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Resolvins AT-D1 and E1 differentially impact functional outcome, post-traumatic sleep, and microglial activation following diffuse brain injury in the mouse

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Highlights

- Diffuse TBI resulted in motor and cognitive impairments in the mouse.
- AT-RvD1, but not RvE1, facilitated functional recovery.
- RvE1-treated brain-injured mice slept significantly more immediately after TBI.
- RvE1, but not AT-RvD1, decreased the injury-induced activation of microglia to TBI.
- AT-RvD1 & RvE1 independently altered sleep, inflammation, and outcome after TBI.

Abstract

Traumatic brain injury (TBI) is induced by mechanical forces which initiate a cascade of secondary injury processes, including inflammation. Therapies which resolve the inflammatory response may promote neural repair without exacerbating the primary injury. Specific derivatives of omega-3 fatty acids loosely grouped as specialized pro-resolving lipid mediators (SPMs) and termed resolvins promote the active resolution of inflammation. In the current study, we investigate the effect of two resolvin molecules, RvE1 and AT-RvD1, on post-traumatic sleep and functional outcome following diffuse TBI through modulation of the inflammatory response.

Adult, male C57BL/6 mice were injured using a midline fluid percussion injury (mFPI) model (6–10 min righting reflex time for brain-injured mice). Experimental groups included mFPI administered RvE1 (100 ng daily), AT-RvD1 (100 ng daily), or vehicle (sterile saline) and counterbalanced with uninjured sham mice. Resolvins or saline were administered daily for seven consecutive days beginning 3 days prior to TBI to evaluate proof-of-principle to improve outcome. Immediately following diffuse TBI, post-traumatic sleep was recorded for 24 h post-injury. For days 1–7 post-injury, motor outcome was assessed by rotarod. Cognitive function was measured at 6 days post-injury using novel object recognition (NOR). At 7 days post-injury, microglial activation was quantified using immunohistochemistry for Iba-1.

In the diffuse brain-injured mouse, AT-RvD1 treatment, but not RvE1, mitigated motor and cognitive deficits. RvE1 treatment significantly increased post-traumatic sleep in brain-injured mice compared to all other groups. RvE1 treated mice displayed a higher proportion

of ramified microglia and lower proportion of activated rod microglia in the cortex compared to saline or AT-RvD1 treated brain-injured mice. Thus, RvE1 treatment modulated post-traumatic sleep and the inflammatory response to TBI, albeit independently of improvement in motor and cognitive outcome as seen in AT-RvD1-treated mice. This suggests AT-RvD1 may impart functional benefit through mechanisms other than resolution of inflammation alone.

Introduction

Each year over 1.7 million people sustain traumatic brain injuries (TBI) in the United States alone (Faul et al., 2002). The consequences of TBI for the individual can include diminished quality of life manifested through a range of symptoms including acute and chronic pain (Tham et al., 2013), loss of neurological function (Arciniegas et al., 2000), and impaired cognitive or emotional ability (Arciniegas et al., 2000, Albensi and Janigro, 2003, Masel and DeWitt, 2010). Few therapies are available to treat these debilitating morbidities and many promising therapeutic agents have failed to achieve efficacy in clinical trials (Margulies and Hicks, 2009). Animal models have been established to reproduce the complex pathophysiology of TBI and offer valuable means through which therapies can be tested on the resulting physiological, sensorimotor, and cognitive deficits. Pharmacological attempts to lessen the burden of TBI include a wide swath of treatment approaches, routinely using experimental compounds largely designed to target the cellular and molecular cascades which contribute to secondary injury in the hours to days following TBI (Margulies and Hicks, 2009, McIntosh et al., 1998).

TBI is induced by mechanical forces which initiate a cascade of secondary injury processes, including inflammation (Werner and Engelhard, 2007). To complicate our understanding of underlying processes, cerebral inflammation has been shown to contribute to both beneficial and detrimental effects on outcome (for review, see (Morganti-Kossmann et al., 2002). Following TBI, the brain is inundated with inflammation-mediating cytokines (Morganti-Kossmann et al., 2001, Frugier et al., 2010, Semple et al., 2010) which prompt a spectrum of responses including cell differentiation, immune activation, and cell death (Allan and Rothwell, 2001). While the role of early-onset inflammation in the pathophysiology of TBI is debatable, clinical and experimental data suggest that chronic over-production of inflammatory cytokines aggravate the primary injury (Schmidt et al., 2005, Lloyd et al., 2008, Cao et al., 2012), and thereby impact outcome. Our lab has previously reported that the cortical primary somatosensory barrel fields (S1BF) are a primary site of neuropathology following experimental diffuse traumatic brain injury (Lifshitz and Lisembee, 2012, Hall and Lifshitz, 2010), with pronounced microglial activation

and the induction of a previously understudied rod morphology of activated microglia (Cao et al., 2012, Ziebell et al., 2012, Taylor et al., 2014). Rod microglia appear to constitute a phenotypically distinct class of activated microglia which present following acute neurological injury including diffuse TBI, infection and seizure (Ziebell et al., 2012, Wirenfeldt et al., 2009, Mukherjee et al., 2013). The relative distribution of microglial morphologies can thereby serve as an indicator neuroinflammation and underlying pathological and reparative processes. The current study further assesses neuroinflammation after diffuse TBI using a semi-quantification method of microglial activation to determine proportions of ramified (unactivated) microglia in relation to morphological phenotypes activated in response to injury—activated and rod microglia.

