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Triiodothyronine may be possibly associated with better cognitive function and less extrapyramidal symptoms in chronic schizophrenia

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ABSTRACT

Objective: Many chronic inpatients with schizophrenia demonstrate enduring psychiatric symptoms and various side effects of antipsychotic drugs. Several biological markers such as prolactin, thyroid hormones and brain-derived neurotrophic factor (BDNF) are reportedly associated with psychiatric symptoms and/or antipsychotic side effects in patients with schizophrenia but to date findings are inconsistent. The objective of the present study was to comprehensively investigate the association of psychiatric and extrapyramidal symptoms with hormones and BDNF in chronic schizophrenia.

Methods: In this study, 93 chronic inpatients with schizophrenia were comprehensively investigated in order to examine the association of psychiatric and extrapyramidal symptoms with prolactin, thyroid hormones (free triiodothyronine (T_3), free thyroxine (T_4), thyroid stimulating hormone), cortisol and BDNF. Symptoms were assessed via the Positive and Negative Syndrome Scale (PANSS), Mini-Mental State Examination (MMSE), and drug-induced extrapyramidal symptoms scale (DIEPSS).

Results: Multiple regression analyses revealed that antipsychotic dose was the only variable that predicted significant variance in PANSS positive subscale scores, that BDNF and free T_3 predicted significant variance in MMSE scores, and that prolactin and free T_3 predicted significant variance in DIEPSS scores.

Conclusion: These findings suggest that BDNF, free T_3, and prolactin may be associated with cognitive function and/or extrapyramidal symptoms in patients with chronic schizophrenia. Notably, free T_3 may be possibly associated with better cognitive function and less extrapyramidal symptoms, although our cross-sectional study could not reveal a causal relationship.

1. Introduction

Schizophrenia is a complex and severe brain disorder with poorly defined etiology and pathophysiology, and is associated with marked impairment in cognitive function (Pedrini et al., 2011). Brain-derived neurotrophic factor (BDNF) is the most widely distributed neurotrophin in the central nervous system (CNS), important for neurogenesis, neuronal survival, and normal maturation of neurodevelopmental pathways. Neurodevelopmental models of schizophrenia implicate reduced BDNF in the CNS, that BDNF reductions reduce synaptic efficiency and connectivity, and may underlie core behavioral signs and symptoms of the disease (Green et al., 2011).

In drug-naïve patients with schizophrenia, Buckley et al. (2007) showed that plasma BDNF levels were significantly reduced in comparison with normal healthy controls and demonstrate a significant negative correlation with positive subscale scores of Positive and Negative Syndrome Scale (PANSS). Similarly, Rizos et al. (2008) reported that serum BDNF levels were significantly reduced in patients compared to normal controls and found negative correlations between serum BDNF and positive *and* negative subscale scores of PANSS. Whereas Chen et al. (2009) showed significantly lower serum BDNF in drug-naïve first-episode patients compared to healthy controls and significant positive correlations between serum BDNF levels and PANSS positive subscale scores.

With regard to chronic patients with schizophrenia, Tan et al. (2005a) reported that serum BDNF levels were significantly lower in medicated patients with chronic schizophrenia than in healthy control subjects, and that PANSS negative subscale scores were significantly and negatively correlated with serum BDNF levels. In contrast to Tan et al.'s (2005a) findings, Reis et al. (2008) showed that serum BDNF levels were significantly *increased* in chronic inpatients with schizophrenia when compared to control subjects and that PANSS negative subscale scores were significantly and positively correlated with serum BDNF levels.

Recently, Green et al. (2011) undertook the first systematic review and meta-analysis of studies examining blood BDNF levels in schizophrenia compared with healthy controls, and examined potential

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effects of age, gender, and medication. Their meta-analysis showed a moderate effect of reduced BDNF in patients with schizophrenia compared with controls. Subgroup analyses revealed reduced BDNF in both drug-naïve and medicated patients, and in both males and females with schizophrenia. Meta-regressions showed an association between reduced BDNF in schizophrenia and increasing age, but no effect of medication dosages (2011).

As for extrapyramidal symptoms, Tan et al. (2005b) showed that patients with tardive dyskinesia had lower plasma BDNF levels than patients without tardive dyskinesia and normal controls. In the patients with tardive dyskinesia, plasma BDNF levels were significantly and negatively correlated with total scores of the Abnormal Involuntary Movement Scale (AIMS), and with PANSS negative subscale scores.

Byerly et al. (2009) have suggested that interactions between BDNF and triiodothyronine (T_3) and/or cortisol may constitute a homeostatic mechanism that links hypothalamic energy regulation controlling body composition, which may also affect brain function. In relation to schizophrenia, Issa et al. (2010) observed a significant negative correlation between BDNF and cortisol levels in postmortem and animal studies. Baumgartner et al. (2000) found that serum thyroxine (T_4) levels of acutely ill schizophrenic patients were elevated while T_3, reverse T_3, and thyroid stimulating hormone (TSH) were normal. Also, Yazici et al. (2002) implicated that higher basal TSH levels may be associated with a poorer treatment response, whereas higher total and free T_3 levels and a blunted TSH response to thyrotropin-releasing hormone may indicate a better response in patients with schizophrenia. In these studies, it is unknown whether thyroid functions interacted with BDNF levels and/or cortisol levels.

