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Journal of Affective Disorders 63 (2001) 85–92

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Research report

The inflammatory response following delivery is amplified in women who previously suffered from major depression, suggesting that major depression is accompanied by a sensitization of the inflammatory response system

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Received 25 September 1999; received in revised form 24 December 1999; accepted 29 January 2000

Abstract

Background: There is now evidence that some patients with major depression show an activation of the inflammatory response system (IRS). This study was carried out to examine whether major depression may induce sensitization with increased IRS responses to the stress of child birth. *Methods:* Serum concentrations of interleukin-6 (IL-6), the soluble IL-6 receptor (sIL-6R), sgp130 (the IL-6 signal transducing protein) and the sIL-1R antagonist (sIL-1RA) were determined in 16 and 50 women with and without a lifetime history of major depression, respectively. Blood was collected 3–6 days before delivery and 1 and 3 days after delivery. On each occasion the women completed the Zung Depression Rating Scale (ZDS). *Results:* Serum IL-6, sIL-6R, sIL-1RA were significantly higher 1 and 3 days after delivery than before. Women who had suffered from a lifetime history of major depression had greater increases in serum IL-6 and sIL-1RA in the early puerperium than women without a lifetime history. Women who had suffered from a lifetime history of major depression had significantly higher IL-6, and sIL-1RA concentrations 1 and 3 days after delivery than women with a negative life-time history. *Conclusions:* The responses of IL-6 and sIL-1RA following delivery are amplified in women who previously suffered from major depression. The results suggest that major depression is accompanied by a sensitization of the IRS.

Keywords: Cytokines; Long term sensitization; Kindling; Post-partum major depression; Immunology

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0165-0327/01/$ – see front matter
PII: S0165-0327(00)00156-7

1. Introduction

There is now evidence that major depression is accompanied by activation of the inflammatory response system (IRS), as indicated by signs of (a) an acute phase response; (b) immune activation, e.g. increased serum and urinary concentrations of neopterin, increased numbers of leukocytes, neutrophils and activated T cells; (c) in vitro immunosuppression, e.g. decreased mitogen-induced lymphoproliferative responses and blunted natural killer cell activity; and (d) increased secretion of proinflammatory cytokines, such as interleukin-1 (IL-1), IL-6 and interferon-γ (IFNγ), and cytokine receptors or receptor antagonists, e.g. the soluble IL-6 receptor (sIL-6R) and the sIL-1R antagonist (sIL-1RA) (Seidel et al., 1996; Maes, 1997; Connor and Leonard, 1998; Maier and Watkins, 1998). It is thought that the increased production of proinflammatory cytokines in depression may underlie the changes in the IRS in that illness (Maes, 1997). It is also hypothesized that increased production of these cytokines may contribute to the etiology of major depression (Maes, 1997; Yirmiya, 1997). In rats, induction of IRS activation by administration of endotoxin may decrease the free consumption of saccharin, a model of anhedonia (Yirmiya, 1996).

Acute or repeated administration of IL-1, IL-6 and IFNs may induce symptoms associated with depression, such as anorexia, weight loss, sleep disorders, anxiety, and inhibition of social, locomotor and exploratory behavior (Gutterman et al., 1982; Maier and Watkins, 1995; Sakic et al., 1997; Anisman et al., 1998; Dantzer et al., 1998; Linthorst and Reul, 1998). It is believed that these behavioral and emotional effects of proinflammatory cytokines are related to their modulatory effects on the serotonergic and catecholaminergic turnover and hypothalamic–pituitary–adrenal axis (Maes, 1997; Yirmiya, 1997).

Several investigators have demonstrated that IRS responses may be subject to learning processes, such as classical conditioning and sensitization. For example, pairing of an unconditioned stimulus (administration of IFNγ) and a conditioned stimulus permits the latter to prolong IFNγ-induced neopterin production in humans (Longo et al., 1999). Adult female mice, which were stressed during postnatal development show enhanced immune reactivity to stressors as compared with unhandled mice (Neveu et al., 1994). LPS-induced increases in serum concentrations of some proinflammatory cytokines were higher in carrageenan- or IFN-sensitized mice (Blanque et al., 1998). Thus, exposure to psychological and organic stressors may induce long-term alterations in IRS responses, which require a restress to get triggered and which get stronger with the passage over time. This phenomenon, called time-dependent sensitization (TDS), can also effect the behavioral, neuronal and endocrine responses to stress exposure (Antelman et al., 1991; Bell et al., 1993). Other key features of TDS are: (a) initiation by simple or intermittent stimuli; (b) cross-sensitization between stressors; (c) greater vulnerability in females, and (d) both context-dependent (conditioned) and context independent (unconditioned) amplification of responses (Bell, 1994).

