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Neuroleptic treatment increases soluble IL-2 receptors and decreases soluble IL-6 receptors in schizophrenia

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Abstract The cytokines interleukin-2 (IL-2) and interleukin-6 (IL-6) increase during immune activation, they are released from activated astrocytes and microglial cells in the central nervous system (CNS), and they are able to enhance the catecholaminergic neurotransmission. This study focused on the soluble receptors of IL-2 and IL-6 (sIL-2R, sIL-6R) as a part of the regulation system of IL-2 and IL-6. We studied serum levels of sIL-2R in 30 schizophrenic patients not under neuroleptic medication during an acute exacerbation of the disease and reexamined these patients under neuroleptic treatment after clinical improvement. The SIL-6R levels of 39 schizophrenic patients were estimated under the same conditions. The results were compared with the levels of sIL-2R and sIL-6R in 42 healthy controls. No difference was found between the schizophrenic patients before neuroleptic treatment and the healthy controls. During neuroleptic treatment, however, there was a significant increase of sIL-2R levels and a significant decrease of the sIL-6R levels between the pre- and post-conditions. In comparison with healthy controls, the treatment group also showed increased sIL-2R levels and decreased sIL-6R levels. These results suggest that treatment with neuroleptics is associated with increased sIL-2R and decreased sIL-6R. Since sIL-2R bind and inactivate IL-2, whereas sIL-6R form an active complex with IL-6, the increase of sIL-2R and the decrease of sIL-6R together may reflect a functional down regulation of these activating cytokines. This suggests that neuroleptic therapy has a differentiated immunomodulatory effect.

Key words sIL-6R · sIL-2R · Immunology · Schizophrenia · Neuroleptics

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Introduction

The function of lymphocytes is determined by the pattern of the cytokines they release. Cytokines activate or recruit specific cell clones, but also mediate suppression and cell death. Cytokines regulate signaling and communication between immune cells and the central nervous system (CNS), as well as within the CNS (Ransohoff and Benveniste 1996). It has been hypothesized that activating cytokines, such as interleukin-2 (IL-2) and interleukin-6 (IL-6), are altered in schizophrenic psychoses (Smith 1991, 1992). The observation of schizophrenia-like symptoms, such as delusions, when cancer patients received high doses of recombinant IL-2, supports this theory (Denicoff et al. 1987).

IL-2 and IL-6 are released from lymphocytes in the blood, and from glial cells in the CNS, which act as immunological effector cells (Plata-Salaman 1991; Sawada et al. 1992; Ransohoff and Benveniste 1996). Both cytokines are also actively transported into the brain (Banks and Kastin 1992; Waguespack et al. 1994) or may cross an at least locally disturbed blood-brain barrier (BBB). Increased cytokine release in the CNS can be induced, e.g., by a viral or bacterial infection, trauma, or ischemia.

Several groups of investigators have reported that the in vitro IL-2 production is decreased in lymphocytes from schizophrenic patients, and this decrease seems to be related to clinical characteristics of the patients (Bessler et al. 1995; Ganguli et al. 1995a; Villlemain et al. 1989). Decreased IL-2 production, found especially in paranoid schizophrenic patients (Wilke et al. 1996), seems to be inversely related to schizophrenic negative symptoms (Ganguli et al. 1995a). IL-2 production may also be related to an early onset of the disorder in schizophrenic patients (Ganguli et al. 1995a).

Serum concentrations of soluble IL-2 receptors (sIL-2R) are increased in schizophrenics (Ganguli and Rabin 1989; Rapaport et al. 1989; Rapaport et al. 1993, 1994; Wilke et al. 1996), particularly in patients with a poor prognosis (Hornberg et al. 1995). However, there are indi-

cations that this increase may be due to the treatment with neuroleptics (Maes et al. 1994, 1996; Pollmächer et al. 1995; Müller et al. 1997a). One of the apparent functions of sIL-2R is to inhibit IL-2 by binding it (Damle et al. 1992).

Increased IL-2 levels have been observed in the cerebrospinal fluid (CSF) of schizophrenic patients in comparison with healthy controls (Licinio et al. 1993). Additionally, high CSF levels of IL-2 are considered a better predictor of a schizophrenic relapse than CSF levels of 5-HIAA, HVA, or psychopathological symptoms (McAllister et al. 1995). However, relapse could only be predicted on the basis of IL-2 levels in CSF, not those in serum.

