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Immunoendocrine aspects of major depression

Relationships between plasma interleukin-6 and soluble interleukin-2 receptor, prolactin and cortisol

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Abstract Recently, a complete bidirectional circuit between the immune and neuroendocrine systems has been documented. Previous reports from this laboratory have shown that there are complex reciprocal relationships between immune and hypothalamic-pituitary-adrenal (HPA)-axis function in major depression. To further examine the immune-endocrine relationships, this study investigates plasma baseline cortisol and prolactin secretion in relation to plasma interleukin-6 (IL-6) and soluble IL-2 receptor (sIL-2R) levels in 34 healthy controls and 56 major depressed patients. There were significant positive correlations between IL-6 or sIL-2R and plasma cortisol in major depressed subjects and in the combined group of major depressed and healthy subjects. There were also significant positive correlations between plasma prolactin and sIL-2R concentrations in major depressed subjects and in the combined groups of normal and major depressed subjects.

Key words Depression · Psychoimmunology · Interleukin-6 · Soluble interleukin-2 receptor · Prolactin · Cortisol · Pituitary

Introduction

Recently, a complete bidirectional circuit between the neuroendocrine and immune systems has been described (Blalock 1984; Berczi 1986). The nervous system may modulate various aspects of immune functions through direct innervation of immune organs (e.g. thymus, spleen, and bone marrow) and the release of hormones, such as hypothalamic-pituitary-adrenal (HPA)-axis hormones and prolactin (Plata-Salaman 1991). Glucocorticoids, for example, have immunosuppressive and anti-inflammatory actions through a variety of mechanisms, including cell death in thymocytes and immature T-cells, inhibitory effects on interleukin-1 (IL-1), IL-2 and IL-6 production and secretion, and redistribution of circulating monocytes, T and B lymphocytes (Fauci 1975; Wyllie 1980; Snyder and Unanue 1982; Berczi 1986; Bloemena 1989; Nieto and Lopez-Rivas 1989; Waage et al. 1990; Rinner et al. 1992). Prolactin is an important immunoregulatory hormone that modulates the immune system, e.g. prolactin activates immunocompetent T lymphocytes and causes expression of IL-2 receptors and Il-2 production in immune cells (Berczi and Nagy 1986; Skwarlo-Sonta 1992).

While the immune system is subject to neural and neuroendocrine control, it exerts a reciprocal effect on the neuroendocrine system, including the HPA-axis (Berczi 1986; Smith and Blalock 1986; Berkenbosch et al. 1987; Del Rey et al. 1987; Plata-Salaman 1991). There is now evidence that, during an immune response, the HPA-axis is activated and that stimulation of the brain catecholaminergic and serotonergic neurotransmission are involved in this phenomenon (Sapolsky et al. 1987; Dunn et al. 1989; Dunn and Welch 1991; Weidenfeld et al. 1989; Matta et al. 1990; Rivier et al. 1989). These neural-neuroendocrine responses are, in part, mediated through cytokines, such as IL-1, IL-2 and IL-6, which are secreted during the immune response (Plata-Salaman 1991; Naitoh et al. 1988; Navarra et al. 1991; Dunn et al. 1989).

Major depression and, in particular, major depression with melancholic features is characterized by increased activity of the HPA-axis (Carroll 1980; Maes et al. 1991 d), alterations in prolactin secretion (Mendlewicz et al. 1980; De la Fuente and Rosenbaum 1981) and by an immune response. The latter is indicated by increased serum levels of soluble IL-2 receptor (sIL-2R) (Maes et al. 1991 c; Nassberger and Traskman-Bendz 1993), increased production of IL-6 by mitogen-stimulated peripheral blood mononuclear cells (PBMC) and increased plasma IL-6 concentrations (Maes et al., submitted). IL-2 is a T cell

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growth factor produced by activated T cells which plays a pivotal role in the generation of an immune response and in T cell proliferation; sIL-2Rs are released from activated T cells into the blood and sIL-2R concentrations appear to correlate with IL-2 secretion in various pathological conditions (Caruso et al. 1993). IL-6 is a pleiotropic cytokine which is a major immune and inflammatory mediator that plays a pivotal role in T and B lymphocyte proliferation or differentiation, T cell activation, hematopoiesis, regulation of antibody production, and the acute phase response (Hirano 1991; Heinrich et al. 1990).

