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Original article

Plasma soluble interleukin-2-receptor in depression: relationships to plasma neopterin and serum IL-2 concentrations and HPA-axis activity

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Summary – The present study examined the plasma concentration of the soluble interleukin-2-receptor (sIL-2R) in depressed subjects in relation to hypothalamic pituitary adrenal (HPA) axis function and plasma neopterin and serum IL-2 concentrations. Plasma sIL-2R concentration was significantly higher in depressed patients (n = 47) than in controls (n = 19). There were no significant correlations between plasma sIL-2R and severity of illness. In the depressed subjects, there was a highly significant relationship between plasma sIL-2R and neopterin concentrations. Depressed patients with pathologically increased plasma neopterin levels had significantly higher plasma sIL-2R values than those with normal serum neopterin. There were no significant relationships between plasma sIL-2R and indices of HPA-axis function in depression. There was no significant effect of dexamethasone administration on sIL-2R levels. Significantly more depressed subjects had measurable serum IL-2 levels than normal controls. Our data support the notion that a moderate activation of cell-mediated immunity may play a role in the pathophysiology of depression.

soluble interleukin-2 receptor / neopterin / depression / hypothalamic-pituitary-adrenal-axis / cortisol / immune disorders

INTRODUCTION

There is increasing evidence that major depression is accompanied by an immune response with – amongst other things – activation of T lymphocytes and cells of the monocyte/macrophage lineage (reviews: Maes, 1995; Maes *et al*, 1995). One of the indices of T cell activation is the increase in soluble IL-2 receptors (sIL-2R) in the blood of depressed subjects (Maes *et al*, 1991b) or depressed subjects who have attempted suicide (Nassberger and Traskman-Bendz, 1993).

The circulating form of the IL-2R p 55 subunit, *ie*, the sIL-2R, is released from activated T cells into the blood, sIL-2R concentrations appear to correlate with T cell activation and IL-2 secretion in various pathological conditions (Caruso *et al*, 1993). The measurement of the sIL-2R in plasma or serum offers an index of disease activity in a variety of disorders, which involves immune activation, such as lupus erythematosus, diabetes mellitus, rheumatoid arthritis, Grave's disease, multiple sclerosis, some hemopoietic malignancies and other cancers and infectious disorders (Caruso *et al*, 1993). Subjects with major depression show also a significantly higher neopterin secretion in blood or urine than normal volunteers (Dunbar *et al*, 1992; Duch *et al*, 1984; Maes *et al*, 1994b). Increased neopterin secretion is another sensitive marker of activation of cell-mediated immunity (Huber *et al*, 1984; Fuchs *et al*, 1992; Wachter *et al*, 1992). Neopterin is released by activated cells of the monocytic/macrophage lineage, and its release is stimulated by products of activated T cells, such as interferon γ (IFNγ) and IL-2 (Wachter *et al*, 1992). Increased secretion of neopterin is observed in autoimmune and inflammatory disorders, such as rheumatoid arthritis, diabetes mellitus, sarcoidosis, infectious disorders and various cancers (Wachter *et al*, 1992). Thus, a significant relationship between circulating sIL-2R and neopterin concentrations may indicate the simultaneous activation of the T lymphocytic and monocytic/macrophage arms of cell-mediated immunity.

However, no research has investigated the relationship between both factors in depression.

Major depression is accompanied by hyperactivity of the hypothalamic pituitary adrenal (HPA) axis (Maes *et al*, 1991c) and there is evidence that glucocorticoids can affect T cell function by regulating IL-2R (Reed *et al*, 1986; Maes *et al*, 1991a) and IL-2 expression or secretion (Boumpas *et al*, 1991; Arya *et al*, 1984; Gillis *et al*, 1979). Circulating sIL-2R levels are significantly decreased in patients with Cushing's disease, whereas hypocortisolemic patients exhibit significantly elevated sIL-2R levels (Sauer *et al*, 1993). However, the relationships between circulating sIL-2R levels and HPA-axis hyperactivity in depression have remained elusive.

