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Brain-derived neurotrophic factor plasma levels in patients suffering from post-traumatic stress disorder

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ABSTRACT

In both animals and humans, stress has been demonstrated to reduce the expression of the Brain-Derived Neurotrophic Factor (BDNF), a neurotrophin (NT) which promotes the proliferation, survival and differentiation of neurons. Although traumatic events have been found to be associated with lower BDNF plasma levels in affective disorders, no study has explored this parameter in patients with post-traumatic stress disorder (PTSD). We, therefore, measured BDNF plasma level in 18 patients with PTSD and in 18 healthy control subjects. Diagnoses were assessed by the Structured Clinical Interview for DSM-IV, while the specific symptoms were examined in the patients by means of the Impact of Event Scale for PTSD and the traumas experienced were assessed by using the Life Events Checklist. BDNF plasma levels were evaluated by means of a standardized Elisa method. The results, while showing significantly lower BDNF levels in PTSD patients, as compared with those of healthy subjects ($p = 0.001$), although obtained in a small sample size, would suggest that this NT may be involved in the pathophysiology of PTSD.

1. Introduction

Post-traumatic stress disorder (PTSD) is a complex syndrome resulting from the exposure to a severe traumatic event that poses effective or threatened death or injury and produces intense fear, helplessness or horror (American Psychiatric Association, APA, 2000; Keane et al., 2006). Clinically, PTSD patients show a wide range of symptoms including re-experiencing (nightmares, intrusive thoughts and flashbacks of the trauma), avoidance (amnesia for the trauma) and hyperarousal (exaggerated startle response, sleep disturbances and impaired learning and concentration). Different brain areas have been supposed to be involved in the pathophysiology of PTSD, in particular the hippocampus, amygdala and cingulate belonging to the limbic system, together with the medial and dorsolateral prefrontal cortex (Bremner, 2003). Different studies have also focused upon the modulation of the stress response and, as such, on the role of the hypothalamic-pituitary-adrenal (HPA) axis and the catecholamine/sympathetic nervous system, so that PTSD has been also depicted as a condition characterized by normal to low cortisol levels, despite hypersecretion of corticotrophin releasing factor (Newport and Nemeroff, 2000).

Neuroimaging studies in patients with PTSD triggered by combat exposure or early childhood physical/sexual abuse, showed a reduced hippocampal size, when compared with healthy individuals or subjects with other types of traumas (Bremner et al., 1995, 1997, 2003; Stein et al., 1997; Villarreal et al., 2002). These structural abnormalities are consistent with the deficits in learning and memory of PTSD patients and provide support for the hypothesis that stress may be associated with hippocampal damage or dysfunction (Bremner et al., 2003). In addition, preclinical studies have suggested that prolonged stress, that leads to atrophy and cell loss in limbic structures (Czéh and Lucassen, 2007), may decrease the expression of the Brain-Derived Neurotrophic Factor (BDNF), a neurotrophin (NT) known to promote neuronal survival and regulate the proliferation and differentiation of nerve cells in both the peripheral and central nervous system (Hartmann et al., 2001). In animal models the exposure to footshock or maternal separation reduces hippocampal BDNF expression through a down-regulation of its mRNA levels (Duman, 2002; Rasmusson et al.,

Abbreviations: APA, American Psychiatric Association; BDNF, Brain-Derived Neurotrophic Factor; CAPS, Clinician Administered PTSD Scale; DSM, Diagnostic and Statistical Manual of mental disorders; DSM-TR, Diagnostic and Statistical Manual of Mental Disorders-Text Revision; EDTA, Ethylenediaminetetraacetic acid; ELISA, Enzyme-Linked Immunosorbent Assay; ANOVA, Analysis of Variance; HPA, Hypothalamic-Pituitary-Adrenal; IES, Impact of Event Scale; IgG, immunoglobuline G; LEC, Life Events Checklist; HCl, Hydrochloric Acid; mRNA, Messanger-Ribonucleic Acid; NT, Neurotrophin; PD, Panic Disorder; PTSD, Post-Traumatic Stress Disorder; SCID-I/P, Structured Clinical Interview for DSM-IV Axis-I Disorders Patient Version; SPSS, Statistical Package for Social Science; TrkB, tyrosine kinase-activating receptor.

