. Phosphodiesterase 2A (PDE2A) plays a crucial role in mediating cognition due to its key function in hydrolyzing cyclic AMP (cAMP) and cGMP, and its broad expression in the hippocampus and frontal cortex, brain regions vulnerable to AD. This suggests the potential involvement of aberrant PDE2A-cAMP/cGMP signaling in the pathogenesis of AD/ADRD. Our results revealed that inhibition of PDE2A reprogrammed mitochondrial homeostasis and rescued oxidative phosphorylation (OXPHOS), akin to changes observed in TBI-induced neuronal damage. This study elucidates how aberrant PDE2A-cAMP/cGMP signaling mediates TBI-induced neuroinflammation and cognitive deficits, deepening our understanding of PDE2A's role in regulating cognition in the brain.

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