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Cerebrospinal fluid neural cell adhesion molecule levels and their correlation with clinical variables in patients with schizophrenia, bipolar disorder, and major depressive disorder

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ABSTRACT

Purpose: Neural cell adhesion molecule (NCAM) plays an important role in neural plasticity, and its altered function has been implicated in psychiatric disorders. However, previous studies have yielded inconsistent results on cerebrospinal fluid (CSF) NCAM levels in psychiatric disorders. The aim of our study was to examine CSF NCAM levels in patients with schizophrenia, bipolar disorder (BD), and major depressive disorder (MDD), and their possible relationship with clinical variables.
Methods: The participants comprised 85 patients with schizophrenia, 57 patients with BD, 83 patients with MDD and 111 healthy controls, all matched for age, sex, and Japanese ethnicity. The CSF samples were drawn using a lumbar puncture and NCAM levels were quantified by an enzyme-linked immunosorbent assay.
Results: Analysis of covariance controlling for age and sex revealed that CSF NCAM levels were lower in all patients ($p = 0.033$), and in those with BD ($p = 0.039$), than in the controls. NCAM levels positively correlated with age in patients with BD ($p < 0.01$), MDD ($p < 0.01$), and the controls ($p < 0.01$). NCAM levels negatively correlated with depressive symptom scores in patients with BD ($p = 0.040$). In patients with schizophrenia, NCAM levels correlated negatively with negative symptom scores ($p = 0.029$), and correlated positively with scores for cognitive functions such as category fluency ($p = 0.011$) and letter fluency ($p = 0.023$) scores.
Conclusion: We showed that CSF NCAM levels were lower in psychiatric patients, particularly bipolar patients than in the controls. Furthermore, we found correlations of NCAM levels with clinical symptoms in patients with BD and in those with schizophrenia, suggesting the involvement of central NCAM in the symptom formation of severe psychiatric disorders.

1. Introduction

Schizophrenia, bipolar disorder (BD), and major depressive disorder (MDD) are serious mental illnesses that show various symptoms, cognitive impairments, and social dysfunctions (American Psychiatric Association, 1994). Although each disorder has been analyzed from several viewpoints (Cai et al., 2015; Lang et al., 2007; Vawter et al., 2000), the comprehensive pathomechanisms remain elusive. However, impaired neural plasticity has been implied in the pathophysiology of schizophrenia, BD, and MDD (Carlson et al., 2006; Goto et al., 2010; Meyer-Lindenberg and Tost, 2014).

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; BACS, Brief Assessment of Cognition in Schizophrenia; BD, bipolar disorder; CNS, central nervous system; CPeq, chlorpromazine-equivalent doses; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; HAMD-21, 21-item version of the Hamilton Depression Rating Scale; IMIeq, imipramine-equivalent doses; MDD, major depressive disorder; MINI, Mini International Neuropsychiatric Interview; NCAM, neural cell adhesion molecule; NCNP, National Center of Neurology and Psychiatry; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.

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Neural cell adhesion molecule (NCAM) plays a key role in neural plasticity, and has been suggested to play a role in the pathophysiology of these psychiatric disorders (Gnanapavan and Giovannoni, 2013; Sandi and Bisaz, 2007; Vawter, 2000). NCAM, alternatively called CD56, is a member of the immunoglobulin superfamily and a synaptic membrane glycoprotein that is widely expressed in neurons and astrocytes in the central nervous system (CNS) (Keilhauer et al., 1985). NCAM is present abundantly at cell membranes, including synapses, and dimerizes to mediate signal transduction and cell-to-cell interaction (Cunningham et al., 1987; Kiselyov et al., 2005; Walmod et al., 2004). NCAM-120, -140, and -180 are the 3 major isoforms generated by alternative mRNA splicing to be expressed in the brain (Cunningham et al., 1987; Ronn et al., 1998). A soluble NCAM-fragment is shown to be generated by ectodomain shedding of the membrane-bound NCAM isoforms (Hinkle et al., 2006; Hubschmann et al., 2005).

NCAM plays an important role in hippocampal synaptic plasticity and learning in rodents (Ronn et al., 2000). Downregulation of NCAM results in phenotypes that mimic those of psychiatric disorders. NCAM-knockout mice display phenotypes related to schizophrenia (Albrecht and Stork, 2012) and depression (Jürgenson et al., 2012). Stress, in turn, decreases NCAM expression in the rodent brain. Levels of NCAM-180, but not NCAM-120 and NCAM-140, isoforms were reduced in the hippocampus, while those of the 3 major isoforms were reduced in the prefrontal cortex after acute stress in rats, presenting memory impairments (Sandi et al., 2005). Reductions in levels of NCAM-140 and NCAM-180, but not NCAM-120, isoforms were also found in the hippocampus after chronic stress, resulting in learning deficits in mice (Bisaz et al., 2011). NCAM total mRNA levels were reduced throughout the brain, particularly in the hippocampus, resulting in a learning deficit in chronically stressed rats (Venero et al., 2002).

