Brain Derived Neurotrophic Factor increases during recovery from psychological stress.

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Abstract:
Objective: *To study the levels of plasma BDNF during recovering from psychological stress.*
Methods: *Blood samples from thirty eight participants in a stress treatment project were analyzed for BDNF in plasma before and after 3 months treatment. Symptom levels were assessed by SCL92, work ability index and a question on stress. Physiological and behavioral measures were collected, all at baseline and after treatment.*
Results: *BDNF increased significantly during the follow up, but the levels of BDNF were not correlated to blood pressure, se-cholesterol, HbA_1C, se-fibrinogen or salivary cortisol even if the two latter decreased significantly. BDNF increase was inversely associated with improvement in depression symptoms contrary to the expected.*
Conclusion: *Plasma BDNF increased during treatment for psychological stress, but was not associated with physiological stressmarkers or improvement of stress symptoms.*

I. Introduction

Psychological strain increases the risk of developing stress-related conditions as cardiovascular disease and depression (1). Moreover, other chronic diseases seem to be aggravated by strain (2). Clear evidence for the role and nature of the mechanisms is however lacking. Contradictionary results from studies on the relationship between i.e. cortisol excretion and stress-related mental disorders are numerous (3). Glucocoticoid resistance has been suggested as explanation for this (3). Brain studies however have demonstrated that reduction of stress is correlated to beneficial changes in amygdala (4).

It has been demonstrated that stress decreases neuronal plasticity and increases neurodegeneration (5). Stress modulates brain-derived neurotrophic factor (BDNF) in hippocampus and amygdala in rodents (6). BDNF is a member of the neurotrophic factor family; neurotrophins induce growth of hippocampus and support neuroplasticity (7). In addition, BDNF facilitate learning and memory and protects against stress-induced neuronal death (8). A "*Neurotrophic model for stress-related disorders*" has been suggested by Duman and Monteggia (9), which states that depression and other stress-related disorders may be a result of decreased level of BDNF and in addition, stimuli that leads to increasing level of BDNF can restore brain neurogenesis and plasticity (10, 11).

Different aspects of lifestyle such as physical exercise and diet can facilitate recovery from depression (12) and brain injury (13). So far, only minor are known regarding psychological stress and BDNF. To investigate the relationship between recovery from psychological stress and circulating levels of BDNF, we analyzed change in plasma BDNF from 38 individuals participating in the COPESTRESS study (14), which is 3 months of intensive treatment in individuals with severe stress. We hypothesized that at baseline low plasma levels of BDNF were related to high score regarding stress and depression and that increase in BDNF was associated to recovery (15).

II. Methods

Material

General practitioners referred participants on sick leave due to common mental disorders to a stress treatment project of which 268 were eligible and randomized to four different treatment groups. 69 were randomized to immediate treatment Bispebjerg Hospital. 60 of these completed the treatment. Details of the inclusion are described earlier (14). Blood samples from the first 38 individuals were taken for analyses of BDNF during the autumn of 2010. Mean age of the 38 participants were 43.2 years (range 28-58), 76.3 pct. were women, 13.2 pct. were smokers, 29.4 pct. blue collar workers, 61.8 pct. white collar workers and 8.8 pct. academics. Nineteen percent took antidepressants as medication, 9.6 pct. antihypertensive medication and 3 pct. cholesterol-lowering medication. At baseline 63.5 pct. reported high degree of stress, while 10.4 pct. reported high degree of stress after treatment. Thirty six pct. was assessed as having a moderate to major depression at

baseline based on Major Depression Inventory. This number was reduced to 9.6 pct. after treatment. After end of treatment were 98 pct. of the participants working full time or started their job part time.

Measures

The following physiological measures were assessed at baseline and after 3 months of treatment:

Weight, height, waist/hip circumference, systolic and diastolic blood pressure (SBP and DBP) were measured at clinical examination. Blood samples for determination of glycated haemoglobin (HbA_1c) were analyzed consecutively, se-cholesterol and se-fibrinogen were drawn and analyzed at the end of data collection, and analyses were performed according to standard procedures at Bispebjerg Hospital. Plasma for measurement of BDNF were kept frozen at -80 ° C until analyses conducted at The Centre of Inflammation and Metabolism, Department of Infectious Diseases, Rigshospitalet, University of Copenhagen as described elsewhere (16).

