Evidence of Increased N-acetyl-aspartate After Repetitive Head Injury

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Introduction

Mild Traumatic Brain Injuries (mTBI) continue to be a growing concern in the world of sports. mTBI has been known to cause short term neurocognitive deficits and may be linked to more long term conditions such as chronic traumatic encephalopathy. To make matters worse, diagnosing concussions is not straight forward as it relies heavily on patient self reporting, and conventional imaging, such as Magnetic Resonance Imaging (MRI), cannot pick up on the metabolic and micro structural changes post mTBI. As a result, advanced imaging techniques such as Magnetic Resonance Spectroscopy (MRS) may be more sensitive to injury. Studies have shown reduced N-acetylaspartate (NAA) after mild brain injury[1-3]; however as many athletes suffer multiple concussions throughout their careers, a history of previous injuries may contribute to a different pattern of chemical changes in the brain. In a study of retired soccer players with a history of repetitive subconcussive trauma, some subjects exhibited an increase in NAA, and although it was statistically non-significant compared to control[4], there were several subjects that exhibited this increased. Therefore our aim is to examine a larger cohort of athletes with repetitive brain trauma to determine if the same phenomenon can be observed. As the data in human studies is cross-sectional and obtained after concussion, the second aim of this study was to determine if these results could be replicated in a more controlled experiment in mice and examine the metabolic effects of a single mTBI compared to repeat mTBIs (rmTBI).

Methods

For aim 1, we studied 84 symptomatic male former NFL players (ages 40-69) with a history of rmTBI and 26 same-age male controls with no history of head injury. Subjects were scanned on a Siemens 3T MRI system (single voxel PRESS, TR/TR=2000/30ms, 2x2x2 cm^3, 128 repetitions) in the posterior cingulate gyrus. For aim 2, we studied 16 three month old male mice using a weight drop model proven to show similar rmTBI deficits found in humans with three experimental groups: single mild injury (n = 4), repetitive mild injury in two days (n = 4), and a control group (n = 6). The mice were scanned pre and post injury using a Bruker 7T MRI system (single voxel PRESS, TR/TE=2000/17 ms, 2x2x2 mm^3, 256 repetitions) in the posterior cingulate gyrus. Both human and mouse data was pre-processed using OpenMRSLab for frequency correction and water suppression then analyzed by LC Model to measure metabolite levels of N-acetyl-aspartate.

Results

When comparing the retired NFL athletes to controls, tNAA was not found to be statistically different in the PCG however 15 subjects (18%) of the athletes had NAA levels one standard deviation (SD) above the mean of the controls and 6 (7%) were above 2 SD. In the mice, we found there was no change in tNAA/tCr levels in the control group ($p = 0.127$, $n = 6$), as expected, and a significant change in the tNAA/tCr levels for the single mild injury and the repetitive mild injury. Interestingly, the single mild injury showed a significant decrease in tNAA/tCr ($p = 0.003$, $n = 4$), while the repetitive mild injury showed a significant increase in tNAA/tCR levels ($p = 0.017$, $n=4$) as shown in Figure 3.

Discussion/Conclusion

The changed levels in NAA in the different brain trauma cohorts supports this previous findings that the type of injury (repetitive or single occurrence) affects the brain differently. Our study echoes a single injury's effect of lowering NAA levels as seen in prior animal and human mTBI studies which has been attributed to neuronal loss. However, increased NAA in repetitive injury has not been previously described. While the mechanism remains unclear, it is possible that increase in NAA is reflective of neuroplastic changes[5] in the brain in an effort to recover from multiple injuries.

References

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