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Research Report

Hydrogen-rich water attenuates brain damage and inflammation after traumatic brain injury in rats

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ABSTRACT

Inflammation and oxidative stress are the two major causes of apoptosis after traumatic brain injury (TBI). Most previous studies of the neuroprotective effects of hydrogen-rich water on TBI primarily focused on antioxidant effects. The present study investigated whether hydrogen-rich water (HRW) could attenuate brain damage and inflammation after traumatic brain injury in rats. A TBI model was induced using a controlled cortical impact injury. HRW or distilled water was injected intraperitoneally daily following surgery. We measured survival rate, brain edema, blood–brain barrier (BBB) breakdown and neurological dysfunction in all animals. Changes in inflammatory cytokines, inflammatory cells and Cho/Cr metabolites in brain tissues were also detected. Our results demonstrated that TBI-challenged rats exhibited significant brain injuries that were characterized by decreased survival rate and increased BBB permeability, brain edema, and neurological dysfunction, while HRW treatment ameliorated the consequences of TBI. HRW treatment also decreased the levels of pro-inflammatory cytokines (TNF-α, IL-1β and HMGB1), inflammatory cell number (Iba1) and inflammatory metabolites (Cho) and increased the levels of an anti-inflammatory cytokine (IL-10) in the brain tissues of TBI-challenged rats. In conclusion, HRW could exert a neuroprotective effect against TBI and attenuate inflammation, which suggests HRW as an effective therapeutic strategy for TBI patients.

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1. Introduction

Traumatic brain injury (TBI), a major cause of death and disability worldwide, is a serious public health problem that accounts for 1.7 million people annually and contributes to 30% of all injury-related deaths in the United States (Lozano et al., 2015). Notably, TBI may result in permanent neurological dysfunction because of primary and secondary damage, which creates a heavy burden for family and society (Davis, 2000). However, no effective treatment for TBI exists, and TBI patients consequently suffer a poor prognosis (Shimoda et al., 2014).

Previous research demonstrated that pro-inflammatory cytokine levels, such as TNF-α, IL-1β and IL-6, increased significantly in the peripheral blood, cerebrospinal fluid and brain tissue after TBI, which had closely correlation with the severity and bad outcome of TBI patients, and the treatment for neuroinflammation after TBI is one opportunity for a therapeutic intervention strategy (Frugier et al., 2010; Kumar and Loane, 2012). Hydrogen-rich water (HRW) provides neuroprotective effects in many diseases, including ischemia-reperfusion injury, stroke, carbon monoxide toxicity, transient ischemia, neonatal hypoxia-ischemia, sepsis, traumatic brain injury, Alzheimer's disease and Parkinson's disease via antioxidant, anti-inflammatory and anti-apoptotic effects (Fu et al., 2009; Fukuda et al., 2007; George and Agarwal, 2010; Hayashida et al., 2014; Sun et al., 2011). Most previous studies on the neuroprotective effects of HRW in TBI primarily focused on the antioxidant effect (Hou et al., 2012; Ji et al., 2012). However, to the best of our knowledge, no study investigated the potential anti-inflammatory neuroprotective effects of HRW on TBI. We hypothesized that HRW treatment would also attenuate brain damage and inflammation in injured brains after TBI in rats. This study investigated the effectiveness of HRW therapy on survival rate, brain edema, blood–brain barrier (BBB) breakdown and neurological dysfunction of TBI induced by a controlled cortical impact (CCI) in rats, which is a well-characterized animal model of focal TBI that resembles many aspects of TBI in patients (Hall et al., 2008). We investigated the effects of HRW treatment on changes in inflammatory cytokines (TNF-α, IL-1β, IL-10 and HMGB1), as well as the novel biochemical marker for detecting the numbers of microglia (Iba1 stained) in the injured brain tissues of TBI animals. In addition, because the proton magnetic resonance spectroscopy (^{1}H-MRS) had recently emerged as a powerful approach for characterizing the microstructural and metabolic responses after TBI (Wei et al., 2012), and the metabolic change of Cho/Cr detected by ^{1}H-MRS was highly sensitive to the pathology of inflammation that contributes to TBI (Brooks et al., 2001; Harris et al., 2012), we also investigated the effects of HRW treatment on Cho/Cr metabolites of injured brain tissues by proton magnetic resonance spectroscopy (^{1}H-MRS) in our study.

2. Results

2.1. HRW treatment meliorated the 14-day survival rate in CCI-induced TBI rats

The 14-day survival rates in the Sham and Sham+HRW groups were nearly 100% (Fig. 1). However, the 14-day survival rates in the CCI+H_2O and CCI+HRW groups were markedly decreased (60% vs. Sham, 80% vs. Sham, respectively, $p<0.05$). HRW treatment markedly ameliorated the 14-day survival rate of TBI rats (60% vs. 80%: $p<0.05$). These data demonstrated that the HRW treatment markedly provided protective effects to rats with CCI (Fig. 1).

2.2. HRW treatment attenuated blood–brain barrier disruption and reduced brain water content in CCI-induced TBI rats

Evans blue (EB) is a non-toxic dye that binds to serum albumin, and this complex seldom passes the BBB. Albumin bound to EB enters the brain tissue when the BBB was disrupted. Thus, the extravasation of EB is an indicator of BBB disruption. Brain water content also reflects the severity of BBB disruption. An obvious increase in EB was observed in the CCI+H_2O and CCI+HRW groups 24 h after surgery compared to the Sham+H_2O and Sham+HRW groups, respectively ($p<0.001$) (Fig. 2A, B). Brain water content also increased in the CCI+H_2O and CCI+HRW groups compared to the Sham+H_2O and Sham+HRW groups, respectively ($p<0.05$) (Fig. 2C). Compared to the CCI+H_2O group, HRW treatment significantly decreased EB extravasation in the CCI+HRW group ($p<0.01$), and brain water content was also dramatically decreased in the CCI+HRW group ($p<0.05$). EB extravasation and brain water content were not statistically different between the Sham+H_2O and Sham+HRW groups ($p>0.05$). These results demonstrated that TBI damaged BBB integrity and produced brain edema, and HRW significantly attenuated these injuries.

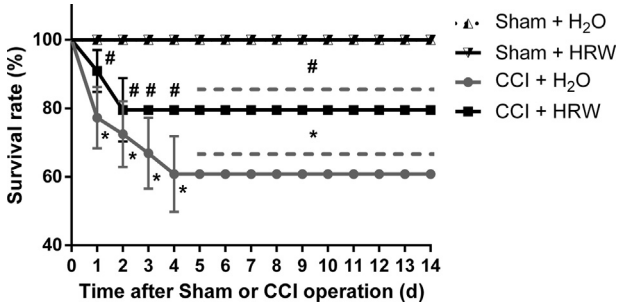

Fig. 1 – HRW treatment improved the 14-day survival rate in TBI rats. Rats were treated with distilled water or HRW 5 min after TBI and once daily (usually 10 AM every day) following surgery in the Sham or CCI group. Values are expressed as survival percentages ($n=10$). *$p<0.05$ vs. Sham group; #$p<0.05$ vs. CCI+H_2O group.

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