Psychoneuroendocrinology (2010) **35**, 364—368

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Acute exercise ameliorates reduced brain-derived neurotrophic factor in patients with panic disorder

Andreas Ströhle [a,*], Meline Stoy [a], Barbara Graetz [a], Michael Scheel [a], André Wittmann [a], Jürgen Gallinat [a], Undine E. Lang [a], Fernando Dimeo [b], Rainer Hellweg [a]

[a] *Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité — Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany*
[b] *Section of Sports Medicine, Department of Internal Medicine III, Campus Benjamin Franklin, Charité — Universitätsmedizin Berlin, Germany*

Received 29 May 2009; received in revised form 16 July 2009; accepted 19 July 2009

KEYWORDS
Panic disorder;
Exercise;
Brain-derived neurotrophic factor;
Anxiety;
Physical activity;
BDNF

Summary The neurotrophin brain-derived neurotrophic factor (BDNF) has been implicated in depression and anxiety. Antidepressants and exercise increase BDNF expression, and both have an antidepressant and anxiolytic activity. To further characterize the association of anxiety, BDNF and exercise, we studied panic disorder patients ($n = 12$) and individually matched healthy control subjects ($n = 12$) in a standardized exercise paradigm. Serum samples for BDNF analyses were taken before and after 30 min of exercise (70 VO_{2max}) or quiet rest. The two conditions were separated by 1 week and the order was randomized. Non-parametric statistical analyses were performed. There was a negative correlation of BDNF concentrations and subjective arousal at baseline ($r = -0.42$, $p = 0.006$). Compared to healthy control subjects, patients with panic disorder had significantly reduced BDNF concentrations at baseline and 30 min of exercise significantly increased BDNF concentrations only in these patients. Our results suggest that acute exercise ameliorates reduced BDNF concentrations in panic disorder patients and raise the question whether this is also found after long-term exercise training and if it is related to the therapeutic outcome.

1. Introduction

The neurotrophin brain-derived neurotrophic factor (BDNF) has been implicated in depression and anxiety (Martinowich et al., 2007; Groves, 2007): a so-called 'neurotrophin hypothesis of depression' has been suggested, mainly based on a correlation of decreased hippocampal BDNF levels and stress-induced depressive behaviors, and vice versa, an enhancement of BDNF expression by antidepressants (Duman and Monteggia, 2006; Sen et al., 2008). Exercise has an anxiolytic and antidepressant activity (Martinsen, 2008; Ströhle, 2009) and also increases BDNF expression (Cotman and Berthold, 2002; Ying et al., 2005; Gómez-Pinilla et al., 2008). In panic

* Corresponding author. Tel.: +49 30 450517034; fax: +49 30 450517934.
E-mail address: andreas.stroehle@charite.de (A. Ströhle).

0306-4530/$ — see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2009.07.013

disorder patients, low BDNF serum concentrations have been associated with low response to cognitive behavioral therapy (Kobayashi et al., 2005). To further characterize the association of anxiety, panic, BDNF levels and exercise, we studied panic disorder patients in a standardized acute exercise paradigm.

2. Methods

Twelve patients (nine women and three men; mean age = 31.9 years, standard error of the mean (SEM) = 2.2; mean age of onset = 23.0 years, SEM = 2.3; 8 smokers) with a diagnosis of panic disorder ($n = 10$, with agoraphobia) but without a comorbid axis-I disorder (Sheehan et al., 1998) were recruited consecutively in our outpatient department. The panic and agoraphobia scale (Bandelow, 1997) indicated a moderate severity of panic and agoraphobia (mean = 24.2, SEM = 4.7). Mean Beck depression scale score was 13.2 (SEM = 2.7) (Beck et al., 1961), Beck anxiety scale (Beck et al., 1988) score was 23.5 (SEM = 6.5) indicating low depression and moderate anxiety in the patients. Mean severity of agoraphobia (Chambless et al., 1985) "alone" was 1.7 (SEM = 0.2) and 1.4 (SEM = 0.1) "accompanied". Patients were antidepressant naive and did not take any psychotropic medication for at least 10 days. Further drug history revealed on demand benzodiazepines use, which was stopped in one patient 3 months before and in an another patient 6 years before. In addition, one patient stopped opipramol 4 months prior to the study. Twelve age- and sex-matched healthy control subjects (mean age = 30.8 years, SEM = 2.5; 5 smokers) with no personal (Sheehan et al., 1998) or family history of a psychiatric disorder were also recruited for the study. All subjects had undergone a thorough medical examination to rule out other illnesses, drug intake and life styles that could interfere with the study. The mean body mass index was 23.3 (SEM = 1.2) in the patients and 23.1 (SEM = 1.3) in the control subjects. The protocol was approved by the local ethics committee for human experiments. After complete description of the study to the subjects, written informed consent was obtained.