The purpose of this study was to further study the finding that depression is characterized by significantly increased circulating sIL-2R levels; and examine the relationships between circulating sIL-2R levels and either neopterin or IL-2 secretion and HPA-axis activity in depression.

SUBJECTS AND METHODS

Subjects

Sixty-six subjects participated in this study: 19 normal volunteers and 47 major depressed patients admitted to the psychiatric ward of the University Hospital of Antwerp, Edegem, Belgium. They were categorized according to DSM-III-R criteria (APA, 1987) on the basis of the semistructured interview according to DSM-III-R criteria (Spitzer *et al*, 1990). The 17-item Hamilton Depression Rating Scale (HDRS) was used to measure severity of illness (Hamilton, 1960). The major depressed subjects were in an acute phase of illness. Patients with other axis-I diagnoses beside major depression, *eg* substance use disorder (6 months before the study), organic mental disorders, schizophrenia or schizoaffective disorder were excluded from this study. We have excluded patients who were treated with lithium, MAOI, antipsychotic dosages of neuroleptics and anticonvulsants or barbiturates and patients who underwent ECT the year previous to hospital admission. Twenty patients had been taking antidepressants, *ie*, maprotiline, clomipramine, amitriptyline, the month prior to the wash-out period; 24 patients had been taking benzodiazepines, while 9 patients were treated with low dosage neuroleptics (*eg*, equivalent of haloperidol < 0.5 mg/day) the month prior to the wash-out period. These drugs were discontinued upon admission and, subsequently, these patients underwent a wash-out period of eight days. In cases of severe agitation, anxiety, sleep disorders or suicidal ideation, a low dosage of benzodiazepines was allowed during the study period (23 patients received the equivalent of ≤ 20 mg di-K-chlorazepate and/or 27.5 mg flurazepam).

Controls were free of any medication during at least one month prior to blood sampling. No one was a regular drinker or had ever taken psychotropic drugs. They were screened and excluded for current, past and family history (first-degree relatives) of psychiatric disorders. All subjects were free of drugs known to interfere with endocrine or immune functions. 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 chronic illnesses known to affect the endocrine or immune status (*eg* autoimmune or inflammatory disorders, such as diabetes, inflammatory bowel disease) and of acute infectious or allergic reactions for at least two weeks prior to the study. Additional analyses were carried out on another study group, which have been described in our previous report on sIL-2R in depression in fourteen normal volunteers and 35 depressed subjects (Maes *et al*, 1991b). In addition to the published baseline plasma sIL-2R data, we measured serum IL-2 in depressed (n = 35) and normal (n = 14) subjects and plasma postdexamethasone (1 mg dexamethasone PO) sIL-2R in the depressed patients (n = 35). These IL-2 and postdexamethasone sIL-2R results have never been published before. Plasma postdexamethasone sIL-2R was determined in the same run as predexamethasone sIL-2R.

Methods

Following an overnight fast, blood was sampled at 08.00 hours for the assay of sIL-2R in all depressed subjects and healthy volunteers, and for the assay of neopterin, basal cortisol and adrenocorticotropic hormone (ACTH) levels in the depressed patients. The same day, depressed patients ingested 1 mg of dexamethasone at 23.00 hours; the next day blood was drawn for assay of cortisol, ACTH and dexamethasone levels. Serum and plasma fractions were stored at – 20°C until thawed for assay. Standardization of sIL-2R measured by the sIL-2R EIA (Eurogenetics, Tessenderlo, Belgium) 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 intraassay CV is 2.0% at a level 208 U/ml. All sIL-2R measurements in controls and major depressed subjects were carried out in the same run. Plasma neopterin concentration was determined by a double antibody radio-

