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Research report

Immune–inflammatory markers in patients with seasonal affective disorder: effects of light therapy

Sy-Jye Leu[a], I-Shin Shiah[b,*], Lakshmi N. Yatham[c], Yech-Mei Cheu[a], Raymond W. Lam[c]

[a]*Graduate Institute of Cell and Molecule Biology, Taipei Medical College, Taipei, Taiwan, ROC*
[b]*Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC*
[c]*Division of Mood Disorders, Department of Psychiatry, The University of British Columbia, Vancouver, British Columbia, Canada*

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Abstract

Background: There is increasing evidence that an activation of the immune–inflammatory system is involved in the pathophysiology of depressive disorders. The purposes of this study were to (1) compare immune–inflammatory markers in patients with seasonal affective disorder (SAD) with those in matched normal controls; and (2) examine the effects of light therapy on the immune–inflammatory markers in patients with SAD. *Methods*: Plasma concentrations of interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R) and soluble IL-2 receptor (sIL-2R) were measured in 15 patients with SAD and 15 age- and sex-matched normal controls. Of the 15 patients, 14 had repeated blood sampling for these variables following 2 weeks of light therapy. *Results*: We found that patients with SAD had significantly increased IL-6 levels compared to normal controls ($P < 0.0005$). There was a trend toward increased sIL-2R in patients with SAD ($P = 0.09$). There was no significant difference in sIL-6R level between the two diagnostic groups ($P = 0.18$), but the product term (IL-6$\times$sIL-6R) was significantly higher in patients with SAD than that in normal control controls ($P < 0.0003$). Furthermore, all 14 patients who completed the study improved with 2 weeks of light therapy and nine of them (64%) had 50% reduction in score of the Hamilton Depression Rating Scale–SAD version post-treatment compared to baseline. However, the initially increased immune markers in SAD patients were not significantly altered by the therapeutic light therapy. *Limitations*: This study was limited to a small sample size and other immune inflammatory markers should be measured for further evidence of immune activation in seasonal depression. *Conclusions*: Our results of increased IL-6, IL-6$\times$sIL-6R, and sIL-2R in patients with SAD suggest an activation of the immune–inflammatory system in winter depression, which is not altered by 2 weeks of successful light therapy.

Keywords: Cytokines; Interleukin-6; Soluble interleukin-2 receptors; Soluble interleukin-6 receptors; Seasonal affective disorder; Winter depression; Light therapy

*Corresponding author. Tel.: +011-886-2-2368-1462; fax: +011-886-2-2365-8619.
E-mail address: ishiah@ms45.hinet.net (I-S. Shiah).

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1. Introduction

Of pro-inflammatory cytokines, interleukin 6 (IL-6) has been the most studied in depression. This pleiotropic cytokine is a major immune and inflammatory mediator. It regulates the synthesis of acute phase proteins and induces proliferation and differentiation of B cells. It is also involved in T-cell activation and induces prostaglandin secretion (Kushner, 1991). IL-6 exerts its action through the interaction with a membrane receptor (i.e. interleukin 6 receptor, IL-6R) and a signal-transducing protein (i.e. gp 130) (Bock et al., 1992). Shedding of membrane receptors generates a soluble form of IL-6R (Mullberg et al., 1993). A parallel increase in plasma concentrations of IL-6 and sIL-6R has been reported in depressed patients in two studies (Maes et al., 1995; Sluzewska et al., 1996), suggesting an activation of immune–inflammatory response in depression. Since it is known that sIL-6R can augment the biological activity of IL-6 (Bock et al., 1992), the parallel increase of plasma IL-6 and sIL-6R in patients with major depression would be expected to induce a further enhancement in the biological activity of IL-6 per se (Maes et al., 1995). Evidence in support of this comes from the observation that in the presence of sIL-6R, the concentrations of IL-6 required for its biological activity were lower than that required in the absence of sIL-6R (Bock et al., 1992). However, another two studies simultaneously measuring plasma IL-6 and sIL-6R levels in patients with major depression and normal controls showed that IL-6, but not sIL-6R, was significantly increased in depressed patients compared to normal controls (Maes et al., 1997; Song et al., 1998). The reason for the discrepancy in the results of plasma sIL-6R levels between the studies is unclear.

