Biological Psychology 99 (2014) 150–159

Contents lists available at ScienceDirect

Biological Psychology

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

Interleukin-6 and soluble interleukin-6 receptor levels in posttraumatic stress disorder: Associations with lifetime diagnostic status and psychological context

Tamara L. Newton[a,*], Rafael Fernandez-Botran[b], James J. Miller[b], Vicki Ellison Burns[c,1]

[a] Department of Psychological and Brain Sciences, University of Louisville, United States
[b] Department of Pathology and Laboratory Medicine, University of Louisville, United States
[c] School of Nursing, University of Louisville, United States

ARTICLE INFO

Article history:
Received 25 May 2013
Accepted 21 March 2014
Available online 30 March 2014

Keywords:
PTSD
Remitted PTSD
Inflammation
IL-6
sIL-6R
Anticipation

ABSTRACT

This study correlated lifetime PTSD diagnostic status with interleukin-6 (IL-6) and soluble IL-6 receptor (sIL-6R) levels, and tested whether these correlations are sensitive to psychological context. Midlife women attended two research visits where blood was drawn (beginning of visits) and saliva and oral mucosal transudate were collected (beginning and end of visits) to measure IL-6 and sIL-6R. Women were classified as PTSD−/− (past and current symptoms below subsyndromal levels), PTSD+/− (past symptoms at or above subsyndromal levels), or PTSD+/+ (past and current symptoms at or above subsyndromal levels). PTSD+/+ women, compared to the other women, showed more negative emotion at the beginning of the visits, higher salivary IL-6 levels at the beginning versus end of visits, and positive correlations between negative emotion, salivary IL-6, and plasma sIL-6R. Their plasma sIL-6R levels exceeded those of the PTSD+/− women. Overall, IL-6 sensitivity to anticipation and to negative emotions, and higher sIL-6R levels, differentiated persistent versus remitted PTSD.

1. Introduction

In the early aftermath of traumatic stress exposure, a symptom profile consistent with posttraumatic stress disorder (PTSD) can be observed in up to three-quarters of persons, depending on the type of trauma (Riggs, Rothbaum, & Foa, 1995). Still, not all trauma-exposed persons show this symptom profile, and among those who do, there are diverse symptom trajectories, with some persons developing persistent, chronic PTSD, and others showing symptom remission with the passage of time following the traumatic event (Berntsen et al., 2012; Bonanno, Galea, Bucciarelli, & Vlahov, 2006; Hobfoll et al., 2009; Layne, Warren, Watson, & Shalev, 2007). Building on our previous research concerning PTSD symptoms and markers of inflammation (Newton et al., 2013), the present study examined how classifying PTSD status by considering both past and current symptoms affects associations with levels of the cytokine interleukin-6 (IL-6). We extended our studies to IL-6 measured in oral fluids (i.e., saliva and oral mucosal transudate), to the soluble IL-6 receptor (sIL-6R), and to consideration of the hypothesis that connections between IL-6 and lifetime PTSD status may be dynamic, or sensitive to psychological context.

Potential connections between PTSD and cytokine levels, particularly those that promote inflammation, have recently received much attention. This has been partially motivated by correlations between PTSD and elevated risk of chronic diseases with inflammatory pathophysiology (Ahmadi et al., 2011), and the question of whether alterations in cytokine levels – inflammatory mediators that are also stress-reactive – might help explain this connection. Generally speaking, across different types of traumatic stressors (e.g., accidents, war zone exposure, civilian assault), across different proinflammatory cytokines (e.g., IL-1β, TNF-α, IL-6), and across both circulating and stimulated cytokine levels, evidence for a pro-inflammatory profile of PTSD and its symptoms is observed, although null and contrary evidence are also apparent (Gill, Saligan, Woods, & Page, 2009; Pace & Heim, 2011; Wong, 2002).