Complex relationships between HPA-axis hyperactivity and immune function have been described in major depression. First, immunosuppressive effects of endogenous HPA-axis hyperactivity in depression are suggested by the negative relationship (a) between post-dexamethasone cortisol values and mitogen-induced lymphoproliferative responses, and (b) between 24-h urinary cortisol excretion and number or percentage of PBMC, such as monocytes, lymphocytes, $CD4^+$ and $CD4^+CD45RA^+$ T cells (Maes et al. 1989, 1991a, 1994). Second, other reports suggest a parallel upregulation of HPA-axis and immune functions in depression: (a) significantly positive correlations were detected between IL-1β or IL-6 production in mitogen-stimulated culture supernatant and post-dexamethasone cortisol values (Maes et al. 1993a, b); and (b) dexamethasone HPA-axis nonsuppressors exhibit increased numbers of $CD4^+$ cells, activated T cells (i.e. $HLA\text{-}DR^+$) and B lymphocytes (Maes et al. 1994). However, no research has examined either the relationships between plasma interleukins or their receptor levels and indicants of HPA-axis function or between these immune variables and prolactin secretion in patients with major depression.

The purpose of this study was to examine the relationships between plasma levels of IL-6 or sIL-2R and cortisol or prolactin secretion in major depressed patients and normal volunteers.

Subjects and methods

Subjects

Ninety subjects participated in this study; 34 normal controls and 56 major depressed subjects. Patients were categorized according to DSM-III-R criteria (APA 1987) on the basis of structural interviews (Schedule for Affective Disorders and Schizophrenia; Endicott and Spitzer 1978). The Hamilton Depression Rating Scale (HDRS) – 24-item version – was used to measure severity of illness (Hamilton 1960). The major depressed subjects were in an acute phase of illness. The authors have omitted patients with other axis-I diagnoses besides major depression, e.g. substance use disorder (6 months before the study), organic mental disorders and schizophrenia. The IL-6 and sIL-2R results were described as part of a larger study on the effects of antidepressants and differences between depressed subjects in an acute phase of illness and in clinical remission; it was shown that treatment with anti-depressants did not affect plasma IL-6 or sIL-2R in the subjects included in this study (Maes et al., submitted). Patients in an acute episode of major depression who had been treated with typical anti-depressants, such as imipramine, amitriptyline, and nortriptyline, before hospitalization were withdrawn from all drugs for at least 1 week prior to the studies. Thirty patients were free of all psychotropic medications for at least 14 days prior to these studies. The others had a wash-out or drug-free period between 7 and 14 days (mean = 8.3 ± 1.99 days). None of the patients had been treated with fluoxetine for at least 2 months prior to the studies. The normal controls were free of any medication during at least 1 month prior to blood sampling. No one was a regular drinker or had ever taken psychotropic drugs. They were screened for current, past and family history of psychiatric disorders by means of structured interviews. No one suffered from any psychiatric disorder; those with a past psychiatric history or psychiatric history in first-degree relatives were excluded. All subjects were medically healthy as screened by physical examination, electrocardiogram, and blood and urine analyses. Criteria for inclusion in this study included normal SGPT, SGOT and GGT, normal hematologic measures, such as hematocrit, serum electrolytes, and normal renal function tests, such as blood urea and serum creatinine. All subjects were free of drug known to interfere with immune or endocrine function. All subjects were free of chronic illnesses known to affect the immune status and of acute infectious or allergic reactions for at least 2 weeks prior to the study.

Methods

After insertion of an intravenous cannula at 8:30 a.m., blood was taken every 15 min until 9:00 a.m. (TO), and then every 30 min until 11:00 a.m. Subjects remained supine during the test period; they were not allowed to eat, drink, sleep or smoke during the study period. Plasma for the determination of IL-6 and sIL-2R was sampled at 8:45 a.m. Cortisol and prolactin values were determined in plasma samples obtained from TO until 2 h later. Plasma was stored at –20° C until thawed for IL-6, sIL-2R, cortisol or prolactin assay. Prolactin assays were complete in 31 normal controls and 33 depressed subjects, cortisol in 32 normal controls and 48 depressed subjects, IL-6 in 32 normal and 56 depressed subjects, and sIL-2R in all subjects.