In addition to increased IL-6, studies of immune–inflammatory markers in depression consistently showed increased plasma concentrations of soluble interleukin 2 receptor (sIL-2R) (Maes et al., 1990; 1991; Nassberger and Traskman-Bendz, 1993; Sluzewska et al., 1994; Maes et al., 1995; Sluzewska et al., 1996). Since activated T cells release a soluble form of IL-2 receptor into the blood and sIL-2R concentrations appear to correlate with IL-2 secretion (Caruso et al., 1993), increased sIL-2R level is considered as an indication of T-cell activation (Caruso et al., 1993). The findings of increased plasma sIL-2R in depressed patients would, therefore, suggest an increase in the numbers of activated T cells in acute depression. Consistent with this, Maes et al. (1992) have shown that patients with major depression had significantly increased numbers of CD^{25+} bearing cells and cells with class II MHC HLA-DR molecules (i.e. interleukin-2 receptor bearing cells) when compared to controls.

Seasonal affective disorder (SAD) is a clinical subtype of recurrent major depression that occurs with a seasonal pattern (Rosenthal et al., 1984). It is a very common psychiatric disorder affecting up to 5–10% of the general population (Rosen et al., 1990). Besides the personal distress, patients with SAD have considerable impairment in occupational and social function (Allen et al., 1993). Winter depression is the most common type of SAD in which patients experience symptoms of clinical depression during the fall and winter, with full remission to normal mood during the spring and summer seasons. A significant proportion of patients with winter depression responds to daily exposure to bright artificial light, known as light therapy (Rosenthal et al., 1988; Terman et al., 1989; Magnusson and Kristbjarnarson, 1991; Eastman et al., 1998; Lewy et al., 1998; Terman et al., 1998). As yet, the pathophysiology of SAD and the therapeutic mechanism of light are still unknown. Given that depressive symptoms (Allen et al., 1993; Tam et al., 1997) and the treatment response to antidepressants (Lam et al., 1995; Ruhrmann et al., 1998) are shared between seasonal and non-seasonal depressions, one may expect that an alteration in immune–inflammatory markers such as IL-6, sIL-6R, and sIL-2R is also involved in seasonal depression and its treatment. The purposes of this study were therefore to determine (1) if there is an increase in plasma levels of IL-6, sIL-6 and sIL-2R in patients with SAD compared to normal controls; and (2) if light therapy has an immunomodulatory effect on these variables in patients with SAD.

2. Methods

2.1. Subjects

We studied a total of 15 patients with SAD (9

males and 6 females) and 15 healthy subjects (8 males and 7 females). All study subjects were physically healthy and were drug free for at least 2 weeks prior to blood sampling and none had taken fluoxetine in the preceding 8 weeks. We excluded those subjects with chronic illnesses known to affect the immune status and with acute infectious or allergic reactions for at least 2 weeks prior to the study. The DSM-IV diagnosis of recurrent major depressive episodes with a seasonal pattern was made by a routine clinical interview, and a structured clinical interview for DSM-III-R (SCID) diagnosis (Spitzer et al., 1990). Those patients that had lifetime history of other Axis I diagnoses were also excluded. The healthy subjects had no lifetime history of psychiatric illness as determined by SCID-non-patient version (Spitzer et al., 1992) and were free of a family history of an Axis I psychiatric disorder in their first-degree relatives. The severity of depressive symptoms was assessed by Hamilton Depression Rating Scale–SAD version (SIGH–SAD) (Williams et al., 1991). SAD patients had a mean 21-item depression score of 19.6 (S.D. = 1.7) and a mean 8-item atypical depression score of 11.4 (S.D. = 2.7) before treatment.

2.2. Procedure

This study was conducted at the Mood Disorders Clinic, UBC Hospital. All study subjects gave their written informed consent for participation in the study, which had been approved by the Clinical Research Ethics Committee of the University of British Columbia. The subjects having fasted since midnight presented for blood sampling at 9:30 am. Venous blood was taken from all the subjects to determine plasma levels of IL-6, sIL-6R and sIL-2R. The blood was immediately centrifuged and serum stored at −80°C until analysis.

The patients with seasonal depression were tested during fall/winter depression between November and March and normal controls were also tested during the same season. All patients were treated with light therapy on an outpatient basis. They took home a light box that delivered 10 000 lux of cool-white fluorescent light with an ultraviolet filter. Exposure time was set for 30 min between 7:00 a.m. and 9:00 a.m. each morning. Fourteen out of 15 patients had repeated blood sampling after 2 weeks of treatment with light therapy. One male patient was non-compliant with the treatment and did not have repeated blood sampling. This patient was included when comparing immune inflammatory markers with normal controls but was excluded when comparing immune–inflammatory markers within SAD patients before and after light therapy.

