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Neuroinflammatory Modulation by Remote Ischemic Conditioning in Mild Traumatic Brain Injury

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Abstract: Traumatic Brain Injury (TBI) is associated with significant disability worldwide. Repetitive mild TBI (r-mTBI) drive neuroinflammation without effective treatments. This study tested Remote Ischemic Conditioning (RIC) in a mouse r-mTBI model. RIC significantly reduced microglial mean fluorescent intensity and density in the motor cortex, and significantly altered cytokines (IL-α, IL-2, IP-10, MIP-2). These findings, alongside the previously demonstrated improvements in motor outcomes, suggest RIC as a promising candidate for clinical translation in r-mTBI treatment.

Extended Abstract

Traumatic brain injury (TBI) is a leading cause of disability worldwide with significant health and socioeconomic consequences. Repetitive mild TBI (r-mTBI), commonly seen in contact sports and military settings, is increasingly recognized for its association with persistent neuroinflammation and progressive neurodegeneration. Despite growing awareness of its long-term consequences, there are currently no effective therapies targeting the underlying pathophysiology of r-mTBI. Remote Ischemic Conditioning (RIC), a non-invasive intervention involving brief, intermittent episodes of limb ischemia and reperfusion, has emerged as a promising strategy to mitigate neuroinflammation and preserve blood brain barrier integrity, both key contributors to r-mTBI pathology. While RIC has demonstrated neuroprotective effects in ischemic stroke, its therapeutic potential in r-mTBI remains unexplored.

This study aimed to investigate whether RIC can improve neuroinflammation in a pre-clinical model of r-mTBI. Thirty-two male C57BL/6 mice were randomly assigned to one of four experimental groups: no RIC/sham, RIC/sham, no RIC/r-mTBI, and RIC/r-mTBI. The RIC protocol consisted of four cycles of 5-minute bilateral hindlimb ischemia followed by 5-minute reperfusion, administered daily over 14 days. Beginning the day after the final RIC session, r-mTBI was induced using a lateral impact model, with one mTBI delivered daily for five consecutive days.

Neuroinflammatory outcomes were assessed using immunohistochemistry to quantify astrocytic and microglial markers in the motor cortex and hippocampus. Whole-brain homogenates were analyzed to profile cytokine and chemokine expression. Mice that received RIC exhibited a significant reduction in microglial mean fluorescence intensity and cellular density in the motor cortex compared to the no-RIC group, suggesting attenuated microglial activation. Additionally, cytokine and chemokine analyses revealed significant alterations in key inflammatory mediators, including IL-1α, IL-2, IP-10, and MIP-2, indicating that RIC modulates the neuroinflammatory profile following r-mTBI.

Overall, RIC demonstrated measurable, though modest, beneficial effects on neuroinflammation in this model of r-mTBI. When considered alongside our prior findings showing improved motor function in the r-mTBI group following RIC, these results further support its potential as a therapeutic strategy. Given its non-invasive nature, low cost, and greater feasibility, RIC represents a promising candidate for translation into clinical applications for r-mTBI. Future studies will focus on elucidating the molecular mechanisms underlying these effects using advanced approaches such as proteomics and transcriptomics, with the goal of optimizing and refining RIC as a targeted intervention for r-mTBI.

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