Cortisol was determined by means of a radioimmunoassay, using kits from Diagnostic Products Corporation, Los Angeles, Calif. The interassay coefficient of variation (CV) was 4.3% (mean = 13.3 μg/dL, $n = 13$). Prolactin was assayed by means of a double-antibody radioimmunoprocedure using reagents from The National Institute of Arthritis and Metabolic Diseases. The interassay CV of duplicate determinations in the same assay was 3.5%. Two indices of hormone secretion were employed, i.e. TO values and the area under the time X concentration curve from TO until 2 h later (labeled as AUC). IL-6 was quantified with a sandwich EIA (Eurogenetics) based on a monoclonal-monoclonal antibody pair and a biotin-streptavidin amplification system. The dynamic range of the immunoassay varies between 0 and 500 pg/mL with an intra-assay coefficient of variation of 3.9% at the 10 pg/mL level. Standardization of sIL-2R measured by the sIL-2R EIA (Eurogenetics) is expressed in arbitrary units and ranges between 20 and 1600 U/mL. Each unit corresponds to approximately 12.5 pg/mL pure recombinant α-chain receptor. The intra-assay coefficient of variation is 2% at a level of 208 U/mL.

Statistics

The independence of classification systems was examined by means of analysis of contingence (χ^2-test). Relationships between variables were assessed by means of Pearson's product moment and Spearman's rank order correlation coefficients or through multiple regression analysis. Group mean differences were ascertained by means of analysis of variance (ANOVA) or analysis of covariance (ANCOVA). Normality of distribution was checked with the test of goodness-of-fit (χ^2-test). Transformations were used to reach normality of distribution or to adjust for heterogeneity of variance between study groups (IL-6, cortisol and prolactin in logarithmic transformation).

Table 1 Correlations between plasma cortisol, prolactin, interleukin-6 (IL-6) and soluble IL-2 receptor (sIL-2R) levels in healthy controls and major depressed subjects. Cortisol values are assessed as area under the time × concentration curve from TO until 2 h later; prolactin is assessed as TO prolactin (r: Pearson's product moment correlation coefficients; r_s: Spearman's rank order correlation coefficients; r_p: Pearson's correlations are pooled over normal and major depressed subjects; exact P-values are given between parentheses)

Variables	Major depression	Healthy controls	Healthy controls and depressed subjects
Cortisol and IL-6	$r = 0.30$ (0.03) $n = 48$ $r_s = 0.31$ (0.03)	$r = 0.28$ (0.1) $n = 30$ $r_s = 0.33$ (0.06)	$r_p = 0.29$ (0.009) $n = 78$
Cortisol and sIL-2R	$r = 0.28$ (0.04) $n = 48$ $r_s = 0.34$ (0.02)	$r = 0.33$ (0.06) $n = 32$ $r_s = 0.24$ (0.17)	$r_p = 0.30$ (0.007) $n = 80$
Prolactin and sIL-2R	$r = 0.50$ (0.003) $n = 33$ $r_s = 0.43$ (0.01)	$r = 0.22$ (0.2) $n = 31$ $r_s = 0.27$ (0.13)	$r_p = 0.33$ (0.007) $n = 64$

Results

Demographic data

There were no significant differences in TO cortisol (9.3 ± 3.7 versus 9.7 ± 4.5 µg/dL; $F = 0.1$, $df = 1/78$, $P = 0.7$), AUC cortisol (51.0 ± 20.4 versus 54.9 ± 24.4 µg/dL; $F = 0.4$, $df = 1/78$, $P = 0.5$). TO prolactin (6.2 ± 3.3 versus 5.9 ± 3.2 ng/mL; $F = 0.2$, $df = 1/62$, $P = 0.6$), AUC prolactin (42.5 ± 40.5 versus 35.8 ± 23.7 ng/mL; $F = 0.7$, $df = 1/62$, $P = 0.6$) between healthy controls and major depressed patients, respectively. Major depressed subjects showed significantly higher sIL-2R values than normal controls (293 ± 69 versus 236 ± 100 U/mL; $F = 10.3$, $df = 1/88$, $P = 0.002$). Major depressed subjects also showed significantly higher plasma IL-6 than normal controls, i.e. real mean after logarithmic transformation with SEM range: 3.5 [3.2–3.9] versus 1.5 [1.2–1.8] pg/mL; $F = 23.4$, $df = 1/86$, $P = 0.00005$. There were no significant differences in men/women ratio (i.e. 18/16 versus 35/21; $\chi^2 = 0.8$, $df = 1$, $P = 0.4$) between normal controls and major depressed patients, respectively. Patients with major depression were somewhat older than normal controls (36.9 ± 9.8 versus 31.9 ± 6.8 years; $F = 7.0$, $df = 1/88$, $P = 0.01$). There were no significant relationships between age and TO cortisol ($r = 0.00$, $P = 0.9$), AUC cortisol ($r = 0.01$, $P = 0.9$), TO prolactin ($r = -0.04$, $P = 0.7$), AUC prolactin ($r = -0.11$, $P = 0.6$), or sIL-2R ($r = -0.10$, $P = 0.6$) – all results of correlation calculations pooled over the two groups. There was a weak but significant negative relationship between age and IL-6 ($r = -0.26$, $P = 0.01$). ANOVAs, factorial design (with diagnosis and gender as groups) did not reveal significant differences between men and women in sIL-2R ($F = 0.00$, $df = 1/86$, $P = 0.9$), IL-6 ($F = 0.9$, $df = 1/84$, $P = 0.7$), TO cortisol ($F = 0.00$, $df = 1/76$, $P = 0.9$), AUC cortisol ($F = 1.4$, $df = 1/76$, $P = 0.2$) or AUC prolactin ($F = 1.6$, $df = 1/60$, $P = 0.2$). Men showed significantly lower TO prolactin values than women (5.3 ± 2.8 versus 7.1 ± 3.5 ng/mL; $F = 5.8$, $df = 1/60$, $P = 0.02$). The above intergroup differences in IL-6, sIL-2R or hormone values did not change after introducing age and sex as covariates in ANCOVAs.