2.3. Biochemical assay

Plasma IL-6 levels were determined by enzyme-linked immunosorbent assay (ELISA). Firstly, ELISA plates were overnight coated with anti-human antibody for IL-6 (R&D Systems Inc.; Minneapolis, MN) at 4°C. After washing with phosphate-buffered saline (PBS) containing 0.1% Tween (pH 7.4), the plates were blocked with 1% bovine serum albumin (BSA) in PBS for 3 h at room temperature. Then, blood samples and standards (recombinant human IL-6 from R&D Systems Inc.; Minneapolis, MN) were added to the plates and incubated at 4°C overnight. Following the overnight incubation, 25 ng/ml of biotinylated anti-human IL-6 antibody (R&D Systems Inc.; Minneapolis, MN) was added to the plates for 2 h at room temperature. After the plates had been washed for 3 times, 0.05 μg/ml of streptavidin horseradish peroxidase (ELISA grade, TAGO Immonologicals; Camarillo, CA) was added to the plates and incubated for 20 min at room temperature. Finally, 3,3′,5,5′-tetramethylbenzidine (TMB) substrate (American Qualex; San Clemente, CA) was added to the plates and incubated for 20 min. The reaction was stopped by adding 50 μl/well of 1 N hydrochloric acid (HCl) and then the plates were read at the optical density 450–650 nm using an ELISA plate reader (E max precision microplate reader, Molecular Devices). Individual concentrations were determined from a standard curve, which was run with recombinant human IL-6. The sensitivity for detection of IL-6 levels was 1 pg/nl.

Plasma sIL-2R and sIL-6R were measured using commercial ELISA kits from BioSource International (Camarillo, CA) and R&D Systems, Inc. (Minneapolis, MN), respectively. All the assays were done according to the manufacturer's instruction. The sensitivity for detection of sIL-2R and sIL-6R was 16.0 pg/ml and 31.2 ng/ml, respectively. The intra- and interassay coefficients of variation for

sIL-2R were lower than 6 and 9%; for sIL-6R were 9 and 7%, respectively.

All the blood samples were measured by duplicated wells and done in the same run. They were performed by the same investigator (Y.-M. Cheu) who was blind to the subjects' status. All data for IL-6, sIL-6R and sIL-2R were within detectable range.

2.4. Statistics

Chi-Square and Students' *t* tests were used to compute differences in sex and age between patients with SAD and normal controls. Paired *t* test was used to compare the 29-item SIGH–SAD scores in patients with SAD before and after light therapy. Repeated measures analysis of variance (ANOVA) and post-hoc analysis with the Mann–Whitney *U* test were used to compare the immune–inflammatory markers between groups. Repeated measures ANOVA and post-hoc analysis with Wilcoxon signed ranks test were used to compare the immune–inflammatory markers within SAD patients before and after light therapy. Relationships between variables were assessed by means of Spearman's correlation coefficient. Values reported are means ±S.D.s, unless otherwise specified. All tests were two-tailed, with significance set at $P < 0.05$. Computer analysis of the data was carried out using the Statistical Package for Social Science (SPSS, 1996).

3. Results

There was no significant difference in sex between patients with SAD and normal controls ($\chi^2 = 0.13$, df = 1, $P = 0.71$). There was also no significant difference in age between the patients with SAD (mean age 35.3 years, S.D. = 8.8) and normal controls (mean age 35.3 years, S.D. = 7.9) ($t = 0.02$, df = 28, $P = 0.98$). Repeated measures ANOVA on data of IL-6, sIL-6R, IL-6×sIL-6 and sIL-2R showed a significant group effect ($F = 14.9$, df = 1,28, $P < 0.002$) and a significant cytokine×group effect ($F = 8.9$, df = 3,84, $P < 0.001$). Post hoc analysis using a Mann–Whitney *U* test showed that patients with SAD had significantly increased IL-6 level (mean ±S.D.: 11.9±6.8 pg/ml) compared to normal (mean ±S.D.: 4.3±3.7 pg/ml) (Mann–Whitney $U = 27.0$, $P < 0.0005$) (Fig. 1A). There was no significant difference in sIL-6R level between the two diagnostic groups (SAD patients vs. normal controls, mean ±S.D.: 50.8±9.5 vs. 45.9±7.9 ng/ml) (Mann–Whitney $U = 80.0$, $P = 0.18$) (Fig. 1B). But, the product term of sIL-6R×IL-6 was significantly higher in patients with SAD (mean ±S.D.: 601.5±350.4) than that in normal controls (mean ±S.D.:200.6±180.0) (Mann–Whitney $U = 23.0$, $P < 0.0003$) (Fig. 1C). There was a trend toward increased sIL-2R in patients with SAD (means ±S.D.: 254.5±282.7 pg/ml) compared to normal controls (means ±S.D.: 133.5±107.7 pg/ml) (Mann–Whitney $U = 72.0$, $P = 0.09$) (Fig. 1D).