Awakening Cortisol Response (ACR) was calculated from saliva cortisol, collected on cotton tampons (Salivette, Saarsted). Participants were instructed to collect first sample of saliva immediately after awakening while still in bed, another sample 30 minutes after awakening. After collection the samples were delivered at the clinic personally within 5 hours. The samples were kept frozen at minus 80 degree Celsius until analysis at The National Research Centre for the Working Environment (17). Difference between salivary cortisol 30 min after- and immediately after awakening were used as ACR(18). Self-reported exercise was measured on a four point score ranging from no exercise in leisure to heavy exercise several times a week.

Psychological symptoms were measured by the Symptom Check List (SCL92) and Major Depression Inventory (MDI).

SCL-92 is a 92-item self-administered questionnaire that consists of nine subscales. The items on the scale are rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). The time frame is the past week. The sum of 9 items from this questionnaire constitutes a depression score (19).

The MDI is a 12-item self-administered questionnaire. Degree of depression can be estimated by analyzing the answers according to specific criteria. Degree can be categorized as mild, moderate or severe (20).

Work-ability was measured by the question: "Assess your work ability on a scale ranging from 0 to 10, where ten points mean that you are at your best. How do you rate your current work ability?".

Degree of stress was measured by the question: "Stress means a situation in which a person feels tense, restless, nervous or anxious or is unable to sleep at night because his/her mind is troubled all the time. Do you feel this kind of stress these days?" The response is recorded on a 5-point Likert scale varying from "not at all" to "very much". The validity of this single-item measure of stress symptoms has been evaluated by Elo et al (21).

Use of antidepressant medication, tobacco and alcohol was recorded too.

Data analyses

All physiological variables and plasma BDNF were transformed logarithmic before analysis. Changes in variables regarding stress symptoms, physiological measurements, exercise and blood measurements including plasma BDNF were tested by pair-wise t-tests for the continuous variables and by Chi^2 tests for the discrete.

Next the association between log BDNF and exercise, symptom scores and physiological variables were tested with adjustment for age, gender and BMI in multiple linear regression analyses. Finally the change in log BDNF was related to baseline values and change in symptoms and physiological variables adjusting for baseline log BDNF, age, gender and BMI.

III. Results

Table 1 gives prevalence and mean values of behavior, symptoms and physiological variables at baseline and at the end of treatment. The sick leave rate decreased significantly as the prevalence of depression. The scores for symptoms and the degree of exercise improved significantly. BDNF increased and se-fibrinogen and ACR decreased significantly as well. Men showed borderline significant higher logBDNF (3.0 (0.3)) than women (2.8 (0.3)) (p=0.06). Age, antidepressant medication, smoking and alcohol consumption were not associated to logBDNF.

Table 2 provides data for the associations between BDNF and symptoms and physiological measures. Except for BMI no statistical association between BDNF at baseline and the tested variables were found. However change in BDNF over time was significantly associated with change in depression score but in the unexpected direction. Those with the lowest depression score showed the highest increase in BDNF and those who diminished their depression score most had the lowest increase in BDNF. Workability index was borderline significantly associated with change in BDNF in the same manner. None of the physiological variables at baseline or changes in these (data not shown) were associated with change in BDNF.

IV. Discussion

This study clearly showed improvement of plasma BDNF during recovering from a stress condition, confirming the second part of our hypothesis. In contrast the increase in BDNF was not associated with improvement in symptom levels as expected. In addition high symptom scores at baseline were more likely to be associated with high levels of BDNF, opposite to the expected (11, 22). The reason for our finding of no association with depression scores at baseline could be that the participants in the study were not depressed to a degree comparable with participants in other studies (23, 24). They were still at the labor market and the length of sick leave was one to three months for most of them.

The association between BDNF and coronary risk factors as blood pressure and se-cholesterol was not significant as reported in a larger study (25).

The main limitations of the study are the small study sample, that the participants were not well-characterized clinically and that the blood sampling was not optimal. Regarding the participants, they were referred patients from their GP, who initially judged that they could benefit from the offered treatment. However, these patients presented quite different clinical conditions, ranging from severe depression to adjustment conditions marked by anxiety and nervousness. Common to all of the participants was a severity, which led to the sick leave, but on the other side of a length which had not yet led to the firing. Thus it must be assumed that the participants represent a sample of a practitioner's patients who usually are referred for psychological or psychiatric treatment. As seen in the materials section, not all of the symptoms diminished during therapy, although the majority of the participants were able to resume work at the end of treatment. The randomization procedure would not affect the results because the intervention was the same for all and the participants served as their own controls in this longitudinal study. The sampling was not optimal for logistical reasons because it was not possible to perform sampling at the same time of day for each of the participants. In addition, the first participants began in early autumn and the last ended in winter. It is difficult to estimate the direction of any bias related to these sampling concerns.

