Eur Arch Psychiatry Clin Neurosci (1996) 246:279–284

ORIGINAL PAPER

I. Wilke · V. Arolt · M. Rothermundt · Ch. Weitzsch
M. Hornberg · H. Kirchner

Investigations of cytokine production in whole blood cultures of paranoid and residual schizophrenic patients

Received: 15 May 1995 / Accepted: 10 May 1996

Abstract In an attempt to define potential immunological dysfunctions in schizophrenia, we determined the production of interleukin-2 (IL-2), interleukin-4 (IL-4), interferon-γ (IFN-γ), and soluble IL-2 receptor (sIL-2R) in a whole-blood assay after stimulation with phytohemagglutinin (PHA) as well as the serum concentrations of sIL-2R. Because $CD_4^+CD45RO^+T$ cells are the main producers of IFN-γ, we determined the percentage of these cells, as well as of panT, $CD4^+T$, and $CD8^+T$ cells, by flow cytometry. A whole-blood count was performed in addition. Two groups of patients were examined, paranoid-type and residual-type schizophrenics. The numbers of both monocytes and neutrophils, but not of lymphocytes, were increased significantly in the schizophrenic sample. The IFN-γ production of the schizophrenics as a whole group, and of the paranoid patients, was reduced significantly in comparison with the control group ($p \leq 0.05$). The residual patients produced less IFN-γ than the controls, but more than the paranoid patients. The latter differences did not reach statistical significance. The production of IL-4, which physiologically antagonizes the production of IFN-γ, was not significantly higher in the patient group. No changes in the lymphocyte subpopulations were observed. The production of IL-2 showed a trend toward reduction in paranoid patients, but not in residual schizophrenics. The serum sIL-2R levels were elevated slightly in schizophrenics when compared with controls. In order to rule out a possible effect of cortisol on cytokine production, 20 schizophrenics were compared with 20 age- and gender-matched controls. However, neither elevated cortisol levels were detected in the schizophrenic sample, nor significant intercorrelations between cortisol levels and cytokine production, or levels of sIL-2R, respectively. In summary, our data reinforce the possibility of immune dysfunction in schizophrenia and point to the possible relevance of disease subgroups in this respect.

Key words Schizophrenia · Immune system · Cytokine · Interferon

Ilona Wilke · Mathias Rothermundt · Christine Weitzsch · Marion Hornberg · Holger Kirchner (✉)
Institute of Immunology and Transfusion Medicine,
University of Lübeck School of Medicine,
Ratzeburger Allee 160, D-23538 Lübeck, Germany

Ilona Wilke · Volker Arolt · Christine Weitzsch · Marion Hornberg
Department of Psychiatry,
University of Lübeck School of Medicine,
Ratzeburger Allee 160, D-23538 Lübeck, Germany

Introduction

A multifactoral etiology of schizophrenia is generally assumed. Although genetic factors undoubtedly exert a major influence on the development of the disease, a variety of immunological abnormalities have also been observed in schizophrenic patients. Changes in the numbers of leukocytes and monocytes (DeLisi 1986) as well as in the percentages of T, T-helper, cytotoxic T, B, and $CD5^+B$ cells have been described (Coffey et al. 1983; Kolyaskina 1983; McAllister et al. 1989; Henneberg et al. 1990; Masserini et al. 1990; Müller et al. 1991). A search for functional changes yielded a reduced production of IFN-α and IFN-γ (Moises et al. 1985; Katila et al. 1989) and IL-2 (Villemain et al. 1987, 1989; Rabin et al. 1988; Ganguli and Rabin 1989; Hornberg et al. 1995), and high serum levels of sIL-2R (Ganguli et al. 1989; Rapaport et al. 1989). In order to determine the capacity of immune cells of schizophrenic patients to produce cytokines, we measured the production of IL-2, IL-4, IFN-γ, and sIL-2R, as well as serum sIL-2R levels. In addition, we determined the percentages of T, $CD4^+T$, $CD8^+T$, and $CD4^+CD45RO^+T$ cells, which are freshly primed or memory T-cells and have been described as being the main producers of IFN-γ (Sanders et al. 1988). We also intended to examine potential differences in cytokine production between patients with acute and residual schizophrenic disease.