All 14 patients who completed the study improved with light therapy and nine of them (64%) had 50% reduction in score of the SIGH–SAD post-treatment compared to baseline. Their post-treatment 29-items SIGH–SAD scores (mean ±S.D.: 11.3±4.9, $n = 14$) were significantly lower than baseline scores (mean ±S.D.: 30.4±6.0, $n = 14$) ($t = 8.5$, df = 13, $P < 0.0001$). In contrast, repeated measures ANOVA on IL-6, sIL-6R, IL-6×sIL-6R and sIL-2R data showed no significant treatment effect ($F = 0.57$, df = 1.13, $P = 0.46$) nor significant treatment×cytokine interaction effect ($F = 0.61$, df = 3.39, $P = 0.62$). Post-hoc comparison using Wilcoxon signed ranks test showed that the plasma IL-6 levels in patients with SAD were not significantly different before (mean ±S.D.: 12.1±7.0 pg/ml, $n = 14$) and after 2 weeks of light therapy (mean ±S.D.: 11.7±8.8 pg/ml, $n = 14$) ($P = 0.42$) (Fig. 2A). Similarly, plasma levels of sIL-6R were not significantly different before (mean ±S.D.: 51.7±9.3 ng/ml, $n = 14$) and after the therapeutic light therapy (mean ±S.D.: 50.6±8.1 ng/ml, $n = 14$) (Wilcox signed ranks test, $P = 0.58$) (Fig. 2B). The product term of sIL-6R×IL-6 also did not significantly differ before (mean ±S.D.: 618.4±357.2, $n = 14$) and after the therapeutic light therapy (mean ±S.D.: 567.7±400.0, $n = 14$) (Wilcoxon signed ranks test, $P = 0.12$) (Fig. 2C). There was no significant difference in the plasma sIL-2R levels before (mean ±S.D.: 261.9±291.9 pg/ml, $n = 14$) and after the therapeutic light therapy (mean ±S.D.: 251.0±270.8 pg/ml, $n = 14$) (Wilcoxon signed ranks test, $P = 0.46$), either (Fig. 2D).

