Eur Arch Psychiatry Clin Neurosci (1997) 247 : 228–233

ORIGINAL PAPER

Ulrich H. Frommberger · Joachim Bauer
Peter Haselbauer · Andrea Fräulin · Dieter Riemann
Mathias Berger

Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission

Received: 22 November 1995 / Accepted: 10 April 1997

Abstract The concentration of cytokines such as Interleukin-6 (IL-6) has been reported to be elevated in depressed and schizophrenic patients and, in healthy persons, upon stress. Interleukin-6 plasma levels were determined in depressed (n = 12) and schizophrenic (n = 32) patients during the acute state of illness and after remission at approximately 8 weeks after admission and were compared with healthy controls (n = 12). Patients were diagnosed according to DSM-III-R by the Structured Clinical Interview (SCID). Severity of illness was assessed for depression by the Montgomery Asberg Depression Rating Scale (MADRS) and for schizophrenia by the Brief Psychiatric Rating Scale (BPRS). Interleukin-6 plasma concentrations were elevated during the acute state either of depression or of schizophrenia if compared to controls. After remission, IL-6 concentrations in depressed and in schizophrenic patients had decreased and did not differ significantly from controls. We hypothesize that the elevated IL-6 levels during the acute state of depression or schizophrenia may reflect an unspecific stress response.

Key words Depression · Schizophrenia · Stress
Interleukin-6, Psychoimmunology

Introduction

A number of studies indicate that psychiatric disorders may be accompanied by alterations of the immune system. Recent investigations revealed that cytokines are involved not only in inflammatory and infectious central nervous system (CNS) diseases (Campbell et al. 1993), but also in neurodegenerative diseases (Bauer et al. 1992) and in functional psychoses (Ganguli et al. 1994; Maes et al. 1995a, b).

U. H. Frommberger (✉) · J. Bauer · P. Haselbauer · A. Fräulin
D. Riemann · M. Berger
Department of Psychiatry, University of Freiburg, Hauptstrasse 5, D-79104 Freiburg, Germany

The cytokine interleukin 6 (IL-6) is a pleiotropic cytokine the functions of which include the induction of the production of acute phase proteins in the liver, haematopoiesis, osteoclast activation, proliferation and differentiation of B lymphocytes and induction of fever in the brain (for review see Kushner 1991).

More recently, cytokines such as IL-6 have been studied in the context of psychiatric disorders (e.g. Bauer et al. 1995; for review see Müller 1997). Psychological stress has been reported to increase plasma IL-6 levels in rats and humans (LeMay et al. 1991; Zhou et al. 1993; Stein and Schluter 1994). Alterations of IL-6 levels have also been found in psychiatric disorders.

In obsessive-compulsive disorder, IL-6 concentrations appear to positively correlate with severity of compulsive symptoms (Maes et al. 1994a). There is evidence that plasma IL-6 levels are also increased in depression (Maes et al. 1995b; Sluzewska et al. 1995, 1996). Recently, an elevation of cytokine production and of acute phase response proteins during acute depression has been reported (Joyce et al. 1992; Maes et al. 1993; Song et al. 1994; Seidel et al. 1995). In other studies depressed patients' IL-6 plasma levels have been shown to be higher in melancholic and non-melancholic depression than in controls (Maes et al. 1993; Maes et al. 1995b). Besides its many other effects, IL-6 has been shown to be capable of stimulating corticotropin-releasing hormone (CRH) synthesis and could be involved in the "overdrive" of the hypothalamic-pituitary-adrenal (HPA) axis and its hyperactivity in major depression (Maes et al. 1994b). Because of its pivotal role in the early phase of the cascade of immune responses, it has been hypothesized that IL-6 hyperproduction may play a pathogenetic role in the immune pathophysiology of major depression (Maes et al. 1993, 1995b).

In schizophrenic patients Ganguli et al. (1994) found a significant correlation between serum IL-6 levels and duration of illness, suggesting either a correlation to treatment or to disease progression in schizophrenia. In remitted schizophrenic patients, however, the mean level of IL-6 did not differ significantly from controls (Shintani et al. 1991). Xu et al. (1994) reported a significant difference in

plasma IL-6 concentration between schizophrenic patients taking neuroleptic drugs and those not taking them, but found no significant difference in the two groups when compared with controls. However, those patients were not severely ill.

