Treatments for Neurotrauma

Potential Treatment for Protection against Blast-induced Neurotrauma and Ocular Injuries

Blast overpressure exposure may lead to severity-dependent brain injury. Lysophosphatidic acid (LPA) is a bioactive lysophospholipid released from activated platelets, astrocytes, choroidal plexus cells, and microglia and is reported to play major roles promoting inflammatory processes through signaling events mediated through specific G-protein coupled LPA receptors (LPARs) (*Eichholtz et al. 1993, Moolenaar 1995*). In particular, LPA is reported to be involved in blood brain barrier disruption, Tau protein phosphorylation and neuroinflammation leading to neurite retraction (*Sayas et al. 2006, Sun et al. 2011*). Prompted by recent reports of elevated LPA and up-regulation of LPARs in both mice and humans following brain injury, and neuroprotective efficacy of LPA antibodies (Lpathomab) in the former, researchers at the Walter Reed Army Institute of Research (WRAIR; Silver Spring, Maryland) in collaboration with Lpath, Inc., (the developer of Lpathomab) (San Diego, California), are evaluating the role of LPA in ameliorating the deleterious effects of blast-induced neurotrauma and ocular injuries (*Crack et al. 2014, Frugier et al. 2011*). Findings to date reveal that a single anti-LPA antibody treatment (25 milligrams per kilogram body weight, intravascular) at one-hour post-blast exposure significantly improved visual acuity and electroretinography and reduced retinal neuropathological changes in rats after blast exposure, reinforcing other indications that therapies targeting LPA may provide effective countermeasures to blast injury. These preclinical findings identify potentially efficacious countermeasures that may in the future be used to treat blast induced ocular injuries and vision dysfunction (Figures 1, 2, 3, and 4).

The research conducted by Lpath, Inc. was partially funded by Psychological Health/Traumatic Brain Injury Research Program (PH/TBIRP). Research at WRAIR was funded by a separate Cooperative Research and Development Agreement between WRAIR and Lpath Inc. The PH/TBIRP award (W81XWH-16-1-0098) is managed by Congressionally Directed Medical Research Programs.

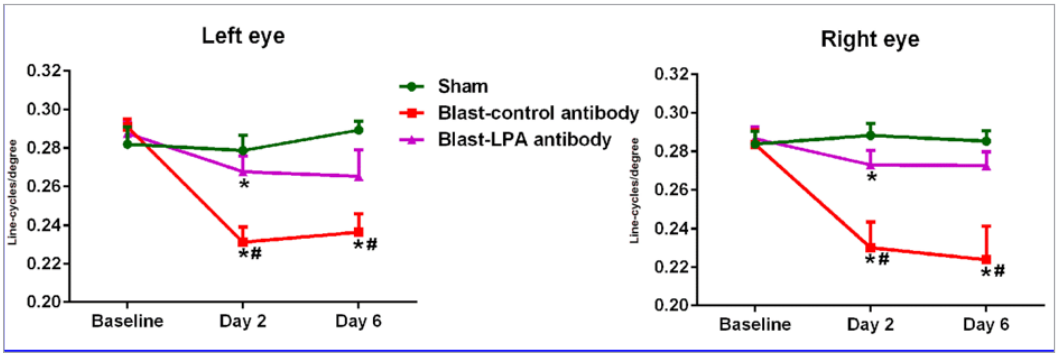

FIGURE 1: Single blast exposure decreases visual acuity and LPA antibody therapy showed significant protection. (Figure used with permission from the authors)