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2002). In humans, lower BDNF plasma levels have been associated with childhood physical neglect in depressed women (Grassi-Oliveira et al., 2008), or with a previous history of trauma in bipolar patients (Kauer-Sant'Anna et al., 2007). Therefore, not surprisingly, BDNF and its intracellular kinase-activating receptor (TrkB) have been implicated in the neurobiology of PTSD. In animals exposed to predator stress, a significant down-regulation of the BDNF mRNA and up-regulation of the TrkB mRNA were found in the hippocampus, so that it has been hypothesized that the consequent changes in neural plasticity and synaptic functioning might mediate some of the clinical manifestations of PTSD (Kozlovsky et al., 2007). Imaging studies support the notion that the neural circuitry of PTSD may involve brain regions implicated in both stress and memory, including hippocampus, amygdala, cingulate, medial and dorsolateral prefrontal cortex (Bremner et al., 1997; Bremner, 2003; Liberzon and Sripada, 2008). Moreover, PTSD has been associated with smaller hippocampal volume (Bremner et al., 2003).

BDNF is also present in the blood stream and derives from different sources, including platelets and the brain (Lommatzsch et al., 2005). Since positive correlations between brain and peripheral BDNF levels have been reported in rodents (Karege et al., 2002a), the blood levels are widely used in clinical settings as a mirror of the same brain parameter. In particular, plasma levels could represent a more reliable and sensitive marker of BDNF variations than serum changes, even in pathological conditions, as suggested by studies on schizophrenia patients (Palomino et al., 2006; Pirildar et al., 2004).

Although recently reduced BDNF plasma levels have been reported in subjects following a sexual abuse, loss of a relative/close friend, or a car/personal accident (Kauer-Sant'Anna et al., 2007), no information is available in PTSD. Therefore, the aim of the present study was to examine serum BDNF levels in PTSD patients and their possible correlations with the characteristics of the disorder and/or of the trauma.

2. Methods

2.1. Participants and assessment

A consecutive sample of 18 drug-free outpatients (12 women and 6 men; mean age ± SD: 42.1 ± 12.5 years) with a DSM-IV-TR (APA, 2000) diagnosis of PTSD were recruited at the Dipartimento di Psichiatria, Farmacologia, Neurobiologia e Biotecnologie of the University of Pisa, Italy.

Exclusion criteria were the following: current or lifetime diagnosis of organic mental disorder, schizophrenia, schizophreniform or other psychotic disorders, bipolar disorders, substance-related disorders, a current diagnosis of depressive disorder, uncontrolled or severe medical conditions, and any current or past psychopharmacological treatment.

Eighteen healthy subjects (11 women and 7 men; mean age ± SD: 38.8 ± 12.1 years) with no current or lifetime psychotropic medication, physical or DSM-IV-TR mental disorders, were recruited as the control group.

The assessment included: the Structured Clinical Interview for DSM-IV Axis-I disorders Patient Version (SCID-I/P, First et al., 1995); the Life Events Checklist (LEC, Gray et al., 2004); and the Impact of Event Scale (IES, Horowitz et al., 1979), for the PTSD symptomatology.

The SCID-I/P was administered to patients and control subjects by psychiatrists (C.C. and A.D.B.) trained and certified in the use of the instruments.

The LEC, administered to patients by the same raters, is a questionnaire measuring the exposure to potentially traumatic events, according to DSM-IV, developed at the National Center for PTSD (Boston Veterans Healthcare System) concurrently with the Clinician Administered PTSD Scale (CAPS), to facilitate the diagnosis of PTSD.

The IES, administered to patients only, is a widely-used scale with excellent psychometric properties, which assesses intrusion and avoidance symptoms that characterize stress response syndromes.

