

STAY INFORMED ABOUT TRAUMATIC BRAIN INJURY (TBI)

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SCIENTIFIC STUDIES

Neurotrauma Biomarker Levels and Adverse Symptoms among Military and Law Enforcement Personnel Exposed to Occupational Overpressure without Diagnosed Traumatic Brain Injury

Military and law enforcement personnel often experience blasts during training and combat operations, a phenomenon called low-level overpressure (LLOP). Those with repeated exposure sometimes report concussion-like symptoms. Research suggests LLOP may affect the central nervous system (CNS), as evidenced by the presence of CNS proteins in the blood. In this study, Boutté et al. examined neurotrauma-associated biomarkers and symptoms in those with LLOP exposure. They recruited 106 active-duty military and law enforcement personnel who routinely engaged in LLOP activities (e.g., heavy-wall breaching, demolitions training, firing high-caliber rifles). Participants completed surveys on operational demographics and medical history. These included questions on the type and number of exposures as well as concussion-like symptoms. The authors also acquired blood samples from 30 of the participants and another 30 from age-matched controls (using a commercial vendor). Participant samples were collected in the morning before training and analyzed for common neurotrauma biomarkers (i.e., GFAP, UCH-L1, NF-L, tau, amyloid β , A β -40, and A β -42). Serum levels of UCH-L1, tau, A β -40, and A β -42 were elevated in the LLOP participants relative to the controls. Tinnitus was reported by 58% of the LLOP participants, memory problems by 32%, and sleep problems by 26%. They also found elevated A β -42 was associated with tinnitus and memory deficits.

Comment

The study found long-term LLOP exposure was associated with neurotrauma biomarkers in the absence of clinically defined brain injury. It presents further evidence that repeated subconcussive forces may lead to subclinical brain dysfunction. The number of exposures necessary to yield symptoms is unknown. As this area of science continues to grow, it may be prudent for clinicians to document this LLOP history in health records for tracking and potential use at a future date. Identification and monitoring of neurotrauma biomarkers could be useful for occupational risk management in military populations.

Boutté et al. (2021) *JAMA Netw Open*, Epub 1 Apr. PMID: 33861330

NK1 Antagonists Attenuate Tau Phosphorylation after Blast and Repeated Concussive Injury

Hyperphosphorylation of tau protein is associated with neurological dysfunction after TBI. This study proposes that mechanical forces exerted on the brain elicit activation of transient receptor potential (TRP) channels, which facilitate the release of neuropeptide substance P. This neuropeptide binds to neurokinin-1 (NK1) receptors increasing kinase activity known to phosphorylate tau. Corrigan et al. sought to (1) confirm the relationships between TRP channels, substance P, NK1 receptors, and tau phosphorylation, and (2) determine whether pharmacological manipulation can alter this pathway. Using rodent models, TBI was delivered by single or repetitive head-impacts or controlled blast. The cerebral cortex was later processed and analyzed for biochemical signatures. In the impact models, substance P immunoreactivity increased 24 hours after TBI (single-moderate and repetitive-mild).

There were no changes in substance P after a single mild TBI. Hyperphosphorylated tau increased 24 hours after injury in all groups except single-mild. Administering the NK1 antagonist EUC-0001 30 minutes after impact significantly reduced the number of immunoreactive cells (i.e., indicators of kinase activity or tau phosphorylation). In the blast model, phosphorylated tau increased 28 days after mild TBI. Treatment with the NK1 antagonist 30 minutes after blast significantly reduced levels of phosphorylated tau and improved neuromotor function 28 days post-injury. The authors also observed neurological changes at 24 hours post-injury, but hyperphosphorylation of tau was not detected at this point. Finally, they examined the role of TRP channels in tau phosphorylation. Using the impact model, the TRPV1 antagonist capsazepine was administered 30 minutes before and after a single moderate TBI. When administered before the injury, capsazepine reduced tau phosphorylation at 24 hours. Administration after the injury had no effect.

Comment

The study found mechanical activation of TRP channels plays a key role in tau hyperphosphorylation in a rodent model. Blocking this process either before (TRPV1) or after (NK1) injury mitigates neuromotor impairment. Pharmaceuticals based on NK1 antagonists could treat brain injury in humans, but more research is needed. Future studies should use transgenic models expressing human tau isoforms or gyrencephalic animals. This would more closely approximate human tau phosphorylation and deposition patterns, allowing a better assessment of NK1's clinical potential.

Corrigan et al. (2021) *Sci Rep*, Epub 23 April. PMID: 33893374

Traumatic Brain Injury and Incidence Risk of Sleep Disorders in Nearly 200,000 US Veterans

Many studies report sleep complaints in TBI patients. However, few have examined clinically diagnosed sleep disorders over the long term (i.e., months to years). Leng et al. addressed this gap in a longitudinal study of nearly 200,000 U.S. veterans. The authors accessed Veterans Health Administration records between October 1, 2001 and September 30, 2015. Their sample consisted of 98,709 veterans with diagnosed TBI and the same number of age-matched controls. Adjusting for demographic factors, they found that veterans with TBI were 41% more likely to develop a sleep disorder compared to controls with a hazard ratio (HR) of 1.41. This disparity was generally consistent across disorders: sleep apnea (HR: 1.28), insomnia (HR: 1.50), hypersomnia (HR: 1.50), and sleep-related movement disorders (HR: 1.33). Injury severity was also a factor. There was an association between sleep disorders and mild TBI (mTBI), but not for moderate or severe TBI. Posttraumatic stress disorder (PTSD) did not increase the risk of sleep disorders. Overall, 23,127 veterans (19.6%) developed one or more sleep disorders within five years of injury. However, the data showed that these conditions could manifest up to 14 years later.