Increased concentrations of IL-6 in the blood have been observed in patients suffering from schizophrenia (Ganguli et al. 1994; Maes et al. 1994). Higher sIL-6R levels are related to paranoid-hallucinatory symptoms (Müller et al. 1997b). In contrast to sIL-2R, sIL-6R do not bind and inactivate IL-6, but rather form a complex with IL-6 which enhances the biological activity of the latter via a signal-transducing protein (Mackiewicz et al. 1992). The same mechanism has been described in the CNS also (Schöbitz et al. 1995).

The significance of IL-2 and IL-6 in schizophrenia can be explained by their influence on catecholaminergic neurotransmission. Data from basic research suggest that IL-6 strongly influences the catecholaminergic system (Norris and Benveniste 1993). In vitro studies have shown that the stimulation of neuronal cells by IL-6 leads to increased release of dopamine (Hama et al. 1991). Animal studies revealed that the application of IL-6 in the peripheral blood leads to increased dopamine turnover in the frontal cortex and hippocampus (Zalcman et al. 1994). The hippocampus – one of the CNS structures involved in schizophrenia – has the most pronounced expression of IL-6 receptors. Accordingly, there are parallel findings for IL-2. The pyramidal layer of the hippocampus shows also a high density for IL-2 receptors (Plata-Salaman and Ffrench-Mullen 1993). Peripheral application of IL-2 causes an increase of catecholaminergic neurotransmission in the hippocampus and frontal cortex (Zalcman et al. 1994).

If an increased concentration of activating cytokines in the CNS is involved in schizophrenia, antipsychotic treatment may have a suppressive effect on these cytokines. Previous studies have reported immunosuppressive effects of neuroleptics (Saunders and Muchmore 1964; Baker et al. 1977; Maes et al. 1994). However, the term immunosuppression is vague and general; the effects need to be specified. Other studies, in contrast, have not detected any suppression of the immune system (Müller et al. 1991). Some in vitro investigations have even observed an immune activating function of neuroleptics (Gallien et al. 1977; Zarrabi et al. 1979). These contradictory results indicate that in vitro and in vivo effects, as well as short-term and long-term effects, must be differentiated (McAllister et al. 1989; Rapaport et al. 1990). Moreover, since the immune system is composed of complex regulatory mechanisms, the effects of its different components must be specified.

An investigation of both sIL-2R and sIL-6R levels has not yet been conducted in parallel with neuroleptic treatment in schizophrenic patients. We hypothesized that neuroleptic therapy of schizophrenic patients is associated with a decrease of sIL-6R serum levels but an increase of sIL-2R levels.

Subjects and methods

sIL-6R

Thirty-nine schizophrenic patients (17 females and 22 males) were diagnosed with the structured clinical interview (SKID; APA 1990) according to the diagnostic criteria of the DSM-III R. The ages of the patients ranged from 18 to 55 years (mean age 31 ± 9 years). All patients and controls gave their informed consent before inclusion in the study.

The patients had been free from neuroleptic treatment for at least 4 weeks. Sixteen of these patients had had a first episode of schizophrenia and had not been treated with neuroleptics before ("neuroleptic naive"). The majority had not been treated with neuroleptics for at least several months. The total duration of the disease before admission to the study ranged from 6 to 300 months (mean duration 54.5 ± 77.9 months).

The positive and negative syndrome scale (PANSS) total score on admission was 46–125 points, and the PANSS positive score 7–36 points. The mean PANSS total score was 96.8 ± 22 points, and the PANSS positive score 23 ± 7 points.

Before being included in the study and after admission to the hospital, 29 patients did not receive any drug therapy; 15 patients received benzodiazepines for a short time (1–3 days). To be included in the study the patients had to be free of inflammatory or immune diseases. This was determined by anamnesis, clinical examination, and routine blood tests (icluding white blood cell differentiation, liver parameters, electrolytes, and blood sedimentation rate).

