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TAURINE IMPROVES FUNCTIONAL AND HISTOLOGICAL OUTCOMES AND REDUCES INFLAMMATION IN TRAUMATIC BRAIN INJURY

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Abstract—We investigated the effect of taurine on inflammatory cytokine expression, on astrocyte activity and cerebral edema and functional outcomes, following traumatic brain injury (TBI) in rats. 72 rats were randomly divided into sham, TBI and Taurine groups. Rats subjected to moderate lateral fluid percussion injury were injected intravenously with taurine (200 mg/kg) or saline immediately after injury or daily for 7 days. Functional outcome was evaluated using Modified Neurological Severity Score (mNSS). Glial fibrillary acidic protein (GFAP) of the brain was measured using immunofluorescence. Concentration of 23 cytokines and chemokines in the injured cortex at 1 and 7 days after TBI was assessed by Luminex xMAP technology. The results showed that taurine significantly improved functional recovery except 1 day, reduced accumulation of GFAP and water content in the penumbral region at 7 days after TBI. Compared with the TBI group, taurine significantly suppressed growth-related oncogene (GRO/KC) and interleukin (IL)-1β levels while elevating the levels of regulated on activation, normal T cell expressed and secreted (RANTES) at 1 day. And taurine markedly decreased the level of 17 cytokine: eotaxin, Granulocyte colony-stimulating factor (G-CSF), Granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma (IFN-γ), IL-1α, IL-1β, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-13, IL-17, leptin, monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF), and only increased the level of MIP-1α in a week. The results suggest that taurine effectively mitigates the severity of brain damage in TBI by attenuating the increase of astrocyte activity and edema as well as pro-inflammatory cytokines.

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Key words: taurine, traumatic brain injury, cytokine, inflammation, Luminex.

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability. It is associated with a complex sequence of inflammatory responses characterized by glial activation, neutrophil and macrophage recruitment, upregulation of adhesion molecules, and secretion of cytokines (Werner and Engelhard, 2007; Lotocki et al., 2009). Brain injury shows the pathophysiology of inflammation including diffuse brain edema and neurological functional deficits. In addition, TBI elicits reactive astrogliosis reflecting the degree of brain injury (Laird et al., 2008).

Clinical and experimental TBI is associated with altered systemic and brain levels of cytokines including interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor-alpha (TNF-α) (Morganti-Kossman et al., 1997; Maier et al., 2001; Ziebell and Morganti-Kossmann, 2010). Recently, a novel Luminex assay was used to detect 23 cytokines in the cerebral cortex of rats at 3 h and 24 h following a moderate fluid percussion injury (mFPI). The results indicated mFPI significantly elevated levels of IL-1α, IL-6, growth-related oncogene (GRO/KC, systemic name: CXCL1); Macrophage inflammatory protein-1α (MIP-1α), and TNF-α in the cortex, but decreased levels of IL-4, IL-12, IL-13, IL-17 and IL-18 (Redell et al., 2013). Luminex is currently the most widely used multiplex biomarker analysis technology with distinct advantages of higher throughput, and smaller sample volume. It consumes less time and is associated with lower cost compared with enzyme-linked immunosorbent assay (ELISA). This method enables a more complete assessment of the cytokine cascade that occurs following TBI. It has also been used for the detection of cytokines in the cerebrospinal fluid (CSF) and serum of patients after TBI (Buttram et al., 2007; Hergenroeder et al., 2010).

Taurine (Tau), 2-aminoethane sulfonic acid, acts as an osmoregulator (Schaffer et al., 2000), neuromodulator, calcium regulator (El Idrissi, 2008), antioxidant (Messina and Dawson, 2000), and provides neuroprotection against excitotoxic cell death (Huxtable, 1989). It has been associated with potent anti-

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Abbreviations: BCA, bicinchoninic acid; CBF, cerebral blood flow; CHI, close head injury; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; G-CSF, Granulocyte colony-stimulating factor; GFAP, glial fibrillary acidic protein; GRO/KC, growth-related oncogene; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IFN-γ, Interferon-gamma; IL, Interleukin; IP-10, γ-Interferon Inducible Protein 10; mFPI, moderate fluid percussion injury; MCP-1, monocyte chemotactic protein-1; MIP-1α, Macrophage inflammatory protein-1α; mNSS, Modified Neurological Severity Score; PBS, phosphate-buffered solution; RANTES, regulated on activation, normal T cell expressed and secreted; SCI, spinal cord injury; Tau, taurine; Tau-CL, taurine chloramine; TBI, traumatic brain injury; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

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inflammatory effects in a variety of models of systemic inflammation, including the spinal cord injury (SCI) (Nakajima et al., 2010), ischemic stroke (Sun et al., 2012), hepatic ischemia reperfusion (Zhang et al., 2010), and lung injury (Abdih et al., 2000). Specifically, taurine has been shown to diminish the production of cytokines, such as IL-1β, IL-6 and TNF-α in SCI and risk of ischemic stroke (Nakajima et al., 2010; Sun et al., 2012). Therefore, we hypothesized that taurine may attenuate TBI-induced inflammatory response.

