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Ropivacaine and Bupivacaine prevent increased pain sensitivity without altering neuroimmune activation following repeated social defeat stress

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ABSTRACT

Objective: Mounting evidence indicates that stress influences the experience of pain. Exposure to psychosocial stress disrupts bi-directional communication pathways between the central nervous system and peripheral immune system, and can exacerbate the frequency and severity of pain experienced by stressed subjects. Repeated social defeat (RSD) is a murine model of psychosocial stress that recapitulates the immune and behavioral responses to stress observed in humans, including activation of stress-reactive neurocircuitry and increased pro-inflammatory cytokine production. It is unclear, however, how these stress-induced neuroimmune responses contribute to increased pain sensitivity in mice exposed to RSD. Here we used a technique of regional analgesia with local anesthetics in mice to block the development of mechanical allodynia during RSD. We next investigated the degree to which pain blockade altered stress-induced neuroimmune activation and depressive-like behavior.

Methods: Following development of a mouse model of regional analgesia with discrete sensory blockade over the dorsal-caudal aspect of the spine, C57BL/6 mice were divided into experimental groups and treated with Ropivacaine (0.08%), Liposomal Bupivacaine (0.08%), or Vehicle (0.9% NaCl) prior to exposure to stress. This specific region was selected for analgesia because it is the most frequent location for aggression-associated pain due to biting during RSD. Mechanical allodynia was assessed 12 h after the first, third, and sixth day of RSD after resolution of the sensory blockade. In a separate experiment, social avoidance behavior was determined after the sixth day of RSD. Blood, bone marrow, brain, and spinal cord were collected for immunological analyses after the last day of RSD in both experiments following behavioral assessments.

Results: RSD increased mechanical allodynia in an exposure-dependent manner that persisted for at least one week following cessation of the stressor. Mice treated with either Ropivacaine or Liposomal Bupivacaine did not develop mechanical allodynia following exposure to stress, but did develop social avoidance behavior. Neither drug affected stress-induced activation of monocytes in the bone marrow, blood, or brain. Neuroinflammatory responses developed in all treatment groups, as evidenced by elevated IL-1 β mRNA levels in the brain and spinal cord after RSD.

Conclusions: In this study, psychosocial stress was associated with increased pain sensitivity in mice. Development of mechanical allodynia with RSD was blocked by regional analgesia with local anesthetics, Ropivacaine or Liposomal Bupivacaine. Despite blocking mechanical allodynia, these anesthetic interventions did not prevent neuroimmune activation or social avoidance associated with RSD. These data suggest that stress-induced neuroinflammatory changes are not associated with increased sensitivity to pain following RSD. Thus, blocking peripheral nociception was effective in inhibiting enhanced pain signaling without altering stress-induced immune or behavioral responses.

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1. Introduction

Numerous clinical studies indicate that psychological stress increases susceptibility to experience pain and exacerbates existing pain (Ashkinazi and Vershinina, 1999, Turner et al., 2002, Greco et al., 2004, Nicholson and Martelli, 2004, DeLeo, 2006). Unfortunately, it is unclear exactly how pain is initiated or amplified by stress. Clinical and preclinical data indicate that enhanced neuroimmune activation elicits adaptive changes in the nervous system that can contribute to exaggerated pain sensation (Maier and Watkins, 2003, Ji and Strichartz, 2004, Tsuda et al., 2005, Campbell and Meyer, 2006). For example, activation of peripheral nociceptors initiates central immune signaling that enhances neuronal excitability, leading to increased pain sensitivity (Griffis, 2011). Inflammatory mediators including IL-1 β play a critical role in driving this response (Maier and Watkins, 2003, Tsuda et al., 2005, Griffis, 2011). For instance, IL-1 β has been shown to directly modulate excitatory synaptic transmission at central terminals, which is associated with enhanced pain responses (Kawasaki et al., 2008, Yan and Weng, 2013, Grace et al., 2014). Furthermore, in response to noxious stimuli, peripheral immune cells have the capacity to traffic to the central nervous system (CNS) and promote an inflammatory environment, thus leading to exaggerated pain responses (Milligan and Watkins, 2009, Grace et al., 2011). Therefore, activation of pain pathways is associated with enhanced neuroimmune signaling, which may underlie the pathophysiology of exaggerated pain symptoms.