The findings of increased levels of antinuclear autoantibodies, antiphospholipid antibodies, white blood cell (WBC) counts and C-reactive protein in depressed and schizophrenic patients has been interpreted as further indications for the involvement of the immune system in these two major psychiatric disorders (Seidel et al. 1995; Spivak et al. 1995). However, not all studies of IL-6 in affective or schizophrenic illness found significant differences between patients and control subjects (Barak et al. 1995; Hornig-Rohan et al. 1995; Katila et al. 1994).

In this study we investigated IL-6 plasma levels in depressed and schizophrenic patients in order to determine its association to the course during inpatient treatment and to contribute to the question as to whether elevation of IL-6 is a state or trait marker in both diseases.

Subjects and methods

The subjects (Table 1) were unselected inpatients with a diagnosis of major depression ($n = 12$) or schizophreniform or schizophrenic ($n = 32$) psychotic episode according to DSM-III-R. Exclusion criteria were a past or current physical disease, allergic conditions, chronic systemic diseases and acute inflammatory processes. We excluded patients using drugs known to affect immunity (except psychotropic medication which may also affect cell-mediated or humoral immunity). Due to the nature of this study as a pilot study only some of the patients ($n = 4$ depressed and $n = 11$ schizophrenic patients) were assessed in drug-free status defined as a condition of no medical drug intake for at least 6 months before admission in the case of schizophrenic patients, or no medical drug intake for at least 2 weeks before admission in depressed patients.

Table 1 Groups' characteristics. MADRS Montgomery-Asberg Depression Rating Scale; BPRS Brief Psychiatric Rating Scale

	Depressed patients	Schizophrenic patients	Healthy controls
Age (years)	46 ± 16	33 ± 11	31 ± 4
Male/female ratio	2/10	18/14	6/6
Duration of illness since onset (years)	5.1 ± 9.8	4.5 ± 6.1	–
Severity of psychiatric illness			
Acute, drug free			
MADRS	48 ± 9	–	–
BPRS	–	42 ± 12	–
Acute, medicated			
MADRS	34 ± 8	–	–
BPRS	–	39 ± 10	–
In remission, medicated			
MADRS	12 ± 9	–	–
BPRS	–	26 ± 5	–

Mean ± SD

However, most of the patients had already received drugs as outpatients or had to be treated immediately.

The psychotropic medication was not standardized during this pilot study. Patients received antidepressants (mostly amitriptyline, trimipramine, maprotiline, moclobemide, lithium) or neuroleptics (e.g. haloperidol, flupentixol, perazine). Antidepressant dosages were up to 200 mg for tricyclics and 600 mg for moclobemide. Neuroleptics were given at dosages up to 25 mg haloperidol or benperidol during the acute phase of illness. The dosages were reduced in remitted state.

Psychometric and immunological assessments (as described below) were done simultaneously on three occasions: at admission, at a mean of 9 days (adaptation to the drug treatment) and at a mean of 8 weeks after admission.

Patients were interviewed and diagnosed according to DSM-III-R by the Structured Clinical Interview (SCID; Spitzer et al. 1987) and assessed for severity by the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham 1962) for schizophrenic patients, or by the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979) for depressed patients (Table 1).

After admission to the hospital, we controlled for inflammatory conditions by screening the sedimentation rate (Westergren), C-reactive protein (CRP), WBC, temperature and a series of immunological tests, including serum complement CH-50, sheep cell agglutination test (Waaler-Rose), latex-fixation test, antistreptolysin O tests (ASO), antiphospholipid antibodies (IgG and IgM), antinuclear antibodies (ANA) and antineutrophil cytoplasmatic antibodies (ANCA). Some patients were found to show slight but non-significant abnormalities in these parameters. These patients were not excluded, because their IL-6 levels did not differ from the IL-6 levels of the other patients. In the literature such subtle abnormalities have been described for psychiatric patients.

After remission from their psychiatric disorder and before discharge from the clinic, patients were investigated again after approximately 8 weeks for CRP, westergren and WBC. Twelve healthy persons served as a control group. Control persons were free of current, lifetime or family history of schizophrenic psychosis or major depression, current medication or acute or chronic inflammatory disease. Their blood samples were collected for measurements of CRP and WBC and showed no abnormalities.

For the determination of IL-6 concentrations, in all cases blood was collected at 8 a.m., since IL-6 appears to be subject to a circadian rhythm (Bauer et al. 1994).

