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ORIGINAL PAPER

Intracellular monocytic cytokine levels in schizophrenia show an alteration of IL-6

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Abstract Several studies have shown an involvement of the immune system, in particular the monocytic system, in the pathophysiology of schizophrenia. Beside others, the monocyte-derived cytokines TNF-α, IL-6 and IL-10 were found to be affected. Since cytokines are secreted by several different cell types, the cellular source is only clear if intracellular levels are measured. Thus, in order to study the monocytic system in schizophrenia, the intracellular levels of TNF-α, IL-6 and IL-10 were determined. The intracellular concentration of TNF-α, IL-6 and IL-10 in CD33 positive monocytes was evaluated in schizophrenic patients and controls with monoclonal antibodies against these cytokines. In addition, in vitro stimulation with lipopolysaccharide (LPS) or poly I/C, which mimic a bacterial and viral infection, was performed before immunocytochemistry. At baseline, monocytic IL-6 levels were significantly lower in schizophrenic patients than in controls. After stimulation with LPS, compared with baseline, monocytic intracellular IL-6 production tended to increase more in schizophrenic patients. The present results provide further support for the hypothesis of an involvement of a dysfunction of the monocytic system in the pathophysiology of schizophrenia and indicate that especially the pro-inflammatory immune response seems to be impaired.

Keywords Cytokines · LPS · Monocytes · Poly I:C · Schizophrenia

Introduction

Growing evidence suggests that cytokines, which mediate inflammatory and immune responses, may be involved in the pathophysiology of schizophrenia. Since cytokines are produced in the central nervous system by microglia, astrocytes, neurons and endothelial cells, they may be implicated in brain signalling and neuropsychiatric disorders [1]. In the recent years, a series of general immunological alterations have been described in schizophrenia [2, 3]. Compared with controls, schizophrenic patients have aberrant proportions of immunocompetent cells and abnormal levels of cytokines, especially pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α, in the peripheral blood and cerebrospinal fluid [4, 5].

So far, results of studies investigating cytokine levels in schizophrenia are somewhat inconsistent. A meta-analysis suggested higher *in vivo* peripheral levels of IL-1RA, sIL-2R and IL-6; the significant differences in levels of peripheral cytokines were taken as evidence for immune activation and an inflammatory syndrome in schizophrenia [4]. After Potvin et al. had excluded the influence of antipsychotic medication, only the increase in IL-6 levels in

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schizophrenia was still valid. Therefore, IL-6 alterations in schizophrenia seem to be related to the disease itself [4].

Environmental factors, such as prenatal infections, may be involved in the aetiology of some cases of schizophrenia [6]. In addition, recent studies investigated the role of postnatal infections on the pathogenesis of this disease [7] and showed higher rates of antibodies to infectious agents in the adult schizophrenic population [8]. There are similar findings also for other psychiatric diseases as Tourette's syndrome [9]. So far, most studies have either analyzed serum, plasma and CSF cytokine levels, *in vitro* cytokine production of a whole-blood assay or infection rates in schizophrenic patients. At present, we are not aware of studies investigating a single immune-competent cell population in regard to cytokine production and changes in production in response to infectious stimuli. Therefore, we performed a pilot study to investigate one cytokine-producing cell subset in particular. The monocytic cell system was chosen for this study because several monocytic-derived cytokines like IL-6 and IL-10 have been found to show abnormalities in schizophrenia and an increase in these monocytic cytokines seems to be relevant for acute psychosis [10, 11].

The aim of the present pilot study was to investigate in schizophrenic patients and controls both monocytic intracellular cytokine secretion and the change in monocytic intracellular cytokine levels after toll-like receptor (TLR) stimulation with either with lipopolysaccharide (LPS), which mimics a bacterial infection, or poly I/C, which mimics a viral infection [12, 13].

