Non-psychotropic cannabinoid based therapy modulates nociceptive signaling molecules, microglia, and pain behavior in a model of post-concussion headache

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Background & Objectives

Headache is a common symptom of post-concussion syndrome which may persist in a substantial portion of patients contributing to a poor quality of life and disability. There is a pressing need to develop novel treatments for post-traumatic headache as current treatments have a number of side effects, are contraindicated or lack efficacy. The Elliott laboratory first established models of post-traumatic headache demonstrating sensitization of trigeminal neurons in rodent models of post-traumatic headache using well-known nociceptive and behavioral markers in the pain and migraine fields1-3. Traumatic brain injury in mice increases expression of calcitonin gene related peptide (CGRP) and inducible nitric oxide synthase (iNOS) in the trigeminal pathway, changes that are accompanied by persistent headache behavior, trigeminal allodynia4,5. The endogenous cannabinoid (eCB) system is a potential therapeutic target for post-traumatic headache. In a series of studies, our laboratory showed CB2R-mediated anti-inflammatory actions in a model of TBI, whereby the reduction of INOS mRNA and protein and substance P immunoreactivity have implications for headache4,6. The cannabinoid receptor type-2 (CB2R) is an ideal analgesic target as it is devoid of psychoactive properties, shows anti-nociceptive actions upon stimulation, and regulates immune function. What is unclear is precisely how anti-nociceptive actions are elicited by the CB2R, and if CB2R stimulation will be effective at alleviating trigeminal hypersensitivity in model of post-traumatic concussion or closed head injury. The objective of this study was to determine the role of the CB2R in the trigeminal pain pathway in a model of post-concussion headache, while identifying mechanisms underlying trigeminal pain after mild TBI.

Methods

Model of Traumatic Brain Injury: Mild traumatic brain injury (TBI) was induced in Sprague Dawley rats utilizing a mild closed head injury. The objective of this study was to determine the role of the CB2R in the trigeminal pain pathway in a model of post-concussion headache, while identifying mechanisms underlying trigeminal pain after mild TBI.

Results

Figure 5: Inducible nitric oxide synthase (iNOS) immunoreactivity in the TNC. Inducible NOS immunoreactivity for incision control (A), single CHI (B), and repeated CHI (C). Noted pattern of NOS IR appears to be from trigeminal afferents and in the soma of second order TNC neurons. Scale bar = 100µm

Summary and Conclusions

- Repeated CHI increased GAFP in the serum and ipsilateral cortex indicating reactive gliosis. GAFP is currently one of the only utilized biomarkers for patients with concussion.
- Increased expression of GAFP and iNOS were observed within the trigeminal pathway in a graded manner respective to the number of injuries and concordant with previous findings in mild TBI.
- CHI altered the calcitonin receptor-like receptor, CRLR, immunoreactivity in the TNC in which a vascular and global response was noted.
- Treatment with JWH133 showed a significant decrease in trigeminal allostynia, similar to the NSAID, Ketorolac. Light testing showed changes in repeated CHI compared to controls that were not seen in single CHI.
- Repeated CHI injured rats showed increased capsacin-induced CGRP in TNC slices, while CHI did not result in a triggered CGRP increase over controls.
- A CB2R agonist, JWH133, blocked capsacin-induced increases in CGRP and PGE2 in TNC and cerebrum slices incubated separately. CHI injured rats showed increased capsacin-induced PGE2 in cerebrum, but not TNC slices, indicating potential for other pain mediators to be important in this pain region.
- CB2R plays a role in the trigeminal nociceptive pathway, although the mechanisms of analgesia will require more in depth investigation.

References:
1. Elliott et al., 2012. Headache, 52: 968-964

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