Sundry Treatments for Blast-related Injuries

Defective Methionine Metabolism in the Brain after Repeated Blast Exposures

Increased oxidative stress in the brain is reported to play a significant role promoting neuronal damage associated with both brain injury and neurodegenerative disorders (*Abdul-Muneer et al. 2013, Cho et al. 2013, Li, O, et al. 2013, Readnower et al. 2010, Wang et al. 2005*). The mechanism(s) leading to increased oxidative stress after blast exposure is still uncertain. Researchers at the Walter Reed Army Institute of Research (Silver Spring, Maryland) explored the mechanism(s) underlying this increase in oxidative stress using preclinical models of repeated blast-induced traumatic brain injury (TBI). In this published 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 (*Arun et al. 2018*). Closely coupled repeated blast exposures (19 pounds per square inch peak total pressure, 8 milliseconds 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 also 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. Total reactive oxygen species, a measure of oxidative stress, increased significantly in the brain after blast exposure. 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 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 (Figure 1).

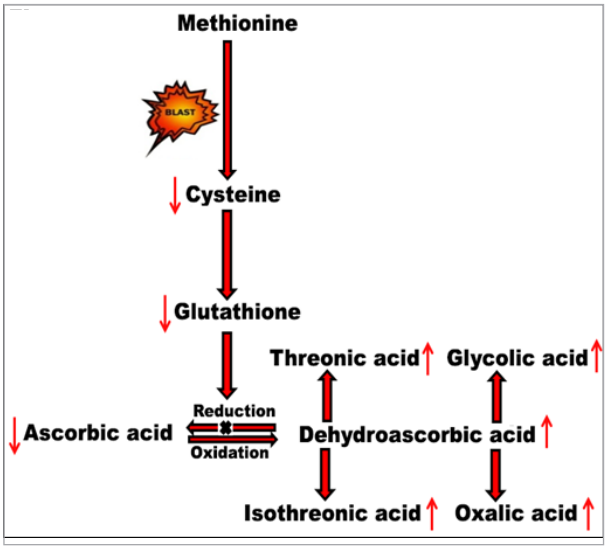

FIGURE 1: Schematic representation of the possible changes in methionine and ascorbic acid metabolisms after repeated blast exposures. (Figure from Arun et al. (2018) used with permission from the authors)

In conclusion, by identifying specific neurobiological underpinnings of blast-induced TBI, these findings identify targets for pharmacological countermeasures to improve outcomes.

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