Table 1 Sociodemographic and psychopathological characteristics of the schizophrenic and the control samples

	Schizophrenics	Controls
No. of subjects	51	39
Men/women	20/31	21/18
Mean age (years)	36.2 ± 12.7	34.6 ± 12.3
Mean duration of illness and range	9.8 (2–33) Paranoid 15.8 (5–31) Residual	– –
PANSS-T	59.0 ± 11.5	–
PANSS-P	30.4 ± 8.4	–
PANSS-N	36.6 ± 12.3	–

Subjects and methods

Blood was obtained from 51 schizophrenic in- and outpatients (31 females and 20 males; mean age 36.2 ± 12.7 years) of the Department of Psychiatry, University of Lübeck, and 39 blood donors (21 females and 18 males; mean age 34.6 ± 12.3 years) as a control group (Table 1). All patients and controls were free of acute or chronic infections, neoplasms, or any chronic diseases. All patients met DSM-III-R and ICD-10 criteria for schizophrenia. A total of 20 patients were paranoid (DSM-III-R 295.3); 25 residual (DSM-III-R 295.6) and 6 patients had other diagnoses (schizoaffective psychosis, disorganized, undifferentiated, or latent type of schizophrenia). The mean duration of the illness was 9.8 years (range 2–33 years) for paranoid schizophrenics and 15.8 years (range 5–31 years) for residual patients. A total of 47 patients received antipsychotic medication and 4 were untreated. The most frequently used drugs were clozapine, chlorprothixene, levomepromazine, haloperidol, promethazine, and biperidene.

A psychopathological evaluation was performed by experienced psychiatrists using the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987). The results are shown in Table 1. We tried to take a detailed history, including family history and nicotine and alcohol intake, from each patient. For each subject a whole-blood count was performed. Serum concentrations of C-reactive protein (CRP) and sIL-2R were measured.

Immunological methods

Peripheral blood mononuclear cells (PBMC) of schizophrenics or blood donors were cultured in a whole-blood technique as has been previously described (Kirchner et al. 1982). Briefly, 50 µl of heparinized blood was mixed with culture medium (RPMI 1640, Gibco Europe, Berlin, Germany, supplemented with 10000 U/ml penicillin, 10 mg/ml streptomycine, and 200 m*M* L-glutamine) at a ratio of 1 : 10 and stimulated with 5 µg PHA /ml (Buroughs-Wellcome, Dartford, UK). All assays were performed in quadruplicate; two unstimulated assays served as controls. The blood suspension was incubated in polypropylene tubes (Greiner, Nürtingen, Germany) at 37° C/5% CO_2 for 48 h (IL-2, IL-4) or 96 h (IFN-γ, sIL-2R), respectively. The supernatants were recovered and kept frozen at –80° C.

Cytokine concentrations were determined by ELISA technique. Recombinant cytokines were used as standards. Each concentration was measured in duplicate. For determination of IL-2 and IFN-γ, we used ELISA kits from Hoffmann-LaRoche, Grenzach-Wyhlen. IL-4 (Research and Diagnostic Systems, Minneapolis) and sIL-2R (T-Cell Sciences, Cambridge) were determined according to the manufacturer's instructions. C-reactive protein concentrations were determined by laser nephelometry (BN 100, Behringwerke AG, Marburg, Germany).

Additionally, in a sample of 20 schizophrenic patients and 20 age- and gender-machted normal controls the serum levels of cortisol were determined by ELISA kits (Boehringer, Mannheim, Germany), in accordance with the manufacturer's instructions. Due to the instructions, the normal range was defined as 55–690 nmol/l.

For the detection of $CD4^+$ and $CD8^+$T cells, 100 µl of blood anticoagulated with ethylenediaminetetraethylacetic acid (EDTA) was added to 10 µl of the appropriate fluoresceine isothiocyanate or phycoerythrine-conjugated monoclonal antibody. The suspension was incubated for 10 min at room temperature and then prepared with a leukocyte preparation system (Coulter Immunoprep EPICS; Coulter Q-Prep EPICS Immunology Work Station, Coulter, Hialeah, USA). For the detection of $CD5^+$ cells and of $CD45RO^+$T cells 50 µl of blood was added to 10 µl of the appropriate monoclonal antibody (FR882, FR884, DAKO GmbH, Hamburg, Germany) and incubated in the dark at 2–8° C for 30 min. One milliliter of red blood cell lysing solution was added. After 5 min, the tubes were mixed and centrifuged for 5 min at 2000 rpm. The pellet was resuspended in 1 ml of phosphate buffered saline (PBS) supplemented with 2% fetal calf serum (FCS) and centrifuged a second time. Again, the pellet was resuspended in 300 µl of PBS. By cytofluorometric analysis (EPICS-Profile II Flow Cytometer, Coulter Electronics, Krefeld, Germany) the percentage of cells positive for the respective marker was determined. By using isotype-matched control monclonal antibodies, nonspecific binding of mouse monoclonal antibody to human cell surface antigens was ruled out.