Methods

Patient and control population

Thirty-one inpatients (age 36.7 years, SD 13.6 years; 58.1% men) with a diagnosis of schizophrenia according to the 4th edition of the Diagnostic and Statistical Manual (DSM-IV) were recruited at the Department of Psychiatry of the Ludwig Maximilian University, Munich, Germany. Diagnoses were made by two experienced psychiatrists. At study inclusion, patients showed a mean value of 92.1 (SD 20.3) on the Positive and Negative Syndrome Scale (PANSS). Thirty-one gender-, age- and ethnicity-matched healthy controls (age 33.7 years, SD 16.1 years; 58.1% men) were recruited via advertisement. All study participants gave their informed consent to participate in the study. The ethics committee of the medical faculty approved the procedure for sample collection and analysis, and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Exclusion criteria consisted of a concomitant organic disease and acute general or genitourinary infections. Blood counts and urine analysis were performed (differential blood count; urea and electrolytes; CK; renal, pancreatic, liver and thyroid parameters; and CRP as an indicator of infections) in order to exclude patients and controls with organic diseases. In addition, an experienced psychiatrist evaluated the controls to ensure that they did not meet the criteria for a DSM-IV diagnosis of mental illness. The schizophrenic patients had to have discontinued antipsychotic medication at least 4 weeks prior to study inclusion. As regards smoking habits, 58.1% of the schizophrenic patients and 20% of the controls were smokers at the time of study inclusion. Patients and controls were all Caucasians living in Bavaria, Germany.

Blood samples

Blood samples were taken from the schizophrenic patients before antipsychotic medication was administered. The samples were obtained in the morning by venipuncture with one 8.5-ml CPDA monovette (Sarstedt, Nümbrecht, Germany).

Antibodies

For detection of the intracellular cytokines and marking of the monocytes, the following fluorescent monoclonal antibodies were obtained from the manufacturers: anti-TNF-α fluoresceine isothiocyanate isomer 1 (FITC), isotype IgG1 (AbD Serotec, Martiensried, Germany); anti-IL-6 phycoerythrine (PE), isotype IgG1,κ (rat) (eBioscience, San Diego, CA); anti-IL-10 R. phycoerythrine (RPE), isotype IgG1(AbD Serotec, Oxford, UK); anti-CD33 Cy 5,5, isotype IgG1κ (mouse); and anti-CD45 allophycocyanine APC, isotype IgG1 (Mouse) (all Caltac Laboratories, San Francisco, CA).

In vitro stimulation

4 × 1 ml CPDA blood was treated as follows:

1. Storage at room temperature (ca. 22°C) for 4 h.
2. Storage in an incubator (Memmert type U25, Heinrich Rhode GmbH, Kirchheim, Germany) at 37°C for 4 h; and addition of 10 µl/ml BFA after 2 h of incubation.
3. Stimulation with 1 µl/ml LPS (stored at 4°C [Sigma, St. Louis, MO]), incubation at 37°C for 4 h; and addition of 10 µl/ml BFA after 2 h of incubation.
4. Stimulation with 50 µg/ml poly I/C (polyinosinic: polycytidylic acid or polyinosinic-polycytidylic acid sodium salt poly I/C, sterile dilution 10 mg and 10 ml NaCl [150 mM], 100 µl aliquoted in 1.5-ml microtubes [Sigma, St. Louis, MO, USA]); incubation at

37°C for 4 h; and addition of 10 µl/ml BFA after 2 h of incubation.

To determine the optimal incubation time for LPS and poly I/C, experiments were performed with several different incubation times. In accordance with the literature on intracellular monocytic cytokines and macrophages, cytokine release peaked after 4 h of incubation [14, 15].

Staining of the intracellular cytokines

Staining was performed using a protocol adapted from previously described methods [16, 17]. 90 µl of each 1 ml of incubated and/or stimulated CPDA blood sample was used for staining in different tubules and about 20 µl of antibodies was added. The cell concentration was 10^6–10^7/ml. We used four-colour immunofluorescence staining with the following antibodies:

Antibody	Immunofluorescence stain (FL)	µg/ml
TNF-α	FITC (FL1)	10
IL-10	PE (FL2)	10
IL-6	PE (FL2)	2.5
CD33	Cy 5,5 (FL3)	5
CD45	APC (FL4)	1

