

Effect of Moderate Hyperthermia on Inflammation Following Experimental Traumatic Brain Injury in Mice

Lesley M Foley¹, Steven L Shein^{2,3}, Vincent A Vagni², T Kevin Hitchens^{1,4}, Chien Ho^{1,4}, and Patrick M Kochanek^{2,5}

¹Pittsburgh NMR Center for Biomedical Research, Carnegie Mellon University, Pittsburgh, Pennsylvania, United States, ²Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States, ³Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States, ⁴Department of Biological Sciences, Carnegie Mellon University, Pittsburgh, Pennsylvania, United States, ⁵Departments of Critical Care Medicine, Pediatrics and Anesthesiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States

INTRODUCTION

In the clinical setting, secondary insults such as hypotension, hypoxia, sepsis, to name a few, can determine the extent of neurological recovery after head injury. For patients with traumatic brain injury (TBI), pyrexia is a regular occurrence, and the commonly held assumption is that a mild to moderate rise in temperature is detrimental to outcome, even though there is a lack of robust clinical evidence to support this [1]. In animal studies, moderately raised temperature (39°C) after TBI was associated with a larger contusion volume, histological damage, increased axonal injury and increased mortality [2]. In this study we examined the inflammatory response in the brain, following TBI and moderate hyperthermia (39°C) by tracking macrophages/monocytes labeled *in situ* with micron-sized superparamagnetic iron oxide particles (MPIO).

MATERIALS AND METHODS

Male C57BL/6 mice were anesthetized with isoflurane in N₂O:O₂ (1:1), the mouse controlled cortical impact (CCI) model was used as previously described [3] with minor modifications [4], a vertically directed CCI was delivered at 6.0 m/sec with a depth of 1.2 mm. 24 H post CCI, mice were randomly divided into 2 groups; normothermic (37°C, n=3) and hyperthermic (39°C, n=4) and re-anesthetized for femoral arterial and venous catheter placement. Animals were placed in a stereotaxic holder and a temperature probe was inserted through a burr hole into the left frontal cortex. MPIO particles were infused iv at a dose of 4.5 mg/kg body weight. 30 min post MPIO infusion normothermia and hyperthermia was induced via a heating lamp and blanket and rigorously controlled for 2 H, after which there was a 30 min cool down period, where hyperthermic mice were allowed to cool naturally and then both groups maintained at 37°C. 7 days post CCI animals were euthanized, perfused and fixed with 4% paraformaldehyde.

Excised brains were imaged using an 11.7-Tesla, 89 mm bore Bruker AVANCE spectrometer, equipped with a Micro2.5 gradient insert. 3D images were acquired with the following parameters: TR = 500 ms, TE = 7 ms, FOV = 1 x 1 x 1.6 mm, 256 x 256 x 256 matrix. MPIO quantification was done with the post-processing method called Phase map cross-correlation Detection and Quantification (PDQ) [5]. Amira, version 4.1.1, was used to create 3D surface renderings.

RESULTS AND DISCUSSION

Mice that were exposed to 2 H of moderate hyperthermia had a more robust inflammatory response following TBI when compared with mice that were maintained at normothermic temperatures for the same time period (Figure 1). This increase was seen throughout the entire brain, not just in the contusion area or injured hemisphere (Figure 1A & 1B). After PDQ analysis, it was found that there were almost twice as many labeled cells in the hyperthermic mice which was significantly different from the normothermic animals (Figure 1C). This model also produces significantly decreased ipsilateral CA1 neuronal survival with exposure to hyperthermia between 24 H and 96 H (data not shown). These findings support previously published studies where mild to moderate elevations in temperature worsen outcomes in experimental models [2,6].

CONCLUSION

Moderate hyperthermia leads to a robust increase in inflammatory cells (mainly macrophages/monocytes) in the injured brain following head injury. Given the role of inflammation in mediating secondary damage after TBI, our data suggest a possible mechanism underlying the exacerbation of brain injury by hyperthermia.

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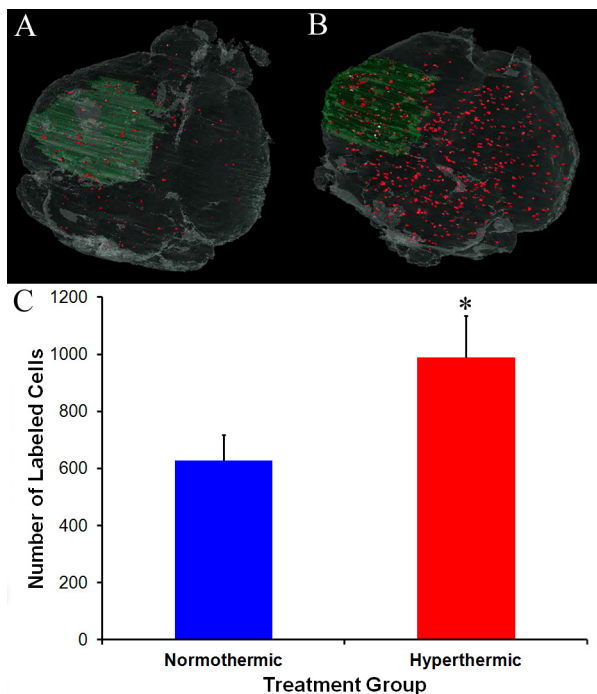


Figure 1. Representative 3D surface renderings of normothermic (A) and hyperthermic (B) mouse brains. White represents the brain volume, green the contusion area and red MPIO particles. (C) PDQ analysis of 3D data sets. *p<0.05 (t-test).

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