The differences between schizophrenic patients and the control group were analyzed by the Student's *t*-test. For the analysis of differences between paranoid schizophrenics, residual schizophrenics, and control group, we used one-way analyses of variance with multiple-range tests with the help of the SPSS-PC program, SPSS Inc., Chicago, USA. In order to find possible correlations between psychopathological findings and immunological data, we determined the Pearson's coefficient *r*. The level of significance was defined as $p \leq 0.05$.

Results

We detected a statistically significant increase in leukocyte numbers, which was due to significantly higher numbers of neutrophils and monocytes in schizophrenic patients ($p \leq 0.05$) (Fig. 1). There were no changes in the num-

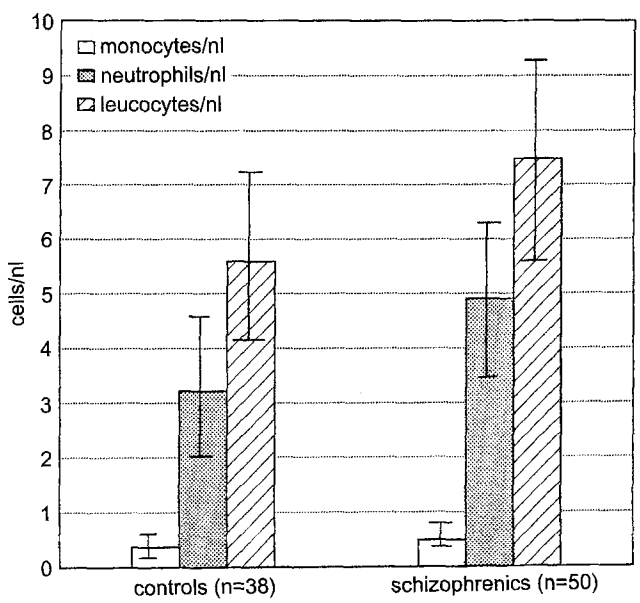

Fig. 1 Numbers of leukocytes, neutrophils, and monocytes in peripheral blood of schizophrenic patients and control subjects. The differences were significant ($p \leq 0.05$) for all three parameters

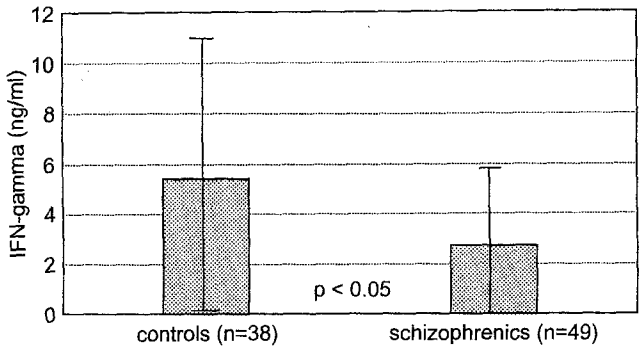

Fig. 2 IFN-γ production in schizophrenic patients and controls after 96 h of stimulation with PHA (5 μg/ml). The difference was statistically significant ($p \leq 0.05$)

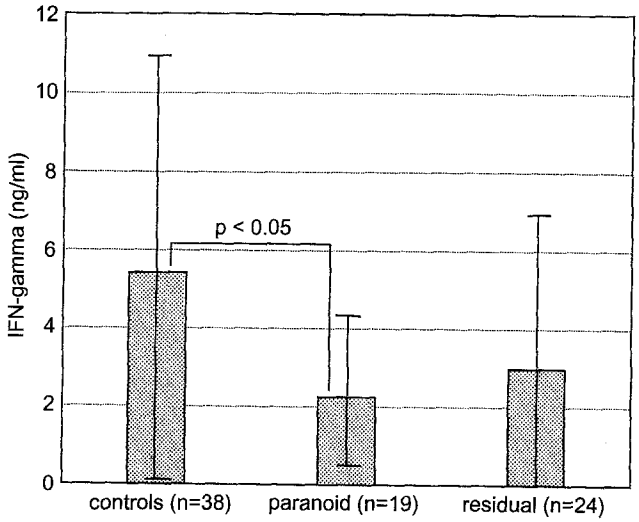

Fig. 3 IFN-γ production in paranoid and residual schizophrenics and controls after 96 h of stimulation with PHA (5 μg/ml). The difference was significant only for paranoid patients vs controls