The Ethics Committee of the Azienda Ospedaliero-Universitaria of Pisa approved all recruitment and assessment procedures. All subjects included provided written informed consent, after receiving a complete description of the study and having the opportunity to ask questions.

2.2. Procedures

All venous blood samples were taken in the morning (between 8:00 and 9:00 am, following an overnight fast). Blood was drawn into EDTA-coated tubes that were kept on ice, centrifugated at 2000 ×g for 10 min at 4 °C and refrigerated at −20 °C. To measure the amount of total BDNF, acidification and subsequent neutralization of the samples were followed before proceeding with the enzyme-linked immunosorbent assay (ELISA) protocol, according to manufacturer's instruction (Promega, Wallisellen, Switzerland). Ninety-six well-plates were coated with anti-BDNF monoclonal antibody and incubated at 4 °C for 18 h. The plates were then incubated in a blocking buffer for 1 h at room temperature, then samples were added. The samples and BDNF standards were maintained at room temperature under shaking for 2 h, followed by washing with the appropriate buffer. The plates were successively incubated with anti-human BDNF polyclonal antibody at room temperature for 2 h, washed and incubated with anti-IgG antibody conjugated to horseradish peroxidase for 1 h at room temperature. The plates were incubated in peroxidase substrate and tetramethylbenzidine solution to produce a colour reaction. The reaction was stopped with 1 M HCl. The absorbance at 450 nm was measured with a microplate reader (Model 550, Bio Rad Laboratories) to determine BDNF values that are expressed as pg/ml.

2.3. Data analyses

Socio-demographic and clinical features were compared between the two groups by using the χ^2 test or *t*-test as indicated in Table 1. BDNF levels were compared between groups using a one-way analysis

Table 1
Socio-demographic and clinical characteristics of PTSD patients (*P*) and healthy control subjects (HC).

	P (*n* = 18)	HC (*n* = 18)
	N	*N*
Gender		
Men	6	7
Women	12	11
Marital status		
Single	5	9
Married/living with partner	9	7
Separated/divorced	2	2
Widows-ers	2	
Education	15	14
>8 y		
Work status		
Employed full/part time	7	9
Students	6	4
Unemployed	3	4
Retired	2	1
Index trauma		
– Sudden unexpected death of someone close to you	6	NA
– Physical or sexual assault	3	NA
– Life threatening illness or injury	4	NA
– Severe accident	5	NA
Age (years, mean ± SD)	42.1 ± 12.5	38.8 ± 12.1
Impact of event scale		
Total score	37.57 ± 14.18	NA
Intrusive	19.00 ± 6.87	NA
Avoidance	18.57 ± 6.93	NA

of variance (ANOVA) test for heterogeneity. The individual differences were assessed using a post-hoc Bonferroni test if the ANOVA was significant. A p-value of $<.05$ was judged as statistically significant. All analyses were carried-out using the Statistical Package for Social Sciences (SPSS), version 12.1, by means of personal computers.

3. Results

The demographic and clinical characteristics of PTSD patients and healthy control subjects are reported in Table 1, together with the frequency of index traumas listed in the LEC.

Patients and control subjects did not show any difference in age, marital status, education or employment. The BDNF levels (mean ± SD, ng/ml) were significantly lower in the patients than in the control subjects (5.3 ± 1.1 ng/ml vs. 7.4 ± 1.5 ng/ml, $p<.001$) (Fig. 1), with no difference between patients who had experienced one (n. 4) and two or more (n. 14) lifetime traumas (5.6 ± 0.6 and 5.2 ± 1.2 ng/ml) (Fig. 2). The patients who had experienced the trauma within one year before the assessment (n. 8) showed similar BDNF plasma levels than those with an older history of trauma (n. 10) (5.1 ± 0.4 and 5.4 ± 0.3 ng/ml, respectively) (Fig. 3).

No correlation was observed between the biological measurement and socio-demographic features or clinical characteristics of PTSD patients.

