



Electroconvulsive Therapy (ECT) increases serum Brain Derived Neurotrophic Factor (BDNF) in drug resistant depressed patients

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Abstract Several findings have suggested that the neurotrophin BDNF could contribute to clinical efficacy of antidepressant treatments. The purpose of this study was to analyse if ECT operates a modulation of serum BDNF levels in a sample of drug resistant depressed patients. The results obtained show significantly higher serum levels of BDNF following ECT. More specifically, while no change occurred in the whole sample between T0 (baseline) and T1 (after ECT) ($p=0.543$) a significant increase has been identified at T2, one month after the end of ECT ($p=0.002$). However, the BDNF augmentation was evident even between T0 and T1 in a subgroup of patients who has low baseline BDNF levels. Although future researches are needed, the results herein presented show for the first time that ECT is associated with changes in serum BDNF and further support the possible involvement of BDNF in antidepressant therapies.

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1. Introduction

Major depression is a severe and life-threatening illness which represents one of the most important causes of disability world-wide. In particular, about 50% of the affected patients experience a chronic course and up to 20% of them shows an insufficient response to drug treatments (Fava et al., 2003; Hussain and Cochrane, 2004). As other chronic diseases, major depression is a complex disorder caused by the interaction between environmental and biological/genetic risk factors. Although the molecular alterations underlying the pathogenesis remains to be clearly established, recent preclinical and clinical studies have suggested an involvement of the neurotrophin Brain Derived Neurotrophic Factor (BDNF) in the aetiology of major depression as well as in the antidepressant drug treatment (Angelucci et al., 2005; Castren, 2004; Duman, 2004; Hashimoto et al., 2004). BDNF is a neurotrophic factor widely expressed in the Central Nervous System (CNS) that plays a major role in brain development, survival and maintenance of neuronal functions and synaptic plasticity. Studies of brain imaging suggest that depressed patients have neuronal atrophy and cell loss in discrete brain regions (Bremner et al., 2000; Krishnan et al., 1993; Kumar et al., 1998, 2000, 2004; Sheline et al., 1996), which are suggestive of a reduction in neuron plasticity. In line with these observations, different studies reported a reduction of BDNF expression in post-mortem brain of depressed subjects (Dwivedi et al., 2001, 2003; Molnar et al., 2003). Extensive research in rodents has shown that stress-related behaviours can alter the expression of BDNF in the limbic system and cortex (Roceri et al., 2002, 2004; Smith and Cizza, 1996; Vollmayr et al., 2001). Furthermore, antidepressant drug treatment enhances BDNF expression and production (Altar, 1999; Castren, 2004; Duman et al., 1997; Nibuya et al., 1995) and the neurotrophin signalling appears to be required for antidepressant activity in animal models of depression (Castren, 2004; Saarelainen et al., 2003; Sairanen et al., 2005). The involvement of BDNF in major depression and antidepressant treatment has gained further support from a series of biochemical studies in humans. A decrease in BDNF serum levels has been associated with major depression (Karege et al., 2002a), an effect that is normalized by antidepressant drug therapies (Aydemir et al., 2005; Shimizu et al., 2003). Moreover a significant correlation between BDNF serum levels and depressive personality traits in a healthy subject was also found (Lang et al., 2004).

Electroconvulsive Therapy (ECT) is one of the eligible therapies for the treatment of major depression (American Psychiatry Association, 2000; UK ECT Review Group, 2003). Preclinical studies have shown that electroconvulsive seizures (ECS) produces a robust increase in BDNF mRNA (Altar et al., 2004; Chen et al., 2001; Duman et al., 1997; Nibuya et al., 1995; Zetterstrom et al., 1997) and BDNF protein (Altar et al., 2003) in different rat brain areas. However, whether or not ECT could affect the peripheral levels of BDNF in depressed patients is still an open question. In order to address this issue, we investigated, in the present study, serum levels of BDNF in a group of drug resistant depressed patients before and after ECT.

2. Experimental procedures

2.1. Subjects

Twenty three patients from the "Villa S. Chiara" Private Clinic (16 females, 7 males; mean age $53,0 \pm 17,39$ years, range 18–79 years) with major depression diagnosis (ICD-10) and planning to receive ECT treatment were recruited after written informed consent approved by the local Ethic Committee. Diagnosis of unipolar depression was confirmed by the diagnostic scale SCAN-IGC. In particular, ten patients met the criteria for major depression without psychotic symptoms and thirteen patients for major depression with psychotic symptoms. Cognitive deficits were evaluated with Mini Mental State examination (mean value $27,9 \pm 2,00$). An independent psychiatrist recommended ECT according to clinical judgement because of the patients' drug resistance. Drug resistance was defined as a failure to respond to at least three courses of antidepressant medications with adequate dose and duration (stage III definition of Thase and Rush, 1997). Patients were maintained on the same drug treatment for at least 3 weeks before ECT treatment and during the entire study period (for the antidepressant treatment: 7 patients were treated with SSRIs, 15 patients were treated with other drug classes and one patient was drug-free). Illness severity and the outcome of ECT treatment was assessed with the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979).

Longitudinal blood sampling and the concomitant MADRS evaluations were performed at T0 (Baseline: the day before ECT treatment), T1 (the day after the last ECT treatment) and T2 (1 month after the end of the ECT treatment). Complete remission was considered when MADRS score after treatment were ≤ 8 at T1 and T2.

2.2. ECT Treatment

A medical history and a physical examination together with blood and urine routine examinations, electrocardiogram (ECG), cerebral CAT scan, and a chest film were requested to screen the general medical conditions. Premedication included atropine sulphate (0,5 mg IV), succinylcholine (0,7 mg/kg IV), thiopental (3,0 mg/kg IV for males, 2,5 mg/kg IV for females).

ECT was performed between 7:00 and 9:00 a.m. using a Thymatron™ DG (Somatics, Inc., Lake Bluff, IL, USA) with standard settings (Abrams and Swartz, 1989) with a bipolar brief pulse square wave. The patients were treated with bilateral ECT. Two stimulus electrodes were placed over the left and right frontotemporal scalp. For each patient, ECT treatment conditions have been set up (charge delivered max 504 mC, current 0.9 A, frequency 30–70 Hz, pulse width 1 ms, duration max 8 s). During ECT, the motor convulsions, the electroencephalogram (EEG), the induced tachycardia (ECG) and, if necessary, the electromyogram (EMG) were monitored. Treatment was given three times a week. The mean number of treatments received was $7,0 \pm 1,97$ (range 3–10) and ECT treatment was completed on the basis of the clinical judgment of the treating physicians.

2.3. BDNF serum determination and statistical analysis

Venous blood samples were collected in the morning after an overnight fast (between 8:00 and 9:00 a.m.) in anticoagulant-free tubes. They were kept at room temperature for 1 h followed by 1 h at 4°C before serum separation by centrifugation at (3000 rpm for 15 min at 4°C). Serum samples were stored at -80°C till the time of assay. BDNF levels were measured by the ELISA method using the human BDNF Quantikine Kit (R D System, Minneapolis, USA), according to the manufacturer's instructions. The BDNF

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