bers of lymphocytes or lymphocyte subpopulations (Table 1). A serum concentration of CRP > 0.5ml/dl, which casts suspicion on the existence of inflammatory processes, was detected in 14 of 37 schizophrenics (37.8%) and in 6 of 33 (15.4%) controls ($p > 0.05$). The production of IFN-γ was reduced significantly in the whole-blood cultures of schizophrenics, in comparison with controls (Fig. 2; Table 2). By separately analyzing the subgroups of schizophrenic patients, the decrease only reached statistical significance in paranoid, but not in residual, schizophrenics, although the IFN-γ production was also lowered in this group (Fig. 3; Table 2). The production of IL-2 did not show any differences in the schizophrenics as a whole group. Paranoid patients tended to have a reduced production of IL-2, whereas residual patients showed a trend toward higher values (Fig. 4; Table 2). Serum sIL-2R levels were higher, especially in residual schizophrenics than in controls, although this difference did not reach the level of significance (Table 2). The production of sIL-2R upon stimulation in vitro did not differ from the controls. Only 8 of 45 schizophrenic patients and 2 of 34 control subjects had IL-4 levels above the detection limit of our assay, which was 3.0 pg/ml.

We also tested the group of untreated schizophrenics ($n = 4$) against the group of treated paranoid and residual schizophrenics ($n = 41$) with respect to parameters IL-2,

Table 2 White blood count and lymphocyte subpopulations in schizophrenics and controls

		Controls	Schizophrenics (whole group)	Paranoid Type	Residual Type	Δ Control/ schizophrenics	Δ Control/ paranoid	Δ Control/ residual	Δ Paranoid residual
Leukocytes (nl)	Mean	5.59	7.48	7.10	7.70	$p \leq$	$p \leq$	$p \leq$	n.s.
	SD	1.50	1.88	1.58	2.21	0.05	0.05	0.05	
	N	39	50	19	25				
Monocytes (nl)	Mean	0.36	0.49	0.48	0.51	$p \leq$	n.s.	$p \leq$	n.s.
	SD	0.14	0.19	0.17	0.21	0.05		0.05	
	N	38	50	19	25				
Neutrophils (nl)	Mean	3.22	4.91	4.95	4.84	$p \leq$	$p \leq$	$p \leq$	n.s.
	SD	1.24	1.40	1.43	1.51	0.05	0.05	0.05	
	N	38	49	20	24				
panT (%)	Mean	70.1	72.7	73.5	72.2	n.s.	n.s.	n.s.	n.s.
	SD	18.0	8.1	8.4	9.0				
	N	38	42	17	19				
$CD4^+T$ (%)	Mean	44.4	46.6	45.6	47.8	n.s.	n.s.	n.s.	n.s.
	SD	12.8	7.9	7.1	8.6				
	N	39	50	20	24				
$CD8^+T$ (%)	Mean	25.3	25.5	25.7	25.2	n.s.	n.s.	n.s.	n.s.
	SD	8.7	6.2	5.2	7.6				
	N	39	50	20	24				
$CD4^+$ $CD45RO^+T$ (%)	Mean	22.4	22.0	21.5	22.8	n.s.	n.s.	n.s.	n.s.
	SD	9.1	6.4	5.6	7.7				
	N	36	41	16	19				