NCAM has been implicated in the pathogenesis of stress-related mental disorders, including schizophrenia and BD (Bisaz and Sandi, 2012; Sandi, 2004). Some previous studies examined NCAM levels in cerebrospinal fluid (CSF) in patients with psychiatric disorders. In an early study of the CSF levels of soluble NCAM, initially described as synaptic membrane protein D2, were unaltered in manic-melancholic patients compared with controls (Jorgensen et al., 1977). Soluble NCAM levels were also unchanged in patients with schizophrenia or mania, although a relative (but not significant) decrease was observed in patients with depression, compared with the controls (Jorgensen, 1988). Subsequently, two studies reported that NCAM levels were high in patients with schizophrenia compared with controls (Poltorak et al., 1997; van Kammen et al., 1998), while another study reported that NCAM levels were low in first-episode schizophrenia patients, but not in multi-episode patients compared with the controls (Vawter et al., 1998b). One study reported increased NCAM levels (especially NCAM-120) in patients with BD and those with MDD compared with the controls (Poltorak et al., 1996). Therefore, the previous studies on CSF NCAM levels in patients with schizophrenia, BD, and MDD were inconsistent. In addition, findings of previous studies of CSF NCAM levels in patients with BD or MDD are not consistent with those of animal studies described above.

The aim of the present study was to determine whether CSF NCAM levels are altered in psychiatric patients (schizophrenia, BD, and MDD), and to investigate the relationship between CSF NCAM levels and clinical variables in a relatively large sample.

2. Methods

2.1. Participants

The study involved 85 patients with schizophrenia (age: 40.9 ± 10.1 years, 51 male patients), 57 patients with BD (age: 43.1 ± 11.6, 30 male patients), 83 patients with MDD (age: 42.4 ± 10.1, 43 male patients), and 111 healthy controls (age: 42.5 ± 15.4, 64 males), that were matched for age, sex, and ethnicity (Japanese). Patients with BD included 18 patients with bipolar I disorder and 39 patients with bipolar II disorder. All participants were recruited at the National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan, by advertising at the NCNP Hospital, on our website, and in local free magazines. Participants were screened for psychiatric disorders by a research psychiatrist by the Japanese version of the Mini International Neuropsychiatric Interview (MINI), a structured interview (Otsubo et al., 2005; Sheehan et al., 1998). Diagnosis was determined according to the criteria in Diagnostic and Statistical Manual of Mental Disorders, 4th edition (American Psychiatric Association, 1994), based on the information from the MINI, additional unstructured interviews, and medical records, if available. Healthy controls were volunteers without a current or past history of contact with psychiatric services. Participants were excluded if they had a medical history of CNS diseases, severe head injury, substance abuse, or mental retardation. The study protocol was approved by the ethics committee at the NCNP, Tokyo, Japan. The study was performed according to the Declaration of Helsinki (World Medical Association, 2000). After describing the study, written informed consent was obtained from every participant.

2.2. Clinical assessments

The Positive and Negative Syndrome Scale (PANSS) was used to evaluate the symptoms in patients with schizophrenia (Kay et al., 1987). The GRID Hamilton Depression Rating Scale, 21-item version (HAMD-21) was used to assess the depressive symptoms in patients with BD or MDD (Hamilton, 1960; Williams et al., 2008). The Young Mania Rating Scale (YMRS) was used to evaluate the manic symptoms in patients with BD (Young et al., 1978). Cognitive functions were evaluated in patients with schizophrenia in accordance with Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004). Daily doses of antipsychotics were converted to chlorpromazine-equivalent doses (CPeq) and those of antidepressants were converted to imipramine-equivalent doses (IMIeq) according to a published guideline (Inada and Inagaki, 2015). Medication status was recorded at the time of lumbar puncture.

2.3. Lumbar puncture

Lumbar puncture was performed in the left lateral decubitus position. Each participant received local anesthesia before puncture. CSF was withdrawn from the L3–L4 or L4–L5 interspace using an atraumatic pencil-point needle (Universe 22G, 75 mm, Unisis Corp., Tokyo, Japan). CSF was collected in a low protein absorption tube (PROTEOSAVE SS, 15 mL Conicaltube, Sumitomo Bakelite Co., Tokyo, Japan) and immediately transferred on ice. The CSF was centrifuged (4000 ×*g* for 10 min) at 4 °C and the supernatant was suspended in 0.5-mL aliquots for storage in a deep freezer at −80 °C. Through a single melting refreeze of the sample, the assay was carried out.

2.4. ELISA

An enzyme-linked immunosorbent assay (ELISA) was performed using a monoclonal sandwich ELISA kit for human NCAM (Duoset, DY2408, R&D systems, Inc.) according to the manufacturer's instructions. The ELISA kit targets NCAM isoforms, including the 3 major isoforms derived from the NCAM gene. The samples were diluted to 1:100 using 1% bovine serum albumin in phosphate-buffered saline. The assay was performed using the samples in duplicate and the mean values were used to determine NCAM levels. The intra-run and inter-run coefficients of variance were <5% and 10% respectively.

2.5. Statistical analysis

Categorical variables were compared between the patients and controls by the chi-square test. Continuous variables between >2 groups of