Brain, Behavior, and Immunity xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

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

Dysregulated relationship of inflammation and oxidative stress in major depression

B.S. Rawdin [a], S.H. Mellon [b], F.S. Dhabhar [c,d], E.S. Epel [a], E. Puterman [a], Y. Su [e], H.M. Burke [a], V.I. Reus [a], R. Rosser [a], S.P. Hamilton [a], J.C. Nelson [a], O.M. Wolkowitz [a,*]

[a] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA
[b] Department of Obstetrics & Gynecology and Reproductive Sciences, University of California, San Francisco, San Francisco, CA, USA
[c] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA
[d] Institute for Immunity, Transplantation, and Infection, Stanford University School of Medicine, Stanford, CA, USA
[e] SilverCreek Technologies, Gilbert, AZ, USA

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Inflammation
Oxidation
Oxidative stress
IL-6
IL-10
F2-isoprostane
Depression
Sertraline

ABSTRACT

Chronic inflammation and oxidative stress have been implicated in the pathophysiology of Major Depressive Disorder (MDD), as well as in a number of chronic medical conditions. The aim of this study was to examine the relationship between peripheral inflammatory and oxidative stress markers in un-medicated subjects with MDD compared to non-depressed healthy controls and compared to subjects with MDD after antidepressant treatment. We examined the relationships between IL-6, IL-10, and the IL-6/IL-10 inflammatory ratio vs. F2-isoprostanes (F2-IsoP), a marker of oxidative stress, in un-medicated MDD patients ($n = 20$) before and after 8 weeks of open-label sertraline treatment ($n = 17$), compared to healthy non-depressed controls ($n = 20$). Among the un-medicated MDD subjects, F2-IsoP concentrations were positively correlated with IL-6 concentrations ($p < 0.05$) and were negatively correlated with IL-10 concentrations ($p < 0.01$). Accordingly, F2-IsoP concentrations were positively correlated with the ratio of IL-6/IL-10 ($p < 0.01$). In contrast, in the control group, there were no significant correlations between F2-IsoPs and either cytokine or their ratio. After MDD subjects were treated with sertraline for 8 weeks, F2-IsoPs were no longer significantly correlated with IL-6, IL-10 or the IL-6/IL-10 ratio. These data suggest oxidative stress and inflammatory processes are positively associated in untreated MDD. Our findings are consistent with the hypothesis that the homeostatic buffering mechanisms regulating oxidation and inflammation in healthy individuals become dysregulated in untreated MDD, and may be improved with antidepressant treatment. These findings may help explain the increased risk of comorbid medical illnesses in MDD.

1. Introduction

Chronic inflammation and oxidative stress have been implicated in the pathophysiology of Major Depressive Disorder (MDD) (Berk et al., 2011; Capuron and Miller, 2011; Chauhan and Chauhan, 2006; Croonenberghs et al., 2002; Forlenza et al., 2007; Khanzode et al., 2003; Maes, 2011a,b, 1999; Miller, 2010; Raison and Miller, 2011; Wolkowitz et al., 2008) as well as a number of serious medical conditions (Maes et al., 2011b), including cardiovascular disease and atherosclerosis (Krishnan, 2010; Lakshmi et al., 2009; Tousoulis et al., 2008; Uno and Nicholls, 2010), chronic renal disease (Cottone et al., 2008), pulmonary disease (Jelic and Le Jemtel, 2008), rheumatoid arthritis (Stamp et al., 2012), certain cancers (Khansari et al., 2009; Maes et al., 2011b; Reuter et al., 2010), metabolic syndrome, obesity and diabetes (Agrawal et al., 2007; Assumpcao et al., 2008; Ferder et al., 2006; Guerrero-Romero and Rodriguez-Moran, 2006), and in the normal physiology of cellular aging and immuno-senescence (Cannizzo et al., 2011; De la Fuente and Miquel, 2009). While inflammation and oxidation have generally been studied separately in these conditions, the interplay between them has been less well-studied, despite mounting evidence that their interaction plays a major role in the pathogenesis of many diseases (Ambade and Mandrekar, 2012; Forlenza and Miller, 2006; Maes et al., 2011e, 2007; Rahman, 2003; Sarandol et al., 2007a). Examining the interplay between chronic inflammatory states and oxidative stress is likely to deepen our understanding of the pathophysiology of MDD and other diseases, offer greater insight into the associations between MDD and co-morbid medical illnesses with inflammatory or oxidative associations (such as diabetes, arthritis, dementia, metabolic syndrome and cardiovascular disease), and potentially guide novel approaches to the treatment of depression and its comorbid systemic diseases (Maes et al., 2011c; Nemeroff and Goldschmidt-Clermont, 2012; Wolkowitz et al., 2011b).

