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Research Report

Suppressed cytokine expression immediatey following traumatic brain injury in neonatal rats indicates an expeditious endogenous anti-inflammatory response

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ABSTRACT

The timing of therapeutic intervention in traumatic brain injury (TBI) is critical. Although immediate cell death cascades have become established in adult TBI, the pathophysiology underlying neonatal TBI is poorly understood. The objective of the present study was to determine the role of cytokine regulation following TBI in neonatal rats. Seven-day-old Sprague-Dawley rats were subjected to TBI using the controlled cortical impact (CCI) injury model. Age-matched littermates that did not receive TBI served as the controls. Immediately following TBI, rats were euthanized, and the brains were divided into the ipsilateral and contralateral hemispheres then flash frozen. A BioRad 23-Plex panel was used to measure cytokine levels. Surprisingly, the data revealed that 18 of the 23 cytokines analyzed were significantly downregulated in the hemisphere contralateral to the TBI impacted hemisphere. IL-5, IL-6 and MIP-3a were significantly suppressed in both ipsilateral and contralateral hemispheres of neonatal TBI rats compared to the control rats. A parallel study processing the plasma of the same cohort of neonatal rats revealed no difference in the same cytokines analyzed in the brain tissue, suggesting highly localized cytokine suppression in the brain during early injury. In stark contrast to the reported early pro-inflammatory response exhibited in adult TBI, the present neonatal TBI study demonstrated a reversed cytokine profile of downregulation. These results suggest a

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robust, immediate anti-inflammatory response mounted by the contralateral hemisphere of the young brain.

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1. Introduction

A traumatic brain injury (TBI) can be defined as a force to the head or to the brain which disrupts proper neurological functions of the brain. Rapid brain acceleration-deceleration, as seen in shaken baby syndrome, can cause diffuse damage or focal damage at the point of impact (coup) and at the opposite pole (countercoup). In addition, traumatic axonal injury (TAI) is present in which axons and blood vessels are sheared, causing contusions, subdural or epidural hematomas, and intracerebral or subarachnoid hemorrhages (Altimier, 2008; Case, 2007).

TBI contributes to a substantial number of deaths and cases of permanent disability annually. To date, numerous studies have detailed both the effects and potential treatments of adult TBI. Many pharmacological and rehabilitative therapies have been tested in adult models (Chung et al., 2013; Wheaton et al., 2011). However, research focusing on neonatal TBI is sparse despite the large young patient population prone to TBI. Indeed, very young children (age 0–4 years) and the elderly (over 65 years) are more likely to sustain a TBI (Andelic et al., 2008; Faul et al., 2010; Levchakov et al., 2006). Falls and drops are the leading cause of TBI-linked death in young children (Karasu et al., 2009). They account for 64% of TBI-related emergency department visits and 42% of hospitalizations. Motor vehicle accidents account for 40% of all TBI-related deaths in young children (Faul et al., 2010), and shaken baby syndrome accounts for a significant portion of TBI in young children as well, especially those under 6 months (Barr et al., 2006; Paiva et al., 2011). Moreover, very few studies detail evidence-based therapy for children who suffered TBI in infancy (Ashton, 2010). Traditional views maintain that the plasticity from young brains enable younger TBI victims to experience a greater recovery. Contrary to these beliefs, more recent research suggests that very early TBI can have a significant negative impact on brain development (Anderson et al., 2005, 2009; Crowe et al., 2012; Maxwell, 2012); however, studies are not conclusive as to exact cell death mechanisms closely associated with neurodevelopmental impairments (Anderson et al., 2005, 2009).

In experimental adult rodent TBI, the brain attempts to repair itself via endogenous repair mechanisms including cell proliferation shortly after TBI (Kaneko et al., 2013; Sun et al., 2009). However, these mechanisms cannot sufficiently remedy secondary cell death and severe inflammatory response (Kaneko et al., 2013; Woodcock and Morganti-Kossmann, 2013). In chronic studies, research indicates neuroinflammation, which can be observed up to 17 years post TBI in humans (Giunta et al., 2012), as a major secondary cell death pathway culminating in neuron loss, impeded cell proliferation and an upregulation of activated microglia cells. All these neuroinflammatory responses can interfere with endogenous repair mechanisms (Acosta et al., 2013; Woodcock and Morganti-Kossmann, 2013). In fact, waves of cytokines and chemokines mediate this inflammatory response throughout the brain (Das et al., 2012; Giunta et al., 2012; Hernandez-Ontiveros et al., 2013; Waters et al., 2013) and facilitate the activation and recruitment of immune cells to the injury (Das et al., 2012; Woodcock and Morganti-Kossmann, 2013). Whether such neuroinflammation accompanies neonatal TBI and the cell death cascades associated with this inflammation remains a needed field of research examination. Investigation of these neuroinflammatory mechanisms will lead to both a greater understanding of the pathology of TBI and insights in potential therapy to arrest the disease evolution (Rovegno et al., 2012).

2. Results

Twenty-three different cytokines were analyzed in this study: IL-1a, IL-b, IL-2, IL-4, IL-6, IL-10, GM-CSF, INF-g, TNF-a, EPO, G-CSF, IL-5, GRO/KC, IL-7, IL-12p70, IL-13, IL-17A, IL-18, M-CSF, MIP-1a, MIP-3A, RANTES and VEGF. Analysis of cytokine levels in the harvested brains exposed sizable downregulation of 18 out of the 23 cytokines in the contralateral hemisphere of TBI inflicted rats relative to the controls. These cytokines included IL-5, IL-6 and MIP-3a which were downregulated in both hemispheres (Fig. 1).

IL-10, IL-18 and IL-17A were significantly downregulated in both the contralateral and ipsilateral hemispheres of the TBI inflicted brains compared to the right hemisphere of the control brains and significantly downregluated in the left hemisphere compared to the left hemisphere of the controls (Fig. 2). IL-1a, IL-4, IL-B, EPO and IL-12p70 levels decreased in the ipsilateral hemisphere of the brain following TBI compared to right hemisphere of the control brains (Fig. 3). IL-2 was significantly downregulated in the ipsilateral hemisphere of the brain with TBI compared to the control brains (Fig. 4). GM-CSF and G-CSF were both significantly decreased throughout the TBI inflicted brains compared to the right hemisphere of the control brains (Fig. 5).

The five remaining cytokines did not signficantly differ between the TBI and control rats. These results indicate an overwhelming downregulation of the entire range of cytokines analyzed. Of note, plasma of the same cohort of neonatal rats revealed no significant change in the cytokine levels analyzed in the brain tissue.

3. Discussion

A significant downregulation of 18 out of the 23 cytokines analyzed was observed in the contralateral hemisphere of the brain following TBI in neonatal rats ($n=10$ per treatment

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