immunoassay (IMMUtest Neopterin, Henning, Berlin, GMBH). Neopterin determinations were carried out in triplicate and in one run. The intra-assay CV was 4.7%. The results that plasma neopterin is significantly higher in major depressed patients than in normal controls, and the relationships between plasma neopterin and amino acid concentrations (*eg* the availability of L-tryptophan to the brain) and IFNγ secretion in depressed subjects have been presented elsewhere (Maes *et al*, 1994b). Plasma neopterin concentrations were used in this study to examine the relationships with sIL-2R levels. Pathologically increased plasma neopterin levels were defined as plasma neopterin ≥ 7 nmol/l (Maes *et al*, 1994b). IL-2 levels in serum were determined by an enzyme-linked immunosorbent assay (Innogenetics IL-2 ELISA kit, Antwerp, Belgium). The intra-assay CV was 8.0% and the sensitivity was 1.6 IU/ml. Intact ACTH (1-39 molecule) was assayed with the Allégro HS-ACTH kit (Nichols Institute, San Juan Capistrano, CA, USA), which is a highly sensitive two-site immunoradiometric assay (IRMA) designed for the assay of intact ACTH only. The sensitivity of the assay was 1 pg/ml. The interassay CV was 5.8% (mean = 39.4 pg/ml, n = 11). Cortisol was assayed with a radioimmunoassay (RIA) kit (Clinical Assays, Gammacoat 125-I Cortisol Radioimmunoassay Kit, Incstar Corporation, Stillwater, MN, USA). The CV was 5.1% for the low (mean = 5.2 mg/dl, n = 20) and 4.0% for the higher (mean = 20.0 mg/dl) secretion ranges. The sensitivity of the assay was 0.1 mg/dl. ACTH non-suppression was defined as postdexamethasone ACTH ≥ 10 pg/ml and cortisol non-suppression as cortisol ≥ 3.5 mg/dl (Maes *et al*, 1991c). Dexamethasone was determined by a radioimmunoassay method (antibodies from Laboratoire d'Hormonologie, Marloie, Belgium). The interassay CV value in our laboratory was 10.0% (mean = 2.44 ng/ml). The lower limit of detection was 0.15 ng/ml.

Statistics

Relationships between variables were assessed by means of Pearson's product moment (r) or Spearman's rank order (r_s) correlations or through multiple regression analysis. Group mean differences were checked with the analysis of variance (ANOVA) or analysis of covariance (ANCOVA). Multiple comparisons among group means were checked with the Dunn test (Howell, 1982). The independence of classification systems was examined by means of analysis of contingence (χ^2-test) or Fisher's exact probability test. Normality of distribution was checked with the Kolmogorov-Smirnov test. Transformations were used to reach normality of distribution or to adjust for heterogeneity of variance between study groups (postdexamethasone cortisol and ACTH and neopterin values in logarithmic transformation).

RESULTS

Demographic data

The mean age (± SD) and men/women ratios in the four study groups were as follows: healthy controls 45.3 (± 12.2) years and 7/12; minor depression 45.1 (± 10.3) years and 2/13; simple major depression 51.0 (± 9.7) years and 3/11 and melancholia 52.3 (± 12.1) years and 4/14. There were no significant differences in age ($F = 1.9$, $df = 3/62$, $p = 0.12$) or in gender ratio ($\chi^2 = 1.5$, $df = 3$, $p = 0.7$) between the four diagnostic groups. No significant relationships between sIL-2R and age were found in any of the four diagnostic groups separately or in the whole sample ($r = 0.15$, $p = 0.23$, $n = 66$). ANOVA, factorial design with the four diagnostic groups and gender as treatments showed no significant differences in sIL-2R values between men (292 ± 112 U/ml) and women (339 ± 106 U/ml) ($F = 0.5$ $df = 1/58$, $p = 0.5$). Although no significant relationships between age or sex and sIL-2R values were found, subsequent statistical analyses were controlled for possible age-sex effects by using both variables as covariates in ANCOVAs or multiple regression analyses.

sIL-2R in major depression

Plasma sIL-2R concentration was as follows: healthy controls 224 (± 107) U/ml; minor depression 364 (± 72) U/ml; simple major depression 371 (± 83) U/ml; and melancholia 369 (± 82) U/ml. By means of ANCOVA with age and sex as covariates, significant differences were found between the four study groups ($F = 9.8$, $df = 3/60$, $p < 10^{-4}$). Dunn test showed a highly significant difference between the combined group of depressed patients and healthy volunteers ($t = 5.6$, $p < 10^{-4}$). No significant differences in sIL-2R values were found between the three depressive categories. In depressed patients, there was no significant relationship between the HDRS-score and sIL-2R values ($r = 0.06$, $p = 0.7$, $n = 47$).