* Corresponding author. Address: 401 Parnassus Ave., San Francisco, CA 94143-0984, USA. Tel.: +1 451 476 7433; fax: +1 415 502 2661.
E-mail address: owen.wolkowitz@ucsf.edu (O.M. Wolkowitz).

0889-1591/$ - see front matter © 2012 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.bbi.2012.11.011

A large body of evidence suggests that MDD is accompanied by activation of inflammatory pathways, reflected by an increased levels of inflammatory cytokines, such as Interleukin (IL)-1β, IL-2, IL-6, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) (Anisman et al., 1999a,b; Maes, 1999; Nassberger and Traskman-Bendz, 1993). Two recent meta-analyses showed significantly higher IL-6 concentrations among depressed versus non-depressed patients but no significant difference in IL-10 concentrations (Dowlati et al., 2010; Hiles et al., 2012). A causal relationship between inflammation and depression is suggested by observational studies of patients undergoing immunotherapy for hepatitis C or cancer who developed depressed mood and neurovegetative accompanying these treatments (Capuron et al., 2001; Dieperink et al., 2000; Kelley et al., 2003; Valentine and Meyers, 1995; Zdilar et al., 2000). Other small-scale studies also suggest antidepressant effects of anti-inflammatory medications (Muller et al., 2006; Nery et al., 2008) as well as anti-inflammatory effects of antidepressants (Abbasi et al., 2012; Felger et al., 2012; Hannestad et al., 2011).

A smaller but growing body of evidence also points to increased oxidative stress in MDD. Elevated plasma and/or urine oxidative stress markers (e.g., increased F2-isoprostanes [IsoPs] or 8-hydroxydeoxyguanosine [8-OHdG], along with decreased anti-oxidant compounds, such as Vitamins C and E) have been reported in individuals with MDD and in those with chronic psychological stress (Forlenza and Miller, 2006; Irie et al., 2001a,b, 2005; Maes et al., 2000), and the concentration of peripheral oxidative stress markers is positively correlated with the severity and chronicity of depression (Forlenza and Miller, 2006; Irie et al., 2003, 2002; Maes et al., 2011a; Miyaoka et al., 2005; Tsuboi et al., 2004; Yager et al., 2010). Antioxidant compounds are also being considered as possible antidepressant treatments (Gibson et al., 2012; Khanzode et al., 2003; Scapagnini et al., 2012; Wolkowitz et al., 2011b).

Inflammation and oxidative stress are inextricably connected in physiologic as well as disease states; they have even been termed "essential partners" in certain diseases (Ambade and Mandrekar, 2012). Under normal physiologic conditions, oxidative stress and activation of the immune system are generally short-lived due to intrinsic negative feedback mechanisms, such as increased production of anti-oxidant compounds or of anti-inflammatory cytokines. In certain chronic disease states, however, both of these systems remain activated and may, indeed, form a positive self-sustaining feedback loop, or a "co-activation" state (Jesmin et al., 2010). Over time, such co-activation may lead to a higher risk of disease and to more serious disease (Ambade and Mandrekar, 2012; Il'yasova et al., 2008; Jesmin et al., 2010; Khansari et al., 2009; Kotani and Taniguchi, 2012; Kregel and Zhang, 2007; Martinon, 2010; Rahman, 2003; Skalicky et al., 2008; Terlecky et al., 2012; Tschopp and Schroder, 2010).

