

AD and TBI: converging on brain energy metabolism

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Cerebral hypometabolism is a shared feature of both traumatic brain injury (TBI) and Alzheimer's disease (AD), but whether these conditions impair metabolism via overlapping or distinct mechanisms remains unclear. TBI acutely disrupts metabolism by damaging the blood-brain barrier, reducing glucose transporter expression, impairing calcium buffering, and oxidizing metabolic enzymes. In contrast, AD-related hypometabolism is linked to direct amyloid- β ($A\beta$) effects on mitochondria, such as impaired respiration, oxidative stress, and altered mitophagy. This study tested whether mitochondrial dysfunction from TBI exacerbates $A\beta$ -induced deficits in a model of AD-related amyloidosis. Using a closed-head injury (CHI) paradigm in APP/PS1 knock-in mice, injuries were delivered at 4–5 months of age—prior to $A\beta$ plaque deposition and mitochondrial decline. Bioenergetics was assessed by Seahorse assay in isolated hippocampal and cortical mitochondria at 1, 4, and 8 months post-injury. At 1 month, injury and genotype interacted: KI mice showed greater dysfunction than TBI or genotype alone, and males were more affected than females. At 4 and 8 months, effects were dominated by $A\beta$, and TBI-related deficits were no longer detectable, suggesting either recovery or convergence of injury and AD mechanisms. These findings define a critical window in which TBI may accelerate mitochondrial decline in AD and underscore the need to consider sex as a biological variable.

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