Antibody concentrations were titrated under standardized conditions (cell concentration, volume, time and wash steps) to find optimal concentrations. Extracellular anti-CD antibodies helped to identify and specify monocytes (especially CD33). CD45 served as the panleucocytes marker. First, both extracellular antibodies—anti-CD33 and anti-CD45—were added to the blood. The tubules were then blended and incubated in the dark for 10–15 min to ensure antigen–antibody bonding. Erythrocytes were lysed by 3 ml water-diluted lysing solution through osmotic lysis to amplify the difference between erythrocytes and leucocytes, for example. The tubules were mixed by Vortex (Vortex-Genie, Bender&Hobein AG, Ismaning, Germany), incubated in the dark for 5 min and then centrifuged at 1,500 rpm for 5 min at 25°C. The supernatant was decanted and resuspended by mechanically disrupting the cell pellet with 20 strokes. To remove unbound antibodies, the cell pellet was washed in 2 ml PBS and centrifuged at 1,500 rpm for 5 min at 25°C. The supernatant was decanted and the cell pellet mechanically disrupted again. Leucocytes were permeabilized by 500 µl diluted FACS Permeabilizing Solution (multiplied by 10 concentrated, buffered solution, <15% formaldehyde, <50% diethylenglycole and Permeabilizing Agenz dilution 1:10 [FACS-Perm-Solution: distilled water], Becton Dickinson, Heidelberg, Germany) and incubated for 10 min. Washing in 2 ml PBS, centrifugation at 1,500 rpm for 5 min at 25°C, decantation of the supernatant and resuspension by mechanical disruption of the cell pellet for isolation of the monocytes followed. The intracellular cytokines were specifically stained by addition of the intracellular antibodies anti-TNF-α, anti-IL-10 and anti-IL-6. Cells were incubated in the dark for 30 min to allow antigen–antibody binding. The final step consisted of a final washing in 2 ml PBS, centrifugation at 1,500 rpm for 5 min at 25°C, decantation of the supernatant and resuspension by mechanical disruption of the cell pellet. To fix cells and products, 200 µl 1% PFA was added and levels of intracellular TNF-α, IL-6 and IL-10 were measured immediately.

Acquisition and analysis

Flow cytometric analysis was performed by using the FACSCalibur flow cytometer with 2 lasers (argon 488 nm, helium-neon 633 nm) and FACSComp Software (Becton Dickinson). A total of 15,000 events were acquired. Neutrophils, lymphocytes and dead cells were excluded in the dot plot by forward and side scatter gating and additional gating of CD33-positive and CD45-positive monocytes towards side scatter. The reference was the baseline (unstimulated) measurement (at room temperature) for each participant. The sums of the gated monocytes from each participant in the condition of non-stimulation or stimulation were incorporated into a histogram analysis (log) with CellQuest software (Becton Dickinson). Analyses were performed twice and independently by two different persons to ensure maximal accuracy; concordance was high. The mean data are given as the results. Figure 1 shows an example of gating monocytes.

Data analysis

The Wilcoxon test for unpaired samples was used for statistical analysis of non-normally distributed data (tested by the Kolmogorov–Smirnov test). No correction for multiple testing was performed since this was an exploratory study. The following formula was applied to determine the (mean) levels of adaption of monocytic cytokine expression from baseline to stimulation with TLR ligands: (stimulated values − baseline values)/baseline values. In addition, a two-way repeated measures ANOVA analysis was performed.

Results

Features of the study population

The distribution of age, gender, age of onset, blood analysis, BMI and smoking status between schizophrenic