Blood was drawn between 9 and 11 a.m. Psychopathology was assessed according to PANSS (Kay et al. 1986). Following clinical improvement under neuroleptic medication, the same 39 patients were reexamined before being discharged. Treatment during this naturalistic study had lasted 1–4 months (mean 2.6 ± 1.8 months) and included butyrophenone derivates, phenothiazine derivates, clozapine, and other atypical neuroleptics. On reinvestigation, the PANSS total score ranged from 44 to 119, and the mean total score was 76 ± 24 points; the mean positive score was 14 ± 6 points (range 7–30 points).

sIL-2R

Due to lack of serum probes or other technical reasons, the sIL-2R levels were only estimated in 30 (14 females and 16 males) of the above-mentioned patients (mean age 31.7 ± 8.6 years). Since we investigated sIL-6R and sIL-2R in parallel, inclusion criteria were the same. Blood was drawn for sIL-2R simultaneously. The total duration of the disease before admission to the study was 6–288 months, and the mean duration was 64.6 ± 84.4 months.

The PANSS total score on admission ranged from 46 to 125 points, and the PANSS positive score from 7 to 36 points (mean values 88.5 ± 20 and 22 ± 7 points, respectively). The mean duration of treatment between the first investigation and the reinvestigation was 2.5 ± 1.4 months. At the reinvestigation, the PANSS total score ranged from 32 to 119 (mean total score 64 ± 28 points). The mean positive score was 12 ± 6 points (range 7–32 points).

Controls

Forty-two healthy volunteers (18 females, 24 males), aged 20–53 years (mean age 29 ± 7.5 years), participated in the study as controls. All controls had to be free from any psychiatric disorder,

acute or chronic infection, immune disorders, or other somatic disease. After the controls gave their informed consent, anamnesis, a short clinical examination, differential white blood cell count, and liver values were obtained.

Laboratory methods

After centrifugation, serum probes were frozen (–80° C) and stored until analysis. SIL-2R and sIL-6R were estimated by using a commercially available double-sandwich ELISA system (R&D Systems, T-Cell Sciences, Cambridge, Mass., USA). Levels for both sIL-6R and sIL-2R were determined according to the manufacturer's instructions. Absorption was measured at 452 nm. Each concentration was measured in duplicate.

Statistics

Differences between the patients at the admission examination and at the reexamination were compared by Student's *t*-test for paired samples. In view of our hypothesis of decreased sIL-6R and increased sIL-2R levels, we used the one-tailed significance test. Differences between controls and both the schizophrenics at the admission examination and the reexamination were compared by the unpaired Student's *t*-test.

Comparisons between the age groups (< 35 years and > 35 years) and smoker/non-smoker groups also used the unpaired student's *t*-test. The influence of age was determined with the Pearson's product-moment correlation. For statistical analysis the SPSS/PC (SPSS Inc., Chicago, IL, USA) program was used.

Results

The mean sIL-2R values in the pretreatment schizophrenic patients were 530 ± 260 U/ml. After treatment, but before release from the hospital, the sIL-2R values increased to 645 ± 331 U/ml. The sIL-2R values of the healthy controls were 448 ± 204 U/ml.

The sIL-6R serum levels were 42.5 ± 14.3 ng/ml in the group of unmedicated schizophrenics. They decreased to 37.6 ± 8.9 ng/ml during the treatment period. The serum levels of the healthy controls were 46.5 ± 13.8 ng/ml (Table 1).

No significant difference was found both between the sIL-2R levels and the sIL-6R levels of unmedicated schizophrenic patients and healthy controls.

The increase of the sIL-2R values during neuroleptic treatment was statistically significant ($t = 1.64$; $P < 0.05$; Table 2). Accordingly, the decrease of the sIL-6R values was also statistically significant ($t = 2.7$; $P < 0.005$).

The reexamination also revealed significant differences between the schizophrenic patients (during therapy) and the healthy controls. SIL-2R levels were significantly higher ($t = 2.9$; $P < 0.004$) and sIL-6R significantly lower ($t = 3.5$; $P < 0.001$) in medicated schizophrenic patients.

Since effects of smoking on the sIL-2R levels and age on the sIL-6R have been reported, possible influences of these variables were determined also.

