Key neurological and neurochemical features in a model of repetitive concussions: Implications for post-concussion headache

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Introduction

Incidence rates for concussion will continue to grow along with the increasing awareness and improvements in diagnosis. Headache is a hallmark feature of post-concussion syndrome. Post-concussion headache (PCH) is highly prevalent in the military with as high as 97.8% reporting having headaches¹, occurring in up to 85% of athletes following ²-⁴. In the Military and sports, return to duty or play guidelines state that a soldier/player should be asymptomatic before returning to physical activity. However, headache following concussion is commonly dismissed. PCH can be a new headache resulting from head trauma or worsening of pre-existing headache disorder. In many patients, it resolves in three months; in others, it persists for much longer. Acute PCH is most likely due to acute inflammatory mechanisms. If headache after concussion is indicative of ongoing neuroinflammation, then headache is an important clinical sign that the neurological system is healing and there is a continued susceptibility to damage. The development of chronic PCH may be due to mechanisms other than Abnormalities within several areas of the trigeminovascular system are common in migraine and other headache disorders. In our previous study, changes in the trigeminovascular system correlated with mechanical allodynia (cutaneous hypersensitivity in response to normally innocuous stimuli) in a model of focal traumatic brain injury. The goal of this study was to characterize the acute neurological and histochemical changes indicative of concussion, particularly headache-like symptoms, implementing a rat model of closed head injury (CHI).

Methods

Male Sprague Dawley rats received either single sCHI, repetitive rCHI or incision without injury (control). Baseline and weekly post-injury neurological assessments included rotorod, periorbital and paw von Frey (mechanical) sensory testing for the presence of allodynia, as well as Barnes maze testing for detecting deficits in memory and learning. The caudal brainstem trigeminal nucleus and somatosensory cortex were examined for differences in calcitonin gene related peptide (Sigma Aldrich, 1:200), gial fibrillary acidic protein (Millipore, 1:200), and β-amyloid precursor protein (Invitrogen, 1:100) using immunohistochecmistry.

Results

Figure 3: Mean thresholds (g) in response to von Frey (mechanical) stimuli in incision-only, sCHI and rCHI groups after injury, n=8-10/group. A) Periorbital thresholds were significantly reduced in sCHI **p<0.01 and rCHI groups **p<0.05 three days after last impact compared to incision thresholds. Seven days after last impact, rCHI thresholds remained significantly reduced ***p<0.001 whereas sCHI returned to baseline. B) Forepaw thresholds were significantly reduced three days after last impact in both sCHI and rCHI groups **p<0.01. Seven days after last impact, rCHI thresholds remained significantly reduced **p<0.05 compared to sCHI and incision groups.

Figure 4: CGRP and β-APP in TNC: Seven days after injury, TNC was assessed for increases in CGRP n=3/group. A-C CGRP staining in the TNC shows increases in both sCHI and rCHI groups while D-F β-APP shows no significant axonal gross pathological injury in the TNC after closed head injury.

Figure 5: GFAP and β-APP in S1FL Sensorimotor Forelimb cortex: Increases in GFAP (A-C) in both sCHI and rCHI groups while only rCHI (D-F) groups show increases in β-APP; n=3/group.

Figure 6: β-APP high power images in Sensorimotor Forelimb cortex (A-B) and corpus callosum (C). β-APP immunoreactivity is negligible in uninjured control cortex (A), while an accumulation of β-APP is shown in CHI cortex (B). β-APP was found to be perinuclear and along axons with occasional swollen axons with a beaded appearance (C).

Results and Conclusion

Periorbital and forepaw von Frey mechanical thresholds were reduced after CHI. Von Frey data is supported by increases in CGRP levels in the caudal medullary trigeminal nucleus compared to controls. Acute deficits in rotorod and Barnes maze were found after CHI. Increases in GFAP and β-APP were seen in CHI rats in the sensorimotor cortex near the impact site. In conclusion, CHI induces increases in nociceptive peptide release in the trigeminovascular system that is accompanied by cortical gliosis and diffuse axonal dysfunction. These histopathological changes occur in areas anatomically associated with the observed neurological and cognitive dysfunction after CHI.

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