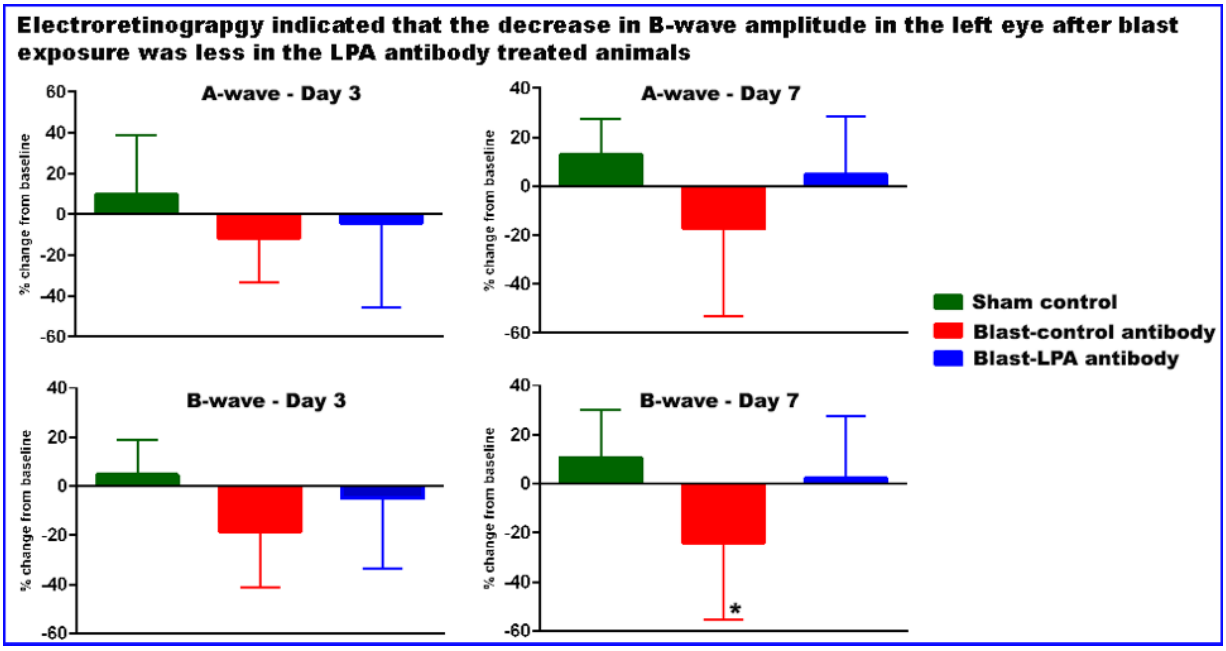

FIGURE 2: Electroretinography indicated that the decrease in B-wave amplitude in the left eye after blast exposure was less in the LPA antibody treated animals. (Figure used with permission from the authors)

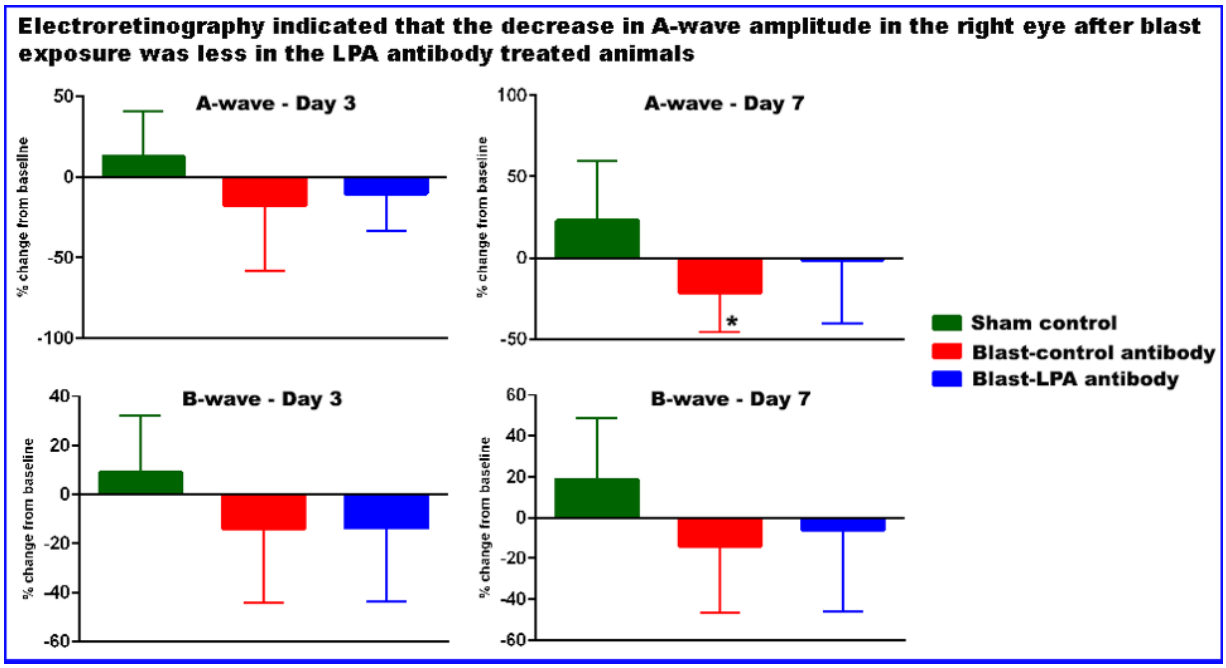

FIGURE 3: Electroretinography indicate that the decrease in A-wave amplitude in the right eye after blast exposure was less in the LPA antibody treated animals. (Figure used with permission from the authors)