The main strengths of the study are the longitudinal design with significant improvement in the clinical condition of the participants during the treatment.

In conclusion this study showed a significant increase in BDNF during treatment for stress, no association between BDNF and other potential physiological stress indicators and significant inverse association between increase in BDNF during 3 months and improvement of depressive symptoms. The negative association between BDNF and psychological stress should be tested in other studies. The mechanism in change in plasma BDNF seems to be independent of experienced stress and other physiological stress markers.

Maria Pedersen and Bo Netterstrøm declare that they have no conflict of interest.
Informed consent was obtained from all patients for inclusion in the study. Feed back to the referral GP was given for all participants.

Table1. Mean values and prevalence of symptoms and physiological measures of 38 participants in a stress treatment programme before and after treatment in 3 months

	Pre treatment	Post treatment	p
Severity of condition			
Behavior			
Sick leave pct.	100	31.4	< 0.01*
Exercise > 2 hours a week, pct.	33.6	47.1	0.05*
Antidepressant medication pct.	19.6	26.1	0.34*
Symptoms			
Work-ability index (WAI) (SD)	2.40 (2.3)	6.00 (2.5)	<0.001
Depression, moderate-severe (MDI) pct.	36.5	9.6	0.02*
SCL92 depression, units (SD)	2.52 (0.76)	0.83 (0.68)	<0.001
Stress score, units (SD)	2.55 (0.78)	1.46 (0.72)	<0.001
Physiological measurements			
Blood pressure			
Sys BP mmHg (SD)	126.74 (14.6)	126.67 (13.3)	0.90
Dia BP mmHg (SD)	77.14 (10.3)	76.78 (10.2)	0.67
Anthropometric measures			

Waist/hip ratio cm/cm(SD)	0.88 (0.07)	0.89 (0.1)	0.59
BMI kg/m^2(SD)	25.20 (4.9)	25.30 (5.1)	0.80
Blood measures			
BDNF mmol/l (SD)	1.09 (0.9)	1.87 (2.6)	<0.001
Cholesterol mmol/l (SD)	5.33 (0.9)	5.24 (1.1)	0.14
Fibrinogen mmol/l (SD)	9.31 (1.6)	8.64 (1.7)	0.003
HbA$_{1C}$ pct. (SD)	5.38 (0.26)	5.34 (0.3)	0.33
ACR nmol/l (SD)	7.40 (8.1)	2.70 (7.0)	0.02

p: Pair-wise t-test

*: Chi^2-test

SCL92: Symptom Check List 92

ACR: Awakening Cortisol Response, Salivary cortisol ½ hour after awakening- salivary cortisol at awakening.

Table 2. Standardized beta coefficients and p-values of multiple linear regression analyses of the relation between BDNF and symptoms and physiological measures

	Regression coefficient for Log BDNF at baseline adjusted for age, gender, and BMI	p-value	Regression coefficient for difference between Log BDNF after and before treatment adjusted for Log BDNF at baseline age, gender and BMI	p-value
Exercise score (ab)	0.16	0.24	0.03	0.81
Exercise score increase			0.18	0.18
SCL92 depression score (ab)	0.15	0.27	-0.24	0.09
SCL92 depression score decrease			-0.31	0.04
Stress score (ab)	0.07	0.65	0.17	0.24
Stress score decrease			-0.06	0.66
Workability score (ab)	0.05	0.77	-0.25	0.08
Workability score increase			-0.24	0.10
Log Systolic BP mmHg	0.29	0.07	0.07	0.63
Log Diastolic BP mmHG	0.16	0.39	0.11	0.47
BMI *kg/m^2	0.40	0.02	-0.04	0.81
Log Cholesterol mmol/l	0.21	0.22	0.10	0.48
Log Fibrinogen mmol/l	0.29	0.17	-0.07	0.72
Log HbA$_{1C}$ pct.	0.01	0.95	-0.03	0.86
Log ACR nmol/l	-0.03	0.86	0.06	0.67

*: not adjusted for BMI

(ab) : at baseline

SCL92: Symptom Check List 92

WAI: Work-ability index

ACR: Awakening Cortisol Response

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