



Relationship between neural activity and immunity in patients with undifferentiated somatoform disorder

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ABSTRACT

It has been suggested that somatoform disorders are related to both the brain and the immune system, and that immune functions may be influenced by cerebral asymmetry. However, few studies have examined the relationship between brain activity and immune function in somatoform disorders. Thirty-two patients with non-medicated undifferentiated somatoform disorder were enrolled in this study. Blastogenic responses to phytohemagglutinin (PHA) were used to measure immunity. Regional cerebral perfusion was measured by 99m-Tc-ethyl cysteinate dimer single photon emission computed tomography (SPECT). Significant hypoperfusion was found at the left inferior parietal lobule and the left supramarginal gyrus in the more immune-suppressed (MIS) subgroup compared with the less immune-suppressed (LIS) subgroup. However, no regions of significant hyperperfusion were found in the MIS subgroup compared with the LIS subgroup. Decreased cerebral blood flow in the left inferior parietal lobule and the left supramarginal gyrus in the patient group was also significantly associated with reduced blastogenic responses to PHA regardless of sex and age. These results suggest that the left inferior parietal lobule and the left supramarginal gyrus might play an immunomodulating role in patients with undifferentiated somatoform disorder. In addition, these results suggest the role of cerebral asymmetry in altered immunity in the patients.

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1. Introduction

Somatoform disorders are a broad group of illnesses that have bodily signs and symptoms that can suggest major medical diseases yet have no associated serious and demonstrable organic disorder. In particular, undifferentiated somatoform disorder (USD) is one subgroup of somatoform disorders which is characterized by one or more unexplained physical complaints lasting for at least 6 months and is below the threshold for diagnosing somatization disorder (Guggenheim, 2000). The prevalence of USD is known to be quite high, ranging from 10.2% to 30.6% (De Waal et al., 2004; Chang et al., 2005; LeiKeiknes et al., 2007).

Somatoform disorders may involve a variety of neuronal pathways (Guggenheim, 2000). In a study using functional magnetic resonance imaging (fMRI), somatoform pain disorder patients showed increased activation in the amygdala, parahippocampal gyrus, anterior/mid-insula, primary and secondary somatosensory cortex and inferior parietal cortex, in comparison to healthy controls (Gundel et al., 2008). The changes in pain memory observed in phantom and chronic pain conditions are also known to be modulated by fronto-medial, fronto-

lateral, parietal, insular and anterior cingulate activation which can influence pain perception (Rainville et al., 1997; Wager et al., 2004; Schreckenberger et al., 2005; Treede, 2006). Moreover, limbic connections may bind stress-regulating and pain-processing systems together, resulting in pain perception triggered by stress without specific noxious stimuli (LeDoux, 2000; Price, 2000; Sandkuhler, 2000).

It has been reported that the activity of cytokines, such as interleukins, tumor necrosis factor, and interferon, is likely to be altered in somatization disorder (Kaplan and Sadock, 1998). In particular, proinflammatory cytokines may not only regulate the mounting of the adaptive immune responses that involve T and B lymphocytes but also trigger a brain–cytokine system that organizes the sickness response (Dantzer, 2005). Therefore, alteration of T cells as well as proinflammatory cytokines can be anticipated in patients with somatoform disorders, who often show sickness behavior (Dantzer, 2005). However, studies that have examined immune activity in somatoform disorder patients are sparse in comparison with those in depressive disorder (Kronfol et al., 1983; Kronfol and House, 1984; Krueger et al., 1984; Andreoil et al., 1990) and anxiety disorder patients (Brambilla et al., 1992; La Via et al., 1996; Koh and Lee, 1998; Rapaport, 1998; Koh and Lee, 2004).

Immune functions may be influenced by cerebral asymmetry. Direct evidence for the existence of a connection between cerebral asymmetry and the immune system has been provided by animal

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studies in which the effects of unilateral cortical lesions on immune response were evaluated (Renoux et al., 1983; Neveu et al., 1986; Barneoud et al., 1987; Neveu, 1988). Renoux et al. (1983) showed that partial ablation of the left frontoparietal cerebral cortex of mice, resulting in relative right-sided activation, decreased immune responses, whereas comparable lesions in the right cortex either had no effect or increased immune responses. In humans, some of the previous studies (Kang et al., 1991; Davidson et al., 1999) found that individual differences in measures of prefrontal activation asymmetry in healthy individuals were related to basal natural killer (NK) cell function, with left-activated subjects exhibiting higher levels of NK cell function than right-activated subjects. In addition, changes in lymphocyte proliferation and NK cell activity have been associated with negative life events only among individuals with greater left frontal cortical activation (Liang et al., 1997).