There were no significant differences in any of the immune or endocrine variables between depressed subjects with a drug-free period of more than 14 days and those with a drug-free period of less than 14 days. There were no significant effects of the drug-free period on the relationships between immune and endocrine variables, which are listed below (tested by means of multiple regression analysis).

Immuno-neuroendocrine relationships

Table 1 lists the relationships (i.e. Pearson's product moment and Spearman's rank order correlations) between AUC cortisol or TO prolactin secretion and plasma levels of IL-6 and sIL-2R. There were significant and positive correlations between AUC cortisol and IL-6 and sIL-2R in major depressed subjects. There was a trend toward a positive relationship between AUC cortisol and IL-6 or sIL-2R in healthy controls. Correlations (Pearson's) pooled over the healthy and depressed study groups showed a significant relationship between IL-6 or sIL-2R and AUC cortisol. Figure 1 shows the correlation between

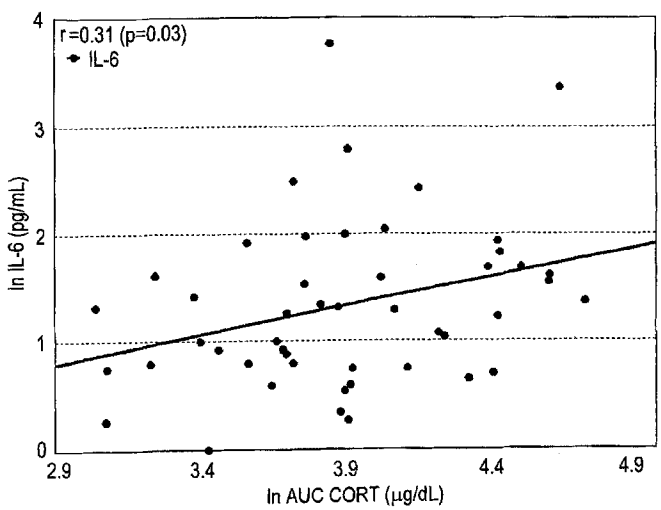

Fig. 1 Relationship between area under the curve (AUC) cortisol and IL-6 in major depression

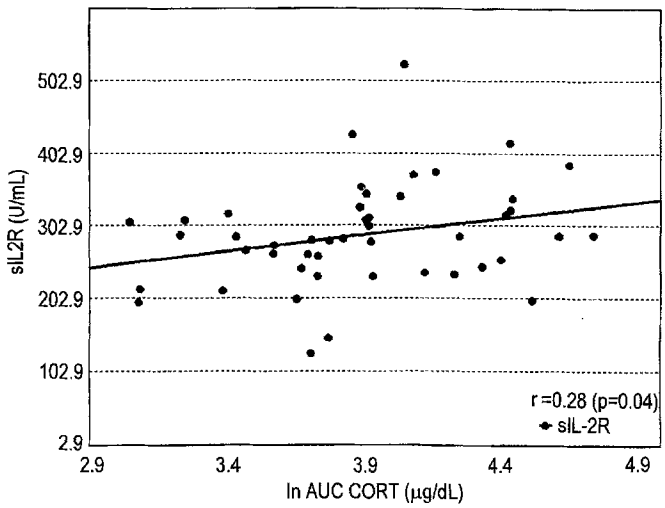

Fig. 2 Relationship between area under the curve (AUC) cortisol secretion and sIL-2R in major depression