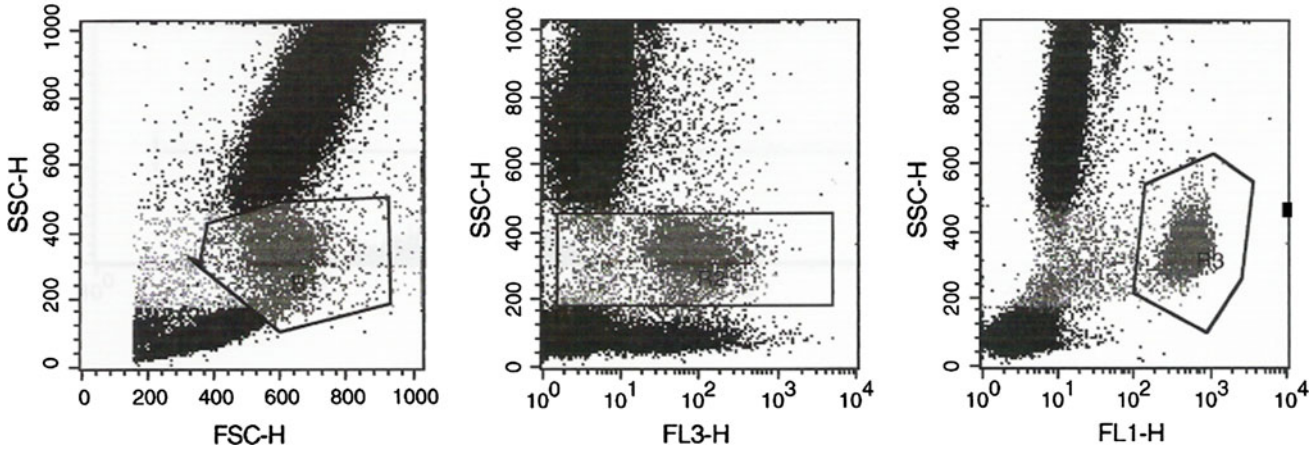

Fig. 1 Monocytes were identified by flow cytometry. **a** Gating of the relevant monocytes (R1 area). Above R1 are neutrophlis; below R1 are lymphocytes. **b** Example of monocytic gating using CD14 as a specfic monocyte marker (R2)

Table 1 The distribution of specific features between the group of schizophrenic patients and controls is shown

	Schizophrenic patients, ($n = 31$)	Mean	Standard deviation (SD)	Healthy controls ($n = 31$)	Mean	Standard deviation (SD)
Sex						
Female	13 (41.9%)	36.7	4.9	13 (41.9%)	36.9	15.0
Male	18 (58.1%)	37.2	13.2	18 (58.1%)	34.0	16.1
Age		36.7	13.6		33.7	16.1
Age of disease onset		31.9	12.9			
WBCs (G/l)		6.59	1.7		5.72	137
Monocytes (%)		7.35	1.92		7.06	1.53
CRP (mg/dl)		0.20	0.19		0.19	0.24
BMI (kg/m^2)	30	25.4	4.32	29	23.3	3.85
Smoking status	18 (58.1%)			6 (20.0%)		

patients and healthy controls was calculated. The results are shown in Table 1.

Schizophrenic patients: lower levels of IL-6 at baseline (before stimulation)

The schizophrenic patients showed significantly lower levels of the monocytic cytokine IL-6 ($P = 0.050$) than the healthy controls. These results were obtained under baseline conditions, meaning that cells were not stimulated. In addition, no significant difference in baseline (unstimulated) monocytic levels of TNF-α and IL-10 between schizophrenic patients and healthy controls were detected. The results are shown in Table 2 and Fig. 2.

Increased IL-6 levels in patients after LPS stimulation compared with baseline

Changes of intracellular cytokine levels after LPS stimulation in comparison with baseline conditions were calculated. Reference values are baseline monocytes at 37°C. The following formula was applied to determine the change in levels of monocytic cytokines (mean) from baseline to after LPS stimulation: (stimulated values − baseline values)/baseline values. The levels of IL-6 change in the schizophrenic group increased after stimulation compared with baseline marginally more than in the control group ($P = 0.051$). This might indicate that monocytes from schizophrenic patients were able to react to LPS stimulation with a higher production of IL-6. No other significant differences were found. The results are summarized in Table 3 and Fig. 3.

No differences for intracellular cytokine levels after LPS stimulation

The intracellular monocytic TNF-α, IL-6 and IL-10 levels did not differ in absolute values after LPS stimulation between the groups. TNF-α from schizophrenic patients showed a slight tendency towards lower levels ($P = 0.060$) than in healthy controls (see Table 4).