Based on the above, we hypothesized that major depression may induce a sensitization of the IRS with a progressive increase in IRS activation upon subsequent exposure to a new stressor. There is now some evidence that in humans, delivery may induce IRS activation, as indicated by increased serum IL-6 and sIL-6R concentrations (Baboonian et al., 1989; Buonocore et al., 1995; Rebelo et al., 1996; De Jongh et al., 1998). Thus, we anticipated to find greater IRS activation, e.g. greater increases in serum IL-6, sIL-6R and sIL-1RA, in the early puerperium in parturients who previously suffered from major depression.

The specific aims of the present study were to examine whether the responses of serum IL-6, sIL-6R and the sIL-1RA following delivery are higher in women with than without a previous history of major depression. The sIL-6R in plasma is generated by proteolysis of the membrane receptor on immune and other cells (Mullberg et al., 1993). The sIL-6R in serum has the potential to mediate IL-6 signals (even in IL-6-insensitive cells) by forming a complex with IL-6, which, in turn, associates with gp130, the signal transducer protein for IL-6 (Saito et al., 1993; Benigni et al., 1996). sGp130 may be generated by proteolysis (shedding) of the membrane receptor components and has the potential to compete with its membrane-bound counterpart and, consequently, may inhibit IL-6 signaling (Narazaki et al., 1993;

Murakami-Mori et al., 1996). Hence, we determined serum sgp130. The IL-1RA is a pure IL-1 receptor antagonist (Dripps et al., 1991), which is mainly derived from monocytes and is released in vivo during an AP response (Dayer and Burger, 1994).

2. Subjects and methods

2.1. Subjects

Sixty-six women, admitted to the hospital (Department of Gynecology, ZOL, Campus St. Jan, Genk, Belgium) for delivery, participated. Exclusion criteria for pregnant women were (i) medical disorders; (ii) past or present axis-I diagnoses, except major depression; (iii) ever have been taking psychotropic medications, except antidepressants; (iv) women who went into labor prematurely (<37 weeks); (v) women with ruptured membranes for more than 12 h; (vi) women with infections before/after delivery; (vii) women who had a cesarean section; (viii) treatment with drugs (including psychotropic drugs, such as antidepressants) known to interfere with immune or endocrine functions; and (ix) medical illnesses and acute infectious or inflammatory reactions for at least 2 weeks prior to the study. Inclusion criteria were: (i) a normal physical examination; and (ii) normal values of blood and urine tests, such as SGOT, SGPT, GGT, hematocrit, serum electrolytes, and renal tests (blood urea and creatinine). The study protocol was approved by the institutional review board of the ZOL, Genk, Belgium. All subjects gave written informed consent after the study design was fully explained.

2.2. Methods

Serum for assay of IL-6, sIL-6R, sgp130 and sIL-1RA was collected at 08:00 h ($\pm$30 min) 3 to 5 days before the anticipated date of delivery (at the Antenatal Clinic) and 1 and 3 days after delivery (while hospitalized at the maternity hospital). During each of these three sessions, women completed the Zung Depression Scale (ZDS) (Zung, 1965). Within 6 to 10 months after delivery, women had a telephone interview by one of the authors trained in the DSM interview techniques. The Structured Clinical Interview of the DSM (Spitzer et al., 1990) was carried out to assess past history (before delivery) of major depression. Telephone interviews aimed to assess a past history of depression according to DSM criteria are commonly used in epidemiologic studies (Kendler and Prescott, 1999). There were 16 and 50 parturient women with and without a past history of major depression, respectively.

The following labor and maternal variables were assessed and controlled for in the statistical analyses: (i) type of delivery, i.e. normal vaginal delivery, or vaginal delivery by means of a forceps or ventouse; (ii) parity, i.e. nulliparae versus multiparae; (iii) duration of pregnancy and labor; (iv) labor induction or not; (v) amniotomy, i.e. spontaneous versus induced; (vi) type of analgesia, i.e. no analgesia, pentazocine 30 mg i.m., or epidural analgesia (10 ml of bupivacaine 0.125% with adrenaline 1/800 000 and with 1 μg/ml sufentanil); (vii) breast feeding or not; and (viii) postpartum complications (such as malleolar edema and use of antibiotics for possible infection) or not.

