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Plasma-soluble interleukin-2 and transferrin receptor in schizoprenia and major depression

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Abstract This study was carried out to examine some components of in vivo immune function in major depression and schizophrenia. Toward this end, plasma concentrations of interleukin-1β (IL-1β) and IL-6, soluble IL-2 receptor (sIL-2R), and transferrin receptor (TfR) were measured in 28 normal controls, 11 schizophrenics and 13 major-depressed patients. Schizophrenic and major-depressed patients showed significantly higher plasma sIL-2R and TfR than normal controls. There was a trend toward higher plasma IL-6 in the psychiatric patients, and particularly in schizophrenic patients, than in normal volunteers. In normal controls and in the total study group, there were highly significant and positive correlations between plasma TfR and sIL-2R concentrations. It is suggested that schizophrenia and major depression are characterized by immune disorders that may indicate activation of cell-mediated immunity such as T-cell activation.

Key words Depression · Schizophrenia · Interleukin-1β Interleukin-2 · Interleukin-6 · Transferrin receptor Psychoimmunology · Cytokines

Introduction

Several lines of evidence point to the involvement of immune disorders in the pathophysiology of major depression and schizophrenia. There is now some evidence that major depression is characterized by the following:

1. Activation of cell-mediated immunity as indicated by an increased number of peripheral $CD4^+$ T cells, increased $CD4^+/CD8^+$ T-cell ratio, T-cell activation, B-cell proliferation, increased numbers of leukocytes, monocytes, and neutrophils, increased serum concentrations of soluble interleukin-2 receptor (sIL-2R), increased production of IL-1β and IL-6 by mitogen-stimulated peripheral blood mononuclear cells (PBMC), and increased secretion of prostaglandins and neopterin (Calabrese et al. 1986; Dunbar et al. 1992; Muller et al. 1989; Tondo et al. 1988; Charles et al. 1992; Maes 1995; Maes et al. 1995)

2. An acute phase (AP) response with lowered plasma levels of negative AP proteins (APPs), such as transferrin (Tf), and increased concentrations of positive APPs such as haptoglobin (Maes 1993; Joyce et al. 1992; Sluzewska et al. 1994; Song et al. 1994)

3. An autoimmune response with increased antinuclear and antiphospholipid autoantibody titers (Deberdt et al. 1976; Gastpar and Muller 1981; Maes et al. 1995)

It has been hypothesized that pathologically increased production of monocytic IL-1β and IL-6 may underlie the various immune/inflammatory disorders in major depression (Maes 1995; Maes et al. 1995). Indeed, IL-1β and IL-6 are pleiotropic cytokines that synergize in T-cell proliferation and activation, B-cell proliferation, autoantibody production, prostaglandin secretion, and the AP response (Maes et al. 1994).

Alterations in the three immune/inflammatory phenomena have also been reported in schizophrenia: (1) alterations in cell-mediated immunity as indicated by higher cerebrospinal fluid (CSF) IL-2 and peripheral blood sIL-2Rs concentrations (Rapaport et al. 1989; Ganguli and Rabin 1989; Licinio et al. 1991), lower IL-2 production by mitogen-stimulated PBMC (Ganguli et al. 1989, 1992; Villemain et al. 1989) and increased number of percentage of T-lymphocytes, $CD4^+$ T cells, and $CD5^+$ B cells (De Lisi et al. 1982; Muller et al. 1991, 1993; Henneberg et al. 1990); (2) an AP response as indicated by significantly increased plasma levels of positive APPs, such as haptoglobin (Smidt et al. 1988); and (3) an autoimmune response as suggested by higher levels of various autoantibodies against cell structures and tissues (De Lisi et al. 1985; Heath and Krupp 1967). It has been hypothesized that excessive in vivo production of IL-2 by lymphocytes may be related to the pathogenesis of schizophrenia (Smith 1991b,

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1992). Interleukin-2 is a T-cell growth factor, produced by activated T cells, that plays a pivotal role in the generation of an immune response and in maintenance of T-cell proliferation (Caruso et al. 1993). Interleukin-2 may induce auditory and visual hallucinations, delusions, paranoia, anxiety, agitation, mental slowing, and other symptoms of schizophrenia (Smith 1991b).