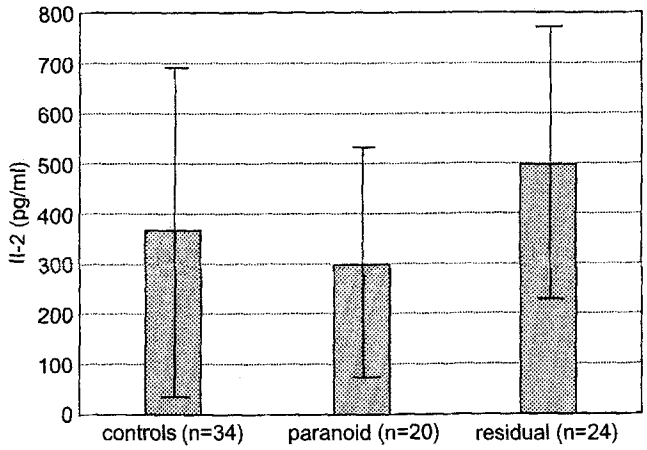

Fig. 4 IL-2 production in paranoid and residual schizophrenics and controls after 48 h of stimulation with PHA (5 µg/ml). The differences were not significant ($p > 0.05$)

IFN-γ, sIL-2R, numbers of leukocytes, total T-cells, CD4+ T-cells, and CD8+ T-cells. However, no significant differences could be detected (data not shown).

To determine serum cortisol levels, 20 schizophrenic patients and 20 age- and gender-matched controls were studied. In only two schizophrenics (885 and 699 nmol/l, respectively) and one control individual (901 nmol/l) serum levels exceeded the normal range (690 nmol/l). No significant differences, neither between schizophrenics and controls, nor between subgroups of schizophrenics, could be detected. In the schizophrenic sample, no significant correlations were observed between the cortisol levels and the production of both IL-2 and IFN-γ, and of sIL-2R levels, respectively (data not shown).

There were no influences of the duration of the illness, family history for psychiatric disorders, or age on immunological data (data not shown). The descriptions of alcohol intake prior to hospital admission were found highly unreliable, due to changing statements concerning types and quantities of alcohol intake. We therefore did not correlate alcohol consumption data to immunological variables. With respect to nicotine, we detected 19 smokers among the schizophrenics with an average consumption of 20 (± 16) cigarettes per day. We were again confronted with high variation, not only of individual statements, but also of nicotine concentration in different brands. Due to these uncertainties, we did not correlate nicotine intake to immunological variables, which had been measured with a much higher degree of precision. We intercorrelated the PANSS total score, positive score, and negative score, each with the following immunological parameters: IL-2, IFN-γ, sIL-2R, numbers of leukocites, total T-cells, CD4+ T-cells, and CD8+ T-cells. No significant correlations could be detected (data not shown).

Discussion

Our results confirm partially findings of others who have described immunological dysfunctions in schizophrenic patients (Moises et al. 1985; Villemain et al. 1987; Ganguli and Rabin 1989; Ganguli et al. 1989; Katila et al. 1989; Rapaport et al. 1989; Hornberg et al. 1995). We feel that the most remarkable result of our investigations was the significantly reduced production of IFN-γ. Similar findings have been reported before, but only as trends (Hornberg et al. 1995; Moises et al. 1985; Katila et al. 1989). It is noteworthy in this respect that some researchers used other methods of stimulation and determination of IFN-γ (Katila et al. 1989). Furthermore, diagnostic subtypes of the disease have not been considered explicitly in these studies. We found a greater reduction in IFN-γ production in acutely paranoid than in residual schizophrenics. This phenomenon was neither caused by a longer duration of illness nor by age differences. Although the difference between paranoid and residual patients was not significant, the reduced production in the acutely paranoid subsample is responsible for the significant difference between the schizophrenic sample as a whole and the controls.

We were able to demonstrate that the reduced IFN-γ was not due to smaller numbers of $CD4^+CD45RO^+$T cells, which are understood as the main producer cells of IFN-γ (Sanders et al. 1988). We also did not detect any significant differences in lymphocyte numbers or subtypes. Furthermore, the secretion deficit was not caused by a higher production of IL-4, a TH2-cytokine which acts antagonis-

Table 3 Cytokine production and sIL-2R in schizophrenic and control subjects

		Controls	Schizophrenics (whole group)	Paranoid Type	Residual Type	Δ Control/ schizophrenics	Δ Control/ paranoid	Δ Control/ residual	Δ Paranoid residual
IFN-γ production (pg/ml)	Mean	5429.0	2736.4	2241.5	2987.5	$p \leq$ 0.05	$p \leq$ 0.05	n.s.	n.s.
	SD	5398.4	3037.3	1943.9	3878.8				
	N	38	49	19	24				
IL-2 production (pg/ml)	Mean	366.9	400.8	297.8	497.9	n.s.	n.s.	n.s.	n.s.
	SD	322.8	260.5	235.6	273.2				
	N	34	50	20	24				
sIL-2R (serum; U/ml)	Mean	344.9	404.5	379.1	430.3	n.s.	n.s.	n.s.	n.s.
	SD	166.4	317.7	195.2	410.5				
	N	39	51	20	25				

tically to IFN-γ (Peleman et al. 1989). These results point to the possibility of an intrinsic defect in the producer cells of IFN-γ, which would parallel similar considerations for the case of a reduced production of IL-2 (Villemain et al. 1989).