After centrifugation, plasma was stored at –20° C until thawed for assay. The intra- and interassay variation for measurement of IL-6 plasma levels was controlled by the fact that all measurements were performed with one batch in one run.

Plasma IL-6 concentration was measured with a bioassay using the IL-6-dependent hybridoma cell line B9 (Aarden et al. 1987) and MTT (Sigma, St. Louis, Mo.) as chromogen. All measurements were done in triplicate. One unit of IL-6/ml is defined as the concentration when B9 cell growth is stimulated half of the maximum. Preliminary tests with exogenously added IL-6 showed near linearity and good reliability of the extinction coefficient between 4 and 9 units/ml. Since the IL-6 concentrations of most of our samples were below this range, we exogenously added 4 units IL-6 (courtesy of T. Kishimoto) in order to lift the baseline (representing zero units of IL-6) of the assay. As a consequence, these 4 units were later subtracted from the results. By this procedure, which has been described previously (Bauer et al. 1994), we improved the accuracy of the measurement of low IL-6 concentrations.

Data analysis

Analysis of variance was applied for comparison of more than two groups, and the two-tailed t-test was applied for unpaired groups. Correlations were determined by Spearman rank correlation coefficient. The level of significance was $p \leq 0.05$.

Table 2 IL-6 levels during the course of treatment in depressed and schizophrenic patients

Groups	IL-6 levels (U/ml)		
	Acute episode		In remission
	Drug free (admission)	Medicated (9 days later)	Medicated (8 weeks later)
Depressed patients	1.48 ± 0.19 ($n = 4$)	1.24 ± 0.33 ($n = 12$; $p \leq 0.05$)	0.98 ± 0.17 ($n = 10$; $p \leq 0.65$)
Schizophrenic patients	1.45 ± 0.53 ($n = 11$; $p \leq 0.02$)	1.31 ± 0.46 ($n = 32$; $p \leq 0.003$)	1.18 ± 0.35 ($n = 32$; $p \leq 0.04$)
Depressed and schizophrenic patients	1.46 ± 0.45 ($n = 15$; $p \leq 0.003$)	1.28 ± 0.42 ($n = 44$; $p \leq 0.002$)	1.13 ± 0.32 ($n = 42$; $p \leq 0.23$)
Healthy controls	1.01 ± 0.18 ($n = 12$)		

NOTE: Comparison between the groups of patients at their different stages vs healthy controls; no. of patients varies because of dropouts; mean ± SD; t-test, two-tailed