The immune profiles of both major depression and schizophrenia may indicate an in vivo immune response, caused by in vivo overproduction of IL-2 in schizophrenia, and of monocytic interleukins (i.e., IL-1β, IL-6), and, consequently, of IL-2, in major depression. These findings are compatible with the existence of an immune or inflammatory response in both disorders, and, consequently, with the hypotheses that these disorders are related to inflammation, infection, or autoimmunity (Maes 1994; Maes et al. 1994; DeLisi 1987; McAllister et al. 1991; Smith 1991a, 1992).

The present study was carried out to examine various immune or inflammatory markers in major depression and schizophrenia, i.e., plasma IL-1β, IL-6, sIL-2R, and TfR. Upon activation, T cells release IL-2Rs in the blood, and this release is related to IL-2 production by activated T cells (Caruso et al. 1993). The TfRs are expressed at the cell surface of proliferating cells, and this phenomenon is tightly coupled to prior expression of the IL-2R (de Jong et al. 1990). Plasma TfRs are a necessary promoting signal for lymphocyte proliferation (Keyna et al. 1991). The TfR plasma concentrations are also an index of erythropoiesis, Tf, or tissue iron deficiency (de Jong et al. 1990; Beguin 1992; Skikne et al. 1990).

Subjects and methods

A total of 52 subjects participated in this study: 28 normal controls (male/female ratio: 18/10; mean age 34.4 ± 15.1 years), 11 schizophrenics (male/female ratio: 7/4; mean age 36.1 ± 4.9 years), and 13 major-depressed patients (male/female ratio: 7/6; mean age 35.2 ± 12.2 years). There were no significant differences either in age ($F = 0.0$; $df = 2/49$; $P = 0.9$) or in gender ratio ($\chi^2 = 0.4$; $df = 2$; $P = 0.8$) between the study groups. Normal controls were recruited through advertisements or through word of mouth. They were screened for past, present, and family history of psychiatric disorder. Subjects with a past, present, or family (first degree) history of mental disorder were excluded from these studies. None of the normal controls had suffered from major medical illnesses, and none had ever taken psychotropic drugs. None of the controls was a regular drinker. The schizophrenic and depressed subjects were all inpatients admitted to the psychiatric ward of the University Hospitals of Cleveland (Cleveland, Ohio, USA). Patients were categorized according to DSM-III-R criteria on the basis of structural interviews (Schedule for Affective Disorders and Schizophrenia; Endicott and Spitzer 1976). All patients were in an acute phase of their illness. The median number of prior psychotic episodes in the schizophrenic patients was 3 (range 1 to more than 10). The median number of prior depressed episodes in the depressed patients was 2 (range 1–14). All subjects were medically healthy as screened by physical examination, serum enzyme and metabolite screening, thyroid-function tests, urine analysis, and electroencephalogram. Schizophrenic or depressed patients who had received oral antipsychotics or antidepressants were withdrawn from all medication for at least 1 week. None of the patients had been treated with parenteral antipsychotic drugs for at least 2 months before hospitalization. Ten schizophrenic patients were treated with antipsychotic drugs (i.e., haloperidol: $n = 5$, 4–10 mg/day; perphenazine: $n = 3$, 4–40 mg/day; loxapine: $n = 2$, 70 mg/day) before the washout period. The other patient was free of any medication for more than 3 months. The median length of the washout or drug-free period was 18 days (range 7 days to more than 90 days). Ten depressed subjects were drug-free for at least 60 days. None of the depressed patients had been taking fluoxetine the last 3 months before these studies were carried out. The 3 remaining depressed patients underwent a washout period of 7 days. Before the washout they were treated with typical antidepressants, i.e., imipramine (100 mg/day). There were no significant differences in smoking habits between the healthy controls and the inpatients, i.e., ratio smokers (> 10 cigarettes/day) nonsmokers ($\chi^2 = 0.1$; $df = 1$; $P = 0.8$).