Taken together, the above-reviewed findings suggest the possibility that somatoform disorders are closely related to both the brain and the immune system. However, few studies have specifically examined the relationship between brain system activity and immune function in somatoform disorders. Lymphocyte proliferative responses to phytohemagglutinin (PHA) were chosen as a measure of cell-mediated immunity because T lymphocytes are one of the sources of lymphokines having some links to the brain (Rohatiner et al., 1983; Ballieu and Heijnen, 1989; Mefford and Heyes, 1990), and alterations of T cells can be anticipated in patients with somatoform disorders (Dantzer, 2005). Therefore, the objective of this study was to examine the relationship between brain activity and immune function in somatoform disorder patients.

2. Methods

2.1. Subjects

The design of this study consisted of three steps. First, immune function was compared between somatoform disorder patients and healthy subjects. Second, the patients were subdivided into two subgroups, the relatively more immune-suppressed (MIS) subgroup and the relatively less immune-suppressed (LIS) subgroup. Finally, regional cerebral perfusion was measured by single photon emission tomography (SPECT) of the brain, and then neural activity was compared between the two subgroups.

The study was reviewed and approved by the Institutional Review Board of Yonsei University College of Medicine at Severance Hospital. Outpatients from the Department of Psychiatry at Severance Hospital (Seoul, Korea) with a diagnosis of undifferentiated somatoform disorder were enrolled in this study. The purpose and procedures of the study were explained to all subjects, and informed consent was obtained from all who decided to participate.

Patients were consecutively selected and interviewed. During the first visit to the outpatient department, a semi-structured interview was conducted using the Korean version (Hahn and Hong, 2000; Hahn et al., 2000) of the Structured Clinical Interview Schedule for the DSM-IV (First et al., 1996) and the diagnosis of USD was made by an experienced psychiatrist.

The psychiatrist directly interviewed healthy control subjects and checked for the presence or absence of physical diseases and psychiatric disorders. Among these volunteers, only those who had no disorders were included in this study. Specifically, we confirmed that each healthy control had no abnormality at his or her most recent regular physical check-up.

The subjects included 32 patients with USD and 42 healthy control subjects. The somatoform disorder patients included 12 men and 20 women, whereas the healthy controls included 23 men and 19 women. The mean age (\pm S.D.) of the somatoform disorder patients was 35.3 (\pm 10.4) years, with a range of 20 to 56 years, while the mean age (\pm S.D.) of the healthy controls was 34.9 (\pm 8.5) years, with a range of 24 to 56 years.

Medical workups as needed were performed on all patients to rule out any medical disorders at either the Department of Psychiatry or at other departments. Only patients who had neither physical diseases nor abnormal laboratory findings were asked to participate in this study. We excluded patients who had a change in diagnosis or who developed any physical disease or additional psychiatric disorders.

Only right-handed subjects were chosen in order to examine the laterality of the brain. Subjects were excluded if they had taken any medication, had smoked cigarettes, or had consumed alcohol within 2 weeks of testing. However, we included subjects who had taken medication but who had undergone a washout period of at least 2 weeks. Among the 38 USD patients who completed the entire testing process, six

subjects were excluded from the data analysis because two had taken antibiotics and four had consumed alcohol.

To determine regions with significant brain activity in the somatoform disorder patients prior to investigating the association between the regional cerebral blood flow and immune parameters, the patients were subdivided into a relatively more immune-suppressed (MIS) subgroup ($N=15$; 2.99–3.91 \log_{10} cpm) and a relatively less immune-suppressed (LIS) subgroup ($N=17$; 4.01–4.70 \log_{10} cpm) by a median split of the blastogenic responses to PHA. The MIS subgroup included six men and nine women, whereas the LIS subgroup included six men and 11 women. The mean age (\pm S.D.) of the former group was 35.1 (\pm 11.9) years and the mean age (\pm S.D.) of the latter group was 34.4 (\pm 10.2) years.

