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Plasma Brain-Derived Neurotrophic Factor in treatment-resistant depressed patients receiving electroconvulsive therapy

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Abstract

There is an increasing evidence that the Brain-Derived Neurotrophic Factor (BDNF) could be involved in the mode of action of antidepressants and, perhaps, of ECT. This study aimed to investigate whether the clinical course of medication-resistant depressed patients following a course of ECT might be associated with changes of plasma BDNF concentrations. Our findings showed that at T0 (baseline) plasma BDNF levels of patients were significantly lower than those of control subjects, and that at T2 (after ECT) were significantly increased in parallel with the decrease of the Hamilton Rating Scale for Depression (HRSD) total score. However, only remitter patients who showed higher baseline BDNF levels than non-remitters reached normalized BDNF levels after ECT. These findings would suggest the potential usefulness of baseline plasma BDNF levels as predictors of response to ECT in treatment-resistant depressed patients.

1. Introduction

Electroconvulsive therapy (ECT) represented for over 70 years, and still represents, one of the most effective treatments for both major depression (MD) and a few other severe psychiatric conditions (Zomberg and Pope, 1993; Pagnin et al., 2004; Taylor, 2008) with an effectiveness rate greater than 60%, although it is not without side effects (MacQueen et al., 2007). The morbidity/mortality of ECT

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ranges between 2 and 4 per 100,000 sessions and 1 per 10,000 patients, similar to that of anaesthetic induction in minor surgery (Fink, 1979; Philbert et al., 1995). In spite of this evidence, its mechanism of action is still elusive (Altar et al., 2004; Frazer et al., 2005). Different parameters, such as cortisol, adrenocorticotropic hormone, corticotrophin-releasing factor, thyroid-releasing hormone, thyroid-stimulating hormone, prolactin, oxytocin, vasopressin, dehydroepiandrosterone sulfate and tumor necrosis factor α, have been proposed as possible substrates of the effect of ECT, but most of the data derived from animal and human research are generally inconsistent (Wahlund and von Rosen, 2003).

Over the past decades, different studies have suggested that Brain-Derived Neurotrophic Factor (BDNF), a neurotrophin recognized to mediate the survival, differentiation and outgrowth of selected neurons during development and adulthood, as well as to modulate the synaptic functions and the neuronal plasticity in several brain areas, might be involved in the pathophysiology of mood disorders (Duman et al., 1997; Duman, 2004). BDNF is also present in peripheral tissues, in particular it is mainly stored in human platelets and circulates in plasma at levels 100-fold lower than those of serum (Yamamoto and Gurney, 1990). It has been suggested that the difference between serum and plasma BDNF may correspond to the amount of BDNF stored in circulating platelets (Fujimura et al., 2002). Although the regulation of BDNF in plasma is still poorly understood and there are other potential cellular sources of plasma BDNF including vascular endothelial and smooth muscle cells, activated macrophages and lymphocytes, the amount of plasma BDNF has been considered to partly reflect BDNF secretion in the central nervous system (Lommatzsch et al., 2005); interestingly, it has been observed that central and peripheral BDNF changes are positively correlated in rodents (Karege et al., 2002). Recently, decreased plasma and serum BDNF levels have been observed in drug-free depressed patients, as compared with those detected in healthy subjects (Shimizu et al., 2003; Gonul et al., 2005; Aydemir et al., 2005; Piccinni et al., 2008a,b).