Statistics

The independence of classification systems has been examined by means of Fisher's exact probability test or through analysis of contingence (χ^2 test). Relationships between variables were assessed by means of Pearson's product moment correlation or through multiple regression analysis. Group mean differences were ascertained by means of analysis of variance (ANOVA) or analysis of covariance (ANCOVA). Multiple comparisons among group means were checked with the Dunn test. Square-root transformations of sIL-2R, IL-6, and TfR were used in order to reach normality of distribution, or to adjust for heterogeneity of variance between study groups.

Methods

Following an overnight fast, blood was sampled at 9:00 a.m. for the determination of IL-1β, sIL-2R, IL-6, and TfR. The IL-1β was determined with a sandwich enzyme immuno assay (EIA) from Cistron, based on a monoclonal-polyclonal antibody combination allowing IL-1β detection in the dynamic range of 20–1000 pg/mL with a detection limit of 20 pg/mL and an interassay precision of 9.4% coefficient of variation (CV) at 30 pg/mL. The IL-6 was quantified with a sandwich EIA (Eurogenetics, Tessenderlo, Belgium) 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 interassay CV of 6.8% at the 35 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 3.0 pg/mL pure recombinant α-chain receptor. The detection limit of the assay is 20 U/mL, and CVs on serum determinations are 10 and 6% at levels of 59 and 382 U/mL, respectively. The TfR was quantified by a heterologous monoclonal antibody pair combined in an EIA system (Eurogenetics) and calibrated against a range of 55 to 1000 arbitrary U/mL. The EIA has a detection limit of 55 U/mL and shows an intraassay CV profile of 4.7, 5.5, and 6.7% at the levels of 125, 250, and 1000 U/mL, respectively.

Results

Figures 1, 2, and 3 show the measurements of sIL-2R, TfR, and IL-6 in normal controls, schizophrenics, and major-depressed patients. Differences between these groups were investigated by means of ANCOVAs with age and gender as covariates. Multiple comparisons among treatment means (i.e., normal controls vs schizophrenics and major-depressed subjects, alone and together) were investigated by means of the Dunn test at a significance level of

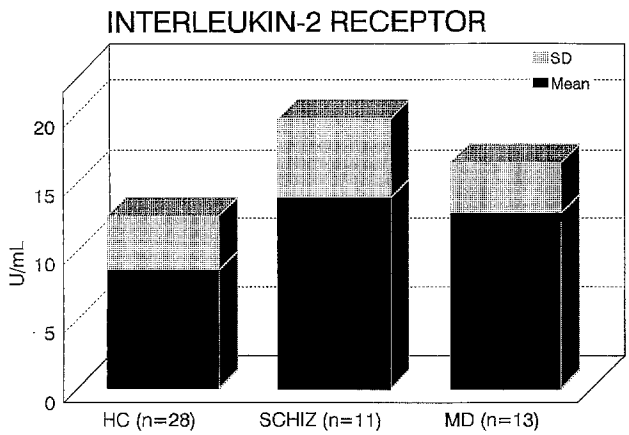

Fig. 1 Plasma soluble interleukin-2 receptor (± SD, in square-root transformation) in healthy controls *(HC)*, schizophrenic patients *(SCHIZ)*, and major-depressed *(MD)* patients

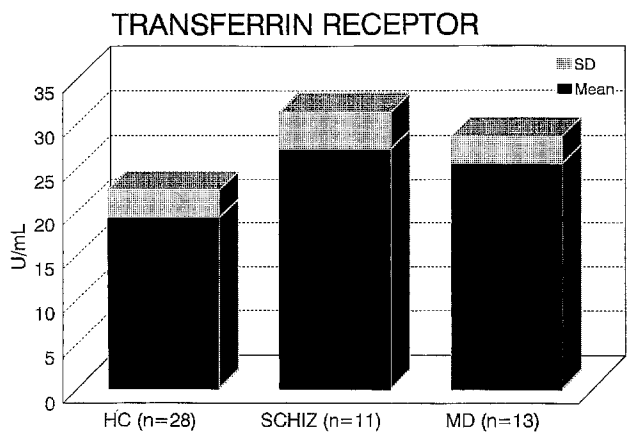

Fig. 2 Plasma transferrin receptor (± SD, in square-root transformation) in healthy controls, schizophrenic patients and major-depressed patients

