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Decreased NT-3 plasma levels and platelet serotonin content in patients with hypochondriasis

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Abstract

Objective: Neurotrophins (NT) are a family of closely related proteins, including brain-derived neurotrophic factor, nerve growth factor, neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). NTs are deemed to regulate several aspects of neuronal survival, development, and function. Although NTs have been associated to a variety of mental disorders, the potential role of NT alterations in hypochondriasis (HC) has never been investigated. **Methods:** In the present study, plasma concentrations of NTs were evaluated in 23 adult patients meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for HC and 22 healthy controls. Platelet serotonin (5-HT) content was chosen as a measure of serotonergic function. Hypochondriacal symptoms were assessed using the Whiteley Index of Hypochondriasis (WIH). **Results:** Plasma NT-3 level (P=.004) and platelet 5-HT (P=.008) were significantly lower in patients with HC compared with controls. Correlation analyses showed that the WIH score was significantly and inversely associated with both NT-3 values (r=−.60, P=.002) and platelet serotonin content (r=−.53, P=.009). We used a multivariate regression model to determine independent predictors of the WIH score. After allowance for potential confounders, plasma NT-3 levels remained the unique independent predictor of the WIH (β=.003, t=−3.5, P=.003). **Conclusions:** Decreased NT-3 concentration, alongside with serotonin dysfunction, may represent a biological correlate of HC.

Keywords: Hypochondriasis; Neurotrophins; Serotonin; Platelet

Introduction

Hypochondriasis (HC) is a disabling disorder characterized by fear or conviction of having a serious physical disease based on misinterpretation of bodily symptoms, persisting despite appropriate medical evaluation and reassurance of good health [1–3]. In HC, nondelusional preoccupation with fears of harboring a severe illness is accompanied by safety behavior, such as repeatedly checking bodily symptoms and seeking medical help, leading to clinically significant impairment or interference with personal and social functioning [4]. Although some authors traditionally regarded HC as a condition of obsessive–compulsive disorder (OCD) spectrum, recent data have clearly demonstrated that HC and OCD are separate entities with distinctive clinical features [5]. Accordingly, patients with HC differ from those with OCD in the presence of somatic symptoms, intense health anxiety, and absence of other type of obsessions, thus being included in the category of somatoform disorders in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*).

Despite being recognized as an important clinical disorder causing overutilization of health care resources and

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psychological disability [6], little is known about the biological basis of HC. It is posited, however, that a better comprehension of the pathophysiological mechanisms underlying HC may represent an important direction for future pharmacological research. Neurotrophins (NTs) play a crucial role in regulating neuronal survival and growth. Alterations of NT levels have been previously reported in several mental disorders [7,8]. Notably, NTs have been implicated in the neurobiology of anxiety [9], OCD [10], and pain perception [11]. Given the anxious and obsessive facets of HC [1–3], and the alteration in pain perception reported in patients with HC [12], a study of NTs in this patient group seemed worthy of investigation. Specifically, we asked whether patients with HC without psychiatric comorbidity could have abnormal levels of specific NTs in serum. In addition, as selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective in patients with HC [13–15], we wanted to determine whether platelet serotonin content, taken as a peripheral indicator of central serotonergic activity, could be altered in this patient group. We tested our hypotheses using a cross-sectional study in which patients with HC were compared with healthy matched controls.

Subjects and materials

Subjects

Twenty-three patients with HC and 22 healthy controls were recruited through physician referrals and direct screening of patients. All patients aged 18 years or older underwent a comprehensive diagnostic assessment performed using the Structured Clinical Interview for *DSM-IV*. All subjects described in the present study met the *DSM-IV* full criteria for HC. Subjects with "subthreshold" HC were not included.

All medical records were carefully checked to ensure that the patient had received an adequate medical assessment to exclude other medical diagnoses that might explain the patient's symptoms. Each patient was examined by a senior internist to confirm that the patient's illness fears and somatic symptoms did not have an identifiable medical cause. A routine blood workup, ECG, and urinalysis were also performed. Exclusion criteria were the following: (a) presence of a current comorbid psychiatric diagnosis of schizophrenia, schizoaffective disorder, major depression, dysthymia, bipolar disorder, OCD, panic disorder, generalized anxiety disorder, social phobia, substance abuse/dependence, or personality disorders; (b) presence of active suicide ideation; (c) presence of any somatic disease that could be the focus of the hypochondriacal concerns; and (d) current use of psychotropic drugs (antidepressants, mood stabilizers, antipsychotics, tranquillizers, or sleep medication).

Hypochondriacal symptoms were assessed by means of the Whiteley Index of Hypochondriasis (WIH) [16]. The WIH is 14-dichotomous-item scale covering hypochondriacal attitudes and concerns. Scores can potentially range from 0 to 14, with higher scores indicating higher disease anxiety. Test–retest reliability and both discriminant and convergent validity have been demonstrated [17]. Additionally, all participants were screened through psychometric rating scales, including the Beck Depression Inventory (BDI), the State–Trait Anxiety Inventory (STAI), and the Yale-Brown Obsessive–Compulsive Rating Scale (Y-BOCS).

Healthy controls were enrolled from within the laboratory staff and the general community. We applied the same exclusion criteria as for patient, but controls also had to be free of psychiatric diseases. The study protocol complied with the Declaration of Helsinki and was approved by our Internal Review Board. All participants gave written informed consent for participating in the study at the time of recruitment.

Quantification of platelet 5-HT content

Blood samples were drawn by venipuncture after an overnight fast and were collected in 10-ml Vacutainer tubes (Becton-Dickinson, Meylan Cedex, France) containing 0.12 ml (0.34 mol/l) EDTA solution. Ten milliliters of blood was divided into two portions. One portion was centrifuged for 5 min at 1000×*g* and the supernatant was kept as plasma. The next portion was centrifuged for 5 min at 10,000×*g* and 4°C, to obtain platelet-rich plasma. After a platelet count was obtained, platelet serotonin concentration was determined according to a previous method [18] using an HPLC system. Concentrations of 5-HT were expressed as nmol/10^9 platelets. Platelet serotonin was determined in a quality control sample with within-series and between-series coefficients of variation of 2.7% and 4.6%, respectively.

Quantification of plasma NT levels

Plasma levels of NTs were determined using commercially available sandwich enzyme-linked immunosorbent assays (Promega, Madison, WI, USA) as described previously [19,20]. All biochemical determinations were done in duplicate and the results were averaged. In all immunoassays, the intra- and interassay coefficients of variation were <6% and <8%, respectively. Since laboratory personnel were blinded to the participants' status, any possible measurement error was likely to be nondifferential.

Statistical analysis

Data were analyzed by the Kolmogorov–Smirnov test to determine distribution. All continuous variables were normally distributed and were expressed as mean±standard deviation (S.D.). Continuous cross-sectional data between patients with HC and healthy controls were analyzed by the Student's *t* test. Categorical data were analyzed by the χ^2 test. Correlations among the study variables were tested by the Pearson's correlation method. Stepwise multiple