Journal of Affective Disorders 185 (2015) 90–96

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Enhanced inflammatory and T-helper-1 type responses but suppressed lymphocyte proliferation in patients with seasonal affective disorder and treated by light therapy

Cai Song [a,b,d,*], Dirk Luchtman [c,e], Zhijian Kang [d], Edwin M. Tam [d], Lakshmi N. Yatham [d], Kuan-Pin Su [b], Raymond W. Lam [d,**]

[a] Research Institute for Marine Drugs and Nutrition, College of Food Science and Technology, Guangdong Ocean University, Zhanjiang, Guangdong, China
[b] Graduate Institute of Neural and Cognitive Sciences, China Medical University Hospital, Taichung, Taiwan
[c] Department of Biomedical Sciences, University of Prince Edward Island, Charlottetown, Canada
[d] Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada
[e] Neurology Department, University Medical Center of the Johannes Gutenberg University Mainz, 55131 Mainz, Germany

ARTICLE INFO

Article history:
Received 10 February 2015
Received in revised form
5 June 2015
Accepted 5 June 2015
Available online 17 June 2015

Keywords:
Seasonal affective disorder
Macrophage activity
Lymphocyte proliferation
Proinflammatory cytokines
Th1 and Th2 cytokines
Light therapy

ABSTRACT

Background: Animals show seasonal changes in the endocrine and immune system in response to winter stressors. Even though increased inflammation has been implicated in the pathophysiology of depression, whether immune disorder is a key mediator in seasonal affective depression (SAD) is unknown. Here, we hypothesized that short photoperiods in winter may induce inflammatory response, which contributes to SAD, and that light treatments should normalize immune function and improve depressive symptoms.

Methods: Twenty patients with a diagnosis of SAD, and a score on the HAM-29 of 20 or higher were recruited for this study. Twenty-one healthy subjects with no personal and family history of psychiatric disorder were matched to patients according to age and sex. Patients and controls were sampled during winter between November and January, inclusive. A subset of SAD patients ($N=13$) was re-sampled after 4 weeks of light therapy. Blood samples were assayed for macrophage activity, lymphocyte proliferation and cytokine release.

Results: SAD patients showed significantly higher macrophage activity and lower lymphocyte proliferation in winter compared to healthy subjects. The concentrations of macrophage-produced proinflammatory cytokines interleukin-1β and tumour necrosis factor-α, and T-helper (Th)-1 produced cytokine, interferon-γ were all significantly increased. In contrast, no significant changes in Th2-produced cytokines were observed. Light therapy significantly improved depressive scores, which was associated with attenuation of decreased lymphocyte functions, increased macrophage activity and level of proinflammatory cytokines.

Conclusion: SAD patients have increased macrophage and Th1 type responses in winter, and light therapy normalized immune functions and depressive symptoms. These results support an inflammatory hypothesis for SAD and an immunomodulatory role of light therapy.

1. Introduction

An immune response initiated in the periphery can be transferred into the brain through cytokine transmitters and modulate brain function. Administration of proinflammatory cytokines in animals can lead to sleep interruption, lethargy, reduction of libido and exploration, poor concentration, and increased stress and anxiety-like behaviour (Dantzer, 2006; Song, 2006). Treatment with tumour necrosis factor (TNF)-α or interferon (IFN)-γ can induce depressive symptoms in healthy human volunteers or cancer patients (Meyers, 1999; Capuron et al., 2000). Increased

Abbreviations: Con, concanavalin; ELISA, a quantitative enzyme-linked immunosorbent assay; HPA, hypothalamic-pituitary-adrenal axis; IL, interleukin; IFN, interferon; MDD, major depressive disorder; PMA, phorbol 12-myristate 13-acetate; PHA, phytohemagglutinin; SAD, seasonal affective depression; SCID, Structured Clinical Interview for DSM-IV Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH–SAD); Th, T-helper; TNF, tumour necrosis factor

* Corresponding author at: Institute for Marine Drugs and Nutrition, College of Food Science and Technology, Guangdong Ocean University, Zhanjiang, China and Graduate Institute of Neural and Cognitive SciencesSciences, China Medical University Hospital, Taichung, Taiwan.
** Corresponding author.
E-mail addresses: cai.song@dal.ca (C. Song), rlam@ubc.ca (R.W. Lam).

http://dx.doi.org/10.1016/j.jad.2015.06.003
0165-0327/

macrophage activity and enhanced production of proinflammatory cytokines have been consistently reported in patients with major depressive disorder (MDD) (Song et al., 1998; Maes et al., 2012; Hoyo-Becerra et al., 2014). The mechanism by which proinflammatory cytokines induced depressive symptoms and neuroendocrine dysfunction has been related to several aspects: (1) directly stimulating the hypothalamic-pituitary-adrenal axis (HPA) axis to secrete corticotrophin releasing factor and glucocorticoids (Leonard, 2014); (2) activating indoleamine 2,3-dioxygenase that may reduce the availability of serotonin (5-HT) precursor tryptophan and decrease 5-HT availability to the brain (Song et al., 1998; Maes et al., 2011) and (3) triggering glial activity in the brain, which may increase CNS inflammation and oxidative stress (Leonard and Maes, 2012; Song et al., 2013). Therefore, proinflammatory cytokines-produced changes in neuroendocrine and neurotransmission are similar to those observed in patients with MDD.