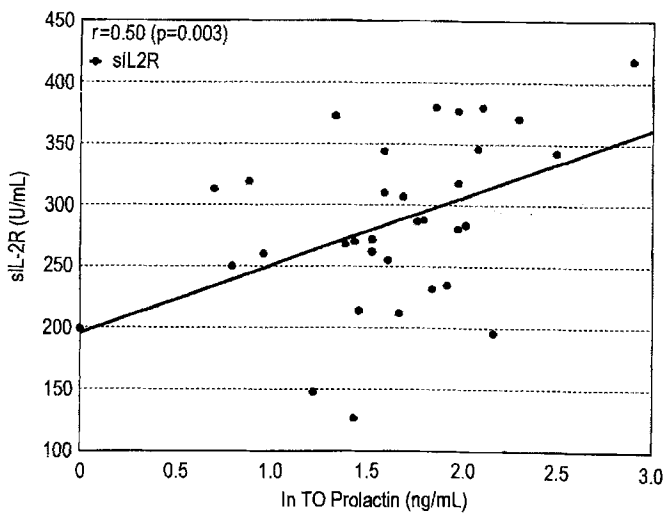

Fig. 3 Relationship between plasma prolactin and sIL-2R in major depression

AUC cortisol and IL-6 in major depression. Figure 2 shows the correlation between AUC cortisol and sIL-2R in major depression. Multiple regression analysis pooled over both groups showed that 14.3% of the variance in AUC cortisol was explained by IL-6 ($F = 4.5$, $P = 0.03$) and sIL-2R ($F = 5.1$, $P = 0.02$) (overall regression: $F = 6.2$, $df = 2/75$, $P = 0.003$). Adjusting for age and sex (through semi-partial correlations or multiple regression analyses with age and sex as covariates) did not change these results. For example, 16.4% of the variance in AUC cortisol in major depressed subjects could be explained by the regression on IL-6 ($F = 7.4$, $P = 0.009$) and age ($F = 3.8$, $P = 0.05$) (overall regression $F = 4.4$, $df = 2/45$, $P = 0.01$).

There were significant and positive correlations between TO prolactin and sIL-2R values in major depressed subjects and in normal and major depressed subjects combined, but not in normal controls. Figure 3 shows the correlation between sIL-2R and TO prolactin in major depressed patients. Adjusting for possible age and sex effects (in multiple regression analyses with age and sex as covariates or through semi-partial correlations) did not change these results. For example, the semi-partial correlation coefficient between sIL-2R and TO prolactin (adjusted for gender) was $r = 0.54$ ($P = 0.001$).

AUC cortisol tended to be increased in subjects with higher IL-6 values (i.e. ≥ 3.5 pg/mL) than in those with lower IL-6 values (61.6 ± 21.4 versus 51.9 ± 23.1 µg/dL, respectively; $F = 2.8$, $df = 1/76$, $P = 0.09$). AUC cortisol (62.2 ± 18.0 versus 50.9 ± 23.5 µg/dL; $F = 5.3$, $df = 1/78$, $P = 0.02$) and TO prolactin (8.3 ± 4.1 versus 5.5 ± 2.7 ng/dL; $F = 8.8$, $df = 1/62$, $P = 0.004$) were significantly increased in subjects with higher (≥ 320 U/mL) than in those with lower sIL-2R values, respectively.

There were significant relationships between sIL-2R and IL-6 values in major depressed subjects ($r = 0.40$, $P = 0.002$) and in the combined group of normal and depressed subjects (pooled $r = 0.21$, $P = 0.048$), but not in normal controls ($r = 0.05$, $P = 0.8$).

Discussion

The major findings of this study are the positive relationships between cortisol secretion and plasma IL-6 and/or sIL-2R and between sIL-2R and prolactin secretion in major depression. A trend towards positive relationships between the neuroendocrine and immune variables was detected in normal controls, while significant relationships were found in the pooled study groups of normal controls and major depressed subjects. These results will now be discussed.