Comment

The study shows relationships between diagnosed sleep disorders and mTBI in a veteran population. Its strengths include a longitudinal design and large cohort. However, a medical record review inherently limits the sample to those who seek treatment. Overall, the study contributes toward an understanding of the nature and timing of sleep disorders after the acute phase of TBI.

Leng et al. (2021) *Neurology*, Epub 3 Mar. PMID: 33658328

Cognitive Impairment after Focal Brain Lesions is Better Predicted by Damage to Structural than Functional Network Hubs

Hubs are highly connected areas of the human brain associated with cognitive abilities. Damage to hubs may underlie the impairments seen after brain injury. Both gray and white matter structures can be hubs (i.e., cortex and fascicles). However, their relative contribution to cognition is unclear. In this study, Reber et al. examined hub metrics in two cohorts with focal brain lesions ($n = 402$; $n = 102$). All participants received MRI scans (three or more months after lesion formation) and a battery of neuropsychological tests. The authors analyzed functional and structural MRI data to yield two metrics: participation coefficient (gray matter connectedness) and edge density (white matter connectedness). In the larger cohort, a regression model showed lesion volume predicted overall cognitive performance. The inclusion of edge density as a variable improved predictive variance. However, participation coefficient did not. The authors repeated this analysis in the smaller cohort and found similar results.

Comment

Historically, research linking the brain and cognition has focused on the cerebral cortex. This study demonstrates that a white matter metric, as opposed to gray matter, is salient for predicting cognitive abilities. Further research is necessary to explore alternative measures. The study also specifically examined acquired brain injury. Results may vary in cases of TBI. These findings contribute to neurocomputational models of brain injury which may inform TBI treatment and diagnostics

Reber et al. (2021) *Proc Natl Acad Sci U S A*, Epub 11 May. PMID: 33941692

A Randomized Trial Comparing Prescribed Light Exercise to Standard Management for Emergency Department Patients with Acute Mild Traumatic Brain Injury

It is estimated that 15–30% of mild TBI (mTBI) patients are at risk of persistent post-concussion symptoms (PCS). Those with PCS may experience chronic symptoms for weeks, months, even years after injury. The emergency department (ED) is often the first place that head injury patients are evaluated. Yet there are no ED-based clinical guidelines for PCS. Varner et al. explored whether light exercise could mitigate PCS in mTBI patients. They recruited 367 adults (intervention: $n = 183$; control: $n = 184$) from three Canadian EDs within 48 hours of injury. All patients were clinically and demographically similar. They were instructed to follow standard-of-care guidelines after discharge (i.e., a symptoms list and plan for resumption of activities). In addition, the intervention group was prescribed 30 minutes of light exercise (i.e., walking) per day. Patients completed the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) at their initial evaluation and then 7, 14, and 30 days after. The authors compared responses between the groups. There was no significant difference in the proportion of PCS patients at 30 days (intervention: 14.6%; control: 13.4%). There were also no group differences in median RPQ scores (intervention: 13; control: 14) or healthcare utilization (i.e., provider visits or unplanned ED visits within 30 days).

Comment

Persistent post-concussion symptoms remain a significant obstacle in TBI clinical care. Light exercise has proven benefits in other domains such as mental health. While the authors did not find a significant effect on the mTBI patients in their sample, light exercise did not appear to be harmful. For the latest recommendations on progressive return to activity (PRA) please refer to the provider resources portal on the TBICoE website: <https://health.mil/About-MHS/OASDHA/Defense-Health-Agency/Research-and-Development/Traumatic-Brain-Injury-Center-of-Excellence/Provider-Resources>

Varner et al. (2021) *Acad Emerg Med*, Epub 28 Feb. PMID: 33481332

Diffusion Imaging Reveals Sex Differences in the White Matter Following Sports-Related Concussion

Sport-related concussions (SRC) may affect men and women differently. Many studies report sex differences in both symptoms and neuropathology, but findings are still inconclusive. In this study, Wright et al. explored the neurological effects of SRC in male and female Australian football players. Over three years, they recruited amateur athletes from clubs around Melbourne. The sample consisted of 14 players with SRC (8 males, 6 females) and 16 age- and education-matched controls (9 males, 7 females). Concussions were diagnosed by team physicians or by postgame neurological assessment. All participants completed a medical history questionnaire, the Sports Concussion Assessment Tool (SCAT), and were scanned by MRI twice: 24 to 48 hours after injury and two weeks later. Questionnaires showed males reported more symptoms and more prior concussions than females. Diffusion tensor imaging (DTI) analysis examined brain white matter tracts, showing SRC participants had increased fiber density in the splenium compared to controls at 48 hours. Also at 48 hours, SRC participants showed increased fractional anisotropy (FA) and decreased apparent diffusion coefficient (ADC) in the corpus callosum, corona radiata, and the superior and inferior longitudinal fasciculus. Finally, male SRC participants showed increased fiber density in the cingulum compared to females at both time points.

Comment

The neuropathology of TBI may differ between the sexes. However, there is little research on the subject. In this study, the authors found indicators of edema in SRC patients compared to controls. They also observed sex differences in the cingulum. Though their sample is small, it contributes to the larger goal of identifying sex differences in TBI pathology. Understanding these patterns could help profile TBI patients and anticipate clinical trajectories for men and women.

Wright et al. (2021) *Cereb Cortex*, Epub 15 Apr. PMID: 33860291

ABOUT

The *Bulletin* is a product of the Traumatic Brain Injury Center of Excellence (TBI CoE) Research Branch and provides a quarterly summary of TBI research and information relevant to health care providers. This issue covers research published from April to June 2021.

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