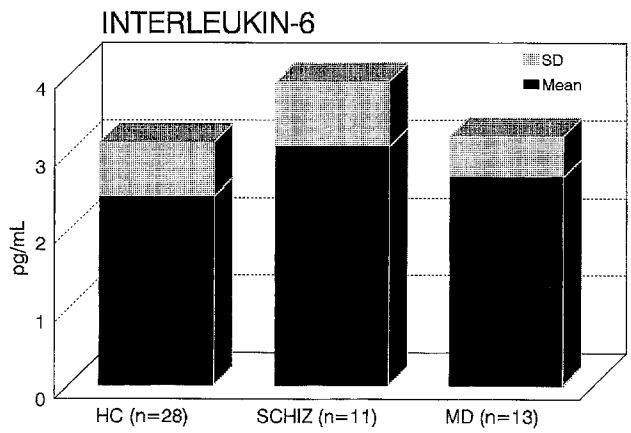

Fig. 3 Plasma interleukin-6 (± SD, in square-root transformation) in healthy controls, schizophrenic patients, and major-depressed patients

$P = 0.017$. Figure 1 shows that plasma sIL-2R levels were significantly higher in depressed and schizophrenic patients than in normal controls ($F = 4.2$; $df = 2/38$; $P = 0.02$; Dunn test: $t = 3.5$; $P = 0.001$). Figure 2 shows that schizophrenics and major-depressed subjects exhibited significantly higher TfR values than normal controls ($F = 20.3$; $df = 2/47$; $P < 10^{-4}$; Dunn test: $t = 6.3$; $P < 10^{-4}$). Figure 3 shows that plasma IL-6 concentrations tended (ANCOVA: $F = 3.1$; $df = 2/47$; $P = 0.052$) to be higher in the combined group of schizophrenic and depressed patients (Dunn test: $t = 1.9$; $P = 0.05$) or in schizophrenic patients (Dunn test: $t = 2.5$; $P = 0.015$) compared with normal controls.

The IL-1β levels were measurable in 3 subjects (i.e., 3 major-depressed subjects). By means of Fisher's exact probability test, a significantly higher occurrence of measurable IL-1β plasma levels was found in major depression compared with normal controls and schizophrenic patients ($P = 0.01$).

In normal controls there was a significant and positive correlation between plasma TfR and sIL-2R concentrations ($r = 0.57$; $P = 0.01$). Up to 46.8% of the variance in TfR values could be explained by the regression on sIL-2R values ($F = 6.1$; $P = 0.02$) and gender ($F = 4.5$; $P = 0.04$) (overall regression: $F = 7.0$; $df = 2/16$; $P = 0.007$). In the combined group of normal, schizophrenic, and major-depressed subjects, multiple regression analysis revealed that 40.4% of the variance in TfR values was explained by sIL-2R ($F = 14.9$; $P = 0.007$) and gender ($F = 10.7$; $P = 0.002$) (overall regression: $F = 13.5$; $df = 2/40$; $P = 0.0001$). The effects of gender ($F = 9.4$; $P = 0.004$) and sIL-2R values (F 5.3; $P = 0.02$) remained significant ($F = 7.1$; $df = 2/40$; $P = 0.003$) after considering the effects of diagnostic classification in a multiple regression analysis pooled over the three diagnostic groups. No significant relationships could be detected between any of the immune/inflammatory variables and length of drug-free period, number of previous depressive or psychotic episodes, or smoking behavior.