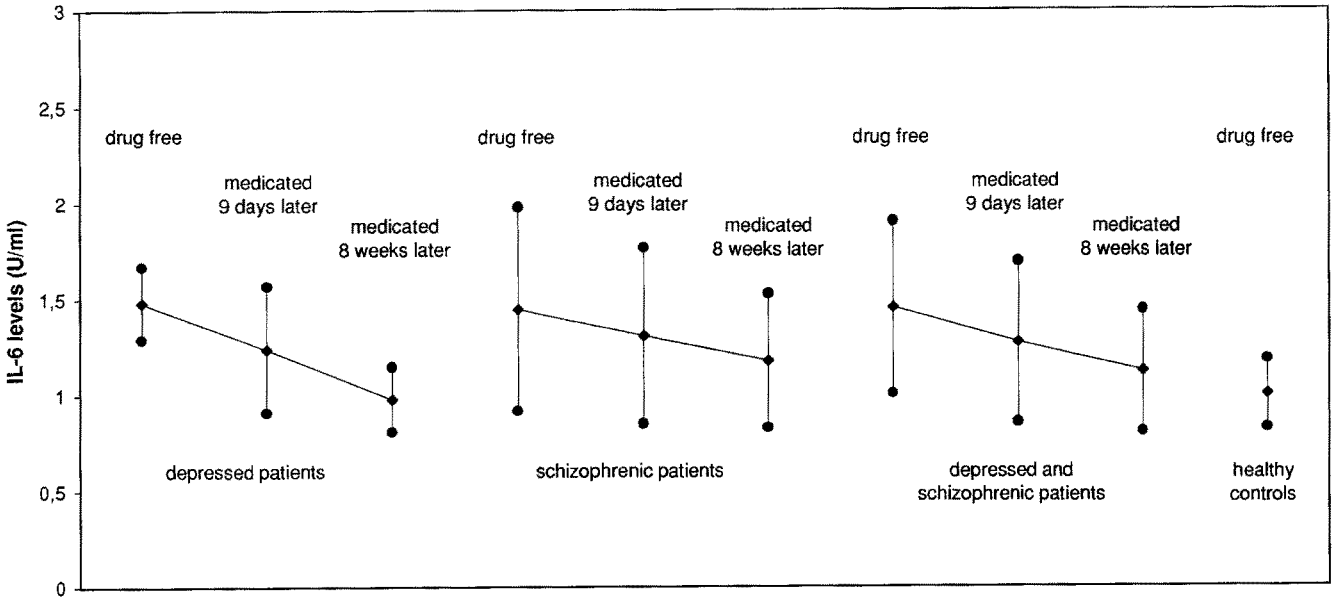

Fig. 1 IL-6 levels during the course of treatment in depressed and schizophrenic patients mean; ± SD

Results

In the acute state, the subgroup of the drug-free depressed patients ($n = 4$), exhibited a higher IL-6 level than control subjects (Table 2). At the second assessment, when also the subgroup of the initially unmedicated depressed patients had received antidepressants, the IL-6 levels of the depressed patients ($n = 12$) were somewhat lower than in the drug-free status but still significantly different ($p \leq 0.05$) from that of the controls.

Similar to the depressed patients, drug-free schizophrenic patients ($n = 11$) in the acute phase showed higher IL-6 concentrations than the controls ($p \leq 0.02$). After a mean of 9 days of drug treatment, at the second assessment, schizophrenic patients ($n = 32$) still exhibited a statistically significant ($p \leq 0.003$) elevation of IL-6 plasma concentration when compared with controls.

In remission, 8 weeks after admission, no significant differences were found between depressed or schizophrenic patients when compared with controls.

When comparing the IL-6 levels of the patients between acute-state medicated status and remitted state, IL-6 levels had significantly decreased in both depressed ($p \leq 0.05$) and schizophrenic patients ($p \leq 0.003$).

The comparison of the course of IL-6 levels during the hospitalization between depressed and schizophrenic patients reveals that in depressed patients the decrease in IL-6 levels is more homogenous than in schizophrenic patients (Fig. 1).

There was no significant correlation between IL-6 plasma concentration during the acute state (medicated status) and (a) age, (b) scores in rating scales for severity of depression or schizophrenia and (c) CRP.

There was a correlation between IL-6 plasma levels and duration of schizophrenic illness; however, this correlation was dependent on the phase of illness. A significant correlation was found for IL-6 concentrations and duration of schizophrenic illness since first onset only during the acute state in medicated schizophrenic patients ($n = 32$, $r = 0.35$, $p \leq 0.05$). No significant correlation was found between IL-6 levels and duration of illness since first onset for medicated depressed patients during the acute state. In remission no significant correlation between IL-6 levels and duration of ill-

ness was found either for schizophrenic or depressed patients.

The improvement of illness between acute medicated and remitted status was correlated to the change in IL-6 levels between both states. In depressed patients change in IL-6 levels and change in MADRS scores correlated non-significantly ($r = 0.21$). In schizophrenic patients a significant correlation ($r = 0.39$, $p \leq 0.05$) was found between change in IL-6 levels and change in BPRS scores.

We controlled for a variety of biological parameters that are related to immunological disorders such as rheumatoid arthritis. We compared patients who showed slight abnormalities in these parameters with those who had no such abnormalities. We did not find significant differences in IL-6 levels between those patients with and those without any increase in such parameters. Our results did not change when excluding those patients with slight abnormalities in the above-mentioned parameters.

Because of the small numbers of patients, we performed an additional analysis by pooling the depressed and schizophrenic patients. This method revealed the same results as in the depressed or schizophrenic patients separately, but with more accuracy and power (Table 2).

Discussion

Our main findings were (a) IL-6 serum levels are elevated during the acute state of both depressive and schizophrenic episodes when compared with controls; and (b) in remission IL-6 levels of depressed patients are at the same level as those of controls, whereas IL-6 levels of schizophrenic patients remain slightly elevated, but to a non-significant extent.

