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Schizophrenia Research 44 (2000) 165–175

SCHIZOPHRENIA RESEARCH

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Relationships between interleukins, neurotransmitters and psychopathology in drug-free male schizophrenics

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Received 28 December 1998; accepted 3 September 1999

Abstract

It has been postulated that altered interleukin (IL) regulation may be involved in the pathogenesis of schizophrenia. We therefore investigated the relationships between interleukins, neurotransmitters, and psychopathology in schizophrenia. IL-1β, IL-2, IL-6, homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) were measured in the plasma of neuroleptic-free male schizophrenics in comparison to age-matched healthy male controls ($n=25$ each). The patients' psychopathology was assessed by the Scale for the Assessment of Positive and Negative Symptoms (SAPS, SANS). The above variables were measured during acute states of illness and after eight weeks of treatment with haloperidol. The plasma levels of IL-2 and HVA were significantly higher in patients compared to controls. In schizophrenic patients, there were significant correlations between IL-2 and HVA, IL-2 and SAPS, and HVA and SAPS during the acute state of illness. The level of IL-6 was significantly correlated to SANS and duration of illness. In schizophrenic patients, the plasma levels of IL-2 and HVA were significantly lowered after treatment with haloperidol. Changes in IL-2 and HVA significantly correlated to those in HVA and SAPS, respectively. These results strongly suggest that the cytokines may modulate dopaminergic metabolism and schizophrenic symptomatology in schizophrenia.

Keywords: Interleukin; Neurotransmitter; Psychopathology; Schizophrenia

1. Introduction

Recently, a new understanding of the interactions between behavioral, neural, endocrine, and immune processes has been described (Ader et al., 1995). These neural–neuroendocrine responses are, in part, mediated through cytokines, such as interleukin (IL)-1, IL-2, and IL-6, which are secreted during the immune response (Plata-Salaman, 1991).

It has been postulated that these cytokines might be overproduced or dysregulated in schizophrenic patients. This postulate is supported by data from several laboratories, including decreased IL-2 production after mitogen stimulation (Villemain et al., 1989; Ganguli et al., 1995; Rothermundt et al., 1998), increased serum IL-2 receptor (Ganguli and Rabin, 1989; Rapaport et al., 1989; Gaughran et al., 1998), increased serum IL-6 (Shintani et al., 1991; Ganguli et al., 1994; Naudin et al., 1997), and increased IL-2 levels in cerebrospinal fluid (CSF) (Licinio et al., 1993; McAllister et al., 1995). Moreover, increased soluble IL-2 receptor concentrations (Rapaport et al., 1994) and decreased IL-2 production (Kim

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0920-9964/00/$ - see front matter
PII: S0920-9964(99)00171-1

et al., 1998) were found in Korean schizophrenics. These findings suggest that certain immune processes are involved in some schizophrenic patients regardless of ethnicity.

There have been some reports that schizophrenia is related to the activation of the inflammatory response system, characterized by increased serum concentrations of IL-6, increased IL-6 receptor (IL-6R), increased IL-1R antagonist (IL-1RA), positive acute phase proteins, and low serum concentrations of CC16, an endogenous anti-inflammatory protein (Kim et al., 1994; Maes et al., 1996, 1997a; Lin et al., 1998).

Abnormal brain dopamine activity has been suggested to be the main neurotransmitter abnormality causing schizophrenia, despite much criticism and qualification (Davis et al., 1991). Recently, another neurotransmitter, serotonin, has become of much interest in schizophrenia research since many of the atypical antipsychotic drugs such as clozapine have been shown to exert potent serotonin-related activity (Schmidt et al., 1995). Moreover, these neurotransmitters play a major role in mediating the psychotic symptoms of schizophrenia (Lieberman and Koreen, 1993).

Interestingly, the relationship between ILs and neurotransmitter abnormalities in schizophrenia has been suggested by several investigators. Smith and Maes (1995) hypothesized that chronic activation of macrophages and T lymphocytes, together with excessive IL-2 and other cytokine secretions, could be the cause of the neurotransmitter abnormalities in schizophrenia. Licinio et al. (1993) found an elevated IL-2 level in CSF of neuroleptic-free schizophrenic patients and postulated that central IL-2 might contribute to increased dopaminergic neurotransmission, autoimmune phenomena, and abnormal brain morphology in some schizophrenics. In particular, IL-1, IL-2, and IL-6 are known to influence the central monoamine activity in a cytokine-specific manner (Zalcman et al., 1994). IL-2 increases hypothalamic and hippocampal norepinephrine utilization and dopamine turnover in the prefrontal cortex, while IL-6 induces profound elevation of serotonin and mesocortical dopamine activity in the hippocampus and prefrontal cortex. IL-1, in contrast, induces a wide range of central monoamine alteration.

If in fact an increased concentration of activated cytokines in the CNS plays a role in schizophrenia, antipsychotic treatment may be able to suppress the level of these cytokines. Actually, typical antipsychotic drugs (e.g. haloperidol) seem to have negative immunoregulatory effects (Boukhris et al., 1988; Bertini et al., 1993; Maes et al., 1995; Leykin et al., 1997) and atypical neuroleptics (e.g. clozapine and risperidone) appear to have complex in vivo immunomodulatory effects (Maes et al., 1996, 1997b). It was also reported that neuroleptic treatment is associated with low serum levels of sIL-6R but high serum levels of sIL-2R (Muller et al., 1997). On the other hand, there was a report that haloperidol at medium dosages did not affect the plasma levels of IL-1RA, IL-6, TNF-α, and sIL-2R (Pollmacher et al., 1997).

Based on these clinical and experimental reports, the present study was conducted to investigate (1) the correlations between interleukins (IL-1β, IL-2, and IL-6), neurotransmitters (HVA, 5-HIAA) and psychopathology (positive, negative symptoms) in drug-free schizophrenic patients, and (2) the possible influence of neuroleptic therapy on these variables.

2. Subjects and methods

2.1. Subjects

Among newly admitted schizophrenics in our acute psychiatric unit, 25 male schizophrenic patients who met DSM-IV criteria for schizophrenia and were neuroleptic-free for at least six months (including 15 neuroleptic-naive, first onset patients) were included in this study. The patients were interviewed using a Structured Clinical Interview for DSM-IV (Spitzer et al., 1995). They had been admitted in an acute psychotic state and informed consent was obtained after the procedure had been fully explained. Table 1 lists the demographic data of the patients.

Patients with a history of any concomitant psychiatric illness, such as drug or alcohol abuse, a history of infection, or a well-known autoimmune disease were excluded from this study. Patients were found to have a normal physical