



US DEPARTMENT OF DEFENSE

BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

Treatment Strategies

Defective Methionine Metabolism in the Brain after Repeated Blast Exposures Might Contribute to Increased Oxidative Stress

Increased oxidative stress in the brain is reported to play a significant role promoting neuronal damage associated with both brain injury and neurodegenerative disorders. The mechanisms leading to increased oxidative stress after blast exposure are still uncertain. Researchers at the Walter Reed Army Institute of Research (WRAIR) explored the mechanisms underlying this increase in oxidative stress using preclinical models of repeated blast-induced traumatic brain injury (TBI). In this study, brain regions of rats exposed to repeated blasts in a blast simulator underwent untargeted profiling of primary metabolism by automatic linear exchange/cold injection gas chromatography - time of flight mass spectrometry and revealed acute and chronic disruptions in the metabolism of amino acids and antioxidants. Closely coupled repeated blast exposures (19 pounds per square inch peak total pressure, 8 millisecond duration) affected the metabolism of the essential amino acid methionine. Methionine sulfoxide, the oxidized metabolite of methionine, showed a sustained increase in the brain after blast exposure which was associated with a significant decrease in cysteine, the amino acid derived from methionine. Glutathione, the antioxidant synthesized from cysteine, similarly decreased as did the antioxidant ascorbic acid. Reductions in ascorbic acid were accompanied by increased levels of its oxidized metabolite, dehydroascorbic acid and other metabolites such as threonic acid, isothreonic acid, glycolic acid, and oxalic acid. In view of the fundamental importance of glutathione in the brain as an antioxidant, including its role in the reduction of dehydroascorbic acid to ascorbic acid, the disruptions in methionine metabolism elicited by blast exposure might prominently contribute to neuronal injury by promoting increased and sustained oxidative stress. These results suggest that increasing the levels of cysteine in the brain by dietary supplementation of cysteine or administration of N-acetyl cysteine could be potential therapeutic strategies against blast-induced TBI. By revealing important neurobiological mechanisms that underlie blast overpressure (BOP)-induced brain injury, these experiments will provide valuable insights into mitigation strategies and therapeutic countermeasures for affected Service Members.