In sIL-2R the influence of age was analyzed by comparison of groups (< 35 years, $n = 22$; > 35 years, $n = 8$). No difference was found between the age groups ($t = 0.56$; n.s.).

Moreover, we divided the patients according to their nicotine use into smokers and non-smokers (smokers = 16, non-smokers = 14) but could not find a difference in the levels of sIL-2R (smokers = 531 ± 241 U/ml, non-smokers = 519 ± 318 U/ml; $t = 0.11$; n.s.).

A comparison of sIL-6R values in patients < 35 years and > 35 years (< 35 years, $n = 26$; > 35 years, $n = 13$) showed no significant difference, neither in medicated nor in unmedicated patients (unmedicated: $t = 0.05$; n.s.; medicated: $t = 0.6$; n.s.). Computing the Pearson's product-moment correlation, there also were no significant correlations between age and both sIL-6R serum levels in unmedicated ($r = 0.04$; n.s.) and medicated patients ($r = 0.03$; n.s.).

Table 1 Comparison of sIL-6R serum levels in unmedicated and medicated schizophrenic patients vs healthy controls

	sIL-6R (ng/ml)	Δ sIL-6R	
Unmedicated schizophrenics ($n = 39$)	42.5 ± 14.3	$t = 2.7$; $df = 38$; $P \leq 0.005$ (paired *t*-Test)	
Medicated schizophrenics ($n = 39$)	37.6 ± 8.9		
Controls ($n = 42$)	46.5 ± 13.8	Controls vs unmedicated schizophrenics ($t = 1.3$; $df = 79$; n.s.)	Controls vs medicated schizophrenics ($t = 3.58$; $df = 70.8$; $P < 0.001$)

Table 2 Comparison of sIL-2R serum levels in unmedicated and medicated schizophrenic patients vs healthy controls

	sIL-2R (U/ml)	Δ sIL-2R	
Unmedicated schizophrenics ($n = 30$)	530 ± 260	$t = 1.64$; $df = 29$; $P \leq 0.05$ (paired *t*-Test)	
Medicated schizophrenics ($n = 30$)	645 ± 331		
Controls ($n = 36$)	448 ± 204	Controls vs unmedicated schizophrenics ($t = 1.4$; $df = 64$; n.s.)	Controls vs medicated schizophrenics $t = 2.9$; $df = 64$; $P < 0.004$)

Discussion

To the best of our knowledge, this is the first published study to investigate in parallel sIL-6R and sIL-2R with regard to treatment effects. The results show opposite, but functionally concurrent, effects of neuroleptic treatment on both types of soluble receptors. Levels in unmedicated schizophrenic patients did not differ from those in controls.

We did not detect any influence of age on sIL-6R serum levels, as described previously (Maes et al. 1994). This might be due to the fact that overall the mean age of the patients and controls was young (31 years). Elderly subjects (> 35 years) who exhibited higher sIL-6R levels (Maes et al. 1995) were underrepresented in our sample. Moreover, the standard deviation was high for both sIL-6R and sIL-2R. An influence of other confounding factors must be mentioned; however, none was significant. This might explain why smoking did not significantly influence sIL-2R levels. Especially sIL-2R levels showed a great variation in unmedicated and medicated schizophrenics, as well as in the pre/post condition. However, this difference did not reach statistical significance.