Our aim was to comprehensively investigate the association of psychiatric and extrapyramidal symptoms with prolactin, thyroid hormones (free T_3, free T_4, TSH), cortisol and BDNF in chronic schizophrenia.

2. Methods

2.1. Subjects

Patients were voluntarily admitted to Hoaki Hospital, Oita, which is a typical psychiatric hospital in Japan. Ninety three inpatients (71 female patients, 22 male patients) who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) for schizophrenia were included in the study. Clinical subtypes included: 70 with residual type, 22 with paranoid type, 1 with disorganized type. Their age was between 43 and 87 years (66.0 ± 8.8) with duration of illness from 11 to 62 years (38.3 ± 9.3) and duration of hospitalization from 1.1 to 50 years (23.5 ± 13.5). None of the patients suffered from clinical hormonal diseases such as thyroid diseases.

Mean chlorpromazine equivalent dose of antipsychotic drugs was 681.2 ± 646.4 mg/day. The chlorpromazine equivalent doses were calculated using the 2006 version of the Equivalent Conversion Table originally reported by Inagaki and Inada (2006) (e.g., equivalent dose of 100 mg chlorpromazine is 1 mg risperidone, 2.5 mg olanzapine, 2 mg haloperidol, etc.).

Forty-four patients had only typical antipsychotics, 19 patients had only atypical antipsychotics, and 30 patients had both. Also, 27 patients had combination therapy with mood-stabilizers, and 74 patients had antiparkinson drugs.

The study design was naturalistic. Symptom assessment, side effect assessment, and blood sampling including hormone and brain-derived neurotrophic factor (BDNF) were obtained from all the patients. The study was approved by the Ethics Committee of Oita University Faculty of Medicine. Written informed consent was acquired from all participants prior to data collection. This study was conducted in accordance with the Declaration of Helsinki.

2.2. Clinical ratings

Psychiatric symptoms were rated by PANSS. Cognitive function and memory function were assessed by Mini-mental State (MMSE), and side effects were measured by drug-induced extrapyramidal symptoms scale (DIEPSS). Although MMSE is a screening tool and very rough method of assessing cognitive and memory function, we selected this because of its simplicity and ease of administration. PANSS ratings were performed by two psychiatrists (SI and TM) whose correlation coefficient was above 0.80 after training.

2.3. Measurement

Serum prolactin (PRL), free T_3, free T_4, TSH, and cortisol were measured using radioimmunoassay by a third party. Serum BDNF levels were measured in duplicate by using R&D systems (Minneapolis, Minnesota). The samples were diluted with assay butter 50 times. Assay diluent standards and samples were added to each well, the plate was covered with the adhesive strip provided. After incubating for 2 h at room temperature, BDNF conjugate was added and the plate was covered with a new adhesive strip. After incubating for 1 h, each well was aspirated and washed 3 times. After removing wash buffer, substrate solution was added. Incubating for 30 min to avoid light, the reaction was stopped with stop solution. Then, the color in the wells changed from blue to yellow. Within 30 min, the optical density of each well was determined using microplate reader set at 450 nm. All reagents necessary were provided by the manufacturer. The standard curve was linear from 5 pg/ml to 5000 pg/ml, and the detection limit was 5 pg/ml. The intra-and interassay coefficients of variation were 5 and 7%, respectively. The recovery rate of the exogenous BDNF in the measured serum samples exceeded 95%.

2.4. Statistical analysis

Pearson's correlation coefficient was used to examine the individual association of PANSS scores, MMSE score and DIEPSS scores with antipsychotic doses (chlorpromazine equivalents), BDNF levels, PRL levels, cortisol levels, TSH levels, free T3 levels, and free T_4 levels. Subsequently multiple regression analysis was used to identify possible demographic variables and independent predictors of PANSS scores, MMSE score, or DIEPSS scores.

3. Results

3.1. Symptoms and hormone levels

The mean of positive subscale scores of PANSS was 15.7 ± 4.6, the negative subscale scores of PANSS were 18.0 ± 4.0, and the general psychopathology scores were 34.7 ± 6.5. The means of MMSE and DIEPSS were 21.9 ± 6.0 and 4.8 ± 3.8, respectively. Means of serum PRL, free T_3, free T_4, TSH, cortisol, and BDNF were 58.9 ± 45.2 ng/ml, 2.7 ± 0.5 pg/ml, 1.1 ± 0.2 ng/dl, 3.9 ± 4.7 μIU/ml, 17.1 ± 5.2 μg/dl, and 12.3 ± 11.1 ng/ml, respectively.

3.2. Correlations

As shown in Table 1, PANSS positive subscale scores, negative subscale scores, general psychopathology scores and DIEPSS scores were significantly and positively associated each other. MMSE scores were significantly and negatively associated with PANSS negative subscale scores, general psychopathology, and DIEPSS scores, but not with PANSS positive subscale scores. Antipsychotic doses (chlorpromazine equivalents) were significantly and positively associated with PANSS positive and negative subscale scores, but not with PANSS general psychopathology, DIEPSS or MMSE scores.