Discussion

The main finding of this study was that major depressed and schizophrenic patients have more significantly increased plasma sIL-2R and TfR concentrations than normal controls. The finding of increased plasma sIL-2R in major depression is in agreement with one of our previous reports (Maes et al. 1991 b) and with the findings of a significantly increased number and percentage of activated IL-2R-bearing T cells in that illness (Maes et al. 1995). The findings of the present study that sIL-2R plasma levels are also increased in schizophrenia are in agreement with reports on increased CSF IL-2 concentrations and serum sIL-2R in schizophrenic subjects (Rapaport et al. 1989; Ganguli and Rabin 1989; Licinio et al. 1991). It has been reported, however, that IL-2 production by mitogen-stimulated PBMC was lower in schizophrenic patients than in normal controls (Ganguli et al. 1989, 1992). Higher numbers of IL-2R bearing T lymphocytes and in vivo production of sIL-2Rs or IL-2 together with lower mitogen-induced IL-2 secretion by PBMC is also characteristic of autoimmune disorders, such as systemic lupus

erythematosus, insulin-dependent diabetes mellitus, rheumatoid arthritis, Grave's disease, and multiple sclerosis (Caruso et al. 1993). There are at least two explanations for these differences between in vivo and in vitro capacity to secrete IL-2R or IL-2 (Caruso et al. 1993): (1) overproduction of IL-2 in vivo causes T-cell exhaustion and, thus, in vitro hyporesponsivity to mitogens, and (2) sIL-2R may bind to its ligand, thereby forming an sIL-2R/IL-2 complex; the latter may compete with cellular IL-2R for IL-2 stimulation, thus inducing down-regulation of the immune response. In any case, our results show that both major depression and schizophrenia are characterized by in vivo activation of T cells.

The study showed that there was a trend toward a higher number of major-depressed subjects with measurable plasma IL-1β than normal controls and schizophrenic patients. However, further interpretation of these data is hampered by the fact that the distribution of IL-1β values below the detection limit is unknown. Nevertheless, the findings may be in accordance with our previous report on higher mitogen-stimulated IL-1β secretion by PBMC in major depression (Maes et al. 1991a). Plasma IL-6 tended to be higher in the combined group of patients and, in particular, in schizophrenic patients than in normal controls. It should be stressed, however, that cytokines act mainly in a paracrine and autocrine manner such that they are released and consumed locally at the site where an immune reaction occurs. Not all cytokines are detectable in peripheral blood, although increased levels of IL-6 may be detected in the plasma of some pathological disorders. Therefore, some groups have argued that disturbances in cytokine synthesis can best be studied under dynamic conditions by stimulating immune-competent cells with polyclonal activators and, consequently, analyzing the pattern of cytokine production (De Groote et al. 1992). Significantly increased mitogen-induced IL-6 secretion by PBMC of major-depressed subjects were found in one study (Maes et al. 1993). Moreover, various other findings in major depression, e.g., the acute phase response and increased levels of prostaglandins, point toward hypersecretion of cytokines, such as IL-6, in that illness (Maes et al. 1994). It should be added that increased plasma IL-6 was detected in major depression in a recent large-scale study performed by this laboratory (Maes 1994, personal communication).

This paper reports significantly higher plasma TfR in major-depressed and schizophrenic patients than in normal controls. The significant positive relationship between plasma TfR and sIL-2R suggests that higher plasma TfR in both psychiatric illnesses is in some way related to immune activation. A highly significant positive relationship between plasma TfR and sIL-2R was also observed in a longitudinal study in normal controls (Maes et al. submitted). Increased TfR levels may indicate proliferation of immune cells. Indeed, TfRs are expressed at the cell surface of normal proliferating cells and are shed off into the plasma (de Jong et al. 1990). Increased plasma TfR is also an index of Tf or tissue iron deficiency (de Jong et al. 1990). In this regard it should be noted that both major depression and schizophrenia are accompanied by an AP response (see Introduction), and that lower plasma Tf levels, which frequently occur in an AP response, are documented in major depression (Maes 1993).

In conclusion, major depression and schizophrenia may be accompanied by in vivo activation of cell-mediated immunity as indicated by higher plasma levels of sIL-2R, TfR, IL-6, and maybe IL-1β. These disorders may point toward T-cell activation, proliferation of immune cells, or to the presence of an acute-phase response with lower Tf plasma levels in both depression and schizophrenia. The findings further underscore that the pathophysiology of both disorders may be related to immune or inflammatory responses such as infection or an autoimmune process.

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