Our results of elevated levels of IL-6 plasma levels during acute depression and schizophrenia are in good agreement with recent reports (Maes et al. 1993; Ganguli et al. 1994; Seidel et al. 1995). In addition, our data support the finding of Ganguli et al. (1994) that IL-6 levels of schizophrenic patients correlate with duration of illness. In our study a correlation is found only if duration of illness is correlated with IL-6 levels of the acute state of illness, but not with IL-6 levels of remission. Ganguli et al. hypothesized that the correlation between IL-6 and duration of the psychiatric disorder might be related to abnormalities in development and functioning of neurons in schizophrenic patients.

The IL-6 levels in remitted schizophrenic patients were still, however non-significantly, higher than those of control subjects. This finding indicates the necessity for subsequent reports to provide information of the psychopathological status of the patient when blood is drawn for IL-6 measurement. Differing results of IL-6 levels between studies might be due to the fact that measures of IL-6 – as we could show – vary during different phases of the disorder. Interleukin-6 as an immunological parameter in schizophrenia appears to be state dependent.

One reason why investigators may come to conflicting results might be the influence of medication. The influence of psychotropic medication on immune function still remains elusive. Xu et al. (1994) reported a significant difference in plasma IL-6 concentration between schizophrenic patients taking neuroleptic drugs and those not taking them. In our study the decline in IL-6 levels from an acute to a remitted state of the patients might be related to the direct action of neuroleptics or antidepressants on immune function or to the time course of psychiatric illness. On the other hand, Ganguli et al. (1994) found no significant difference between IL-6 levels of neuroleptic-naive vs previously medicated schizophrenic patients, or between schizophrenic patients in an acute episode vs in remission. In the case of depressed patients Maes et al. (1995b) did not find significant differences in IL-6 levels between groups of acutely depressed patients treated with antidepressants of various types and patients who were in remission and drug free. They concluded that elevation of IL-6 plasma levels might be a trait marker in depression. Our data which are derived from the same patients in acute and remitted state do not support the notion that IL-6 is a trait marker. The results instead suggest that the elevation of IL-6 levels is a state marker of acute depression.

Two recent reports support our findings that IL-6 levels vary during the course from acute to remitted state. In depressed (Maes et al. 1995b) and in schizophrenic patients (Seidel et al. 1995) it was found that elevated IL-6 levels measured at admission decreased during treatment. However, these findings were not supported by other investigators. Mean IL-6 levels were not found to be different between schizophrenic patients in remission and controls (Shintani et al. 1991). Some investigators even did not find detectable plasma levels of IL-6 in patients and controls (Katila et al. 1994).

At the moment it still remains unclear as to whether and how IL-6 contributes to the pathogenetic process of depression and schizophrenia. Several authors discuss the hypotheses of autoimmune processes, a viral infection or reactivation of nonspecific factors in schizophrenia (Ganguli et al. 1994; Maes et al. 1995a). In our study we controlled for a variety of parameters involved in autoimmune processes, such as complement CH-50, and compared patients who showed abnormalities in these parameters with those who had no slight abnormalities. We would have expected, for example, complement CH-50 to be reduced if autoimmune processes would be involved in an acute state of depression or schizophrenia. The patients in this study did not exhibit an abnormality such as a reduction in complement CH-50. We found slight abnormalities, e.g. CH-50 86 U/l or ASL 312 U/ml, only in some patients and they did not differ in IL-6 levels from those without any abnormalities in laboratory parameters. The difficult question remains as to whether our data do support the hypothesis of an autoimmune response in acute depression or schizophrenia. The question remains unresolved because we found slight alterations of immunological parameters in only some patients so that the elevation of IL-6 levels during acute phase might be due to a primary autoimmune process in at least some pa-

tients. Yet, we do not know whether increased IL-6 levels in psychiatric patients are of immune origin. Interleukin-6 might even be of central origin because glutamate and norepinephrine in CNS might contribute to increased IL-6 synthesis via microglia or astrocytes.

We prefer another interpretation of our findings: stress has been found to be sufficient to increase IL-6 levels (Stein and Schluter 1994). One might argue that psychological stress, e.g. negative life events which often precede depression and psychosis could increase IL-6 levels. Stress might cause alterations in synaptic neurotransmission of adrenaline, norepinephrine or glutamate. Subsequently, astroglia or microglia might be stimulated (De Rijk et al. 1994; Maimone et al. 1993; Norris and Benveniste 1993; Sawada et al. 1992) and induce increased IL-6 production, however in different ways.