Table 2 Values of monocytic intracellular cytokines at baseline (before stimulation at 37°C)

Monocytes at baseline	Study group	*n*	Mean	SD	Min./Max.	Z	Rank	*P* value
TNF-α	Schizophrenic patients	31	46.5	49.1	3.9/234.8	−0.8	29.6	0.402
	Healthy controls	31	47.9	35.5	4.0/140.5		33.4	
IL-6	Schizophrenic patients	31	99.0	30.5	60.1/205.5	−2.0	27.0	**0.050**
	Healthy controls	31	110.9	29.8	75.7/220.0		36.0	
IL-10	Schizophrenic patients	31	116.8	47.0	60.9/238.8	−0.9	31.7	0.927
	Healthy controls	31	111.7	36.8	49.7/207.5		31.3	

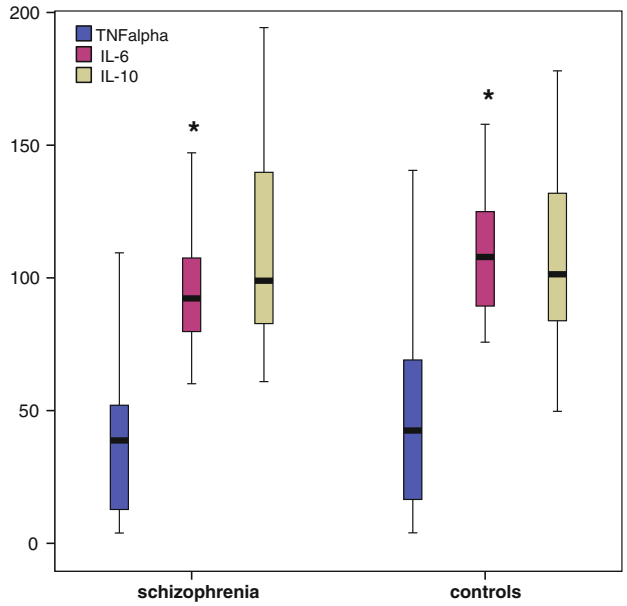

Fig. 2 *Box plots* represent levels of TNF-a, IL-6 and IL-10 at baseline (unstimulated condition). *Asterisk* marks a significant difference between schizophrenic patients and controls

Lower TNF-α levels in patients after LPS stimulation

ANOVA analysis showed that after LPS stimulation, the intracellular cytokine levels of TNF-α were significantly lower in schizophrenic patients than in controls ($P = 0.002$). No significant change in levels was found for any of the other cytokines. The results are shown in Table 5.

No differences were found in all poly I-/C-stimulated experiments

After stimulation with poly I/C, the monocytic intracellular cytokine levels were just slightly lower in schizophrenic patients than in healthy controls, but the difference was not significant. Also, no differences were found between both groups in regard to changes in cytokine levels from baseline to after stimulation (see Tables 6,7 and Fig. 4).

Discussion

The present study investigated whether intracellular monocytic cytokine levels differ between schizophrenic patients and healthy controls. Our analysis showed that at baseline (unstimulated condition), intracellular monocytic IL-6 levels were lower in schizophrenic patients than in controls. The rate of adjustment of monocytic intracellular IL-6 production from baseline to stimulation with LPS was increased in schizophrenic patients. However, the total levels of IL-6 after LPS stimulation were still higher in the control population. These results might point towards an impaired monocytic baseline level of IL-6 that cannot be compensated even upon stimulation.

