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The acute response of plasma brain-derived neurotrophic factor as a result of exercise in major depressive disorder

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) and other neurotrophins are believed to play an important role in affective disorders. In this study we investigated plasma-BDNF response during an incremental exercise test in 18 patients suffering from moderate major depressive disorder (MDD) and 18 controls. The patients were not treated with antidepressants or neuroleptics. Possible associations between plasma plasma-BDNF levels, dexamethasone suppression test cortisol levels and Montgomery-Åsberg Depression Rating Scale (MADRS) scores were also tested. No difference in basal BDNF levels between patients and controls was found. BDNF increased significantly during exercise in both male and female patients as well as in male controls, with no significant differences between the groups. BDNF levels declined after exercise, but after 60 min of rest BDNF levels showed tendencies to increase again in male patients. No correlation between BDNF and cortisol or MADRS scores was found. We conclude that unmedicated patients with moderate depression and normal activity of the hypothalamic-pituitary-adrenal axis do not have a disturbed peripheral BDNF release during exercise. The BDNF increase 60 min after interruption of exercise in male patients might indicate up-regulated BDNF synthesis, but this needs to be further investigated in future studies.

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a member of the mammalian neurotrophin family (Hallbook, 1999), which regulates crucial functions of the central nervous system such as cell survival, cell differentiation, axonal growth, and the function and plasticity of synapses (Huang and Reichardt, 2001). Its potential role in major depressive disorder (MDD) has led to extensive research during recent years. For example, one early post-mortem study noted elevated levels of BDNF in hippocampal brain tissue in subjects treated with antidepressants at the time of death compared with subjects who had not been treated with antidepressants (Chen et al., 2001). The impact of BDNF is also supported by studies on BDNF in serum, showing significantly lower BDNF levels in unmedicated MDD patients as compared with MDD patients treated with antidepressants and healthy controls (Aydemir et al., 2005; Karege et al., 2002). The lowered BDNF levels have furthermore been reported to normalize with antidepressant treatment (Gervasoni et al., 2005; Shimizu et al., 2003). The peripheral BDNF alterations may be related to CNS activity, as animal studies have shown a passage of BDNF across the blood-brain barrier (Pan et al., 1998). It is not known, however, to what extent serum or plasma BDNF correlates with BDNF in the CNS in humans.

The interest of BDNF alterations in major depression is also increased by findings implicating a relation between BDNF, monoaminergic activity (Garcia et al., 2003; Ivy et al., 2003; Mattson et al., 2004) and the function of the hypothalamic-pituitary-adrenal (HPA) axis (Holsboer and Barden, 1996; Schule et al., 2006).

Another interesting aspect of BDNF is that it may have a role in the potential effect of exercise in MDD. In animal models, exercise has been shown to up-regulate BDNF mRNA transcription, and this has been reported to be further accelerated when exercise has been combined with antidepressant medication (Russo-Neustadt et al., 2000; Russo-Neustadt et al., 2001). It has also been shown that rodents with access to a running wheel for voluntary exercise or in a cognitively stimulating environment display higher BDNF levels in certain parts of the brain, including the hippocampus (Mattson et al., 2004). Much less is known about the effect of exercise on BDNF in humans. There is, however, one study of the acute effects of exercise, in which patients suffering from multiple sclerosis and healthy controls performed a standardised 30-min exercise. The results showed an acute elevation of s-BDNF without any significant differences between groups. Neither were there any significant differences in baseline s-BDNF (Gold et al., 2003).

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The effect of physical exercise in MDD has been examined in several recent studies. Dimeo et al. (2001) found a clinically relevant and statistically significant reduction in depression scores after an aerobic training program in patients with moderate to severe MDD (Dimeo et al., 2001). Likewise, moderate aerobic exercise was found to be a significantly better treatment of mild to moderate MDD compared with low-intensity aerobic exercise or flexibility training (placebo) (Dunn et al., 2005). There is a possibility that this effect is partly mediated by neurotrophins, including BDNF.

