Injury Models

The Role of PP2A Methylation in Susceptibility and Resistance to TBI and Alzheimer's Disease-Induced Neurodegeneration

An award granted to the Taub Institute for Research on Alzheimer's Disease and the Aging Brain (Columbia University), managed through CDMRP's Peer Reviewed Alzheimer's Research Program, hypothesized that upstream regulators of tau phosphorylation status would be sensitive to the effects of blast. Two proteins that regulated the activity of tau phosphatase, PP2A, were investigated. Overexpression of PP2A methyltransferase, LCMT-1, was posited to result in decreased PP2A activity; while the PP2A methylesterase, PME-1, was expected to increase PP2A activity. Increases in PP2A activity were hypothesized to result in global dephosphorylation of tau, leading to cognitive impairments. Increases in in LCMT activity were expected to beneficially maintain or increase tau phosphorylation status. Preliminary experiments showed that tau phosphorylation transiently (24-hour time frame) increased in response to blast in all mice including controls, leading the research team to conclude that tau phosphorylation had reached saturation using the experimental blast model. LCMT overexpression did not appear to overcome the effects of blast on tau phosphorylation. Soon after these preliminary experiments were completed, the research team also observed significant blast-related eye damage. The team posited that cognitive and behavioral results for this study may have been skewed by this damage, as many of these tests require visual cues. Shockwave exposure led to vitreous detachment, photoreceptor degeneration, pigmentary changes, and subretinal hemorrhage in 50 percent of eyes examined from shockwave-exposed mice. As such, an animal model using blast-naïve mice to control for blast-related eye injury was created. Tau was extracted from shockwave-exposed mice and introduced via cannula into blast-naïve animals. Mice were infused shortly prior to testing on each day of a two-day radial arm water maze task with vehicle or tau purified from blast or sham mice. Infusion of tau from shockwave-exposed mice significantly impaired performance when compared to tau from sham-exposed animals. Tau from shockwave-exposed animals also impaired contextual fear conditioning when infused into wild type mice. Similar experiments were done in naïve LCMT and PME -overexpressing mice. The studies showed that LCMT overexpression was protective against the impairments, whereas PME exacerbated the impairment effects. The grant demonstrated that tau phosphorylation status is transiently altered after TBI, and that its status is closely modulated by its upstream regulators. The animal models may suggest new targets for modulating tau phosphorylation status, so that positive cognitive, behavioral and memory outcomes can be achieved after mTBI. It also illustrates that blast studies should account, and control for, blast-related eye damage. This damage can impede further cognitive and behavioral testing after blast which may rely on visual cues.