Before the experiment a treadmill spiroergometry was performed to determine the maximum oxygen uptake (mean VO_{2max}: patients 38.1 (SEM = 1.7), control subjects 39.7 (SEM = 1.7) ml/kg/min) ($Z = -0.382$, $p = 0.71$). No participant had signs of cardiovascular abnormalities during the ergometry. All subjects were studied twice on different days separated by 1 week. From 09:30 h the subjects were studied in a supine position in a soundproof room with a single bed. On the first day subjects were randomly assigned to one of the two conditions "quiet rest" or "exercise" (treadmill walking for 30 min at 70% VO_{2max}. from 1020 to 1050 h); the other condition was used on the second study day. Visual analogue scale (VAS) ratings for arousal (apprehension and vigilance) and anxiety were recorded in the subjects before and after "exercise" and "quiet rest" in parallel to blood samples before and after exercise (1015 and 1050 h).

BDNF serum concentrations were quantified by a modified fluorometric ELISA as described in detail elsewhere (Hellweg et al., 2003; Ziegenhorn et al., 2007). Briefly, rethawed serum samples were diluted with assay buffer containing a variety of protease inhibitors ("complete" Protease Inhibitor Cocktail Tablets purchased from Roche Diagnostics, Germany) and 10 μg/ml unspecific IgG antibodies ("PolyMak 33" purchased from Boehringer Mannheim, Germany) to overcome the possible interference of serum-derived proteins and human anti-mouse antibodies with assay results, thereby increasing the signal to noise ratio. Due to the high amount of BDNF in the serum as first described by Radka et al. (1996) samples were diluted 1:200 prior to BDNF measurements (i.e., 1 vol. serum + 199 vol. assay buffer). The BDNF content was expressed as equivalents of recombinant human BDNF. The assay has a detection limit of 1 pg/ml, inter- and intra-assay variations are 34.1 and 6.7%, respectively. Determinations of recovery, specific, and unspecific neurotrophin binding for BDNF involved quadruplicate fluorescence determinations for each serum sample. Because the intra-assay variation is much less than the inter-assay variation, the corresponding pre- and post-exercise samples of each subject were always measured in the same BDNF assay. Because BDNF concentrations were not normally distributed (Ziegenhorn et al., 2007) non-parametric statistical analyses were performed, using Mann–Whitney *U*-test, Wilcoxon signed paired test and Spearman correlation coefficient with Bonferroni's correction were appropriate.

3. Results

Subjective arousal at baseline was significantly increased in patients (mean VAS 23.0, SEM = 3.9), when compared to healthy control subjects (mean VAS 4.1, SEM = 1.1) ($Z = -4.60$, $p < 0.001$). In the whole sample ($n = 24$), there was a negative correlation of BDNF concentrations and VAS arousal ratings at baseline ($r = -0.42$, $p = 0.006$) (see Fig. 1); distinguished by groups, no significant correlation was found (patients $r = 0.319$, $p = 0.138$; controls $r = -0.390$, $p = 0.098$). VAS arousal and anxiety were not significantly changed by exercise. However, there was as a trend for a correlation of post-exercise VAS arousal and BDNF concentrations in the patients ($r = 0.576$, $p = 0.063$).

Compared to healthy control subjects, patients with panic disorder had significantly reduced BDNF concentrations at baseline ($Z = -2.85$, $p = 0.003$) and 30 min of aerobic

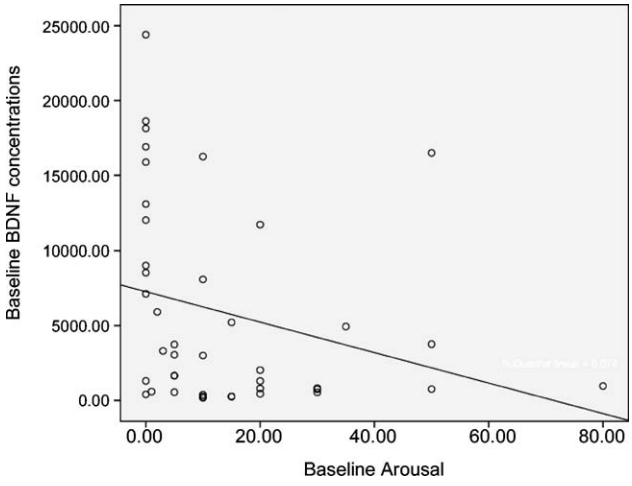

Figure 1 Baseline BDNF concentrations and VAS arousal in patients and control subjects.