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Research article

In schizophrenia serum level of neurotrophin-3 (NT-3) is increased only if depressive symptoms are present

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ABSTRACT

Aim: Neurotrophin-3 (NT-3) is a neurotrophic factor responsible for promoting development, survival and function of neurons. NT-3 may be involved in the etiopathology of schizophrenia and mood disorders. However it must be cleared up if changes of NT-3 level are associated with schizophrenia itself or are secondary to certain symptoms (e.g. negative or depressive). The aim of this study was to examine whether the presence of negative or depressive symptoms affects peripheral NT-3 concentration in patients with schizophrenia.

Methods: Data for 69 Caucasian adult hospitalized patients with chronic paranoid schizophrenia was compared with 27 healthy subjects. Level of NT-3 was measured in blood serum using enzyme-linked immunosorbent assay. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale for Schizophrenia (CDSS).

Results: Patients were stratified into three sub-groups: non-depressed with no dominating negative symptoms (DEP-/NEG-), non-depressed with dominating negative symptoms (DEP-/NEG+) and depressed with dominating negative symptoms (DEP+/NEG+). Mean NT-3 concentration was higher in the DEP+/NEG+ subgroup (202.61 ± 258.76 pg/mL) compared with the DEP-/NEG+ (83.79 ± 215.75 pg/mL), DEP-/NEG- (83.79 ± 215.75 pg/mL) and control (36.47 ± 73.84 pg/mL) sub-groups ($p = 0.016$).

Conclusion: We found that in schizophrenia serum level of neurotrophin-3 (NT-3) is increased only if depressive symptoms are present. There was no difference in NT-3 level between schizophrenia patients and controls.

1. Introduction

Schizophrenia is one of the most disruptive psychiatric disorders, affecting at least 1% of the population. Positive symptoms, such as delusions or hallucinations, are the most common, but the majority of patients present also negative symptoms or depression [1,2]. Depression and psychosis occur simultaneously in about 25% of patients suffering from schizophrenia, according to current knowledge. Depressive and negative symptoms may manifest in all stages of the disease. Clinically, they may be associated with poor response to treatment, but also may lead to progressive deterioration and may be predictor of suicide [3].

The neurodevelopmental theory of schizophrenia surprisingly is not new, as it has already been presumed by Bleuler and Kraepelin in the 19th century [4]. It states that the environmental and genetic disruptions, occurring in early (e.g. prenatal or perinatal) stages of development may later manifest clinically as schizophrenia. One of such interruptions may involve the dysfunction of neurotrophic factors in the brain. Neurotrophic factors (neurotrophins) have many effects on the nervous system, such as stimulation of neurogenesis, neuronal growth, plasticity and synaptic transmission. Neurotrophin-3 (NT-3) is a neurotrophic factor in the NGF (Nerve Growth Factor) family of neurotrophins. It was discovered in 1990 by Jones et al. [5]. NT-3 is responsible for promoting growth, maturation, survival and function of neurons and may be associated with the etiopathology of schizophrenia [6,7]. The role of NT-3 is probably the development of neurons in the brain at early stages – its level is physiologically higher in fetus and lower in adults [8]. Moreover, it was discovered that NT-3 is required for appropriate development of thalamocortical pathways in mice, which may suggest the link between NT-3 and the abnormal brain development in the course of schizophrenia [9].

While there is a growing body of evidence for the involvement of NT-3 in the etiology of depression [10], less is known about its role in schizophrenia [8]. Moreover, since many patients with schizophrenia may experience depressive symptoms, it must be cleared up whether changes in NT-3 expression are associated with schizophrenia itself or

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secondary to its specific symptoms, e.g. negative or depressive. Our previous study has already found that there were no differences in BDNF or NT-3 levels between patients with schizophrenia and controls, but in depressed patients with schizophrenia serum levels of BDNF were lower, while of NT-3 were higher compared with healthy controls [11]. This is the replication of the former study, with more patients included. The main objective of this study was to assess serum NT-3 levels in patients with schizophrenia and to compare these levels between patients with dominating negative or depressive symptoms.

2. Methods

This was a cross-sectional study. Eligible participants were European Caucasian adult patients with paranoid schizophrenia. All study patients were hospitalized and underwent a structured interview according to ICD-10 and DSM-IV criteria of schizophrenia. Control group consisted of mentally and somatically healthy subjects. Health status of the control subjects was determined on the basis of basic physical and psychiatric examination, including vital signs and an interview. Only subjects who were physically, neurologically and endocrinologically healthy with normal laboratory values (blood routine tests, biochemical tests including TSH, liver and kidney parameters and ECG) were eligible to enter the study. Subjects with substance abuse/dependence were excluded from the study. All patients and volunteers included in the study expressed their written informed consent for participation in this study and the study protocol was approved by the local Bioethics Committee.

Clinical symptoms of schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS) and its sub-scores for positive (PANSS-P), negative (PANSS-N) and general (PANSS-G) symptoms. Severity of depression was assessed using the Calgary Depression Scale for Schizophrenia (CDSS) [12]. For each patient all scales were done on the same day, by one rater.

NT-3 level was measured in blood serum. The blood samples were collected between 7 a.m. and 8 a.m., after ensuring at least 8 h of overnight fasting. Blood was drawn to Sarstedt S-Monovette tubes, centrifuged at 3000 rpm for 10 min at 20 °C and then stored in NUNC CryoTubes (USA) at −80 °C for up to 12 months. Level of NT-3 was measured in serum samples using ELISA (enzyme-linked immunosorbent assay) method. ELISA assays were performed using commercial kits (catalogue number: ELH-NT3-1, intra-assay: CV < 10%, inter-assay: CV < 12%) manufactured by RayBiotech (USA), according to protocol provided by its manufacturer. Absorbance was measured at 450 nm with a Diagnostic Pasteur LP 400 microplate reader (Germany).

