Neurocognitive and Psychological Health Treatment Strategies

Trigeminal Sensitization in a Preclinical Model of Traumatic Brain Injury (TBI): Implications for Posttraumatic Headache (PTH)

It is estimated that nearly a quarter of Service Members wounded in combat during Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) suffer from TBI. PTH, the most common and persistent symptom of post-concussive syndrome (PCS), shares features with migraine headache, such as increased sensitivity of touches to the face and increased sensitivity to light. The changes that underlie PTH, brought on by blast-induced inflammation, are thought to involve the sensitization of the trigeminal pain neural network; however, the precise mechanisms which bring about these changes remain poorly understood. Calcitonin gene-related peptide (CGRP) and nitric oxide (NO) are signaling molecules thought to drive sensitization of the trigeminal pain network following blast injury. In work performed under an FY11 Peer Reviewed Medical Research Program (PRMRP) Investigator-Initiated Research Award, researchers at Jefferson Medical College utilized a rodent controlled cortical impact (CCI) model to elucidate the respective roles of CGRP and NO in PTH pathophysiology. Blocking CGRP in the trigeminal pain circuit returned mechanical pain sensitivity of CCI rats to levels found in normal rats. In contrast, blocking NO had no effect on mechanical pain sensitivity. Blocking CGRP also decreased the expression of iNOS, one isoform of the enzyme that synthesizes NO, demonstrating that these two molecules mediate PTH pain sensitivity in an interdependent manner. Photosensitivity, a common symptom of PTH, was attenuated in the CCI rodents following inhibition of either CGRP or NO. CGRP expression levels remained high during inhibition of NO, however, which suggests that CGRP and NO contribute to PTH photosensitivity via independent pathways. These results support the conclusion that both CGRP and NO play important roles in the trigeminal network sensitization contributing to PTH, but that, while co-modulators of mechanical pain sensitization, they may modulate PTH pain sensitivity independently. Following its ameliorating effects on both mechanical and PTH pain sensitivity, this work suggests that CGRP inhibition is a therapeutic target worth pursuing in the effort to treat PTH. For many Service Members who suffer from PTH, CGRP offers a promising target for developing a treatment that not only relieves pain from PTH but potentially reduces side effects through more effective targeting empowered by a thorough knowledge of the pathways involved in PTH-associated sensitization of the trigeminal pain network.