However, extrinsic variables may also affect the production of IFN-γ. Among these variables are the effects of IL-10, another antagonistic TH2-cytokine, which could not be ruled out by this study. Because cortisol has a suppressive effect on the production of IL-2 and IFN-γ (Fowell et al. 1991; Mendelson and Glascow 1966), it must be questioned whether reduced cytokine levels in schizophrenia might be due to elevated cortisol levels. It is noteworthy in this respect that Kronfol and House (1991), who measured cortisol and lymphocyte response to mitogenes in schizophrenic patients, found elevated cortisol levels in schizophrenics, but no effect of cortisol on lymphocyte mitogenic response. They concluded that immune abnormalities in psychiatric disorders cannot be explained solely on the basis of increased cortisol values. When we tested 20 schizophrenics against age- and gender-matched controls, we detected only very few individuals (2 schizophrenics and 1 control) in which cortisol levels were elevated. Furthermore, we did not find any significant correlations between cortisol levels and the production of cytokines, or sIL-2R, respectively. Due to these non-significant results, it seems unlikely that changes in cortisol levels had a major influence on the cytokine production of our patients.

It is one major finding of this study that the production of IFN-γ is significantly reduced only in acutely paranoid, but not in residual, schizophrenics. This observation points to the possibility that the IFN-γ production may be associated with acute psychotic exacerbation in schizophrenia. Hence, there is an indication that this phenomenon might be understood as a state marker of schizophrenic psychoses. If this be the case, it must also be considered whether the IFN-γ production is primarily reduced (in the case of an intrinsic cellular defect) or if the deficit production is a secondary consequence ("exhaustion") of an initial excess production in vivo, which has not yet been observed directly in any study. This question has likewise been raised for the production of IL-2 (Ganguli et al. 1995a). Due to its cross-sectional procedure, our study can only provide first indications, which should be followed by employing longitudinal study designs.

In contrast to other researchers (Villemain et al. 1987, 1989; Ganguli et al. 1989), but also to our own previous findings (Hornberg et al. 1995), we did not detect a significant reduction in the IL-2 production in the whole sample of schizophrenic patients. Interestingly, there was a trend toward lower IL-2 production in the acutely paranoid schizophrenics, but not in residual patients, who tended towards a higher IL-2 production than the controls. Similar subgroup differences were reported by Rabin et al. (1988) and Ganguli et al. (1992). We observed a similar phenomenon for the case of sIL-2R. Unlike other researchers (Ganguli et al. 1989; Rapaport et al. 1989; Hornberg et al. 1995), we only observed a trend to higher serum levels of sIL-2R, which was stronger in residual than in paranoid patients, but did not reach statistical significance. There are two possible explanations for these differences. Firstly, even slight changes in immunological laboratory procedures can produce major variation of results. The most important difference in this respect is represented by the fact that we have used the whole-blood method, by which the cellular components are left in their natural milieu and are handled with extreme care. Also, different choices of ELISAs should be conceived as being sources of variance. However, we used the same methods in this study which we have used before (Hornberg et al. 1995); nevertheless, with different results. Secondly, in this study we differentiated subgroups of schizophrenics, whereas before we recruited patients of all subgroups during a period of clinical recovery. This observation illustrates the fact that the sampling of probands also substantially contributes to variation. Although the other cited studies are based on similar subgroup selections, there may still be differences which we are still unable to detect.

The higher leukocyte numbers ($p \leq 0.05$) were due to significantly elevated numbers of neutrophils and monocytes ($p \leq 0.05$). This elevation was not caused by the higher number of patients with an elevated CRP. Abnormal leukocyte counts have been reported by several groups in the literature (review: DeLisi 1986). Müller et al. (1993) reported elevated numbers of CD3+ and CD4+ cells, whereas our group did not observe such results (Hornberg et al. 1995). Because flow cytometry is a highly standardized method, it contributes probably far less to variation than differences in the sampling of patients and perhaps also of controls. It is our impression that further studies are needed to ascertain these differences.