Our aim was to investigate the interaction of taurine with the cascade of inflammation in a rat model of TBI using Luminex technology. We also examined the impact of taurine in cerebral edema, astrocyte activity and neurological function after TBI.

EXPERIMENTAL PROCEDURES

Animals

Adult male Sprague–Dawley rats, weighing between 260 and 300 g and obtained from the Experimental Animal Laboratories of the Academy of Military Medical Sciences (Beijing, China) were used for all experiments. Animal care was in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (Institute for Laboratory Animal Research, the National Academy of Sciences, Washington, DC, USA). Rats were housed under standard conditions of temperature (23 ± 2 °C) and light (12-h light/dark cycle), and were provided with food and water *ad libitum* during the experiment.

Experimental groups

In this study, 72 rats were randomized into three groups (n = 24 in each group): (1) sham group: rats were subjected to identical surgical procedures except for brain injury, and administered saline only; (2) TBI group: rats were subjected to FPI and received saline only; and (3) Tau group: TBI rats were administered taurine (200 mg/kg/day, Sigma, St. Louis, MO, USA) by tail intravenous injection, once daily for either 1 or 7 days after TBI. The three groups were then divided into two subgroups (n = 12 for each time-point in each group) at 1 and 7 days post-injury, respectively. All rats were sacrificed 1 and 7 days after TBI for further analysis. The number of animals used in each group was present in Tables 1 and 2.

Table 1. The number of animals used in each group 1 day after TBI

Experimental measures	Sham group	TBI group	Tau group
Water content	7	8	7
Immunofluorescence	3	3	3
Cytokine	9	8	7

Table 2. The number of animals used in each group 7 days after TBI

Experimental measures	Sham group	TBI group	Tau group
mNSS	12	9	12
Water content	8	6	9
Immunofluorescence	3	3	3
Cytokine	8	6	9

FPI model

TBI model was modified from previous study (Kelley et al., 2006). Rats were intraperitoneally anesthetized with 10% chloral hydrate (10 μl/100 g), and then immobilized in a stereotaxic frame. After exposing the skull, a 5.0-mm craniotomy was performed over the left parietal bone, 4.5 mm posterior from bregma and 2.5 mm lateral to the sagittal suture, ensuring the integrity of the dura. A female Luer-Lock fitting was then cemented to the skull with cranioplastic cement. The rats were connected to the fluid percussion device (University of Virginia, USA) via the Leur–Lock fitting, and an overpressure of 1.8 atm was delivered causing a moderate brain injury. Body temperature was monitored by a rectal probe, maintaining at 37 ± 1 °C with a heating pad during the experiment. After surgery, the skin was closed with staples and rats were allowed to recover from anesthesia.

Neurological function evaluation

The Modified Neurological Severity Score (mNSS), previously described by Chen et al., was used to evaluate post-injury functional impairment (Chen et al., 2001). As a composite of the motor, sensory and reflex tests, the mNSS was graded on a scale of 0–18 (normal score 0; maximal deficit score 18). The higher the score, the worse was the sensorimotor function. These tests were performed by two observers blinded to the experiment on all rats before injury, and at days 1, 3, 5 and 7 after TBI.

Evaluation of cerebral edema

Fresh brains from the three groups were removed at 1 or 7 days post-injury. A 30-mg section of penumbral region from each extracted brain was obtained for the

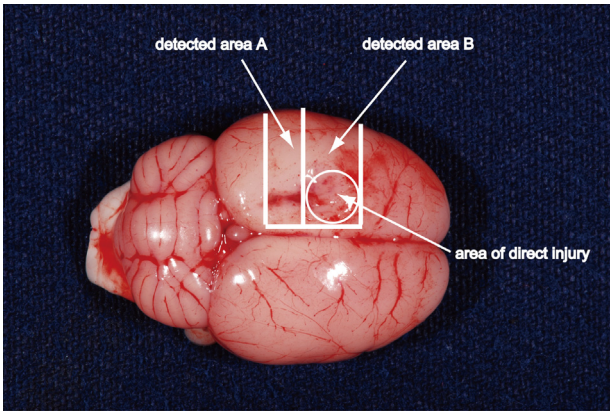

Fig. 1. Schematic representation of the area of direct injury induced by FPI. Detected areas A and B were obtained for the evaluation of brain water content and cytokine concentrations, respectively.

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