Modeling PTSD and repetitive concussive injury in animal models

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Background

A large body of evidence from human studies have shown that >44% of active duty soldiers who experience a loss of consciousness as a result of brain trauma also meet the criteria for PTSD after deployment. Combat-related mTBI have been demonstrated to double the risk for PTSD in veterans. However, numbers are largely underestimated given the complex neurological background of mTBI and PTSD, the clinical heterogeneity and large degree of overlap between both conditions, which make them extremely challenging to diagnose and manage individually or co-morbidly. This work aims to address the paucity of neurobiological studies that has been carried out to examine the interrelationship between TBI and PTSD. We consider, given the heterogeneity of clinical presentation in TBI and PTSD patients that the most efficient way to identify the neurobiological areas of interrelationship between both conditions is to develop and utilize a relevant animal model whereby many variables can be effectively controlled and then translated to the human population.

Method

We have recently developed a model of PTSD, which involves: 21 days of unpredictable repetitive exposures at different times of the light and dark cycle to danger-related predator odor while under restraint, a daily psychosocial stressor involving unstable social housing and a physical trauma in the form of inescapable footshock. This model has now been combined with our repetitive concussive head injury model that has been extensively characterized from acute (24hr) to 24 months (chronic) post-injury. In this work we extend the neurobehavioral analysis of our comorbid model at chronic timepoints to attempt to demonstrate persistent PTSD like behavior. We have also included the aspect of multiple re-exposures at different timepoints of the mouse life span to mimic the role of multiple military-deployments. We plan to utilize our state of the art proteomic and lipidomic (mass-spectrometry) technology to identify brain, peripheral tissue and plasma biomarker profiles and critical molecular pathways that correlates with the severity of neurobehavioral, histopathological and endocrine features of our comorbid model at multiple extended timepoints post-exposure.

Results and Conclusion

Animals exposed to stressful trauma alone demonstrate similar traits with the human condition as defined by the DSMV; this includes evidence of recall of traumatic memories, anxiety and impaired social behavior. Repetitive mTBI animals demonstrate deficits in spatial learning and memory, dis-inhibitory-like behavior, which is accompanied by the persistent thinning of the corpus callosum, axonal injury and astroglial activation in white matter tracts post-injury. Combination of both stress and

mTBI results in overlapping and heterogeneous outcomes in behavior, notably the abrogation of impaired social behavior and contextual fear memory in PTSD animals following repetitive mTBI. Further assessments of chronic effects of stress-injury and biochemical analyses of tissue and plasma profiles are currently ongoing. Our model thus far seems to suggest a complex neurobehavioral background for both mTBI and PTSD, with heterogeneous and overlapping features. Our proteomic and lipidomic profiling will explore the neurobiological basis of this complex inter-relationship between mTBI and PTSD.