Table I shows that, in depression, there were no significant differences in sIL-2R values between cortisol or ACTH non-suppressors and suppressors. In depression, there were no significant relationships between plasma sIL-2R values and either postdexamethasone cortisol ($r = 0.02$, $p = 0.9$, $n = 47$) or ACTH ($r = 0.04$, $p = 0.8$, $n = 47$) values. No significant relationships between sIL-2R values and either basal cortisol ($r = 0.09$, $p = 0.6$, $n = 47$) or basal ACTH ($r = 0.06$, $p = 0.7$, $n = 47$) could be found. Also, the semi-partial correlation

Table I. Measurements of the soluble interleukin-2 receptor (sIL-2R) in depressed patients divided according to HPA-axis function, neopterin secretion and drug state.

Variables	*Yes/no ratio*	*sIL-2R (U/l)*		*Results of ANCOVAs (df = 1/43)*	
		Yes	*No*	*F-statistic*	*p-value*
Cortisol non-suppression (cortisol ≥ 3.5 mg/dl)	13/34	374 (75)	365 (80)	0.1	0.7
ACTH non-suppression (ACTH ≥ 10 pg/ml)	14/33	392 (76)	358 (77)	1.9	0.2
Increased neopterin (neopterin ≥ 7 nmol/l)	21/26	408 (73)	335 (65)	13.2	0.001
Antidepressants*	20/27	367 (83)	369 (75)	0.09	0.8
Neuroleptics*	9/38	374 (49)	367 (83)	0.05	0.8
Benzodiazepines*	24/23	359 (77)	377 (79)	1.6	0.2
Benzodiazepines**	23/24	360 (73)	376 (82)	0.8	0.6

All results are expressed as mean (SD). *Use of antidepressants, low-dosage neuroleptics, or benzodiazepines before the eight day wash out period; **use of benzodiazepines during the study period.

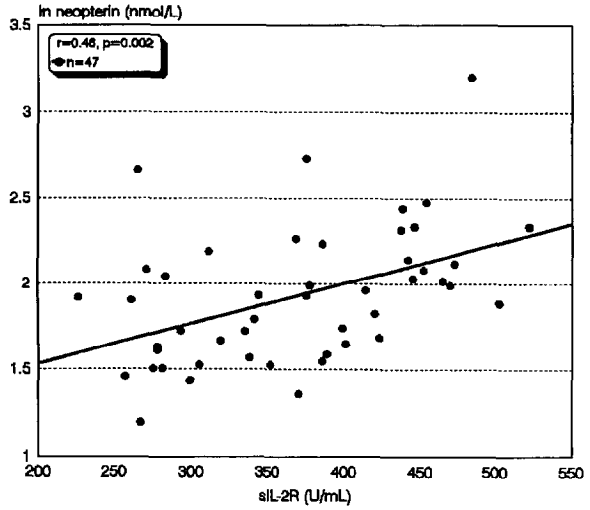

Fig 1. Relationship between plasma neopterin and sIL-2R concentrations in the blood of depressed subjects.

coefficients between sIL-2R and the adjusted post-dexamethasone ACTH or cortisol values (adjusted for dexamethasone levels and age) were non-significant.