Statistical procedures were performed with STATA 15.1 (StataCorp, College Station, USA) and GraphPad Prism 7.01 (GraphPad Software, La Jolla California, USA). Simple descriptive statistics (means, standard deviations) were generated for continuous variables. For discrete variables number of patients and percentages are given. Normality of distribution was tested with Shapiro-Wilk test. Study variables had no normal distribution and therefore were analyzed using Wilcoxon rank sum test or Kruskal-Wallis and post-hoc Dunn tests. All comparisons were adjusted using Bonferroni correction for multiple comparisons. The difference between proportions was analyzed by Fisher's exact or Chi-Square tests. Associations were tested by Spearman's correlation coefficients and adjusted linear regression models. The significant level was set at $p < 0.05$ (two sided).

3. Results

Data for 69 patients and 27 healthy controls were collected. Demographic and clinical characteristics, as well as serum NT-3 levels are detailed in Table 1. All patients were treated with antipsychotics. Dose of all antipsychotics was converted to defined daily dose (DDD). Antipsychotic treatment in the study groups was highly heterogeneous. The majority of patients were on monotherapy with quetiapine (n = 27, 39.1%) or polytherapy (n = 15, 21.7%), other antipsychotics taken by study subjects were: olanzapine (n = 12, 17.3%), risperidone (n = 11, 15.9%), aripiprazole (n = 2, 2.9%), flupenthixol (n = 1, 1.4%) and sulpiride (n = 1, 1.4%). Apart from occasional use of benzodiazepines, study subjects were not taking other medications.

Each study patient was classified as depressed (with CDSS > 6) or non-depressed (with CDSS ≤ 6) and with dominating negative symptoms (PANSS-N > PANSS-P) or without dominating negative symptoms (PANSS-N ≤ PANSS-P). Of 69 patients with schizophrenia, twenty (29.0%) patients met criteria for depression (DEP + sub-group), while fifty (72.5%) patients met criteria for dominating negative symptoms (NEG + sub-group). Patients were divided into three sub-groups: non-depressed with no dominating negative symptoms (n = 19, 19.8%; DEP-/NEG- sub-group), non-depressed with dominating negative symptoms (n = 34, 35.4%; DEP-/NEG + sub-group) and depressed with dominating negative symptoms (n = 16, 16.7%; DEP +/NEG + sub-group). There was no difference in the severity of positive ($p = 0.10$) or negative ($p = 0.14$) symptoms between DEP-/NEG + and DEP +/NEG + groups. Also, these sub-groups did not differ in terms of combined dose of antipsychotics ($p = 0.06$) or duration of schizophrenia ($p = 0.60$).

Mean NT-3 concentrations between the whole schizophrenia group (92.90 ± 204.74 pg/mL, median: 15.25 pg/mL) and in the control group (36.47 ± 73.84 pg/mL, median: 13.80 pg/mL) did not differ significantly ($p = 0.28$). When NT-3 was analyzed in the study sub-groups, we have found significant differences. NT-3 concentration was highest in the DEP +/NEG + sub-group (202.61 ± 258.76 pg/mL, median: 37.50 pg/mL, interquartile range: 15.98–504.68 pg/mL) and lowest in the DEP-/NEG- sub-group (16.80 ± 15.97 pg/mL, median: 13.55 pg/mL, interquartile range: 11.26–17.67 pg/mL), with the control group (36.47 ± 73.84 pg/mL, median: 13.80 pg/mL, interquartile range: 8.79–17.67 pg/mL) and DEP-/NEG + (83.78 ± 215.75 pg/mL, median: 14.52 pg/mL, interquartile range: 9.05–36.07 pg/mL) in-between, see Table 1 and Fig. 1.

Regression analysis (adjusted for age, sex and duration of schizophrenia) confirmed that of all included study variables (i.e. dose of antipsychotics, PANSS score and sub-scores, CDSS score, sub-group [DEP + or DEP- and NEG + or NEG-]), only being in the DEP + sub-group was associated with increased NT-3 concentration ($R^2 = 0.18$, standardized coefficient (β) = 0.42, $p = 0.029$). There were no differences for NT-3 levels between men and women ($p = 0.34$). There were no correlations between NT-3 and duration of schizophrenia, type of antipsychotic medication(s) and antipsychotic dose, CDSS or PANSS scores, both in the whole study group and in individual sub-groups. Also, level of NT-3 was not correlated with age ($p = 0.09$).

4. Discussion

The aim of this study was to examine whether the presence of negative or depressive symptoms affects peripheral NT-3 concentration in subjects with schizophrenia. Similarly to our previous study [11], we did not find differences in NT-3 levels between patients with schizophrenia and controls. In our study NT-3 concentration was highest in the DEP +/NEG + sub-group and lowest in the DEP-/NEG- sub-group, with the control group and DEP-/NEG + in-between. This indicates that the presence of depressive symptoms has more effect upon NT-3 level than negative symptoms. Consequently, we have stated that in schizophrenia serum level of neurotrophin-3 (NT-3) is increased only if depressive symptoms are present.

No other studies analyzing NT-3 level in regard to depression in schizophrenia have been reported to date, so it was not possible to compare results of this study to previous findings. Also, the data on the association between increased serum level of NT-3 in schizophrenia and depressive, but not with negative symptoms has been replicated. This may indicate that negative symptoms have origin and underlying