Human behaviour and mood also fluctuates with the seasons. At the extreme end of seasonality lies seasonal affective disorder (SAD, or winter depression), a subtype of major MDD characterized by recurrent episodes of depression in the winter and normal mood in the summer. Symptoms of SAD include increased sleep and sleep need, increased appetite with carbohydrate craving and weight gain, and decreased energy and feeling fatigued, which have been likened to a winter "hibernation" response. So far, the aetiology of SAD is unknown, but major hypotheses include photoperiodism, circadian phase shift and neurotransmitter dysfunction (Lam and Levitan, 2000).

In the past decade, several studies demonstrated that the changing seasons exert fundamental effects on the immune system. In animal studies, immune function is enhanced during the short photoperiods of winter as an adaptive response to energetic stress, such as low temperature, reduced food availability, etc. (Nelson et al., 2002). These seasonal changes in immune function are mediated via the duration of melatonin secretion, which acts as a signal of the changing photoperiod from long in summer to short in winter (Nelson et al., 2002; Haldar and Ahmad, 2010). Since melatonin is secreted only at night, it is increased in the winter short photoperiod and decreased in the summer long photoperiod. Melatonin receptors have been found in lymphocytes and macrophages in both humans and animals (Calvo et al., 1995; Lopez-Gonzalez et al., 1992). Melatonin can enhance macrophage activity, elevates antibody response, and increases cytokine production from macrophage and T-helper 1 (Th1) lymphocytes (Nelson et al., 2002; Shafer et al., 2001) but decreases anti-inflammatory response from Th2 lymphocytes (Kuhlwein and Irwin, 2001; Shearer et al., 2002). In human subjects, macrophages and Th1 cell-produced proinflammatory cytokines IFN-α, IFN-γ and interleukin (IL)-6 were increased in winter when compared to summer, while Th2-produced cytokine IL-10 was decreased (Maes et al., 1994; Kuhlwein and Irwin, 2001; Shearer et al., 2002). These studies indicate that immune cells, immune cell subsets, and cytokine releases exhibit significant seasonal variation, and these seasonal changes are mediated through photoperiodic changes.

Given that inflammation may contribute to the aetiology and symptoms of MDD and that seasonal variation is seen in immune function, a hypothesis could be that an increased immune-inflammatory response in winter is a mediating factor in SAD. Few studies have investigated immune changes in SAD patients, with only preliminary evidence showing higher plasma levels of IL-6 (Leu et al., 2001). However, changes in immune cellular functions and the balance between proinflammatory and anti-inflammatory cytokines and between Th1 and Th2 cell-produced cytokines in SAD are unclear. Furthermore, whether bright light therapy, an effective treatment for SAD (Lam et al., 2006), can modulate immune changes has not been studied. Thus, the present study aimed to investigate two hypotheses in SAD patients: (1) the shorter photoperiod of winter leads to the activation of macrophages, production of proinflammatory cytokines, increase in Th1 responses and shift in dynamic balance between Th1 and Th2; and (2) treatment with bright light will normalize these immune changes. To test these hypotheses, both cellular (macrophage activity and lymphocyte proliferation) and humoral immune functions (proinflammatory cytokines and Th1 and Th2 cell-produced cytokines) were measured in the blood samples from SAD patients during the four seasons of the year, and in healthy subjects and depressed SAD patients in winter, before and after light therapy.

2. Materials and methods

2.1. Subjects

This study was approved by the clinical research ethics board at the University of British Columbia and written, informed consent was obtained from all participants. Patients were recruited from the Mood Disorders Clinic at UBC Hospital in Vancouver, Canada. Inclusion criteria for SAD patients included: (1) DSM-IV criteria for MDD with a seasonal (winter pattern) as determined by the Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1995) modified to include criteria for seasonal pattern, (2) psychotropic drug-free for at least 2 months, (3) in winter, a score on the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH–SAD) (Williams, 1988) of 20 or higher (indicating moderately severe depression), (4) in summer, a score on the SIGH–SAD of 12 or less (indicating clinical remission). Exclusion criteria for SAD patients included: (1) other major psychiatric diagnoses, including bipolar disorder and psychotic disorders; (2) active alcohol/substance abuse or dependence within the past 12 months; (3) medical conditions or use of medications that may affect immune function; (4) retinal diseases that precluded the use of bright light therapy. Healthy control subjects were recruited by advertisement and matched to SAD patients by age. Inclusion criteria for healthy subjects included: (1) no current nor past history of mood disorder as determined by a SCID interview, (2) no family history of mood disorder, (3) score on the Seasonal Pattern Assessment Questionnaire (Rosenthal et al., 1987) of 6 or less, psychotropic drug-free for at least 2 months. The same exclusion criteria as for SAD patients were also used.

2.2. Procedure

After screening procedures for eligibility, 20 medication-free SAD patients (15 females and 5 males, age 39.0 ± 9.3 years) and 21 age-matched healthy subjects (13 females and 8 males, age 35.7 ± 12.3 years) were sampled during winter. Thirteen of the SAD patients (9 females and 4 males) had repeated blood sampling after 4 weeks of treatment with a standard regimen of light therapy, consisting of 10,000 lx fluorescent white light box fitted with a ultraviolet filter (Lam et al., 2006). Patients used the light box at home for 30–60 min in the early morning upon awakening, typically between 07:00 and 10:00 (Lam et al., 2006; Desan et al., 2007). Clinical response was determined by SIGH–SAD ratings at baseline and post-treatment. The intravenous blood samples were drawn into a heparinised syringe at 8:00–10:00 am.

2.3. Lymphocytes and monocyte/macrophages separation

Blood samples were diluted with RPMI-1640 with l-glutamine and phenol red (Sigma, Canada) at 1:1, and layered on the top of Histopaque (1.077). Then the tubes were centrifuged at 1650 rpm for 25 min at room temperature. Lymphocytes and monocytes/