The aim of the current study was to examine the relationship between inflammation and oxidative stress in the plasma of un-medicated subjects with MDD before and after antidepressant treatment, and in un-medicated subjects with MDD compared to non-depressed healthy controls. We hypothesized that un-medicated subjects with MDD would show stronger positive correlations between oxidative stress and inflammatory markers than the same subjects after antidepressant treatment and than healthy non-depressed controls.

2. Methods

2.1. Subjects

Twenty subjects with MDD, diagnosed with the Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 2002), and 20 matched healthy controls (matched by sex, ethnicity and age ±3 yr) were enrolled. Subjects were recruited by fliers, craigslist postings (http://sfbay.craigslist.org), and newspaper advertisements and, in the case of depressed subjects, clinical referrals. Subjects gave written informed consent to participate in this study, which was approved by the University of California, San Francisco (UCSF) Committee on Human Research and were paid for their participation. SCID interviews were conducted by an experienced clinical psychologist and were clinically verified by a separate psychiatric interview with a Board-certified psychiatrist. Depressed subjects with psychosis, post-traumatic stress disorder or bipolar histories were excluded, although other co-morbid anxiety disorders were allowed when the depressive diagnosis was determined to be the primary diagnosis. Seven of the depressed subjects had one or more secondary co-morbid psychiatric diagnoses as follows: three with generalized anxiety disorder, two with obsessive compulsive disorder, two with binge eating disorder (one of whom was in remission) and one with social anxiety disorder. Healthy controls were also screened with the SCID, and were required to have no present or past history of any DSM-IV Axis I or Axis II diagnosis. Potential subjects were excluded if they met SCID criteria for alcohol or substance abuse within 6 months of entering the study. Subjects in both groups were medically healthy (assessed by physical examination, review of systems and screening routine laboratory tests), had no acute illnesses or infections, and had not had any vaccinations within 6 weeks of entering the study. All subjects (depressed and control) were free of any psychotropic medications, including antidepressants, antipsychotics and mood stabilizers, as well as any hormone supplements, steroid-containing birth control or other interfering medications or Vitamin supplements above the U.S. Recommended Daily Allowances (e.g. Vitamin C, 90 mg/day), for a minimum of 6 weeks before entry into the study (with the exception of short-acting sedative-hypnotics, as needed, up to a maximum of 3 times per week, but none within 1 week prior to testing). The sample described in the present report incorporates the smaller sample previously reported on, which was used to test a different set of hypotheses (Dhabhar et al., 2009).

2.2. Procedures

Subjects were admitted as outpatients to the UCSF Clinical and Translational Science Institute's Clinical Research Center at 8:00 am, having fasted (except water) since 10:00 pm the night before. Before proceeding with testing, all subjects were required to test negative on a urine toxicology screen (measuring the presence of abused drugs) and, in women of childbearing capacity, a urine pregnancy test. After the subjects had sat quietly for 45 min, blood samples were obtained for the assay of serum IL-6, IL-10 and for the oxidative metabolite, plasma F2-IsoP. Severity of depression in the depressed subjects was ascertained with the observer-rated 17-item Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1967). Depressed and control subjects were also rated with the Inventory of Depressive Symptomatology, 30-item self-rated version (IDS) for purposes of comparing the two groups, since the HDRS-17 is not intended for use in non-depressed populations, and since the IDS shows greater sensitivity at lower levels of depressive severity (Rush et al., 1996). The IDS was also used in analyses in which depressive severity was utilized as an independent variable across groups. Scores on the IDS range from 0 to 84 and are highly correlated with scores on the HDRS-17 (Inventory of Depressive Symptomatology (IDS) and Quick Inventory of Depressive Symptomatology (QIDS), 2012). Ratings and blood assays were performed blind to each other.

Following these baseline behavioral and biochemical tests, the MDD subjects were treated in an open-label manner with sertraline for 8 weeks, after which blood was re-drawn for F2-IsoP and cytokine assays, and depression ratings repeated. Sertraline dosing

Please cite this article in press as: Rawdin, B.S., et al. Dysregulated relationship of inflammation and oxidative stress in major depression. Brain Behav. Immun. (2012), http://dx.doi.org/10.1016/j.bbi.2012.11.011