2.2. Psychometric measures

Each subject completed a self-administered questionnaire including the psychometric measures such as the Korean version (Kim et al., 1984) of the Symptom Checklist-90-Revised (SCL-90R) anxiety, depression and somatization subscales (Derogatis et al., 1976) about 40 min before giving a blood sample and 90 min before SPECT scanning. In addition, each patient was individually interviewed and the extent of his or her depression was measured by a psychiatrist using the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960).

2.3. Preparation of peripheral blood lymphocytes

All blood samples were obtained between 9:00 a.m. and 10:30 a.m. to control for circadian periodicity (Williams et al., 1979). In each instance of venipuncture, vacutainers (Becton Dickinson Co., Franklin Lakes, NJ, USA) were used to simultaneously collect blood for all immune assays. The peripheral blood lymphocytes were isolated from heparinized blood by Ficoll-Hypaque (Pharmacia, Piscataway, NJ, USA) gradient separation and washed three times with RPMI 1640 medium (Hazelton Biologicals, Inc., Denver, PA, USA). Cells were suspended in an RPMI 1640 medium containing 10% heat-inactivated fetal calf serum (J.R. Scientific, Woodland, CA, USA), 10-mM HEPES, and 100 units/ml penicillin, and 100- μ g/ml streptomycin (hereafter referred to as complete medium).

2.4. In vitro culture of lymphocytes

Peripheral blood lymphocyte proliferation was measured by the uptake of a labeled probe, tritiated-thymidine (3 H-TdR). Briefly, lymphocytes were suspended in a complete medium with or without 10 μ g/ml of phytohemagglutinin (PHA) at a concentration of 10^6 cells/ml. The cell suspension (0.2 ml/well) was distributed in 96-well round-bottomed microtiter plates. Multiple PHA concentrations (0, 1, 5, 10, 20, 40 μ g/ml) were used to establish the dose–response curve, which was found to be linear. Plates were incubated for 48 h at 37 °C in a humidified 5% CO₂ incubator. After incubation, the plates were pulsed with 10 μ l (1.0 μ Ci)/well of 3 H-TdR (New England Nuclear, Boston, MA, USA) for 6 h. The cells were harvested into glass fibers using a cell harvester (Flow Laboratories, McLean, VA, USA), and incorporation of 3 H-TdR (counts per minute, cpm) was measured using a β -counter (Beckman, LS 5000TA, Palo Alto, CA, USA).

All samples were assayed in triplicate, and the mean cpm for the triplicate wells was calculated and compared with a standard curve. Data are expressed as the log of the difference between the stimulated and unstimulated samples, measured in cpm (\log_{10} cpm), in an attempt to minimize interassay variance.

2.5. SPECT scanning procedure

The subject was placed in a quiet room with eyes closed. Scanning was performed in the resting state approximately 50 min after intravenous injection of 740 MBq (20 μ Ci) of 99m-Tc-ethyl cysteinyl dimer (ECD) (Bristol-Myers Squibb, N Billerica, MA, USA). Brain perfusion studies were performed with a brain-dedicated annular crystal gamma camera with low energy, high-resolution parallel-hole collimators (Digital Scintigraphics Inc., Waltham, MA, USA). Its spatial resolution was 5.8 mm full-width at half-maximum (FWHM). We used a 128 \times 128 matrix with 3° angular increment for 30 min to obtain axial images, using the filtered back projection method and a Butterworth filter (cut-off frequency 1.1 cycle/cm at an order No. 10). Attenuation correction was performed by Chang's method (attenuation coefficient = 0.15) (Chang, 1978), and sagittal, coronal and transverse images were reconstructed.

2.6. Statistical parametric mapping analyses

Statistical parametric mapping (SPM) (Friston et al., 1991; Friston et al., 1995) was used to determine differences between 99m-Tc-ECD SPECT images of the two groups. Using SPM 2 software (Wellcome Department of Cognitive Neurology, London, UK), we spatially normalized all images onto the 99m-Tc-ECD SPECT standard template to remove inter-subject anatomical variabilities (Friston et al., 1991; Friston et al., 1995). Spatially normalized images were then smoothed by convolution using an isotropic Gaussian kernel with 10-mm FWHM to increase the signal-to-noise ratio and accommodate the variations in subtle anatomical structures. To minimize edge effects, voxels with values less than 80% of the

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