Activation of IL-6 is closely related to activation of HPA axis (Maes et al. 1993), the latter being known to be involved in depression and in the stress response (Black 1994; Stein and Schluter 1994). The contrasting findings of increased activation of cell-mediated or humoral immune response and signs of immunosuppression in major depression may be the result of the activity of multiple feedback systems which may reflect homeostatic devices (Maes et al. 1995b). The low levels of IL-6 in psychiatric illness could indicate a self-limiting process during the immune response in functional psychoses.

Psychological stress could subsequently trigger immunological response such as IL-6 or HPA-axis activation. Because of the feedback loops between IL-6 and HPA axis, it remains unclear what parameter is initiating the stress reaction. To test these possibilities one has to study prospectively depressed patients in remission and to assess which parameter is increasing at what time point and is influencing other parameters involved in the stress reaction.

Acute psychiatric illness might be such a relevant stressor, able to activate acute-phase response and HPA axis.

According to the stress hypothesis we might interpret the different course of IL-6 in levels of depressed and schizophrenic patients during treatment. The homogenous decrease of IL-6 levels in depressed patients might be related to a perceived relief of the distressing symptoms. In schizophrenic patients, however, we found a different pattern. A considerable number of patients exhibited a more inhomogenous course of IL-6 levels during treatment and time to remission of psychotic symptoms (Fig. 1). According to the stress hypothesis this might be related to a perception of the patients that quality of life during remission of the schizophrenic symptoms does not necessarily increase. A considerable number of schizophrenic patients perceive the remission of symptoms and then occurring problems as sequelae of the psychotic episode and the difficulties in everyday life as even more distressing than the period of psychotic features (D. Naber 1997, pers. commun.). Thus, by the stress hypothesis, our findings of significantly higher IL-6 levels at admission, the decrease in IL-6 levels during treatment and the inhomogenous pattern of the decrease in IL-6 in schizophrenic patients' levels might be interpreted, and stress might be one source of variation in IL-6 research literature.

In conclusion, since we found that the decline in IL-6 levels occurs in both the depressed and schizophrenic patients, and since studies showed that mere stress, independent of psychiatric illness, leads to an elevation of serum IL-6 levels (LeMay et al. 1991; Zhou et al. 1993; Stein and Schluter 1994), we interpret our findings as a reflection of the unspecific stress perceived by patients due to the acute illness itself as well as to the admission to the hospital and its psychosocial consequences.

References

Aarden LA, de Groot ER, Schaap OL, Lansdorp PM (1987) Production of hybridoma growth factor by human monocytes. Eur J Immunol 17:1411–1416

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders (DSM-III-R), 3rd edn, revised. American Psychiatric Press, Washington DC

Barak V, Barak Y, Levine J, Nisman B, Roisman I (1995) Changes in interleukin-1 beta and soluble interleukin-2 receptor levels in CSF and serum of schizophrenic patients. J Basic Clin Physiol Pharmacol 6:61–69

Bauer J, Ganter U, Strauss S, Stadtmüller G, Frommberger U, Bauer H, Volk B, Berger M (1992) The participation of interleukin-6 in the pathogenesis of Alzheimer's disease. Res Immunol 143:650–656

Bauer J, Hohagen F, Ebert T, Timmer J, Ganter U, Krieger S, Lis S, Postler E, Voderholzer U, Berger M (1994) Interleukin-6 serum levels in healthy persons correspond to the sleep-wake cycle. Clin Investig 72:315

Black PH (1994) Central nervous system-immune system interactions: psychoneuroendocrinology of stress and its immune consequences. Antimicrob Agents Chemother 38:1–6

Campbell IL, Abraham CR, Masliah E, Kemper P, Inglis JD, Oldstone MBA, Mucke L (1993) Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6. Proc Natl Acad Sci USA 90:10061–10065

De Rijk RH, Boelen A, Tilders FJH, Berkenbosch F (1994) Induction of plasma interleukin-6 by circulating adrenaline in the rat. Psychoneuroendocrinology 19:155–163

Ganguli R, Yang Z, Shurin G, Chengappa KNR, Brar JS, Gubbi AV, Rabin BS (1994) Serum interleukin-6 concentration in schizophrenia: elevation associated with duration of illness. Psychiatry Res 51:1–10

Hornig-Rohan M, van Bell CT, Kuhn P, Amsterdam JD (1995) Acute phase proteins in affective illness. Biol Psychiatry 37: 607 (Abstract)