As extracellular cytokines have a relatively short half-life, we focused specifically on intracellular monocytic cytokines. Interest in the monocytic cell population in schizophrenic patients has grown because these patients have recently been found to show a high inflammatory set

Table 3 Change in intracellular cytokine levels after LPS stimulation. Reference values are baseline monocytes at 37°C

Adjustment: stimulated versus baseline	Study group	*n*	Mean	SD	Min./Max.	Z	Rank	*P* value
TNF-α	Schizophrenic patients	31	0.36	51	−50/190	−1.6	27.9	0.116
	Healthy controls	31	0.74	79	−10/280		35.1	
IL-6	Schizophrenic patients	31	0.78	35	30/200	−2.0	36.0	0.051
	Healthy controls	31	0.62	40	0/170		27.0	
IL-10	Schizophrenic patients	31	0.67	34	10/160	−0.5	30.4	0.617
	Healthy controls	31	0.75	38	30/200		32.7	

The following formula was applied to determine the change in levels of monocytic cytokine expression (mean) from baseline to after LPS stimulation: (stimulated values − baseline values)/baseline values

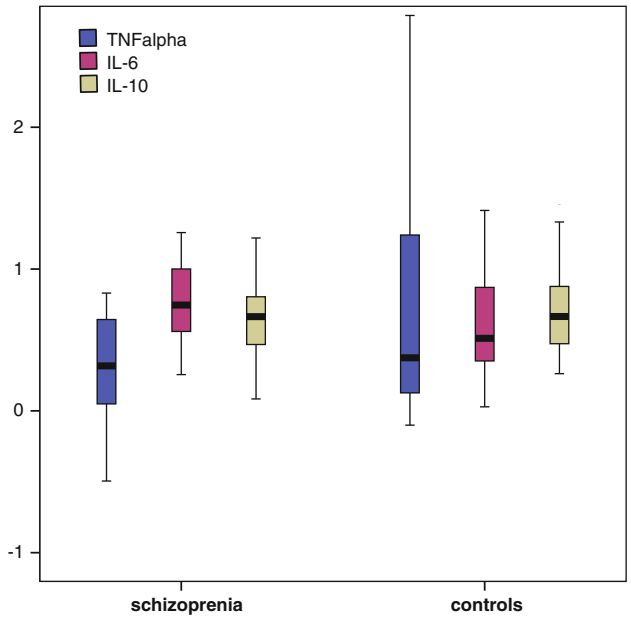

Fig. 3 *Box plots* represent the change of intracellular cytokine levels after LPS stimulation compared with baseline

Table 5 ANOVA analysis of LPS-stimulated monocytes

	F value	*P* value
TNF-α		
(Intercept)	100.666	0.000
Group	1.357	0.249
Time	20.328	0.000
Group:time	10.182	0.002
IL-6		
(Intercept)	795.133	0.000
Group	0.911	0.344
Time	215.621	0.000
Group:time	0.243	0.624
IL-10		
(Intercept)	458.322	0.000
Group	0.004	0.949
Time	162.970	0.000
Group:time	0.4503	0.505

The reference category is baseline monocytes (at 37°C) of healthy controls

point of circulating monocytes at the transcriptome level [18]. To our knowledge, this is the first pilot study to investigate intracellular monocytic cytokine levels in schizophrenia and to show a disturbed monocytic function—in the form of differences in cytokine levels—in this population.

Cytokine levels reported from investigations of monocytic cytokines and studies looking at whole blood differ greatly because cytokines are not only produced by monocytes. For example, TNF-α is secreted by macrophages, monocytes, neutrophils, T cells and NK cells. IL-6 in plasma is also produced in muscle and osteoblasts [19]. Of course, our measurements from a single-cell population represent after secretion only part of the total amount of extracellular cytokines. The sum of extracellular cytokines depends on the secretion of each single cell and on the total number of cytokine-producing cells.

Serum cytokine levels have not yet been fully evaluated. Singh et al. found IL-6 to be decreased in both medicated and unmedicated schizophrenic patients [20]. This finding is in contrast to that of a meta-analysis (including 2,298 schizophrenic patients and 1,858 controls) which found that levels of IL-6 were elevated in schizophrenia [4]. For TNF-α, altered cytokine levels have been measured in serum and revealed an increase in TNF-α in untreated schizophrenic patients and in treated patients with acute psychotic symptoms [21, 22]. These results are again not only from monocytes and represent serum baseline levels without stimulation. In the present study, we focused specifically on monocytes, and cytokine levels in serum were not measured in addition. Therefore, future studies are needed which use this pilot study as a basis to compare intracellular and extracellular cytokine levels.