This is a first report that plasma IL-6 may be related to indicants of cortisol secretion in major depression. The findings concur with a previous report that IL-6 production in mitogen-stimulated culture supernatant was positively related to HPA-axis hyperactivity in depression as well as in normal controls (Maes et al. 1993b). It is known that glucocorticoids inhibit the production of monocytic IL-6 by preventing IL-6 gene transcription (Waage et al. 1990; Zanker et al. 1990). Thus, despite inhibitory effects of glucocorticoids on IL-6 production, a significant, albeit weak, positive correlation between IL-6 and cortisol secretion was found. There are at least two mechanisms that may explain this positive relationship: 1) a common denominator, such as psychological stress, may underlie both increased IL-6 secretion (LeMay et al. 1990; Zhou et al. 1993) and HPA-axis hyperactivity (Janowsky and Risch 1984). However, it is unlikely that psychological stress, related to the acute phase of illness, is involved in increased plasma IL-6 in major depression. Indeed, IL-6 levels are also significantly increased in the absence of disease activity (i.e. major depressed subjects in complete clinical remission), suggesting that the immunologic perturbations are present even in the inactive phase of major depression (Maes et al., submitted). 2) A second hypothesis is that plasma IL-6 may stimulate

HPA-axis function. Indeed, IL-6 is known to stimulate hypothalamic corticotropin releasing hormone (CRH), pituitary adrenocorticotropic hormone (ACTH) and adrenal glucocorticoid secretion (Naitoh et al. 1988; Navarra et al. 1991; Woloski et al. 1985; Fukata et al. 1989; Tominaga et al. 1991). IL-6 may stimulate the HPA-axis at concentrations known to occur in human plasma (Navarra et al. 1991; Woloski et al. 1985; Naitoh et al. 1988). However, as pointed out by Fukata et al. (1993) the detection of a particular cytokine in the blood does not mean that it plays a role as an immune-derived mediator in causing hyperglucocorticoidemia, even if it is known to be effective.

This is also a first report that cortisol secretion may be positively related to plasma sIL-2R in major depressed subjects and in the combined group of normal and major depressed subjects. It is known that glucocorticoids block T cell proliferation through the inhibition of IL-2 gene and IL-2R expression (Larsson 1980; Arya et al. 1984; Reed et al. 1986; Tsokos and Balow 1986; Maes et al. 1991b) and that endogenous hypercortisolism results in an in vivo inhibition of the IL-2 system (Sauer et al. 1994). Thus, despite possible inhibitory effects by glucocorticoids on IL-2R production, this study found a positive correlation between both factors. There are at least two mechanisms that may explain these relationships: (1) T cell activation (as indicated by increased sIL-2R levels) with concomitant IL-2 secretion may have increased the blood levels of ACTH and cortisol (Atkins et al. 1986; Denicoff et al. 1989; Lotze et al. 1985). However, these stimulatory effects of IL-2 were only reported at pharmacological doses. (2) A common mechanisms, such as increased IL-6 secretion, may underlie both increased plasma sIL-2R and cortisol secretion. Indeed, IL-6 plays a pivotal role in T cell activation, it increases IL-2R expression on T cells and increases IL-2 responsiveness (Vink et al. 1990). This thesis is underscored by the findings that plasma IL-6 and sIL-2R are positively correlated in major depression.

The third finding of this study is that plasma sIL-2R was significantly and positively related to prolactin secretion in major depressed subjects. Several studies have documented direct mitogenic and immunoregulatory effects of prolactin on T lymphocytes, such as stimulation of IL-2R expression and IL-2 production (Skwarlo-Sonta 1992). To our knowledge, no effects of IL-2 at physiological concentrations on pituitary prolactin have been reported. Other cytokines such as IL-6 (Spangelo et al. 1989; Yamaguchi et al. 1990) may stimulate the release of pituitary prolactin. However, the present study was unable to detect a significant relationship between plasma IL-6 and prolactin secretion. In addition, immunization may result in lower serum prolactin concentrations (Skwarlo-Sonta 1992). Thus, the positive relationship between prolactin and sIL-2R levels, found in the present study, may well reflect this immunoregulatory role of prolactin on T lymphocytes in vivo.

In the present study, no significant differences in cortisol or prolactin secretion were found between major depressed subjects and normal controls. A moderately increased baseline secretion of cortisol in blood or urine has been reported by some (Sachar 1967; Carroll et al. 1976) but not all authors (Christie et al. 1986; Maes et al. 1991d). An increased escape of ACTH and cortisol from suppression by dexamethasone, on the other hand, has frequently been reported in depression (for a review: Maes et al. 1991d). Our previous result that IL-6 production is significantly and positively related to postdexamethasone cortisol values suggests that IL-6-related mechanisms may play a role in HPA-axis hyperactivity in major depression. In any case, the findings of the present study indicate reciprocal relationships between the neuroendocrine and immune systems in major depression.

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