Table I shows that depressed patients with pathologically increased plasma neopterin concentrations (*ie*, ≥ 7 nmol/L; Maes *et al*, 1995a) had significantly higher plasma sIL-2R values than patients with normal neopterin secretion. There was a significant and positive relationship between plasma sIL-2R and neopterin in the depressed patients ($r = 0.46$, $p = 0.002$, $n = 47$). Figure 1 shows the regression of plasma neopterin on sIL-2R values. Since neopterin values are also significantly and positively related to age ($r = 0.43$, $p = 0.003$), we have carried out a multiple regression analysis to control for age effects. It was found that 34.0% of the variance in plasma neopterin concentrations could be explained by the regression on sIL-2R ($F = 10.6$, $p = 0.002$) and age ($F = 8.8$, $p = 0.005$) (overall regression: $F = 11.3$, $df = 2/44$, $p = 0.0002$).

Table I shows also the sIL-2R measurements with respect to drug usage in the month before the wash out period and benzodiazepines during the study period. Neither previous treatment with psychotropic drugs or use of benzodiazepines during the study period had any effect on the sIL-2R levels in depressed patients.

Analyses of IL-2 and postdexamethasone sIL-2R values

Repeated measures ANOVA showed that administration of 1 mg of dexamethasone did not significantly alter plasma sIL-2R levels in depressed patients ($n = 35$), *ie*, predexamethasone sIL-2R 322 (± 91) U/ml *versus* postdexamethasone sIL-2R 320 (± 78) U/ml ($F = 0.01$, $df = 1/33$, $p = 0.9$). The pre- and postdexamethasone sIL-2R values were significantly and positively related ($r = 0.90$, $p < 10^{-4}$, $n = 35$). We found that 9 of 35 depressed patients had measurable IL-2 levels (minor depression 3/11 or 27.3% and major depression 6/24 or 25.0%), whereas no measurable IL-2 levels were detected in the healthy volunteers ($n = 14$). These differences were significant by Fisher's exact probability test ($p = 0.034$). The IL-2 concentrations in the depressed patients with positive IL-2 levels were 21.0, 15.8, 11.0, 39.2, 69.4, 60.3,

499.8, 23.0 and 17.2 IU/ml. A significant and positive correlation between sIL-2R and IL-2 concentrations was found in the study group as a whole ($r_s = 0.30$, $p = 0.03$, $n = 49$), but not in the depressed study group ($r_s = 0.10$, $p = 0.6$, $n = 35$). IL-2 values were not related to age or sex.

DISCUSSION

The major findings of this study are that i) depression is characterized by increased plasma sIL-2R concentrations compared to controls; ii) plasma sIL-2R values are significantly and positively correlated to plasma neopterin concentrations in depressed patients; and iii) no significant relationships between plasma sIL-2R values and HPA-axis activity are found in depression.

The finding that sIL-2R circulating levels are significantly higher in unipolar depressed patients, irrespective of depressive subtyping, than in controls, is in agreement with previous results (Maes *et al*, 1991b; Nassberger and Traskman-Bendz, 1993). The results provide further support that depression is associated with an increased number or percentage of activated (IL-2R bearing) T cells in the peripheral blood (Maes *et al*, 1992; 1993). Significant and positive relationships between circulating sIL-2R levels and the number or percentage of IL-2R bearing T cells have been described in cancer patients before as well as after therapy with IL-2 (Bogner *et al*, 1992). The importance of these findings in depression is that activated T cells can readily cross the blood brain barrier and may modulate the function of neurally active brain cells through, for example, secretion of cytokines (Plata-Salaman, 1991).