Of interest in the present study are connections between PTSD and the cytokine IL-6. In addition to being a predictor of chronic diseases itself (Ridker, Hennekens, Buring, & Rifai, 2000), IL-6 has proinflammatory properties that include stimulating synthe-

* Corresponding author at: Department of Psychological and Brain Sciences, University of Louisville, 317 Life Sciences, Louisville, KY 40292, United States. Tel.: +1 502 852 0070.
E-mail address: tlnewton@louisville.edu (T.L. Newton).
[1] Vicki Ellison Burns is now at the Lansing School of Nursing and Health Sciences, Bellarmine University.

http://dx.doi.org/10.1016/j.biopsycho.2014.03.009
0301-0511/

sis of C-reactive protein, a widely used indicator of systemic inflammation (Gabay & Kushner, 1999; Ridker, 2003). Supporting a proinflammatory model of PTSD, the results of some studies have shown that circulating IL-6 levels are greater among persons with a current PTSD diagnosis compared to healthy controls (Maes et al., 1999) or trauma-exposed persons without PTSD (von Känel et al., 2010). Other studies, however, have either shown null effects (McCanlies et al., 2011; Vidovic et al., 2011), or elevations of IL-6 levels only when PTSD is comorbid with major depressive disorder (Gill, Luckenbaugh, Charney, & Vythilingam, 2010). Thus, a clear picture of the connections between PTSD and IL-6 has not yet emerged.

In a previous report by our group, analyzing the association of PTSD symptom severity with markers of inflammation in a sample of midlife women, plasma IL-6 levels measured at an initial, baseline research visit were significantly, negatively correlated with past, but not current, symptom severity (Newton et al., 2013). This observation shows that PTSD symptom history has significance for current IL-6 levels, but because the direction of the correlation is negative, it appears to be at odds with the proinflammatory model of PTSD. One way to reconcile this may be to consider that for some persons, but not all, past symptoms subside. Thus, perhaps lower plasma IL-6 levels are linked with decreases in symptom severity, a pattern that could be revealed only by classifying participants using both past and current symptoms, rather than considering them separately.

To test this idea, the present study identified three groups of women: **PTSD**−/− (no evidence of past or current syndromal or partial/subthreshold PTSD); **PTSD**+/− (presence of past, but not current, syndromal or partial/subthreshold PTSD); and **PTSD**+/+ (presence of past and current syndromal or partial/subthreshold PTSD). We specifically aimed to clarify the prior observation that severe past symptoms predicted lower IL-6 levels (Newton et al., 2013) by examining whether the PTSD+/− group – persons previously, but no longer, reporting syndromal or subsyndromal symptoms – showed lower IL-6 levels than the PTSD+/+ group. The main goal was to examine whether these groups differed in terms of IL-6 levels in two oral fluids: saliva, a product of salivary glands, and oral mucosal transudate (OMT), fluid that has filtered through the oral mucosa from systemic sources (i.e., serum or plasma) (Nishanian, Azia, Chung, Detels, & Fahey, 1998). However, we also included plasma IL-6 in order to more directly compare this group-based analytic approach to one using continuous symptom scores, as in our previous study. Levels of IL-6 from these three different fluids all show correlations with various psychosocial factors (Chiang, Eisenberger, Seeman, & Taylor, 2012; Sjogren, Leanderson, Kristenson, & Ernerudh, 2006), suggesting central nervous system control, but their intercorrelations are small to moderate (Fernandez-Botran, Miller, Burns, & Newton, 2011; Sjogren et al., 2006), perhaps reflecting the somewhat different origins of IL-6 in each of the fluids. For example, as we previously showed, levels of IL-6 (and also its soluble receptor, sIL-6R) tend to be higher in OMT than in saliva and plasma, suggesting production by the oral mucosa (Fernandez-Botran et al., 2011)

As a second goal, the present study aimed to clarify another pattern observed in our prior report: severe past PTSD symptoms predicted higher plasma IL-6 levels at a visit that included a trauma assessment, compared to an initial baseline visit that did not include any trauma-related questions. Further, the blood used for IL-6 assays had been drawn at the beginning, rather than the end, of each research visit, implying that this response was anticipatory to confronting trauma-related content. In contrast, when past PTSD symptoms were reported as absent or low, plasma IL-6 levels were higher at the initial baseline visit compared to the trauma assessment visit, suggesting an anticipatory response to the novelty or unfamiliarity of the first visit (Al'Absi & Lovallo, 1993; Ohman, Hamm, & Hugdahl, 2000). These results further emphasize the importance of assessing PTSD symptom history, and also suggest that connections between PTSD symptoms and IL-6 levels may be dynamic, or sensitive to psychological context, and especially to anticipation. In the present study, we further evaluated this by taking advantage of the fact that oral fluids were collected at the beginning and at the end of both research visits. A pattern in which correlations between PTSD and IL-6 levels are higher at the beginning of a visit than at the end underscores the role of anticipation, compared to a pattern in which correlations are similar at both assessments (suggesting a static relationship, or a visit effect), or one in which correlations are higher at the end of a visit compared to the beginning (suggesting a reactivity response).