4. Discussion

The results of the present study showed significantly lower BDNF plasma levels in PTSD patients, with respect to those of healthy control subjects. This was particularly true for both patients who had experienced multiple trauma in their lifetime and those reporting only one, despite the small size of this latest sample may affect the results requiring a confirmation in larger samples. Further, no significant difference was observed in plasma BDNF of patients who had experienced the trauma less than one year before the time of assessment and those who had experienced it more than one year before. To our knowledge, this is the first study exploring BDNF plasma levels in patients with a DSM-IV-TR diagnosis of PTSD. Recently, some clinical studies reported reduced plasma or serum BDNF levels in major depression (Gonul et al., 2005; Karege et al., 2002b; Lee et al., 2007; Piccinni et al., 2008a), while suggesting that this NT might be involved in the pathophysiology of mood disorders (Shimizu et al., 2005). On the contrary, BDNF serum levels were unmodified in patients with panic disorder (PD) (Kobayashi et al., 2005). Interestingly, reduced BDNF serum levels were found in PD patients who were poor responders to cognitive-behavioral psychotherapy, as compared with good responders (Kobayashi et al., 2005), however no associations of the BDNF gene polymorphisms with PD have been found yet (Lam et al., 2004; Shimizu et al., 2005).

A large wealth of preclinical studies, while reporting BDNF changes in different stress conditions, strongly support its role in stress reaction (Duman, 2002; Hartmann et al., 2001; Rasmusson et al., 2002). This contrasts with the paucity of clinical data on BDNF alterations in patients who had faced traumatic or stressful experiences. Depressed patients with an early life stress had lower BDNF levels than those without it (Grassi-Oliveira et al., 2008). Lowered BDNF serum levels were reported also in another stress-related disorder, the burnout syndrome, where it seemed to be associated with some symptoms of including altered mood and cognitive functions (Onen Sertoz et al., 2008).

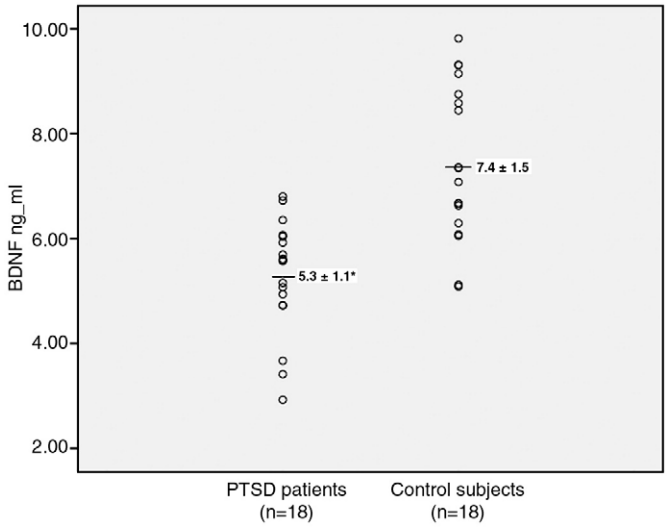

Fig. 1. Scattergrams of BDNF plasma levels in PTSD patients and healthy control subjects. A statistically significant difference between the two groups was observed (*$t=-4.96$; $p<.001$).