Possible influences of pharmacological compounds may contribute to a lowered production of IFN- and IL-2. In this study we were not able to detect significant differences between treated and untreated schizophrenics with respect to these TH1-cytokines and other immunological parameters, but the sample of untreated patients was very small ($n = 4$). However, there is some evidence in the literature against a major influence of neuroleptic treatment on immune functions. Moises et al. (1985) did not detect an in vitro effect of haloperidol, neither on the proliferation of lymphocytes nor on the IFN-γ production. In two clinical studies lymphocyte subpopulations were not influenced by neuroleptic treatment (McAllister et al. 1989; Müller et al. 1991). The production of IL-2 was not affected by neuroleptic treatment in three studies (Bessler et al. 1995; Rabin et al. 1988; Villemain et al. 1989), nor was the level of sIL-2R in the supernatants (Rapaport and Lohr 1994). A decreased production of IL-2 was also found in untreated schizophrenics (Bessler et al. 1995; Ganguli et al. 1995a). Interestingly, Maes et al. (1994) and Pollmächer et al. (1995) described elevated levels of sIL-2R in clozapine-treated schizophrenics. However, Ganguli et al. (1995b) have been unable to reproduce this finding. It can be concluded that the influence of neuroleptic treatment has not yet been ruled out and deserves further study.

Immunological dysfunction could be a pathogenetic factor in schizophrenia by causing brain damage, perhaps associated with viral infections or the induction of autoantibodies. On the other hand, it cannot be excluded that immunological abnormalities represent epiphenomena caused either by the illness itself or by the factors causing schizophrenia, e.g. brain damage or changes in neurotransmitter metabolism. It is remarkable that many groups recently reported immunological findings in schizophrenia, but these findings were heterogenous and difficult to reproduce by others. Our group, in fact, has thus far studied three series of schizophrenic patients and has also found partially divergent results. Our present data may serve as a partial solution to the problem, because it turned out that a proper classification of schizophrenic patients into subgroups may aid working out immunological dysfunctions.

References

Bessler H, Levental Z, Karp L, Modai I, Djaldetti M, Weizman A (1995) Cytokine production in drug-free and neuroleptic-treated schizophrenic patients. Biol Psychiatry 38:297–302

Coffey CE, Sullivan JL, Rice JR (1983) T-lymphocytes in schizophrenia. Biol Psychiatry 18:113–119

DeLisi LE (1986) Neuroimmunology: clinical studies of schizophrenia and other psychiatric disorders. In: Nasrallah HA, Weinberger DR (eds) Handbook of schizophrenia, vol 1.Elsevier, Amsterdam, pp 377–396

Fowell D, McKnight A, Powrie F, Dyke R, Mason D (1991) Subsets of CD4+ T-cells and their role in the induction and prevention of autoimmunity. Immunol Rev 123:37–64

Ganguli R, Rabin BS (1989) Increased serum interleukin-2 receptor in schizophrenic and brain-damaged subjects. Arch Gen Psychiatry 46:291–292

Ganguli R, Rabin BS, Belle SH (1989) Decreased interleukin-2 production in schizophrenic patients. Biol Psychiatry 26:424

Ganguli R, Brar JS, Solomon W, Chengappa KNR, Rabin BS (1992) Altered interleukin-2 production in schizophrenia: association between clinical state and autoantibody production. Psychiatry Res 44:113–123

Ganguli R, Brar JS, Chengappa KNR, DeLeo M, Yang ZW, Shurin G, Rabin BS (1995a) Mitogen-stimulated interleukin-2 production in never-medicated, first-episode schizophrenic patients. Arch Gen Psychiatry 52:668–671

Ganguli R, Brar JS, Rabin BS (1995b) Clozapine-induced increase in plasma levels of soluble interleukin-2 receptors (comment) Arch Gen Psychiatry 52:878

Henneberg A, Riedl B, Dumke H-O, Kornhuber HH (1990) T-lymphocyte subpopulations in schizophrenic patients. Arch Psychiatr Neurol Sci 239:283–284

Hornberg M, Arolt V, Wilke I, Kruse A, Kirchner H (1995) Production of interferons and lymphokines in leukocyte cultures of patients with schizophrenia. Schizophr Res 15:232–242