Infectious agents may also be involved in the pathogenesis of schizophrenia. In this study, we investigated the effects of in vitro stimulation with LPS and poly I/C (models for bacterial and viral infections, respectively) on intracellular cytokine levels. We found hints for an association between LPS stimulation and schizophrenia in

Table 4 Values of LPS-stimulated monocytic intracellular cytokines (37°C)

LPS-stimulated monocytes	Study group	*n*	Mean	SD	Min./Max.	Z	Rank	*P* value
TNF-α	Schizophrenic patients	31	51.2	41.0	5.1/177.9	−1.9	27.2	0.060
	Healthy controls	31	75.4	54.3	7.8/196.9		35.8	
IL-6	Schizophrenic patients	31	171.6	45.8	98.1/335.2	−0.4	30.7	0.720
	Healthy controls	31	178.7	60.2	82.3/351.1		32.3	
IL-10	Schizophrenic patients	31	191.1	76.0	96.0/410.0	−0.4	30.6	0.688
	Healthy controls	31	194.3	75.9	89.0/451.0		32.4	

Mean values represent the fluorescence intensity of the cytokines TNF-α, IL-6 or IL-10 in monocytic cells after LPS stimulation

Table 6 Change in intracellular cytokine levels after poly I/C stimulation

Poly I:C-stimulated monocytes	Study group	*n*	Mean	SD	Min./Max.	Z	Rank	*P* value
TNF-α	Schizophrenic patients	31	41.6	33.8	4.1/143.1	−1.3	28.6	0.203
	Healthy controls	31	54.3	43.4	6.5/205.0		34.4	
IL-6	Schizophrenic patients	31	149.4	41.4	88.4/293.9	−1.0	29.2	0.321
	Healthy controls	31	161.1	47.2	82.5/300.9		33.8	
IL-10	Schizophrenic patients	31	170.1	58.4	98.6/354.9	−0.7	30.0	0.504
	Healthy controls	31	176.5	59.8	79.5/327.7		33.0	

Reference values are baseline monocytes at 37°C. The following formula was applied to determine the change in levels of monocytic cytokine expression (mean) from baseline to after poly I/C stimulation: (stimulated values − baseline values)/baseline values

Table 7 Change in intracellular cytokine levels after poly I/C stimulation

Adjustment: stimulated versus baseline	Study group	*n*	Mean	SD	Min./Max.	Z	Rank	*P* value
TNF-α	Schizophrenic patients	31	0.07	0.35	−0.6/0.9	−0.8	29.7	0.426
	Healthy controls	31	0.23	0.71	−0.4/3.6		33.3	
IL-6	Schizophrenic patients	31	0.54	0.26	0.1/1.3	−1.0	33.8	0.321
	Healthy controls	31	0.47	0.31	−0.1/1.3		29.2	
IL-10	Schizophrenic patients	31	0.50	0.22	−0.0/0.8	−0.9	29.6	0.394
	Healthy controls	31	0.61	0.37	0.0/1.6		33.5	

Reference values are baseline monocytes at 37°C. The following formula was applied to determine the change in levels of monocytic cytokine expression (mean) from baseline to after poly I/C stimulation: (stimulated values − baseline values)/baseline values