Cytokines are elevated and regulate inflammation following TBI (Semple et al., 2010, Ziebell and Morganti-Kossmann, 2010). These cytokines, including pro-inflammatory interleukin-1 beta (IL-1β), can also serve dual roles as sleep regulatory substances (SRSs) which influence sleep–wake behavior through action on the sleep circuits within the brain (Krueger et al., 1995, Krueger et al., 2007, Krueger et al., 2001). The elevation of IL-1β following midline fluid percussion brain injury in the mouse has previously been documented to correspond temporally with an acute increase in post-traumatic sleep during the first six hours post-injury (Rowe et al., 2014). These data suggest a relationship between inflammation and SRSs such that post-traumatic sleep may serve as an indicator of SRS action.

While inflammation is an essential component of the repair process, excessive or prolonged inflammation can aggravate injury-related damage (Bachstetter et al., 2013). Therapies which resolve the inflammatory response may promote neural recovery without exacerbating the primary injury. Certain derivatives of omega-3 fatty acids loosely grouped as specialized pro-resolving lipid mediators (SPMs) have been shown to promote the resolution of inflammation resulting from multiple induction pathways (for review, see (Recchiuti and Serhan, 2012). These lipid mediators of inflammation are described as eicosanoids or docsanoids depending on their derivation from either eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) respectively Serhan et al., 2002 and encompass subclasses including resolvins, protectins, lipoxins, and maresins (Recchiuti and Serhan, 2012). Dietary supplementation with precursors of SPMs, particularly DHA, has shown therapeutic potential by reducing lesion size and improving neurological function following a model of ischemic stroke (Belayev et al., 2009) and TBI (Rowe et al., 2014, Bachstetter et al., 2013) in rats by decreasing axonal injury and preserving cognitive function. Further, DHA supplementation after experimental stroke led to increased brain levels of another docosanoid, neuroprotectin D1 (NPD1) Belayev et al., 2011, a lipid mediator of inflammation which was then shown to ameliorate the functional and histological consequences of

experimental stroke on its own (Bazan et al., 2012). Therefore, pharmacotherapy targeting SPMs provides a pleiotropic approach to regulating inflammation resulting from TBI, rather than genetically or chemically targeting a single signaling pathway.

Considering the similar inflammatory pathophysiologies of stroke and TBI, these data suggest that SPMs may regulate inflammation resulting from TBI. In the current study, two lipid mediators of inflammation, resolvin E1 (RvE1) and aspirin-triggered resolvin D1 (AT-RvD1), are tested for their impact upon post-traumatic sleep, sensorimotor and cognitive outcome, and microglial activation after diffuse experimental brain injury in the mouse. These endogenous SPMs are proposed to bring the injury-induced inflammatory response to conclusion as evidenced by a reduction in post-traumatic sleep, shift in the microglial morphology profile, and thereby improvement in functional outcome. We hypothesize that RvE1 and AT-RvD1 will improve functional outcome from diffuse TBI through modulation of the inflammatory response.

Section snippets

Animals

Male C57BL/6 mice (Harlan Laboratories, Inc., Indianapolis, IN) were used for all experiments (n=73). Mice were housed in a 12 h light/12 h dark cycle at a constant temperature (23±2 °C) with food and water available *ad libitum* according to the Association for Assessment and Accreditation of Laboratory Animal Care International. All mice used in this study were singly housed. Mice were acclimated to their environment following shipment for at least 3 days prior to any experiments. After surgery, …

Resolvin treatment did not influence the initial induction of diffuse TBI

We have previously reported suppression of the righting reflex response in mice following mFPI (Rowe et al., 2014a) as an injury-induced deficit and indicator of injury severity. Diffuse brain injury resulted in a significant suppression of the righting reflex in brain-injured mice, compared to anesthetized, uninjured shams, regardless of drug treatment (Fig.

2). A one-way ANOVA comparing only brain-injured treatment groups showed no significant difference of righting reflex times, indicating …

Discussion

The current study was designed with the proof-of-principle goals to: (1) test the administration of SPMs AT-RvD1 and RvE1 for therapeutic effect on translational outcomes of motor and cognitive function; (2) investigate a potential mechanism for SPM interactions in the injured brain by evaluating their effects upon microglial activation; (3) further probe the relationship between sleep and inflammation following diffuse brain injury in the mouse. One SPM, AT-RvD1, showed significant efficacy in …

Conclusion

In the diffuse brain-injured mouse, AT-RvD1 treatment, but not RvE1, mitigated motor and cognitive deficits. RvE1 treatment significantly increased post-traumatic sleep in comparison to all other groups. RvE1 treated mice displayed a higher proportion of ramified microglia and lower proportion of rod microglia in the cortex compared to saline or AT-RvD1 treated brain-injured mice. Increased post-traumatic sleep in the RvE1-treated brain-injured mice may be associated with active resolution of …

Acknowledgments

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