

Brain Injury Animal Models (Ramot)

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Blast Brain Injury: a combat zone-like mouse model. From the experimental lab to the war against terror and back to the lab.

Improvised explosive devices (IEDs) are one of the main causes for casualties among civilians and military personnel in the present war against terror. IEDs induce various degrees of cognitive, emotional and behavioral disturbances but the knowledge of the exact brain pathophysiology following exposure to blast is poorly understood. We have developed a blast injury model for mice that resembles, as much as possible, the conditions in the battlefield or at a terror-attack site. As such, the outcomes of the "real-life-like" exposure to the blast in our model may vary from severe to mild brain injury under controlled conditions for each mouse, and possible confounds are minimized. In the mild to moderate group no alterations in neurological assessment or brain gross pathology were found in the blasted mice.

At 7 days post blast, cognitive and behavioral tests revealed significantly decreased performance at both 4 and 7 meters distance from the blast. At 30 days post-blast, clear differences were found for animals at both distances in the object recognition test, and in the 7 m group in the Y maze test. Using MRI, T1 weighted images showed an increased BBB permeability one month post-blast. DTI analysis showed an increase in fractional anisotropy and a decrease in radial diffusivity. These results may represent myelin reorganization and axonal-outgrowth inhibition.

Cellular and biochemical studies are underway in order to further correlate these blast-induced cognitive and behavioral changes and to identify possible underlying mechanisms that may help develop treatment- and neuro-protective modalities. In a cutting edge set of recent experiments, groups of mice were implanted pre or post blast with ALZET mini pumps containing Ex-4. Ex-4 is a long-acting glucagon-like peptide-1 receptor (GLP-1R) agonist, which comprises 39 amino acids, which can enter the brain and activates anti-apoptotic pathways. We used 2 different paradigms: 1) mini pumps were implanted immediately following trauma, and 2) mini pumps were implanted 48 hr prior to the exposure to blast. Behavioral tests were conducted at two times, 7 and 30 days post trauma using the novel object recognition test. In the pre-injury treatment groups, mice subjected to mTBI showed impaired cognitive behaviors that were reversed by Ex-4. In the novel object recognition test 7 days post injury these differences reached statistical significance. Alike differences were found when the mice were examined 30 days post trauma. Similar protection was found for groups that were treated with Ex-4 immediately following the injury. These findings may offer a new therapeutic strategy to treat damages induced by mTBI and blast. Further studies are investigating this disorder to gain better understanding of the mechanisms involved in mTBI as well as blast to optimize treatment.

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