Katila H, Cantell K, Hirvonen S, Rimon R (1989) Production of interferon alpha and gamma by lymphocytes from patients with schizophrenia. Schizophr Res 2:361–365

Kay SR, Fiszbein A, Opler LA (1987) The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 13:261–276

Kirchner H, Kleinicke Ch, Diegel W (1982) A whole blood technique for testing production of human interferon by leukocytes. Immunol Method 48:213–219

Kolyaskina GI (1983) Blood lymphocytes in schizophrenia – immunological and virological aspects. Adv Biol Psychiatry 12:142–149

Kronfol Z, House JD (1991) Immunity, cortisol and psychiatric disorders. In: Kurstak E (ed) Psychiatry and biological factors. Plenum, New York, pp 223–227

Maes M, Meltzer HY, Bosmans E (1994) Immune-inflammatory markers in schizophrenia: comparison to normal controls and effects of clozapine. Acta Psychiatr Scand 89:346–351

Masserini C, Vita A, Basile R, Morselli R, Boato P, Peruzzi C, Pugnetti L, Ferrante P, Cazzullo CL (1990) Lymphocyte subsets in schizophrenic disorders. Schizophr Res 3:269–275

McAllister CG, Rapaport MH, Pickar D, Paul SM (1989a) Effects of short-term administration of antipsychotic drugs on lymphocyte subsets in schizophrenic patients. Arch Gen Psychiatry 46:956–957

McAllister CG, Rapaport MH, Pickar D, Podruchny TA, Christison G, Alphs LD, Paul SM (1989b) Increased numbers of $CD5^+B$-lymphocytes in schizophrenic patients. Arch Gen Psychiatry 46:890–894

Mendelson J, Glascow LA (1966) The in vitro and in vivo effects of cortisol on interferon production and action. J Immunol 96:345–349

Moises HW, Schindler L, Leroux M, Kirchner H (1985) Decreased production of interferon gamma in leukocyte cultures of schizophrenic patients. Acta Psychiatr Scand 72:45–50

Müller N, Hofschuster E, Ackenheil M, Eckstein R (1993) T-cells and psychopathology in schizophrenia: relationship to the outcome of neuroleptic therapy. Acta Psychiatr Scand 87:66–71

Müller N, Hofschuster E, Ackenheil M, Hofschuster E, Hempel W, Eckstein R (1991) Cellular immunity in schizophrenic patients before and during neuroleptic treatment. Psychiatry Res 37(2):147–160

Peleman R, Wu J, Fargeas C, Delespesse G (1989) Recombinant interleukin-4 suppresses the production of interferon-γ by human mononuclear cells. J Exp Med 170:1751

Pollmächer T, Hinze-Selch D, Mullington J, Holsboer F (1995) Clozapine-induced increase in plasma levels of soluble interleukin-2 receptors (letter). Arch Gen Psychiatry 52:877

Rabin BS, Ganguli R, Cunnick JE, Lysle DT (1988) The central nervous system – immune system relationship. Clin Lab Med 8:253–268

Rapaport MH, Lohr JB (1994) Serum soluble interleukin-2 receptors in neuroleptic naive schizophrenic subjects and in medicated subjects with and without tardive dyskinesia. Acta Psychiatr Scand 90:311–315

Rapaport MH, McAllister CG, Pickar D, Nelson DL, Paul SM (1989) Elevated levels of soluble interleukin-2 receptors in schizophrenia. Arch Gen Psychiatry 46:291–292

Sanders ME, Makoba MW, Sharrow SO, Stephany D, Springer TA, Young HA, Shaw S (1988) Human memory T-lymphocytes express increased levels of 3 cell adhesion molecules (LFA-3, CD2 and LFA-1) and 3 other molecules (UCHL-1, Cdw29 and Pgp-1) and have enhanced interferon-gamma production. J Immunol 140:1401–1407

Villemain F, Chatenoud L, Galinowski A, Homo-Delarche F, Ginestet D, Loo H, Zarifian E, Bach JF (1989) Abberant T-cell mediated immunity in untreated schizophrenic patients: deficient interleukin-2 production. Am J Psychiatry 146:609–616

Villemain F, Chatenoud L, Guillibert E, Pelicier Y, Bach JF (1987) Decreased production of interleukin-2 in schizophrenia. Ann NY Acad Sci 469:669–675