Joyce P, Hawes C, Mulder R, Sellman J, Wilson D, Boswell D (1992) Elevated levels of acute phase plasma proteins in major depression. Biol Psychiatry 32:1035–1041

Katila H, Appelberg B, Hurme M, Rimon R (1994) Plasma levels of interleukin-1 beta and interleukin-6 in schizophrenia, other psychoses, and affective disorders. Schizophr Res 12:29–34

Kushner I (1991) The acute phase response: from Hippocrates to cytokine biology. Eur Cytokine Netw 2:75–80

LeMay LG, Vander AJ, Kluger MJ (1991) The effects of psychological stress on plasma interleukin-6 activity in rats. Physiol Behav 47:957–961

Maes M, Scharpe S, Meltzer HY, Bosmans E, Suy E, Calabrese J, Cosyns P (1993) Relationships between interleukin-6 activity, acute phase proteins, and function of the hypothalamic-pituitary-adrenal axis in severe depression. Psychiatry Res 49:11–27

Maes M, Meltzer HY, Bosmans E (1994a) Psychoimmune investigation in obsessive-compulsive disorder: assays of plasma transferrin, IL-2 and IL-6 receptor, and IL-1β and IL-6 concentrations. Neuropsychobiology 30:57–60

Maes M, Meltzer HY, Stevens W, Cosyns P, Blockx (1994b) Multiple reciprocal relationships between in vivo cellular immunity and hypothalamic-pituitary-adrenal axis in depression. Psychol Med 24:167–177

Maes M, Bosmans E, Calabrese J, Smith R, Meltzer H (1995a) Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. J Psychiatr Res 29: 141–152

Maes M, Meltzer H, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R, Desnyder R (1995b) Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. J Affect Disord 34:301–309

Maimone D, Cioni C, Rosa S, Macchia G, Aloisi F, Annunziata P (1993) Norepinephrine and vasoactive intestinal peptide induce IL-6 secretion by astrocytes: synergism with IL-1ß and TNFα. J Neuroimmunol 47:73–82

Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389

Müller N (1997) Die Rolle des Zytokinnetzwerks im ZNS und psychische Störungen. Nervenarzt 68:11–20

Norris GJ, Benveniste EN (1993) Interleukin-6 production by astrocytes: induction by the neurotransmitter norepinephrine. J Neuroimmunol 45:137–146

Overall JE, Gorham DR (1962) The Brief Psychiatric Rating Scale. Psychol Rep 10:799–812

Seidel A, Arolt V, Hunstiger M, Rink L, Behnisch A, Kirchner H (1995) Cytokine production and serum proteins in depression. Scand J Immunol 41:534–538

Shintani F, Kanba S, Maruo N, Nakaki T, Nibuya M, Suzuki E, Kinoshita N, Yagi G (1991) Serum interleukin-6 in schizophrenic patients. Life Sci 49:661–664

Sluzewska A, Rybakowski J, Laciak M, Mackiewicz A, Sobieska M, Wiktorowicz K (1995) Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. Ann NY Acad Sci 762:474–476

Sluzewska A, Rybakowski J, Bosmans E, Sobieska M, Berghmans R, Maes M, Wiktorowicz K (1996) Indicators of immune activation in major depression. Psychiatry Res 64:161–167

Song C, Dinan T, Leonhard B (1994) Changes in immunoglobulin, complement and acute phase protein levels in the depressed patients and normal controls. J Affect Disord 30:283–288

Spitzer RL, Williams JB, Gibbon M (1987) Structured clinical interview for DSM-III-R (SCID). Biometrics Research Department, New York State Psychiatric Institute, New York

Spivak B, Radwan M, Bartur P, Mester R, Weizman A (1995) Antinuclear autoantibodies in chronic schizophrenia. Acta Psychiatr Scand 92:266–269

Stein TP, Schluter MD (1994) Excretion of IL-6 by astronauts during spaceflight. Am J Physiol 266:E448–E452

Xu HM, Wei J, Hemmings GP (1994) Changes of plasma concentrations of interleukin-1alpha and interleukin-6 with neuroleptic treatment for schizophrenia. Br J Psychiatry 164:251–253

Zhou D, Kusnecov AW, Shurin MR, Paoli M de, Rabin BS (1993) Exposure to physical and psychological stressors elevates plasma interleukin-6: relationship to the activation of hypothalamic-pituitary-adrenal axis. Endocrinology 133:2523–2530