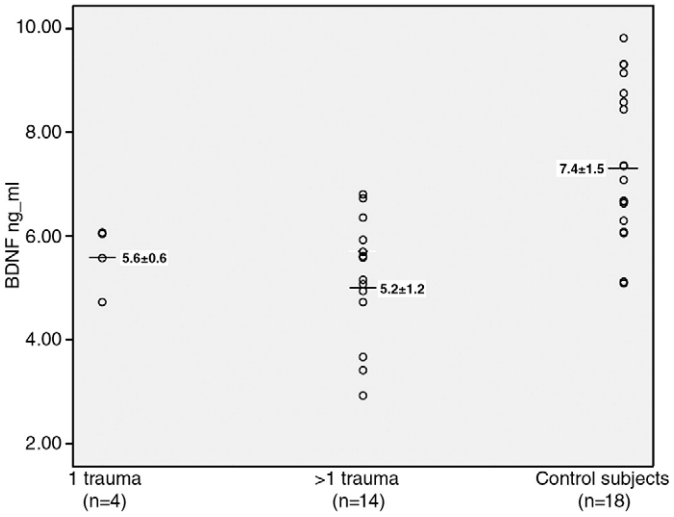

Fig. 2. Scattergrams of BDNF plasma levels in PTSD patients with one trauma or two or more traumas and healthy control subjects. No significant difference between plasma BDNF levels in PTSD patients with one trauma with respect to those with two or more traumas was demonstrated by using a post-hoc Bonferroni t-test in the ANOVA analysis.

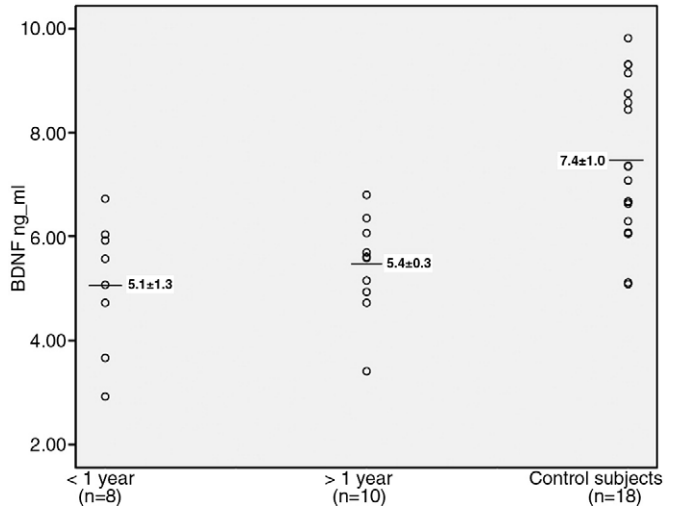

Fig. 3. Scattergrams of BDNF plasma levels in PTSD patients who had experience the trauma less or more than one year before the time of the assessment and healthy control subjects. No significant difference between plasma BDNF levels in PTSD patients who had experience the trauma less or more than one year before the time of assessment was demonstrated by using a post-hoc Bonferroni t-test in the ANOVA analysis.

In spite of its originality, some bias of this study should be acknowledged. The first limitation is represented by the small sample size, so that the findings should be considered preliminary, however all the patients recruited were drug-free and no patient presented comorbid psychiatric diagnoses that might have affected the results, such as major depression or bipolar disorder. The second is common to studies addressing the relationship between BDNF and psychiatric disorders, as it is linked to the extent to which blood BDNF levels may reflect brain BDNF concentrations. We investigated the changes of BDNF in plasma, because poor platelet plasma BDNF is minimally affected by the amount of BDNF stored in platelets and, therefore, may represent a more reliable and sensitive marker of BDNF variations occurring in the brain and periphery (Fujimura et al., 2002; Lommatzsch et al., 2005; Pliego-Rivero et al., 1997; Radka et al., 1996). Nevertheless, plasma BDNF have shown high inter-individual variability. It should also be mentioned that our absolute plasma BDNF values were higher than those observed in recent publications (Lommatzsch et al., 2005; Begliuomini et al., 2008). We hypothesized that the methodological procedure in assaying plasma BDNF levels might be crucial, thus, as previously reported (Piccinni et al., 2008a,b, 2009), we chose to assay total BDNF in plasma by acidification and subsequent neutralization procedures, that may increase the amount of detectable BDNF, while others might have measured the amount of the free mature form only. Therefore, according to us, different methodological procedures might contribute to explain the controversial data present in literature (Karege et al., 2005; Palomino et al., 2006). It's also important to recall that our data represent preliminary observation since the limited sample size, further studies in larger samples should be is low.

5. Conclusion

In conclusion, our findings suggest a possible role of BDNF in the patophysiology of PTSD, however further studies should replicate these findings in larger samples, as well as explore the possible relationships between BDNF changes and specific PTSD symptoms.

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