Brain, Behavior, and Immunity 47 (2015) 228–237

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Effects of insomnia disorder and knee osteoarthritis on resting and pain-evoked inflammatory markers

Phillip J. Quartana [a,*], Patrick H. Finan [b], Gayle G. Page [d], Michael T. Smith [b,c]

[a] Center for Military Psychiatry and Neuroscience, Walter Reed Army Institute of Research, USA
[b] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, USA
[c] Center for Behavior and Health, Johns Hopkins University School of Medicine, USA
[d] School of Nursing, Johns Hopkins University, USA

ARTICLE INFO

Article history:
Received 31 July 2014
Received in revised form 4 December 2014
Accepted 5 December 2014
Available online 20 December 2014

Keywords:
Osteoarthritis
Insomnia disorder
Sleep
Inflammation
Cytokines
Pain
Stress

ABSTRACT

Osteoarthritis is the most prevalent arthritic condition. Systemic inflammatory cytokines appear to have an important role in the onset and maintenance of the disease. Sleep disturbances are prevalent in osteoarthritis and associated with alterations in systemic inflammatory cytokines, suggesting a common pathophysiology across these conditions. A comparative investigation of the effects of insomnia disorder and osteoarthritis on pain-evoked cytokine responses has yet to be undertaken. We examined the influence of symptomatic knee osteoarthritis and insomnia disorder on resting C-reactive protein (CRP), interleukin (IL)-6, and IL-10 levels, and pain-evoked IL-6 and IL-10 responses. Participants were $N = 117$ older adults (mean age = 59.7 years; 61.8% women) rigorously evaluated for knee osteoarthritis and insomnia disorder using established diagnostic guidelines. Results revealed no association of osteoarthritis or insomnia disorder with CRP. Resting IL-6 was greater in osteoarthritis participants versus those without osteoarthritis, although this association was largely attributable to BMI. IL-10 was highest among participants with osteoarthritis or insomnia disorder. Growth curve modeling revealed that participants with insomnia disorder had greater pain-evoked IL-6 responses than participants without insomnia disorder or osteoarthritis. These findings highlight the utility of laboratory pain testing methods for understanding individual differences in inflammatory cytokines. Moreover, our findings provide evidence for amplified pain-evoked pro-inflammatory cytokine reactivity among older adults with clinically diagnosed insomnia disorder, even after controlling for individual differences in BMI and age. Additional research will be required determine whether an amplified pain-related cytokine response contributes to OA, and possibly other age-related disease, associated with insomnia disorder.

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1. Introduction

An estimated 27 million individuals in the United States have osteoarthritis (OA) (Neogi, 2013). Although local inflammatory cytokines are a critical pathophysiological component of OA (Wojdasiewicz et al., 2014), studies support an important role for systemic cytokines concerning incident OA (Livshits et al., 2009) and related joint and muscular pathology among older adults (Barker et al., 2014; Brinkley et al., 2009; Santos et al., 2011; Stannus et al., 2010; Stannus et al., 2013). As a result, it can be hypothesized that variables that influence systemic cytokines, perhaps particularly in the context of acute pain or injury, may enhance risk for OA and other age-related disease processes through elevations in systemic inflammatory cytokines. In the current study, we explored the possibility that a common pathophysiology of insomnia disorder and OA might be represented through associations of these factors with inflammatory markers both at rest and in the context of pain provocation.

The extant literature supports the hypothesis that insomnia and OA may be co-morbid and share reciprocal risk, at least in part, through systemic inflammation. First, sleep problems are evident in OA samples (Abad et al., 2008). OA patients report difficulties with sleep continuity (Wilcox et al., 2000), and these sleep problems have been correlated with greater joint pain, pain-related inference, and depressive symptoms (Leigh et al., 1987; Wilcox et al., 2000). Sleep problems have also been associated with greater pain report in OA samples, in addition to manifold other chronic pain conditions (Edwards et al., 2009a; Haack et al., 2012; Quartana et al., 2010; Smith et al., 2009; Tang et al., 2012;

* Corresponding author at: Center for Military Psychiatry and Neuroscience, Walter Reed Army Institute of Research, 503 Robert Grant Ave., Silver Spring, MD 20910, USA. Tel.: +1 301 319 9777.
E-mail address: phillip.j.quartana2.civ@mail.mil (P.J. Quartana).

http://dx.doi.org/10.1016/j.bbi.2014.12.010
0889-1591/Published by Elsevier Inc.

Vitiello et al., 2014). Second, pain-evoked pro-inflammatory cytokine response has been shown to be exaggerated in OA versus pain-free control participants (Lee et al., 2011), and resting levels of the pro-inflammatory cytokine, interleukin (IL)-6 has been linked to prevalent and 5-year incident OA (Livshits et al., 2009). Other inflammatory cytokine markers have been prospectively linked to worsening OA, joint space narrowing, muscular pathology, and poorer physical function (Barker et al., 2014; Brinkley et al., 2009; Santos et al., 2011; Stannus et al., 2010, 2013). Third, greater non-painful stress-evoked inflammatory cytokine response has been associated with self-reported sleep problems (Heffner et al., 2012; Prather et al., 2013). Finally, there is emerging empirical data supporting the notion that treating insomnia disorder can effectively mitigate pain and functional impairment through early-treatment reductions of sleep problems in OA patients (Vitiello et al., 2014). Moreover, pre-surgical sleep problems are diminished following total hip replacement surgery (Fielden et al., 2003). These data further highlight the possibility that OA and insomnia disorder possess a shared pathophysiology; the extant literature suggests systemic inflammatory markers as a viable candidate.

