Changes of Plasma Concentrations of Interleukin-1α and Interleukin-6 with Neuroleptic Treatment for Schizophrenia

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A significant difference of plasma interleukin (IL)-1α concentration was found between schizophrenic patients taking neuroleptic drugs ($n = 38$) and those not taking them ($n = 14$; $P < 0.02$); Kruskal-Wallis analysis revealed a significant difference of plasma IL-6 concentration among the patients taking neuroleptic drugs, those not taking them, and healthy control subjects ($H = 7.1$, d.f. $= 2$, $P < 0.05$); also, there was a significant difference of plasma IL-6 concentration between the patients taking neuroleptic drugs ($n = 32$) and those not taking them ($n = 13$; $P < 0.01$). No significant differences were found between the three groups in the concentrations of IL-1β, IL-2 and tumour necrosis factor(TNF)-α. The present results suggest that neuroleptic treatment may change IL-1α and IL-6 production in schizophrenic patients.

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Recently, the relationship between cytokines and schizophrenia has been investigated by several research groups. Villemain *et al* (1987) found that production of interleukin (IL)-2 *in vitro* by lymphocytes was decreased in schizophrenia, but Smith (1991) proposed that excessive production of IL-2 and interferon-γ might play an aetiological role in schizophrenia. Andrews (1990) suggested that the slow-wave sleep deficit and the absence of rheumatoid arthritis in schizophrenia might be related to macrophage activation and IL-1 production. Recently, Shintani *et al* (1991) reported that there was a significant difference in the variation and distribution of serum IL-6 concentrations between schizophrenic patients who were taking neuroleptic drugs, and healthy control subjects. In view of interactions between the cytokines in biological processes and the effects of IL-1, IL-6 and tumour necrosis factor (TNF) on the central nervous system (Arai *et al*, 1990; Selmaj *et al*, 1990; Van Snick, 1990), it might be important to assess them in schizophrenia.

Method

Fifty-two schizophrenic patients (38 men and 14 women), aged 19–61 years, of whom 14 patients (10 men and 4 women) had not taken neuroleptic drugs for at least three months, and ten healthy control subjects (7 men and 3 women), aged 21–60 years, came to the Schizophrenia Association of Great Britain in Bangor, North Wales, from all parts of the UK. These patients had been ill for 1.5 to 30 years since the onset of illness, or since their first admission to hospital. Their diagnoses were made by the psychiatrists who treated them initially, and were confirmed when they came for interview and blood collection. They were divided into two groups – fairly well and actively ill – according to their clinical state at the time of the interviews. The 'fairly well' patients included those who were in remission, working or capable of full-time work, or who were slightly psychotic; the 'actively ill' included those who were not capable of work, or those with visibly psychotic symptoms. No patients who were severely ill were included in this study. The neuroleptic drugs, which these patients had been taking for at least six months, included chlorpromazine, clozapine, flupenthixol, fluphenazine, haloperidol, sulpiride, thioridazine, trifluoperazine and zuclopenthixol. The dose ranges of them have been listed in a previous study (Wei *et al*, 1992*a*). Some patients were taking more than one of these drugs.

The patients and healthy control subjects travelled the day before their blood collection, and did not eat from 10 p.m. of that day until the blood samples were taken the next morning. They were asked about their health and medical histories, including mental and physical illnesses, infectious diseases, as well as any drugs they were taking for therapeutic, nutritional, or addictive reasons. They all signed the consent forms before blood collection.

Venous blood samples were drawn from the ante-cubital veins between 8 and 9 a.m. in the morning. Of the blood sample, 5 ml was put into a blood tube with K^+EDTA and cooled to 2–4°C immediately. The plasma was separated by centrifugation at 2000 r.p.m. at 4°C for 15 minutes, and aliquots of 0.5 ml were stored at −45°C until they were assayed within ten weeks after the blood samples were taken. The five cytokines in the plasma were determined by radioimmunoassay (^{125}I-RIA systems, Amersham International p.l.c., Amersham, UK). The intra-assay coefficients of variation of the cytokines were 6–8%; for inter-assay they were 15–19%. All samples were processed in duplicate and blindly.

The Mann–Whitney *U* test and Kruskal-Wallis one-way analysis of variance were used to analyse the data.

Results

The Mann–Whitney *U* test showed that the concentration of plasma IL-1α was significantly lower in the patients not taking neuroleptic drugs than in those taking them ($P < 0.02$), and also was lower than in healthy control subjects, but not significantly ($P > 0.05$). There was a significant difference between the patients taking and not

Table 1
Concentrations of plasma IL-1, IL-2, IL-6 and TNF-α (fmol/ml)

Cytokines	Neuroleptic-treated Mean (s.d.)	n	Neuroleptic-free Mean (s.d.)	n	Healthy controls Mean (s.d.)	n
IL-1α	19.0 (15.5)[1]	38	12.1 (3.4)	14	17.9 (11.1)	10
IL-1β	28.7 (4.3)	28	28.3 (3.6)	8	28.0 (5.3)	8
IL-2	70.1 (25.4)	35	71.6 (10.9)	14	72.6 (8.5)	10
IL-6	5.95 (1.20)[2]	32	4.81 (1.13)	13	5.04 (1.78)	9
TNF-α	2.95 (0.43)	26	3.03 (0.32)	7	3.16 (0.59)	7

1. $P<0.02$ (v. neuroleptic-free, two-tailed test).
2. $P<0.01$ (v. neuroleptic-free, two-tailed test).
The significance was estimated by the Mann–Whitney U test.

taking neuroleptic drugs and the concentration of plasma IL-6 ($P<0.01$), but no significant difference between either of the two groups of schizophrenic patients and healthy control subjects. No significant differences of plasma IL-1β, IL-2 and TNF-α were found between the three groups (Table 1).