All serum specimens for each of the IRS variables were assayed in a single run with a single lot number of reagents and consumables employed by a single operator. IL-6, sIL-6R, sgp130 and sIL-1RA were quantified by means of ELISA methods (Eurogenetics, Tessenderlo, Belgium) based on appropriate and validated sets of monoclonal antibodies. The intra-assay CV values were less than 8% for all assays. In order to obtain an index of the synergizing effects between serum IL-6 and sIL-6R (Saito et al., 1993; Benigni et al., 1996), we computed the product term IL-6 $\times$ sIL-6R (Sluzewska et al., 1996).

2.3. Statistics

Group mean differences were ascertained by means of analyses of variance (ANOVA) or analysis of covariance (ANCOVA). Repeated measure (RM) design ANOVAs were employed to examine the between-subject variability with diagnosis (a past history of depression) and the maternal/labor variables as factors, and the within-subject variability with the baseline and two postpartum conditions as time factor; and two-way interactions between time $\times$ diagnosis and time $\times$ maternal/labor vari-

ables. All results of RM design ANOVAS were corrected for sphericity. Tests on simple effects were carried out in order to examine significant main effects or significant interaction patterns (Howell, 1982). Comparisons among treatment means and diagnosis were ascertained with the Dunn test (Howell, 1982).

3. Results

Fig. 1 shows the effects of delivery on the ZDS, serum concentrations of IL-6, sIL-6R, sgp130 and sIL-1RA and on the product term IL-6 × sIL-6R. There were no significant differences in age between women with (mean age = 28.4±3.8 years) and without (mean age = 27.3±3.3 years) a history of major depression ($F = 1.1$, df = 1/64, $P = 0.3$). RM design ANOVAs with serum IL-6, sIL-6R, sgp130 and sIL-1RA as dependent variables and labor induction, type of analgesia, type of delivery, breast feeding, postpartum complications, parity and amniotomy as factors, did not show any significant interactions between time × diagnostic groups.

Fig. 1 shows that there was no significant effect of time on the ZDS score ($F = 0.7$, df = 2/115, $P = 0.5$) and that the interaction pattern time × diagnostic classification was not significant ($F = 2.5$, df = 2/115, $P = 0.08$). Analyses on simple effects did not show any effect of time on the ZDS score in women with or without a past history of major depression. RM design ANOVA performed on the IL-6 data showed a significant effect of time ($F = 19.6$, df = 1/67, $P = 0.0004$). Analyses on simple effects showed (i) significant effects of time in women with ($F = 18.3$, df = 2/94, $P < 10^{-3}$) and without ($F = 3.2$, df = 2/94, $P = 0.02$) a past history of depression; and (ii) significantly higher IL-6 values in women with than without a past history of major depression 1 ($F = 7.4$, df = 1/141, $P = 0.007$) and 3 ($F = 5.3$, df = 1/141, $P = 0.02$) days after delivery, but not before delivery ($F = 0.05$, df = 1/141, $P = 0.8$).

RM design ANOVA showed a significant effect of time on serum sIL-6R ($F = 24.6$, df = 2/79, $P < 10^{-3}$). Dunn tests showed significantly higher serum sIL-6R concentrations in women with a past than without a past history of depression ($t = 3.01$, $P = 0.003$). RM design ANOVAs performed on the product term IL-6 × sIL-6R showed a significant effect of time ($F = 25.8$, df = 2/71, $P < 10^{-3}$) and a significant time × diagnostic group interaction ($F = 4.1$, df = 2/72, $P = 0.02$). Analyses on simple effects showed: (i) significant effects of time in women with ($F = 25.3$, df = 2/94, $P < 10^{-3}$) and without ($F = 4.6$, df = 2/94, $P = 0.01$) a past history of major depression; and (ii) a significantly higher product term IL-6 × sIL-6R in women with and without a past history of depression, 1 ($F = 7.1$, df = 1/141, $P = 0.008$) and 3 days after ($F = 9.1$, df = 1/141, $P = 0.003$) delivery, but not before delivery ($F = 0.03$, df = 1/141, $P = 0.8$).

RM design ANOVA performed on the sgp130 data showed no significant effect of time ($F = 2.9$, df = 2/94, $P = 0.06$) and no significant time × diagnostic group interaction ($F = 1.1$, df = 2/94, $P = 0.2$). Dunn test showed no significant difference in serum sgp130 between women with and without a past history of depression ($t = 0.63$, $P = 0.05$). RM design ANOVA performed on the sIL-1RA data showed a significant effect of time ($F = 12.6$, df = 2/89, $P = 0.00008$) and a significant time × diagnostic group interaction ($F = 5.0$, df = 2/89, $P = 0.009$). Analyses on simple effects showed (i) a significant effect of time in women with ($F = 16.4$, df = 2/98, $P < 10^{-3}$), but not without ($F = 1.1$, df = 2/98, $P = 0.3$) a past history of major depression; and (ii) significantly higher serum sIL-1RA concentrations in women with than without a past history of depression, 1 ($F = 14.0$, df = 1/147, $P < 10^{-3}$) and 3 ($F = 13.3$, df = 1/147, $P < 10^{-3}$) days after delivery, but not before delivery ($F = 1.5$, df = 1/147, $P = 0.2$). There were no significant correlations between any of the IRS variables and the time interval between the last episode of major depression and childbirth.