Systemic levels of C-reactive protein (CRP) and pro-inflammatory cytokines, such as interleukin-6 (IL-6), have been linked to prevalent and incident OA, progression of structural abnormalities, and pain and functional impairment among individuals with and without OA (Barker et al., 2014; Cesari et al., 2004; Livshits et al., 2009; Santos et al., 2011; Stannus et al., 2010, 2013). These inflammatory biomarkers are also sensitive to stress (Steptoe et al., 2007), sleep disturbance (Faraut et al., 2012) and pain (Edwards et al., 2009a). Systemic inflammation appears to be evident in the context of insomnia disorder as well (Burgos et al., 2006; Vgontzas et al., 2002). Preliminary studies have found interactions between non-painful stress and sleep problems on the pro-inflammatory cytokine, IL-6 (Heffner et al., 2012; Prather et al., 2013). Experimental sleep deprivation increases circulating IL-6 levels and spontaneous pain in healthy participants (Haack et al., 2007), though some studies have shown no effect of total sleep deprivation on resting pro-inflammatory cytokine levels (Matzner et al., 2013; Ruiz et al., 2012). To our knowledge, whether pain-evoked inflammatory cytokines are elevated by the presence of insomnia disorder among individuals with or without OA has not been systematically explored. This is important because pain is the most clinically significant symptom of OA, and many individuals who develop OA have a history of physical trauma (i.e., post-traumatic osteoarthritis; (Schenker et al., 2014)). Lastly, no human studies have considered anti-inflammatory cytokine responses to pain. IL-10 is an immunoregulatory, anti-inflammatory cytokine that is believed to have an important role in the modulation of OA pathology (Wojdasiewicz et al., 2014) and sleep–wake regulation (Opp, 2005). Knowing whether OA and insomnia disorder interact with pain to promote differential activity of anti-inflammatory cytokines, such as IL-10, can broaden our understanding of immunoregulatory mechanisms underlying these constructs.

If systemic inflammatory markers emerge as a common pathophysiologic element of OA and insomnia disorder, then we would anticipate additive (i.e., main) effects of these conditions on pain-evoked cytokine response. There are potentially important implications if data support this hypothesis. First, if insomnia disorder is related to greater pain-evoked inflammatory cytokine response compared to good sleepers, then we can tentatively advance the argument that insomnia disorder might enhance risk for the onset (e.g., following acute injury or owing to age-related processes), maintenance, or exacerbation of OA, in part, through common inflammatory mechanisms. It is also stands to reason that if OA is associated with greater pain-evoked inflammatory cytokine response versus pain-free controls, it might represent a risk variable for the onset, maintenance, and exacerbation of insomnia disorder symptoms. A first and important precondition of this line of reasoning, and the goal of the present study, was to determine whether OA and insomnia disorder are associated with exaggerated resting and pain-evoked markers of inflammation relative to appropriate controls. We examined resting CRP, IL-6, and IL-10, as well as pain-evoked IL-6 and IL-10, among participants carefully screened for a diagnosis of symptomatic KOA and/or insomnia disorder. Control groups were participants without evidence of symptomatic KOA and those who met criteria as normal sleepers based on clinical evaluation (Edinger et al., 2004). Based on prior studies (Edwards et al., 2008, 2009b; Lee et al., 2011), we hypothesized that we would observe pain-evoked increases in IL-6 irrespective of diagnosis. We further hypothesized that the presence of a KOA or insomnia disorder diagnosis would be associated with greater resting levels of CRP and IL-6, and that pain-evoked IL-6 and IL-10 responses would be greater among participants with KOA or insomnia disorder versus those without KOA or normal sleepers.

2. Methods

2.1. Participants

The data for the current study were part of a larger study designed to examine the effects of insomnia and osteoarthritis on laboratory measure pain sensitivity and the efficacy of cognitive behavioral therapy for insomnia disorder among symptomatic KOA patients. The data presented here are from the baseline assessment alone. Intervention data will be presented elsewhere. Participants ($N = 117$) were recruited via advertisements in community media outlets and physician offices for individuals with and without knee pain and/or individuals with or without trouble sleeping. General and study group-specific inclusion/exclusion criteria are presented in Table 1. Sixty-three participants received a diagnosis of KOA and insomnia disorder (KOA + insomnia disorder)[1], $n = 17$ met criteria for KOA without insomnia disorder (KOA + normal sleeper), $n = 17$ met criteria for insomnia disorder without KOA (no KOA + insomnia disorder), and $n = 20$ did not meet criteria for either KOA or insomnia disorder (no KOA + normal sleeper). Demographic, pain, sleep and mood characteristics of these participant groups are provided in Table 2. All participants included in the study provided informed consent in accordance with the Johns Hopkins University Institutional Review Board requirements.

2.2. Procedures

Eligible participants arrived at the laboratory visit during which they completed a standardized laboratory pain testing protocol with accompanying blood draws (see Fig. 1). Sessions were conducted between 14:00 and 16:00 to control for circadian variation in cytokine levels (Vgontzas et al., 2005). At the beginning of the session, and 30 min prior to pain testing, an I.V. line was placed in the antecubital vein and a 0.45% saline solution was infused to maintain catheter patency. Blood samples (10 ml) were drawn 5 times throughout the baseline assessment, twice during rest and prior the onset of the pain testing procedures, and 3 times following the pain testing procedures (immediately and 30 and 60 min following). All samples were collected with EDTA vacutainers, placed on ice and centrifuged at 4 °C within 30 min following all blood draws. Plasma was aliquoted and stored at −80 °C until batch assayed.

[1] KOA + insomnia disorder participants were oversampled for enrollment in a randomized controlled trial of Cognitive Behavioral Therapy for Insomnia (CBT-I) in patients with KOA with insomnia disorder. These data will be presented elsewhere.