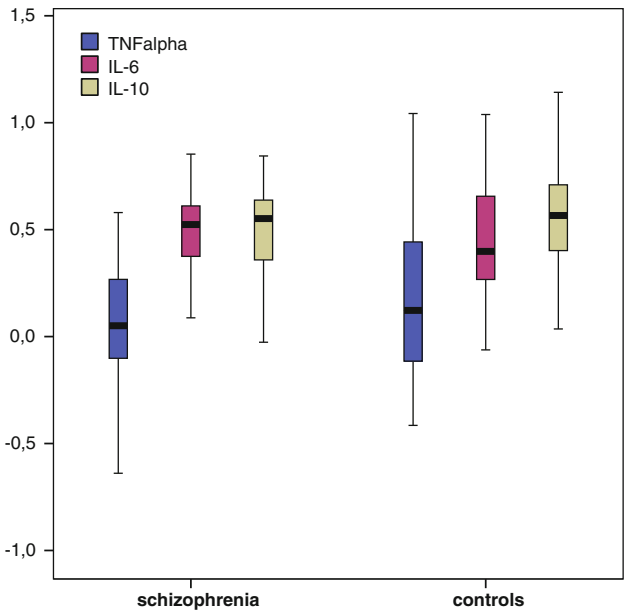

Fig. 4 *Box plots* represent the change of intracellular cytokine levels after poly I/C stimulation compared with baseline

regard to TNF-α levels: baseline monocytic intracellular TNF-α levels did not differ significantly between schizophrenic patients and controls but showed a trend towards a smaller increase in schizophrenic patients after stimulation with LPS. This might be interpreted as a sign of an impaired reaction upon bacterial infection. Our findings are interesting because previous studies have shown that particularly intracellular bacteria like *Chlamydia* or the parasite *Toxoplasma gondii* are more prevalent in patients with schizophrenia [23, 24], and our results might point towards a disturbed TNF-α upregulation in models of bacterial stimulation. Besides, our ANOVA analysis of the LPS-stimulated sample showed that schizophrenic patients had less TNF-α than healthy controls. This finding might provide further evidence for an association between schizophrenia and monocytic TNF-α levels.

Antipsychotic medication can also modulate the immune system and might thus affect the susceptibility for infections [10]. In our study, schizophrenic patients were free of antipsychotic medication for at least 4 weeks.

One explanation of how an altered immune balance caused by infectious agents could contribute to psychiatric symptoms is the 'kindling hypothesis', which is used to convey the concept of the development of persistent hypersensitivity to a given stimulus. While a certain stimulus is mandatory for the initiation of the immune response, that is, the release of cytokines and other mediators of immune activation, kindling is associated with an increased release of cytokines after re-exposure to the same stimulus or with release of the same amount in response to a weaker stimulus [25]. For example, stress-associated release of IL-6 was shown to reactivate (prenatal) conditioned processes

[26]. This phenomenon might be due to the memory function of the immune system [27, 28]. In addition, this mechanism is the key in triggering immune activation and inflammation and might be responsible for the increased IL-6 response to LPS in the schizophrenia group. A sensitization process of the immune system would be in line with the infection hypothesis of schizophrenia: an infection in early childhood may sensitize the immune system so that a re-infection or other stimulation of the immune system in later stages of life might cause a boosted release of cytokines, resulting in neurotransmitter disturbances. Even small stimuli can cause an upregulation upon stimulation and lasting changes intrinsic to the NMDA receptor [29].

In addition to this mechanism, infectious agents have been suggested to contribute to the pathogenesis of psychiatric diseases by activating microglia cells (monocytes in the brain) [7, 30, 31]. Within the brain, microglia are resident, monocyte-derived and cytokine-producing cells that have been implicated as active contributors to neuron damage in neurodegenerative diseases [32]. However, the degree to which parallels can be drawn between peripheral cytokines and processes in the CNS remains controversial. It is known that peripheral cytokines influence brain cells through various mechanisms such as passive transport into the CNS, second messengers and active transport during pathological conditions [5, 33].

Our results provide further support for the hypothesis of an involvement of the immune system in the pathophysiology of schizophrenia and indicate that especially the pro-inflammatory immune response seems to be impaired. However, all our findings need to be interpreted with caution because of the pilot study character of the present results.

Conclusion

In conclusion, our pilot study found that in an unstimulated condition intracellular monocytic IL-6 levels were lower in schizophrenic patients than in controls. Additionally, the rate of adjustment of monocytic intracellular IL-6 production from baseline to stimulation with LPS was increased in schizophrenic patients. An explanation for these results might be that either a pre-existing innate immune dysfunction of the monocytic system is the cause or it could be due to an acquired condition of the immune system through higher rates of previous chronic infections.

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Conflict of interest The authors declare that they have no conflict of interest.

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