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Therapeutic Potential of n-3 PUFAs TBI Mediated Visual Dysfunction

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Institution Receiving Award: TENNESSEE, UNIVERSITY OF, HEALTH SCIENCE CENTER
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View Technical Abstract

PUBLIC ABSTRACT

Traumatic brain injury (TBI) and non-rupturing ocular trauma are known to cause damage to the cornea, retina, and optic nerve leading to significant visual impairments. Research sponsored by the Department of Veterans Affairs (VA) showed that as many as 75% of Service members who suffered a TBI have visual dysfunction. There is no drug or treatment available that will effectively limit the post-trauma visual impairments from retinal and optic nerve damage. The research idea to be tested in this proposal is to determine the protective effect of n-3 PUFAs (polyunsaturated fatty acids, namely, DHA, docosahexaenoic acid, and EPA, eicosapentaenoic acid) in animal models of mild TBI to prevent vision loss. N-3 PUFAs will be fed before and after the injury to assess their effectiveness as a preventive or augmentative therapy as well as post-trauma acute therapy, respectively.

The basis or rationale behind this research idea derives from our preliminary studies. The beneficial effects of n-3 PUFA for neuronal development and neuroprotection have been known for years. However, their benefit in TBI-mediated visual dysfunction has not been tested. We used "fat-1 transgenic mice (Fat1^+)," genetically modified mice that harbor "fat-1" gene (Omega-3 fatty acid desaturase) from C. elegans, which is absent in mammals, and can convert n-6 fatty acids to n-3 fatty acids and thus produce relatively higher levels of n-3 PUFAs in every tissue, compared to their wild type (WT) littermates fed on the same diet. After subjecting Fat1^+ mice to mild TBI, we found significantly smaller visual deficits than in WT mice in a one-month follow-up study. Through histological analysis of the optic tract of the brain, we observed significantly reduced microglial activation in Fat1^+ mice compared to their littermate controls (indicative of reduced optic nerve axon injury), which provides compelling evidence that systemic augmentation of n-3 fatty acids is protective against TBI-mediated retinal (neuronal) damage. We hypothesize that n-3 PUFA supplementation for primary prevention or treatment in the immediate aftermath of closed-globe ocular trauma (or mild TBI) is a promising therapeutic approach for reducing the visual deficits commonly produced by such trauma.

The critical barriers in reducing vision loss among active duty Soldiers and in Veteran and civilian populations who suffered a TBI are the lack of existing preventive, augmentative, or acute therapies. Our long-term goal is to develop strategies for prophylactic as well as therapeutic use of n-3 PUFAs for resolution of neuro-inflammation by administering as pre- and post-trauma medication. The objective of this proposal is to determine the therapeutic benefit of n-3 PUFAs in animal models of mild TBI in preserving functional vision. The goal of this study will remain focused on the amelioration of visual dysfunction associated with mild TBI using preclinical testing in animal models (Specific Aim 1). In Specific Aim 2, we will attempt to understand novel mechanisms by which n-3 PUFAs may modulate neuro-inflammation in this mouse model.

The main purpose of our research efforts is to ensure that the invaluable gift of sight may be preserved so that those in harm’s way can come home without any long-term visual deficits. The purpose of this study is determining the effectiveness of n-3 PUFAs in successfully reducing neuroinflammation after mild TBI in mouse models and identifying the mechanism of action. If found effective, n-3 PUFA supplementation can be fast-track FDA-approved, as these are safe and have been in human consumption for centuries, into use as an effective treatment for the visual damage before and after closed-head brain injury in human clinical trials. The effects of TBI can vary from permanent visual dysfunction to personal distress in Soldiers and the Veteran population. As much as 80% of Soldiers with eye trauma cannot return to their active duty. From 2000-2017, in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF), deployment-related eye injuries and blindness have represented a total cost of U.S. $45.5 billion (B), with $44.4B of that cost incurred toward a lifetime of long-term benefits, lost wages, and family care.

This novel therapeutic strategy could make a significant improvement over existing treatments available for TBI-mediated vision loss by providing protection against vision loss and resulting enduring benefits, so that Service members can go back to their military duties or join the civilian workforce and have a better quality of life. The n-3 PUFA can be supplemented through diet (pills) to active duty Soldiers in the battlefield and thus could be the first as a "preventive therapy" for TBI injuries among Soldiers in the battlefield or athletes who are at risk of TBI (for example, football players). Along with its therapeutic potential, n-3 PUFAs have many other long-term health benefits that may include protection from neuro-psychiatric, neuro-degenerative, diabetic, and oncologic diseases that are common in the Veteran population. Our determination of the novel mechanism by which neuro-inflammation and microglial activation is regulated by a group of bioactive lipids and their enzymes may provide novel target and avenues for novel therapeutic development for vision loss from TBI, other than use of n-3 PUFAs.

Back to Search Results

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