With regard to correlations between variables,

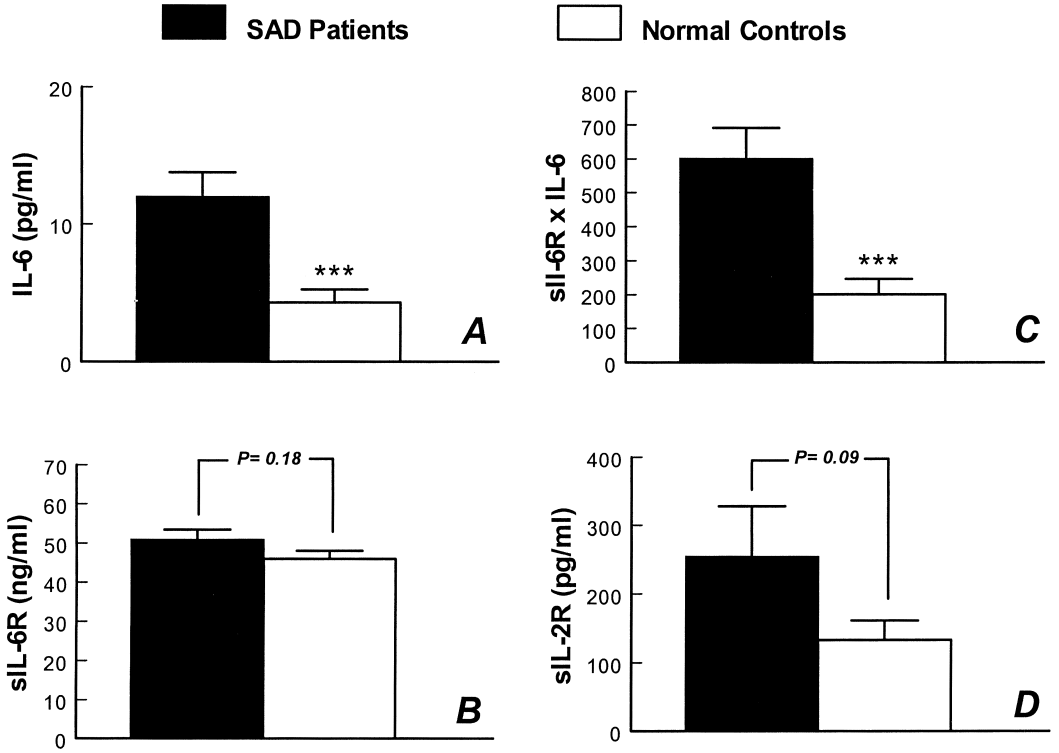

Fig. 1. (A–D) Comparison of immune–inflammatory markers (mean ±S.E.M.) between patients with seasonal affective disorders (SAD) ($n=15$) and normal controls ($n=15$) (***$P<0.0005$).

there was a significant positive correlation between IL-6 and the product term of IL-6×sIL-6 in patients with SAD (Spearman's $r=0.986$, $P<0.001$, $n=15$). But there was no significant correlation between IL-6 and either sIL-6 or sIL-2R levels. In addition, no significant correlations were found between the SIGH–SAD scores and any immune–inflammatory markers in patients with SAD. There were no significant correlations between the mean change in SIGH–SAD scores and those in the immune–inflammatory markers in patients with SAD before and after light treatment (data not shown). There were also no significant correlations between age or sex and any immune–inflammatory markers in SAD patients or normal controls (data not shown).

4. Discussion

The major findings of the present study included that 1) patients with SAD had significantly increased IL-6 levels and the product term of sIL-6×IL-6, as well as a trend toward increased plasma sIL-2R levels, and 2) the initially increased immune markers in SAD patients were not significantly altered by 2 weeks of successful light therapy.

This is the first report that plasma IL-6 concentrations are significantly increased in patients with SAD. This finding is consistent with previous reports that plasma IL-6 levels were significantly increased in patients with non-seasonal depression (Maes et al., 1995; Sluzewska et al., 1996; Maes et al., 1997; Sluzewska et al., 1997; Song et al., 1998) and that mitogen-induced culture supernatant IL-6 production was significantly increased in patients with melancholic depression (Maes et al., 1993), suggesting that an activation of immune–inflammatory system exists in both seasonal and non-seasonal depressions.

We did not find significant difference in plasma sIL-6R levels between SAD patients and normal controls. However, the product term of sIL-6R×IL-6