Since increased sIL-2R levels have been reported in schizophrenics (Ganguli and Rabin 1989; Maes et al. 1996; Rapaport et al. 1989, 1993, 1994), we investigated the role of neuroleptic medication. Three studies dealt with patients treated with neuroleptics at the time of inclusion in the study (Ganguli and Rabin 1989; Rapaport et al. 1989, 1993); thus, a treatment effect cannot be excluded. Only one study of schizophrenic patients without neuroleptic treatment showed increased levels of sIL-2R (Rapaport et al. 1994). Since these patients were Koreans, not Caucasians, racial or other genetic factors may have played a role. Indeed, Korean patients showed significantly different sIL-2R serum levels than Caucasians (Rapaport et al. 1994). Increased sIL-2R levels in the group of neuroleptic-treated schizophrenic patients compared with those in controls, however, were also observed in our study. An increase of IL-2R during neuroleptic treatment has been described previously especially for clozapine (Pollmächer et al. 1995) and risperidone (Maes et al. 1996). Other authors have mentioned that sIL-2R levels did not differ in neuroleptic-treated patients regardless of whether they received clozapine, haloperidole, or fluphenazine (Ganguli et al. 1995b). This fits with our own results because the study included patients treated with both typical and atypical neuroleptics. It has been described that an acute single-dose administration of 5 or 10 mg haloperidol does not influence the sIL-2R levels (Rapaport et al. 1991); our patients, however, received chronic treatment with neuroleptics including haloperidol (mean 2.5 months). The increase of sIL-2R levels indicates that neuroleptics have immunomodulatory effects. It is known from in vitro investigations that increased sIL-2R could mediate an immunosuppressive effect due to its IL-2 binding capacity, thus reducing Il-2 availability (Barral-Netto et al. 1991; Brivio et al. 1991; Damle et al. 1992). An increase of sIL-2R is also observed during treatment with immunosuppressive drugs such as cyclosporin-A, which induces a state of relative IL-2 deficiency and reduces stimulatory signals for lymphocyte proliferation and activation (Hornung et al. 1992; Maes et al. 1994).

The other findings of our study, the decrease of sIL-6R levels during neuroleptic treatment and decreased sIL-6R levels in neuroleptic-medicated schizophrenics, also implies a down regulation of an immune-activating compound. As discussed above, sIL-6R form an immune-stimulating complex with IL-6 which enhances the biological activity of IL-6, including that in the CNS (Mackiewicz et al. 1992; Schöbitz et al. 1995). Whereas neuroleptic treatment has a down-regulating effect on sIL-6R levels in schizophrenic patients (Maes et al. 1995), it has also had an inhibiting effect on the m-RNA of activating cytokines (Schleuning et al. 1989) as well as the release of cytokines in vitro (Schleuning et al. 1994).

However, it is not clear whether changes of sIL-2R and sIL-6R in the blood can influence the function of IL-2 and IL-6 in the CNS, but four possible interrelations can be discussed:

1. The most simple and intriguing possibility is that the immunomodulatory effect of neuroleptics takes place in the CNS-cytokine network also.

2. It is possible that less IL-2 is transported across the BBB, because a larger amount is bound to molecules that cannot easily cross the BBB.

3. Increased serum concentrations of sIL-2R lead to increased concentrations of sIL-2R in the CSF, since the diffusion of proteins across the BBB depends on serum concentrations (Tibbling et al. 1977; Reiber and Felgenhauer 1987). In case of a disturbed BBB, sIL-2R can pass through it (Müller and Ackenheil 1995). Parallel to the results of in vitro investigations, it can be speculated that higher CSF-sIL-2R concentrations may bind IL-2 and mediate a decrease of the CSF-IL-2 levels. Increased CSF-IL-2 levels have been described in schizophrenic patients (Licinio et al. 1993), lower IL-2 levels seem to protect from a schizophrenic relapse (McAllister et al. 1995).

4. Since neuroleptic treatment seems to increase the permeability of the BBB for certain compounds (Müller et al., submitted), more sIL-2R may cross the BBB and inhibit further activation by IL-2. SIL-6Rs, however, may be less available despite increased BBB permeability.

Of course, these suggested functional peripheral immune system–CNS interactions in schizophrenia are speculative, but much evidence including the interactions of IL-2, IL-6, and the catecholaminergic neurotransmission supports this view. The question arises as to whether sIL-2R and sIL-6R serum levels do not differ between unmedicated schizophrenics and controls. A disturbance of the cytokine network within the CNS (Müller 1997) may not necessarily be accompanied by a disturbed cytokine system within the peripheral immune system. It has been suggested that unmedicated acute schizophrenics may

have a defect in the presentation or recognition of antigens by T-lymphocytes (Müller et al. 1991, Müller et al., submitted; Russo et al. 1994), hypothetically associated with a relative lack of activation of the peripheral immune system and an insufficient control of activating cytokines in the CNS by the peripheral immune system.

Our findings show that treatment with neuroleptics is associated with differentiated regulatory effects on the cytokines in the peripheral immune system. Further studies have to show whether these immunological effects are related to the therapeutic efficacy in schizophrenia.

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