Neuroprotective strategies for traumatic brain injury (TBI) and TBI-induced acceleration of Alzheimer's disease

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While chronic neurodegeneration following traumatic brain injury (TBI) has long been viewed as irreversible, we have recently shown that pharmacologically stabilizing brain energy can halt neurodegeneration and fully restore cognitive function in mice one year post-TBI, equivalent to decades in humans. We have also identified key pathways driving post-TBI neurodegeneration involving pathologically acetylated-tau (ac-tau), which we have shown additionally accelerates the progression and severity of Alzheimer's disease (AD) (termed "TBI-AD"). Using amyloid-prone 5xFAD mice, an AD model that develops non-mutant tau pathology akin to human disease, TBI was shown to rapidly increase ac-tau, worsening AD pathology and symptoms. Two mechanistically distinct oral therapies converging on reducing ac-tau prevented TBI-AD: p300/CBP acetyltransferase inhibition (via FDA-approved NSAID diflunisal) and NAD^+-dependent sirtuin1 activation (using P7C3-A20 to restore NAD^+ homeostasis). Single-nucleus RNA sequencing identified tauopathy-associated microglial signatures in both human and mouse TBI-AD, which were reversed by these ac-tau-lowering strategies. Notably, human data revealed reduced long-term dementia risk in TBI patients using p300/CBP-inhibiting NSAIDs, compared to other NSAIDs, highlighting translational potential for targeting ac-tau in TBI-AD.