Another question is whether this increased sIL-2R concentration in the blood of depressed patients is accompanied by increased serum IL-2 concentrations. It is known that most cytokines are rapidly cleared from the blood and that cytokine blood concentrations give only a crude estimation of their production. Moreover, IL-2 levels are not always measurable in the peripheral blood. Nevertheless, we found that there were significantly more depressed patients with measurable serum IL-2 levels than controls. Likewise, we detected a significant and positive relationship between IL-2 and sIL-2R concentrations in the study group as a whole, which reflects in part the higher number of depressed patients with measurable serum IL-2 levels. On the basis of the above, it may be suggested that unipolar depression is associated with a moderate *in vivo* activation of T cells, with increased numbers of IL-2R bearing T lymphocytes and increased sIL-2R and IL-2 concentrations in the blood. This condition is - at first sight - in sharp contrast to the diminished *in vitro* responsiveness of immune cells to mitogens (Maes *et al*, 1989) and the reduced delayed-type hypersensitivity (DTH) skin response (Hickie *et al*, 1993) in major depression. However, in patients with immune and autoimmune disorders, the corresponding activation of immune cells is often accompanied by signs of immunosuppression, such as diminished *in vitro* responses of T cells to various antigenic stimuli (Caruso *et al*, 1993) and diminished DTH (Wachter *et al*, 1992). This hyporesponsiveness of peripheral blood mononuclear cells (PBMC) to various stimuli may – amongst other things - be explained by products of the immune response, such as overproduction of cytokines, which renders the immune cells refractory to respond properly to antigenic stimulation, prostaglandin secretion, and the presence of sIL-2Rs, which may compete with IL-2 for binding to cellular IL-2Rs (Caruso *et al*, 1993). Downregulation of some immune functions may also be caused by other concomitants of immune activation, such as HPA-axis hyperactivity and lower availability of plasma L-tryptophan (Maes *et al*, 1994b).

The second finding was the significant positive relationship between plasma neopterin and sIL-2R in depressed patients. Thus, it appears that depression is characterized by an interrelated upregulation of the monocytic (*ie*, neopterin) and T lymphocytic (*ie*, sIL-2R) arms of cell-mediated immunity. It is conceivable that increased production of IFNγ and IL-2 by activated T cells of depressed subjects (Maes *et al*, 1994b; present study) may have stimulated cells of the monocytic/macrophage lineage to secrete neopterin, through induction of guanosine-5'-triphosphate (GTP) cyclohydrolase I activity (Wachter *et al*, 1992; Huber *et al*, 1984; Werner *et al*, 1987).

The third finding was that there are no significant relationships between circulating sIL-2R levels and HPA-axis activity. Moreover, the administration of a single dose of dexamethasone 1 mg did not affect plasma sIL-2R concentrations in depressed subjects nine hours later. These findings are in agreement with previous results showing that there are no significant relationships between HPA-axis function and number or percentage of IL-2R bearing T lymphocytes in depression, and that dexamethasone administration did not affect the number or percentage of these activated T lymphocytes (Maes *et al*, 1994a). Nevertheless, it has been reported that suprapharmacological doses of dexamethasone

may inhibit IL-2R gene expression in PBMC (Reed *et al*, 1986) and that dexamethasone is able to suppress the *in vitro* sIL-2R production in culture supernatants of mitogen-stimulated PBMC in normal controls (Maes *et al*, 1991b). However, since we did not measure the effects of dexamethasone on plasma sIL-2R in healthy volunteers, it cannot be elucidated whether the lack of significant relationships between plasma sIL-2R and HPA-axis activity is restricted to depressed patients. In this respect, other authors reported no effects of dexamethasone administration on IL-2R (Boumpas *et al*, 1991), while Lamas *et al* (1993) found that glucocorticoids may increase expression of IL-2R on T cells by regulating IL-2R gene transcription. Some of the above controversies can be explained by the findings of Sauer *et al* (1993) that glucocorticoids may modulate sIL-2R levels *in vivo* depending on the state of immune activation and the duration of exposure to glucocorticoids. For example, the lack of any effect of glucocorticoids on sIL-2R or number or percentage of IL-2R bearing T lymphocytes in depression could be explained by the fact that activated T cells are less sensitive to the inhibitory effect of glucocorticoids (for review, Maes *et al*, 1991b).

In conclusion, depression is accompanied by increased plasma sIL-2R values and this increase in sIL-2R appears to be related to increased plasma neopterin and serum IL-2 secretion. The findings support the hypothesis that some functions of the monocytic and T lymphocytic arms of cell-mediated immunity are activated in depression or in some categories thereof (Maes *et al*, 1995b).

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