Kruskal-Wallis analysis revealed a significant difference in the concentrations of plasma IL-6 among the three groups ($H=7.1$, d.f. $=2$, $P<0.05$), but no significant differences in the plasma concentrations of the other four cytokines. No significant differences were found between fairly well and actively ill patients in the concentration of the five cytokines.

Discussion

IL-1 and IL-6 have been shown to have direct effects on the central nervous system, including glial growth, neural differentiation, regulations of appetite, pain, sleep and fever, and on the neuroendocrine system (Arai *et al*, 1990; Van Snick, 1990; Hama *et al*, 1991). Although the glial cells may be a major cellular source of IL-1 and IL-6 in the brain (Arai *et al*, 1990; Van Snick, 1990), the effects of IL-1 and IL-6 on the central nervous system may also depend on their production in the periphery. A recent study in mice indicated that recombinant human IL-1α might enter the brain from the blood in an intact form by a saturable transport system (Banks & Kastin, 1991). Such passage is likely to provide a basis for the direct effects of the peripheral interleukins on the functions of the brain.

The present study demonstrated that there were significant differences in plasma concentrations of IL-1α and IL-6 between the patients taking and not taking neuroleptic drugs (see Table 1), suggesting that neuroleptic treatment could change production of the two interleukins. Thus, the clinical effects of neuroleptic drugs on schizophrenia may be partially related to the alteration of IL-1α and IL-6 production. The influence of acute febrile infections on chronic schizophrenia has attracted the attention of psychiatrists, because the prominent symptoms such as stupor, mannerisms, hallucinations, and delusional ideas may disappear during such an illness (Slater & Roth, 1972). This effect may be due to the induction of IL-1 and IL-6 production, as both the interleukins are involved in fever during infections. However, we failed to find a significant change of IL-1α and IL-6 with the clinical state of these patients. The relation of IL-1α and IL-6 to the symptoms of schizophrenia remains to be further explored.

In spite of a considerable overlap in the cellular sources and biological activities of IL-1, IL-6 and TNF-α (Arai *et al*, 1990; Selmaj *et al*, 1990; Van Snick, 1990), we did not find significant changes of plasma IL-1β or TNF-α in the patients with or without neuroleptic treatment (see Table 1), suggesting that the effect of neuroleptic treatment on the production of IL-1α and IL-6 may be specific, and that there might be a close relationship between these two interleukins. A previous study has shown a significant correlation between the concentrations of plasma IL-1α and IL-6 in healthy subjects (Wei *et al*, 1992*b*).

Although IL-2 has been suggested to play a role in schizophrenia (Villemain *et al*, 1987; Smith, 1991), we did not find any abnormality of the plasma IL-2 concentration in those patients either taking or not taking neuroleptic drugs (see Table 1). There were no significant differences in the five cytokines between healthy control subjects and either of the two groups of paients, with or without neuroleptic treatment, although the mean levels of plasma IL-1α were lower in neuroleptic-free patients compared with healthy control subjects (see Table 1).

In conclusion, the present findings do not seem to support the hypothesis of immunological abnormality in schizophrenia, but do not exclude a role for some individual cytokines, such as IL-1α and IL-6, in the action of neuroleptic drugs.

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Objective Evaluation of Pain Perception in Patients with Schizophrenia

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The pain thresholds of patients with schizophrenia often seem to differ from those of healthy subjects. In the present study we assessed the pain thresholds of ten patients with schizophrenia, and of ten controls, by measuring the leg flexion nociceptive reflex threshold: the stimulation threshold at which this reflex is triggered, is known to be correlated with the pain threshold. Our conclusion is that, in most cases, the increase in pain threshold is the result of 'attitude' and not of alterations in brain function.

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Clinicians have often observed in the course of their everyday work that the pain perception thresholds of patients with schizophrenia seem to be higher than those of healthy subjects. It has frequently been observed that these patients can incur even quite severe traumatic lesions without apparently experiencing any pain (Lewis, 1937; Rosenthal *et al*, 1990). It is difficult, however, to determine whether this absence of pain is due to these patients' mental disease condition or to its treatment, since most neuroleptic, normothymic or anxiolytic drugs are known to have strong analgesic effects and some of them, such as carbamazepine or levomepromazine, are prescribed specifically with a view to obtaining pain relief.

Until now, pain has usually been assessed subjectively, by means of verbal or visual intensity scales and questionnaires. It is now possible, however, to evaluate pain threshold levels objectively using the leg flexion nociceptive reflex as an index. This reflex, which is known as the RIII reflex, can be elicited by applying percutaneous electrical stimulation of the sural nerve and recording the reflex motor response in the muscles on the posterior side of the thigh. Studies carried out on healthy subjects have shown that the stimulation threshold at which the RIII reflex is triggered is correlated with the subject's subjective pain threshold (Willer *et al*, 1979). Willer *et al* have shown that the amplitude of the RIII reflex response is proportional to the perceived pain intensity. This polysynaptic reflex of spinal origin is largely controlled, like the subjective pain threshold, by supra-spinal influences. Attentional factors, mental calculation and stress can therefore all lead to a decrease in the amplitude of this reflex (Willer *et al*, 1979), whereas effort raises the threshold at which the reflex is triggered (Guieu *et al*, 1992).

The purpose of the present study was twofold: firstly to measure the threshold stimulation level at which the RIII reflex was triggered in patients with