A third goal of the present study was to examine whether the predicted associations also extend to sIL-6R, endogenous regulators of the bioavailability and cellular targets of IL-6 (Heaney & Golde, 1996; Rose-John, Scheller, Elson, & Jones, 2006; Scheller, Chalaris, Schmidt-Arras, & Rose-John, 2011). The few studies that have examined connections between sIL-6R and trauma-related symptoms have revealed positive correlations between serum sIL-6R levels and post-trauma psychological distress (Sutherland, Alexander, & Hutchison, 2003), PTSD symptoms (Miller, Sutherland, Hutchison, & Alexander, 2001), and syndromal PTSD, especially when comorbid with major depression (Maes et al., 1999). Thus, available evidence predicts positive associations between sIL-6R levels and PTSD, but does not provide any basis for predictions with respect to psychological context.

2. Method

2.1. Participant recruitment and selection

Physically healthy women with histories of divorce or separation were recruited from the community as part of a broader investigation of recovery from intimate partner violence (IPV) and inflammation at midlife (Newton et al., 2011). A phone interview assessed inclusion criteria (history of divorce; 45–60 years of age; postmenopausal defined as cessation of menses for ≥12 months), and exclusion criteria (no English language skills; ongoing divorce-related legal issues; psychiatric hospitalization in the preceding 6 months; active suicidal ideation; current IPV – i.e., IPV involving an ex-partner in the preceding year, or any IPV history with a current partner, defined by a score ≥ 1 on the Slapped, Threatened and Throw screener (Paranjape, Rask, & Liebschutz, 2006); chronic disease other than unmedicated hypertension; use of prescription or over-the-counter medications with inflammatory effects (including psychotropics and botanicals); blood or needle phobia; use of street drugs; current alcohol use disorder defined as ≥5 on the alcohol use disorders identification test consumption questions (Dawson, Grant, Stinson, & Zhou, 2005)).

Of 577 callers, 96 were eligible and interested in participation; 82 attended the first research visit. This visit included a blood draw and urine sample for additional eligibility checks on menopausal status (follicle-stimulating hormone levels ≥ 25 mIU/mL), use of street drugs and alcohol (urine toxicology screen; blood ethanol), and general health status (comprehensive metabolic profile, thyroid stimulating hormone, HbA1c, complete blood count). Sixty-nine women were eligible for, and attended, the second research visit. At this visit, the Clinician Administered PTSD Scale for DSM-IV (CAPS) (Blake et al., 2000) was used to assess current (i.e., last 30 days) and past (i.e., worst lifetime episode) PTSD symptoms. Because the interview for past PTSD symptoms was added after data collection had begun, it was not administered to the first five particpants, and these participant are not included in the present study sample. Also, one woman did not meet the PTSD group definitions, described below, leaving 63 women for the current sample.

2.2. Procedure

Women participated in two research visits, beginning between 8 a.m. and 1 p.m., and were compensated $140.00. Visit 1 began with three brief interviews to confirm intact cognitive functioning (Pfeiffer, 1975), absence of psychotic symptoms (First, Spitzer, Gibbon, & Williams, 2001), and absence of active suicidal ideation (Kroenke & Spitzer, 2002). This was followed by collection of the first sample of saliva and oral mucosal transudate (OMT). (Procedures for collecting oral fluids are described below, under Biological Measures). A nursing evaluation then assessed acute medical conditions, blood pressure, and body measurements. Blood was drawn via antecubital venipuncture and collected with appropriate anticoagulants for assessment of IL-6 and sIL-6R (sodium citrate), and the eligibility labs described above (EDTA for complete blood count and hemoglobin A1c, lithium heparin for all others). A urine sample was obtained for the toxicology screen and urinalysis. Women then