4. Discussion

The major findings of this study are that parturients who previously had suffered from a major depressive episode had significantly greater responses in serum IL-6, the product term IL-6 × sIL-6R and sIL-1RA than parturients without a previous history of depression. This indicates increased activation of the IRS and in particular of the monocytic–macrophage arm of cell-mediated immunity in par-

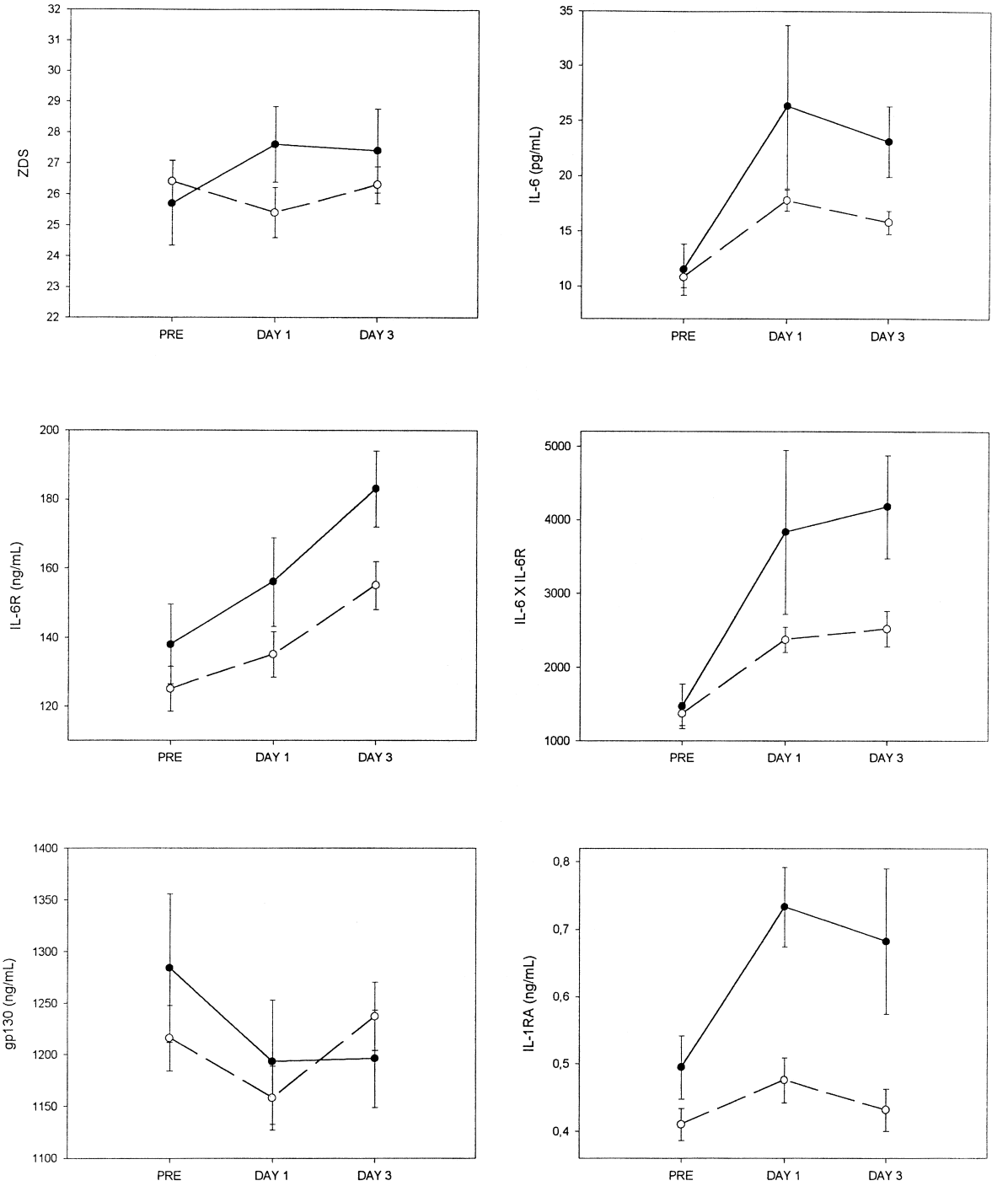

Fig. 1. Mean (S.E.M.) serum concentrations of interleukin-6 (IL-6), IL-6 receptor (sIL-6R), the product term IL-6 × IL-6R, gp130, and the IL-1R antagonist (sIL-1RA) in women, divided in those with (●) and without (○) a past history of major depression, at the end of term (PRE) and 1 (DAY1) and 3 (DAY3) days after delivery.

