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Research Report

The effects of hyperbaric oxygen on macrophage polarization after rat spinal cord injury

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ABSTRACT

The immunoreactive responses are a two-edged sword after spinal cord injury (SCI). Macrophages are the predominant inflammatory cells responsible for this response. However, the mechanism underlying the effects of HBOT on the immunomodulation following SCI is unclear now. The present study was performed to examine the effects of hyperbaric oxygen therapy (HBOT) on macrophage polarization after the rat compressive injury of the spinal cord. HBOT was associated with significant increases in IL-4 and IL-13 levels, and reductions in TNF-α and IFN-ɣ levels. This was associated simultaneously with the levels of alternatively activated macrophages (M2 phenotype: arginase-1- or CD206-positive), and decreased levels of classically activated macrophages (M1 phenotype: iNOS- or CD16/32-positive). These changes were associated with functional recovery in the HBOT-transplanted group, which correlated with preserved axons and increased myelin sparing. Our results suggested that HBOT after SCI modified the inflammatory environment by shifting the macrophage phenotype from M1 to M2, which may further promote the axonal extension and functional recovery.

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1. Introduction

Spinal cord injury (SCI) results in severe neurological damage and requires extremely expensive, long-term care. It is estimated that 40 new cases of SCI per million people occur every year worldwide (Ackery et al., 2004; van den Berg et al., 2010). The annual incidence in Beijing, China was 60.6/10 million in 2002, nearly 10 times the incidence 10 years earlier (Li et al., 2011). Experimental studies and clinical observations have revealed that SCIs are greatly enlarged more often by secondary injury than by the primary insult (Rawe et al., 1981; Wrathall et al., 1996). Secondary injury caused by damage to the neuronal cell membranes and alterations in both spinal cord blood flow (Young and Flamm, 1982) and metabolism (Demediuk et al., 1985) exacerbate the effects of the initial mechanical trauma.

The inflammatory responses play an important role in the secondary damage after SCI (Trivedi et al., 2006). Macrophages/microglia are the predominant inflammatory cells responsible for this response, and can be polarized into the"classically activated" M1 phenotype or the"alternatively activated"M2 phenotype depending on the signals within the lesion microenvironment (Kigerl et al., 2009). This divergence is referred to as macrophage polarization. Classically activated macrophages are the product of exposure to T helper (Th)1 cytokines, such as interferon (IFN)-ɣ and tumor necrosis factor (TNF)-α, alternatively activated macrophages are activated via Th2 cytokines, such as interleukin (IL)-4, IL-10, and IL-13. M1 phenotype produce high levels of oxidative metabolites (e.g., nitric oxide and superoxide) and proinflammatory cytokines that are essential for host defense and tumor cell killing but that also cause collateral damage to healthy cells/tissue (Gordon, 2003; Kigerl et al., 2009). Conversely, M2 macrophages promote angiogenesis and matrix remodeling while suppressing destructive immunity (Zhang et al., 2013). After spinal cord injury (SCI), CNS macrophages promote secondary injury and repair. The divergent effects might be attributed to distinct macrophage subsets and the activation of specific intracellular signaling cascades. In general, M1 macrophages are detrimental, whereas M2 macrophages are protective (David and Kroner, 2011; Kigerl et al., 2009; Loane and Byrnes, 2010). Thus, to increase the number of these alternatively activated macrophages (M2 phemotype) may promote functional recovery after SCI.

Hyperbaric oxygen therapy (HBOT) is a treatment by which 100% oxygen is administered to a patient at a pressure greater than atmospheric pressure at sea level (i.e. one atmosphere absolute, ATA; Gill and Bell, 2004). HBOT promotes healing of damaged tissue, decreases inflammatory response and promotes capillary angiogenesis by increasing tissue oxygen levels by 10–15-fold (Gill and Bell, 2004; Knighton et al., 1981; Tompach et al., 1997). The previous report showed that acute HBOT enhanced cerebral IL-10 protein levels after traumatic brain injury (TBI; Tai et al., 2010). Lim et al. (2013) found that treatment of TBI with HBOT during the acute phase of injury can attenuate microgliosis and expression of the proinflammatory cytokine TNF-α, resulting in a neuroprotective effect. Thus, it can be speculated that the effect of HBOT during the acute phase may be correlated with immunomodulatory effects(Chen et al., 2014). However, there are no reports to define the role of HBOT in the inflammatory responses, especially of the macrophage polarization after rat SCI.

The present study was thus designed to investigate the effects of HBOT on the macrophage activation after the rat compressive injury of the spinal cord.

2. Results

2.1. Functional analysis

All animals had normal motor function before SCI (BBB=21±0). In the sham group, all animals recovered to a score of 21 at 1 days post-injury. From day 7 after SCI, locomotor performance improved gradually in the two experimental groups. In comparison, rats in the HBOT group showed higher scores at days 14 ($P<0.01$), 21 ($P<0.01$) and 28 ($P<0.01$) compared with those in the NBA group. Four weeks after injury, the final BBB scores in the NBA ($n=6$) and HBOT ($n=6$) groups were 9±0.07 and 11.87±0.08, respectively ($P<0.01$, Fig. 1).

2.2. Macrophage polarization

To determine whether HBOT affects macrophage polarization, we quantified the populations of M1 and M2 phenotypes. iNOS and CD16/32 (M1 phenotype) immunostaining in mid-sagittal sections at 3 days post-injury identified relatively high numbers of positive cells gathered around the injury epicenter, and extending proximally and distally from the injury epicenter in the rat NBA group (Fig. 2Aa and Ca). Both the robust iNOS- and CD16/32-immunopositive products were located mainly in the membrane of the stained cells. The numbers of iNOS- or CD16/32 positive cells were relatively small in the HBOT group (Fig. 2Ab and Cb). Quantification analysis showed that the HBOT group showed decreased numbers of iNOS and CD16/32-expressing macrophages when

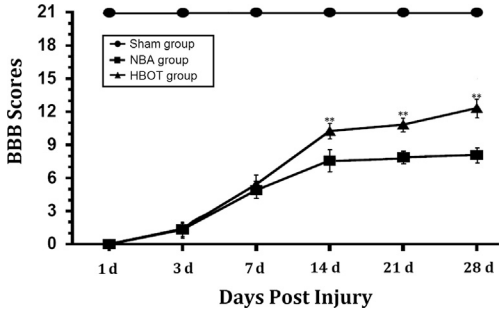

Fig. 1 – The open-field locomotion of rats in different treatment groups was analyzed by the Basso–Beattie–Bresnahan (BBB) locomotor rating scale. The animals in the sham group recovered to normal locomotor activity, scored as 21, following short paralysis immediately after injury. $n=6$ for each group. In comparison, rats in the HBOT group showed higher score at days 14 ($P<0.01$), 21 ($P<0.05$) and 28 ($P<0.01$) than those in the NBA group. By the end of 4 weeks after injury, the final BBB scores in the NBA, and HBOT groups were 9±0.07 and 11.87±0.08, respectively ($P<0.01$, Fig. 1). Data are presented as the mean±SEM, $^{*}P<0.05$, $^{**}P<0.01$.

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