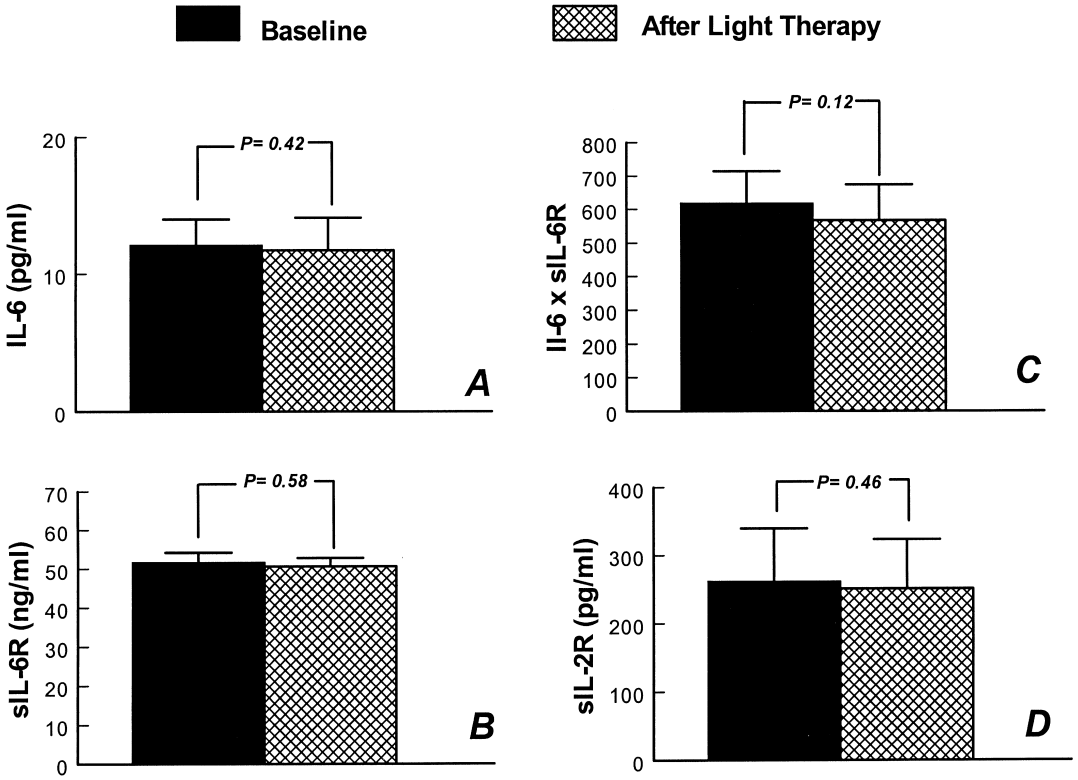

Fig. 2. (A–D) Comparison of immune–inflammatory markers (mean ±S.E.M.) in patients with SAD before ($n=14$) and after 2 weeks of light therapy ($n=14$).

was significantly higher in SAD patients than normal controls. Furthermore, the average product term of sIL-6R×IL-6 was three times higher in SAD patients than that in normal controls. This is consistent with two previous studies of patients with non-seasonal depression (Maes et al., 1995; Sluzewska et al., 1995), which also reported that the average product term of sIL-6R×IL-6 was three times higher in depressed patients than that in healthy subjects. As mentioned in the introduction, sIL-6R has a potentiating effect on the IL-6 activity. The significant increase in the product term of sIL-6R×IL-6 in patients with SAD would, therefore, suggest that SAD patients had a significantly higher biological activity of IL-6 than normal controls. This appears to support an activation of the immune–inflammatory system in seasonal depression.

As mentioned in the introduction, sIL-2Rs are released from activated T cells into the blood (Caruso et al., 1993). They are considered as an index of T cells activation. In the present study, we found a trend (a two-tailed $P=0.09$) towards increased plasma sIL-2R levels in patients with SAD. This trend, albeit did not reach significance, might suggest that T-cell activation is also involved in seasonal depression, because IL-6 plays an important role in T cell activation (Kushner, 1991) and we found a significant increase in plasma IL-6 levels and the product term of sIL-6R×IL-6 in patients with SAD. If this is the case, one may expect that the increased IL-6 in SAD patients activates T-cells, which would in turn lead to an increase in the release of sIL-2R into the blood. Further studies that examine HLA-DR$^+$ and CD25$^+$ T cells and sIL-2R

levels in a larger number of SAD patients are needed to verify this.

With regard to the effects of light therapy on the immune–inflammatory markers, we did not find any significant change in plasma levels of IL-6, sIL-6R, and sIL-2R levels or the product term of sIL-6R× IL-6 in patients with SAD following 2 weeks of light therapy. This is consistent with the finding reported by Maes et al. (1995) that treatment with fluoxetine (mean: 81.2 days) or the typical antidepressants including nortriptyline, amitriptyline, and imipramine (mean: 85.4 days) did not significantly affect plasma IL-6, sIL-6R and sIL-2R levels in a group of patients with non-seasonal depression. Taken together, our results and the findings of Maes et al. (1995) might suggest that an activation of immune–inflammatory system (as measured by plasma IL-6, sIL-6R and sIL-2R levels) is a trait marker for patients with seasonal and non-seasonal depressions. However, an alternative explanation could be that these increased immune–inflammatory markers in SAD patients take longer time to normalize, despite the therapeutic effect of light therapy. In this regard, it is of worth to note the results of two longitudinal studies. Frommberger et al. (1997) showed that plasma IL-6 levels were significantly elevated in 12 depressed patients during the acute state of illness compared to 12 normal controls. The increased plasma IL-6 levels in depressed patients significantly decreased after remission (8 weeks since admission) and they did not significantly differ from those in normal controls. Similarly, Seidel et al. (1995) showed that mitogen-induced IL-6 and sIL-2R levels were significantly increased in 39 patients with major depression shortly after admission compared to 39 normal controls. These elevated supernatant IL-6 and sIL-2R levels significantly decreased and tended to reach control values over a 6-week period of time. Further longitudinal studies of immune function in patients with SAD are needed to clarify this trait or state marker issue.

In conclusion, our findings of increased IL-6, IL-6×sIL-6R, and sIL-2R in patients with SAD suggest an activation of the immune–inflammatory system in winter depression, which is not altered by 2 weeks of successful light therapy. Studies of other immune inflammatory markers in patients with SAD are needed for further evidence of immune activation in this condition.

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