In this study we hypothesized that patients with major depression and no current antidepressant treatment have an altered plasma plasma-BDNF response during an acute exercise test as compared with healthy controls. If such a difference existed, it might be related to the pathophysiology in MDD and the possible therapeutic mechanism of physical exercise in MDD. Plasma-BDNF levels were thus examined during the course of an incremental exercise test. Possible associations between plasma-BDNF levels, post-dexamethasone cortisol, and depression rating scale scores were also tested.

2. Methods

2.1. Subjects

The patients were recruited from wards and the emergency room at the psychiatric clinic at the University Hospital in Lund. Patients were asked whether they were willing to participate in the study, and if so, they were referred to us. Patients who declined participation were not recorded and their number is therefore unknown. For inclusion the patients had to meet the diagnostic criteria for moderate or severe major depressive disorder according to DSM-IV, score more than 21 on the Montgomery-Åsberg Depression Rating Scale (MADRS) and accept participation. The exclusion criteria were pregnancy and cardiovascular disease. The control group was randomly selected from the municipal population register in Lund, Sweden, and invited by letter. This method of selection has the benefit of being randomized, but since the register only contains information about date of birth and sex, we were unable to match for anything more than this. Patients and controls were sex- and age-matched ±5 years, and the inclusion criteria for control subjects were good physical health and no history or current mental or somatic disorder or drug abuse. The control subjects were paid for participation.

Major depressed patients (9F + 9M) and healthy controls (9F + 9M) participated in the study. The median ages were as follows: for MDD men 33 (22–54) years, for MDD women 34 (24–53) years, for control men 34 (24–54) years, and for control women 35 (23–54) years. There was no significant difference in age between patients and controls (Wilcoxon sign rank test).

The research examination of the patients started within a week from inclusion. The day before the exercise test, the patients were examined by two research physicians, both residents in psychiatry. The interview was structured and included the SPIFA (Structured Psychiatric Interview for General Practitioners; Dahl et al., 2002; von Knorring et al., 1999), the CPRS (Comprehensive Psychopathological Rating Scale) and a reevaluation with the MADRS.

All people included in the study were screened by blood tests and physically examined regarding somatic diseases. Patients with ongoing or a history of cardiovascular diseases were excluded from the study as well as patients who had been treated with antidepressants, neuroleptics or mood stabilizers in the last 2 weeks. However, as described below, none of the included patients had in fact been treated with neuroleptics or antidepressants the last month before the exercise test.

Before examination, the patients were interviewed according to the Structured Clinical Interview of DSM-IV-II to screen for an axis-II diagnosis.

The samples were composed of five patients with a history of recurrent depressive episodes, while the remaining 13 patients were experiencing their first episodes of depression. Sixteen patients had not been treated with antidepressants or neuroleptics in the last 6 months. One patient ended treatment with mirtazapine 34 days before the exercise test. One patient used diclofenac intermittently. One patient had ended bupropion treatment 2 months before the examination. Two patients had taken zopiclone and one patient had taken zolpidem occasionally, but not on the day before the examination.

Eight patients received an additional DSM-IV axis-I diagnosis, and three patients received an axis-II diagnosis. One patient with fibromyalgia was treated with ibuprofen and carisoprodol occasionally but had not taken any medication for 5 days before the exercise test. One patient was treated with sumatriptan occasionally against migraine. This patient had, however, not taken any medications for 7 weeks preceding the examination. One patient received budesonide against an allergic reaction 1 week before examination and was treated with terbutaline a couple of weeks before examination; one patient was occasionally treated with furosemide against benign oedema in the legs, the last time 3 days before the exercise test. One patient had been treated for ulcerous colitis 2 years before examination but was without any current symptoms of the disease at the time of study. Two patients used oral contraceptives. One patient had psoriasis eczema; one had had a cold, without fever, 4 days before the examination. None of the patients suffered from any cardiovascular diseases. Three controls used oral contraceptives.