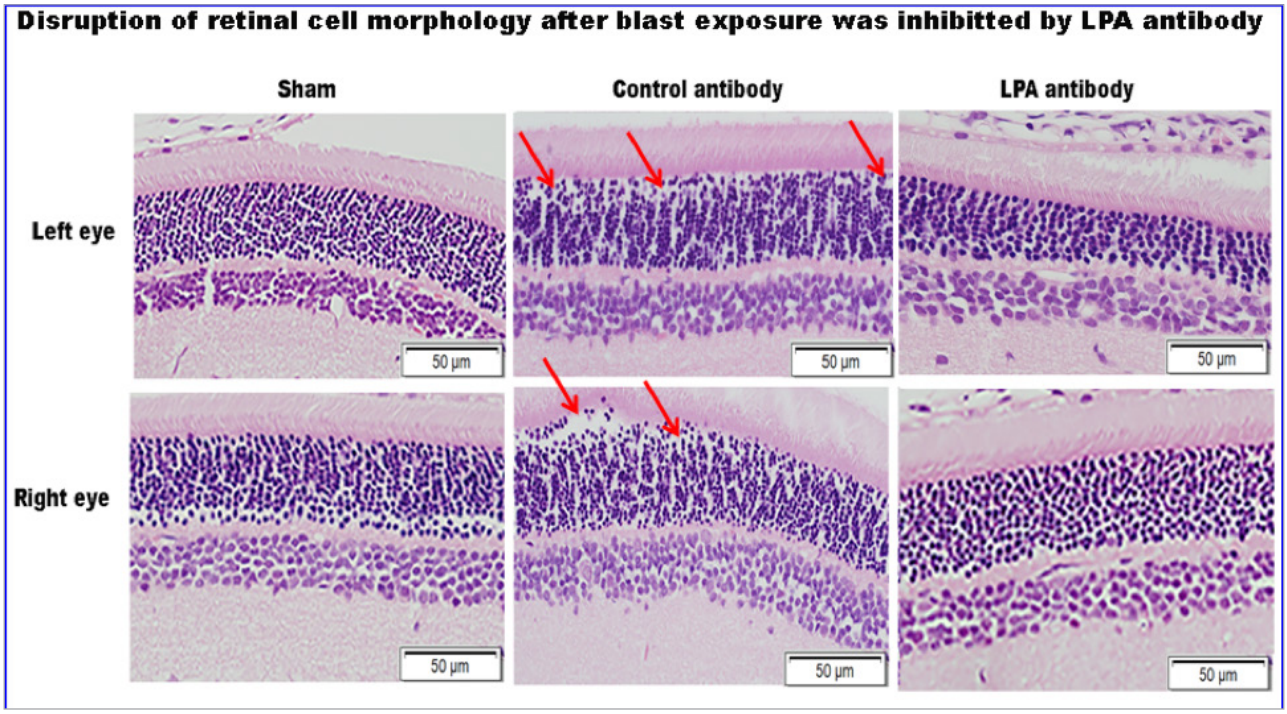

FIGURE 4: Disruption of retinal cell morphology after blast exposure was inhibited by LPA antibody. (Figure used with permission from the authors)

REFERENCES:

Crack, P. J., Zhang, M., Morganti-Kossmann, M. C., Morris, A. J., Wojciak, J. M., Fleming, J. K., Karve, I., Wright, D., Sashindranath, M., Goldshmit, Y., Conquest, A., Daglas, M., Johnston, L. A., Medcalf, R. L., Sabbadini, R. A., and Pebay, A. 2014. "Anti-Lysophosphatidic Acid Antibodies Improve Traumatic Brain Injury Outcomes." J Neuroinflammation 11:37. doi: 10.1186/1742-2094-11-37.

Eichholtz, T., Jalink, K., Fahrenfort, I., and Moolenaar, W. H. 1993. "The Bioactive Phospholipid Lysophosphatidic Acid Is Released from Activated Platelets." Biochem J 291 (Pt 3):677-80.

Frugier, T., Crombie, D., Conquest, A., Tjhong, F., Taylor, C., Kulkarni, T., McLean, C., and Pebay, A. 2011. "Modulation of LPA Receptor Expression in the Human Brain Following Neurotrauma." Cell Mol Neurobiol 31 (4):569-77. doi: 10.1007/s10571-011-9650-0.

Moolenaar, W. H. 1995. "Lysophosphatidic Acid, a Multifunctional Phospholipid Messenger." J Biol Chem 270 (22):12949-52.

Sayas, C. L., Ariaens, A., Ponsioen, B., and Moolenaar, W. H. 2006. "GSK-3 Is Activated by the Tyrosine Kinase Pyk2 During LPA1-Mediated Neurite Retraction." Mol Biol Cell 17 (4):1834-44. doi: 10.1091/mbc.E05-07-0688.

Sun, Y., Kim, N. H., Yang, H., Kim, S. H., and Huh, S. O. 2011. "Lysophosphatidic Acid Induces Neurite Retraction in Differentiated Neuroblastoma Cells via GSK-3beta Activation." Mol Cells 31 (5):483-9. doi: 10.1007/s10059-011-1036-0.