Electroconvulsive seizures (ECS) have been shown to increase the levels of BDNF mRNA, proteins and the tyrosine kinase receptor B (TrkB) mRNA in the rat hippocampus, while chronic ECS administration blocked the down-regulation of BDNF mRNA in the same area in response to restraint-induced stress (Lindefors et al., 1995; Nibuya et al., 1995; Angelucci et al., 2002). Preclinical observations in animals on the ECS-induced mossy fiber sprouting of hippocampal neurons (Duman and Vaidya, 1998; Vaidya et al., 1999; Lamont et al., 2001) and neurogenesis (Parent et al., 1997; Madsen et al., 2000) have anticipated more recent studies indicating a possible relationship between the neurotrophic effect of ECT and the increase of the brain levels of *N*-acetylaspartate (Michael et al., 2003; Lang et al., 2007), an index of neuron functionality (Tsai et al., 1995; Sager et al., 2001). A few studies in depressed patients have shown that ECT may increase the amount of serum and plasma BDNF (Taylor, 2008). The first evidence of serum BDNF levels increase in treatment-resistant depressed patients receiving ECT was recently published (Bocchio-Chiavetto et al., 2006) and subsequently confirmed only in responders (Okamoto et al., 2008). A similar finding was reported also for BDNF plasma levels (Marano et al., 2007). These results suggest that one of the putative mechanisms of ECT might be mediated by BDNF and related substances (Taylor, 2008). Two of the abovementioned studies (Marano et al., 2007; Okamoto et al., 2008) included both unipolar and bipolar depressed patients with a 2:1 ratio (Marano et al., 2007). Although the relationship between the polarity of a patient's illness and the ECT outcome is still controversial, most observations up-to present suggest that the unipolar/bipolar distinction may have no predictive value in determining ECT outcome (Daly et al., 2001).

Many factors including sex, age, diagnosis, presence of psychosis, duration of index episode, medication treatment failure prior to ECT and medication during ECT course, have been proposed as predictors of response to ECT in patients suffering from depression (Bloch et al., 2005; Kho et al., 2005; Pluijms et al., 2006), however no agreement exists on the predictive values of such variables (Dombrovski et al., 2005). The aim of the present study was, therefore, to assess plasma BDNF levels in depressed patients who failed to respond to medications and received ECT, as well as to explore the possible correlation between the biological parameter and the clinical changes along the ECT course.

2. Experimental procedures

2.1. Subjects

Eighteen inpatients (9 men and 9 women, mean age ± SD 44.9 ± 17 years) who met the DSM-IV-TR (APA, 2000) criteria for current major depressive episode (MDE) with or without psychotic features (16 bipolar disorder and 2 major depressive disorder) were selected at the Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, University of Pisa, between September 2006 and December 2007. Subjects were eligible if they were 18 years or older, not suffering from a major neurological or medical illness that limited the use of ECT, and had a chronic (>2 years) or recurrent MDE. Participants were required to have at least three MD treatment fails, including an adequate trial with a tricyclic antidepressant (TCA) (Thase and Rush, 1997; Fava, 2003). More specifically, treatment non-response in patients with bipolar depression was defined as persisting depressive symptoms despite 2 trials of at least 8 weeks, consisting of 1 trial with mood stabilizer(s) plus a (TCA) (200 mg/day of imipramine or the equivalent, or the maximum tolerable dose) and one trial with a selective serotonin reuptake inhibitor (SSRI) (40 mg/day of fluoxetine or the equivalent) combined with mood stabilizer(s) and a TCA. Diagnosis was confirmed by means of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). For each patient, an attending-level ECT psychiatrist recommended ECT according to clinical judgment based on the patient's failure to medication trials and severity or urgency of illness.

Fifteen healthy subjects (3 men and 12 women, mean age ± SD: 36.9 ± 9.2 years), with no history of past or current chronic physical or mental disorders and not taking regular medications, were recruited as the control group.

A written informed consent was obtained from all subjects to participate in the study, which was approved by the Ethics Committee of the University of Pisa, after procedure and effects were fully explained.

2.2. ECT treatment procedures

Before undergoing ECT, each patient was screened for general medical conditions through an accurate clinical evaluation including the collection of a detailed medical history, a physical and neurological examination, blood and urine tests, electrocardiogram, chest film, and a cerebral computed tomography scan. Anesthesia was induced with intravenous thiopental (2–4 mg/kg i.v.) and