Related to these findings, psychosocial stress disrupts homeostatic communication pathways between the CNS and peripheral innate immune system, leading to dysregulated and heightened neuroinflammation (Wohleb et al., 2014, Reader et al., 2015, Weber et al., 2017). Repeated social defeat (RSD) is a rodent model of psychosocial stress that recapitulates many of the human immune and behavioral responses to stress (Wohleb et al., 2014, Reader et al., 2015, Weber et al., 2017). For example, exposure to RSD increases the production and release of Ly6C^{hi} monocytes into circulation that exhibit a pro-inflammatory gene expression profile similar to that observed in CD14⁺/CD16⁺ peripheral monocytes found in chronically stressed humans (Powell et al., 2013). Furthermore, RSD promotes the recruitment of Ly6C^{hi} monocytes to stress-responsive brain regions, where they differentiate into macrophages and propagate inflammatory signaling (Wohleb et al., 2013). Notably, these neuroimmune responses are associated with the development of anxiety-like behavior and social avoidance following stress (Ramirez et al., 2016, McKim et al., 2017).

It is apparent that exposure to either psychosocial stress or painful stimuli is associated with enhanced neuroimmune signaling and increased production of inflammatory mediators that ultimately result in behavioral alterations. Therefore, understanding the mechanism that mediates the relationship between stress and the development of an altered response to pain may lead to novel therapeutic strategies for the management of human chronic pain states. Ropivacaine and Liposomal Bupivacaine are long-lasting local anesthetics that are extensively used for intraoperative anesthesia and postoperative analgesia (Kuthiala and Chaudhary, 2011). The role of local anesthetics in modulating immune function has been previously described (Colucci et al., 2013), but the effect of local anesthetics on stress-induced pain sensitization and neuroimmune activation is unknown.

Here we developed a model of regional analgesia in mice using repeated, low-volume, subcutaneous injections of Ropivacaine or Liposomal Bupivacaine to block sensation of pain during repeated social stress. We assessed the effects of Ropivacaine and Liposomal Bupivacaine on the development of mechanical allodynia and social avoidance in mice following exposure to RSD. Furthermore, we determined whether either drug treatment affected

neuroimmune responses to stress, including increased Ly6C^{hi} monocytes in circulation, enhanced myelopoiesis in the bone marrow, recruitment of brain macrophages, and augmented IL-1 β expression in the brain and spinal cord. Taken together, our results show that blocking peripheral nociception is effective in preventing increased pain signaling without blocking immune or behavioral responses associated with stress.

2. Methods

2.1. Mice

Male C57BL/6 (6–8 weeks old) and male CD-1 (12 months, retired breeders) mice were purchased from Charles River Breeding Laboratories (Wilmington, MA), and allowed to acclimate to their surroundings for 7–10 days prior to experiments. Resident C57BL/6 mice were housed in cohorts of three and aggressor CD-1 mice were individually housed. All mice were housed in 11.5" \times 7.5" \times 6" polypropylene cages. Rooms were maintained at 21 °C under a 12-h light–dark cycle (lights on at 0600) with *ad libitum* access to water and rodent chow. All procedures were in accordance with the National Institutes of Health Guidelines and were approved by the Ohio State University Institutional Laboratory Animal Care and Use Committee.

2.2. Repeated social defeat

Mice were subjected to repeated social defeat (RSD) stress as previously described (McKim et al., 2017). In brief, an aggressive male intruder CD-1 mouse was introduced into cages of established male cohorts (3 per cage) of C57BL/6 mice for 2 h between 17:00 and 19:00 for six consecutive nights. During each cycle, submissive behavior (e.g., upright posture, fleeing, and crouching) was observed to ensure defeat of the resident mice. A new intruder was introduced if an attack on the resident mice was not initiated within the first 5–10 min, or if the intruder was defeated by any of the resident mice. At the end of the 2 h period, the intruder was removed and the residents were left undisturbed until the following day when the paradigm was repeated. To avoid habituation, different intruders were used on consecutive nights. As described previously in studies with RSD, inter-male aggression observed during each cycle resulted in minor tissue damage inflicted by the intruder mouse. The mice were monitored at least twice daily for any indication of distress or illness. Mice that were injured or moribund were removed from the study. Consistent with previous studies using RSD (Sawicki et al., 2015, McKim et al., 2016a, McKim et al., 2016b), less than 5% of mice met the early removal criteria. Control mice were left undisturbed in their home cages. All social behavior and biological measures were obtained 12 h after the final cycle. This time point was selected because sympathetic nervous system and hypothalamic–pituitary–adrenal axis activation returns to baseline by 12 h after the final cycle (Wohleb et al., 2013).

2.3. Pain behavior

Tactile mechanical sensitivity was analyzed by measuring threshold responses to a calibrated von Frey rigid tip (IITC Life Science Inc., Woodland Hills, CA). Mice were placed on a mesh platform in a clear compartment (8 cm \times 12 cm \times 5.5 cm) that allows unrestrained exploration, locomotion, and grooming. The rigid tip was applied to the mid-line of the plantar surface of the right hind paw to determine the smallest force that repeatedly elicits withdrawal of the hind paw from the tip. A lower withdrawal threshold in grams (g) is indicative of increased pain sensitivity or mechanical allodynia. Baseline measurements were performed 24 h prior to

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