turients with a past history of depression. Although the delivery-induced increases in serum sIL-6R did not differ significantly between parturients with and without a past history of depression, the former showed higher serum sIL-6R concentrations, before and after delivery, than parturients without a past history of depression. These findings are in agreement with previous reports on increased serum sIL-6R concentrations in major depression (Maes et al., 1995; Sluzewska et al., 1996). Since no significant differences in sgp130 were found in parturients with or without a past history of depression, IL-6 signaling in those subjects is not likely to be differently modulated by changes in serum sgp130. Since also the responses in the product serum IL-6 × sIL-6R are significantly greater in parturients with a past history of depression and since the sIL-6R augments the biological activity of IL-6 (Bock et al., 1992), our findings suggest higher IL-6 signaling in parturients with than without a past history of major depression.

Previous research has shown that women with a past history of depression are at an increased risk to develop maternity blues or postpartum depression (Hapgood et al., 1988) and that maternity blues may grade into postpartum depression (Lee, 1982). However, in the present study, no significant differences in the ZDS scores could be found between parturient women with and without a previous history of depression and no significant alterations in the ZDS score in either one of those two study groups could be found in the early puerperium. These findings indicate that the increased IRS responses in the early puerperium in women with a past history of depression are not associated with an increase in depression severity in the early puerperium.

It has been shown that delivery may trigger activation of the IRS as characterized by increased serum IL-6 and sIL-6R (Rebelo et al., 1996; De Jongh et al., 1998). The findings of the present study suggest that women who previously suffered from a major depressive episode have a greater vulnerability to develop activation of the IRS in response to delivery. Thus, exposure to a previous depressive episode may magnify the size of the IRS response in the early puerperium. As described in the Introduction, the IRS is sensitizable to restress whereby cross-sensitization between stressors and conditioned or unconditioned amplification of responses may occur (Bell, 1994). Therefore, one plausible explanation, which was the a priori hypothesis for this study, is that major depression may induce sensitization in the IRS, and that the restress of delivery triggers the activation of the sensitized IRS.

Previously, the syndrome progression manifested by either increased frequency, severity or spontaneity of depressive episodes has been attributed to sensitization (Post and Weiss, 1998). Post and Weiss (1998) proposed kindling, i.e. the progressive development of seizures generated by repeated low levels of electrical stimulation of limbic structures (Baudry, 1986), as a valid model of preclinical sensitization in depressive disorders. For example, the greater role for psychological stressors in association with the first episode of depression than with subsequent episodes is explained by sensitization to stressors (Post, 1992). It is thought that stressors and the biochemical concomitants of the episodes themselves can induce the protooncogene c-fos, which then affects the expression of hormones, neurotransmitters and receptors (Post, 1992). Both psychosocial stressors and depressive episodes may leave residual traces which increase the vulnerability to further occurrence of affective disorders (Post, 1992; Poirier-Littre, 1994). The role of the sensitizable IRS as an important factor in the kindling model of affective disorders may be suggested by: (i) the results of the present study that major depression is accompanied by a sensitization in the IRS; (ii) previous findings that psychological stress may activate the IRS to produce greater amounts of proinflammatory cytokines (Maes et al., 1998a,b); and (iii) previous findings showing that proinflammatory cytokines induce c-fos (mRNA) expression (Callahan and Piekut, 1997; Herkenham et al., 1998) as well as the turnover of those neurotransmitters and hormones related to the pathophysiology of depression (reviews: Maes, 1997; Yirmiya, 1997). Moreover, proinflammatory cytokines, such as IL-1, may induce sensitization in stress hormones. For example, exposure of IL-1 primed rats 1–2 weeks later to footshocks results in exaggerated cortisol responses as compared to vehicle-primed controls, suggesting that IL-1 induces longlasting hyperresponsiveness to stressors (Tilders and Schmidt, 1998).

Acknowledgements

The research reported was supported in part by the Staglin Investigator Award to Dr. M. Maes (NARSAD); the Funds for Scientific Research, Vlaanderen, Belgium (FWO); and the CRC-MH, Antwerp, Belgium.

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