2.2. Exercise test

All participants performed an exercise test on a computerized ergometer cycle (Rodby 380, Siemens Elma, Solna, Sweden) in a standardised way (Atterhog et al., 1979). Every participant was weighed on a physician's beam scale, dressed in light underwear and wearing no shoes. The height of every participant was measured and the body mass index (BMI) was calculated. The subjects rated their perceived capacity (RPC) based on metabolic equivalents (MET) (Wisen et al., 2002). They were instructed not to take part in any sporting activities on the day of the test or on the preceding day, nor to eat, drink caffeine-containing beverages or smoke during the 2 h preceding the test.

The exercise test was designed with an initial workload of 30 W for women and 50 W for men. The workload was thereafter increased in small steps (5 W/30 s for women and 5 W/20 s for men) until a heart rate (HR) of 125 ± 5 bpm was attained.

The exercise was then followed by a period of constant workload, lasting 6 min ('sub-maximal workload'). Subsequently the workload was again increased in small steps (as described above) until exhaustion ('maximal workload') (Wisen and Wohlfart, 2004). The ECG (ECG Megachraft, Siemens-Elema, Solna, Sweden) and heart rate were continuously monitored, and the blood pressure was determined every second minute. Baseline BDNF was taken at 14:00h after 60 min of resting sitting in a chair, right before the exercise test took place. During the exercise test blood samples were taken at sub-maximal and maximal workload. After the exercise, the subjects rested in a supine position and blood samples were drawn after 30 min and 60 min. At each time of blood sampling during the exercise test, the workloads as measured in W and self-rating of perceived exertion (RPE) (Borg, 1982) were registered.

The blood samples were immediately placed on ice and centrifuged at 4 °C and 3000 rounds per min for 10 min within 1 h of collection. Plasma was stored at −70 °C until analysis of BDNF.

2.3. Dexamethasone suppression test (DST)

The subjects were given 1 mg of Decadron (dexamethasone) orally at 22:00h on the same day that they performed the exercise test. Blood samples for analysis of cortisol were drawn 7 h before Decadron administration (baseline), and the day after at 08:00h and 15:00h.

2.4. Chemical analyses

Analysis of BDNF concentration in plasma samples was performed using the ChemiKine sandwich ELISA kit (Chemicon International USA) and conducted according to manufacturer's guidelines. A microplate reader (Milenia, kinetic analyser, DPC, USA) set at 450 nm was used to determine plasma-BDNF values (intra-assay and inter-assay levels of variation were less than 15%). Maximum detectable concentration was 1875 pg/ml.

2.5. Statistical analyses

For statistical analysis, non-parametric tests were used. For paired variables Friedman's test and the Wilcoxon sign rank test were used. To analyse correlations, we used Spearman's rank test. Analyses were computed using SPSS version 14.0. A P-value of $P<0.05$ (two-tailed) was considered significant.

2.6. Ethical approval

The study was approved by the Lund University Medical Ethics Committee. Patients signed a written informed consent.

3. Results

Median, minimum and maximum MADRS scores for patients and controls were 24 (17–42) and 0 (0–1), respectively. Median basal BDNF levels (pg/ml) were 487 (80–1238) for male patients, 223 (79–836) for male controls, 367 (113–815) for female patients and 382 (106–1875) for female controls.

The BDNF levels during and after exercise were normalized to the baseline BDNF level for each subject. Females and males were analysed separately. Fig. 1 and Table 1 illustrate median plasma-BDNF levels during the exercise test for patients and controls. There were no differences in plasma-BDNF levels at (I) baseline, (II) sub-maximal workload, (III) maximal workload, (IV) 30 min after conclusion of the exercise test or (V) 60 min after conclusion of the exercise between patients and controls in either the females or the males (Wilcoxon sign rank test). No BDNF was obtained at maximal workload from one of the female controls.