Increased BDNF serum concentration in fibromyalgia with or without depression or antidepressants

Christoph Laske a,*, Elke Stransky a, Gerhard W. Eschweiler a,b, Reinhold Klein c, Andreas Wittorf a, Thomas Leyhe a,b, Elke Richartz a, Niklas Köhler a, Matthias Bartels a, Gerhard Buchkremer a, Klaus Schott a

a Department of Psychiatry and Psychotherapy, University of Tuebingen, Osianderstrasse 24, D-72076 Tuebingen, Germany
b Geriatric center, University of Tuebingen, Germany
c Department of Internal Medicine, University of Tuebingen, Germany

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Abstract

Fibromyalgia (FM) is still often viewed as a psychosomatic disorder. However, the increased pain sensitivity to stimuli in FM patients is not an “imagined” histrionic phenomena. Pain, which is consistently felt in the musculature, is related to specific abnormalities in the CNS pain matrix. Brain-derived neurotrophic factor (BDNF) is an endogenous protein involved in neuronal survival and synaptic plasticity of the central and peripheral nervous system (CNS and PNS). Several lines of evidence converged to indicate that BDNF also participates in structural and functional plasticity of nociceptive pathways in the CNS and within the dorsal root ganglia and spinal cord. In the latter, release of BDNF appears to modulate or even mediate nociceptive sensory inputs and pain hypersensitivity. We were interested, if BDNF serum concentration may be altered in FM. The present pilot study assessed to our knowledge for the first time BDNF serum concentrations in 41 FM patients in comparison to 45 age-matched healthy controls. Mean serum levels of BDNF in FM patients (19.6 ng/ml; SD 3.1) were significantly increased as compared to healthy controls (16.8 ng/ml; SD 2.7; \( p < 0.0001 \)). In addition, BDNF serum concentrations in FM patients were independent from age, gender, illness duration, preexisting recurrent major depression and antidepressive medication in low doses. In conclusion, the results from our study indicate that BDNF may be involved in the pathophysiology of pain in FM. Nevertheless, how BDNF increases susceptibility to pain is still not known.

Keywords: Brain-derived neurotrophic factor (BDNF); Fibromyalgia (FM); Controls; Pain

1. Introduction

Fibromyalgia (FM) is a generalized chronic pain disorder of the musculoskeletal system associated with disturbances in serotonin metabolism. The aetiology and pathogenesis of FM has not yet been fully understood. In the last years there is growing evidence that biological as well as psychosocial stress play a key-role in the pathogenesis of FM. According to the classification criteria of the American College of Rheumatology (1990), diagnosis of FM is based on the examination of the so-called 18 tender points which are sensitive to pressure (Wolfé et al., 1990). The prevalence of FM is estimated to range between 1.3% and 4.8% in the general population (Biever et al., 2004). FM coincidences frequently with psychiatric disorders such as major depression, dysthymia, anxiety, and somatoform disorders (Epstein et al., 1999; McBeth and Silman, 2001).

Brain-derived neurotrophic factor (BDNF) is a member of the nerve growth factor family. BDNF and seroto-
nin (5-hydroxytryptamine, 5-HT) co-regulate one another and play an important role in neuronal survival and synaptic plasticity in the central nervous system (CNS) (Mattson et al., 2004). Recent findings have suggested an involvement of BDNF in the pathogenesis of major depression (Angelucci et al., 2004; review in Laske and Eschweiler, in press), which is often associated with pain syndrome (Ohayon and Schatzberg, 2003). In addition, BDNF is a mediator of pain in the peripheral nerve system (PNS) (Siuciak et al., 1994; Malcangio and Lessmann, 2003; Lever et al., 2003). To our knowledge, BDNF serum concentrations have not yet been described in patients with FM.

Pathophysiological loops and key players in FM are mediated by BDNF (as regards serotonin, depression and pain). This has erased our interest to examine BDNF serum concentration in patients suffering from FM with or without depression or antidepressants in comparison to healthy controls.

2. Materials and methods

2.1. Subjects and clinical assessment

FM patients \( (n = 41, 36 \text{ females and } 5 \text{ males, mean age of } 51.6 \text{ years}) \) were recruited from the Rheumatology Outpatient Clinic of the Department of Internal Medicine. Diagnosis was met according to the criteria of the American College of Rheumatology (Wolfe et al., 1990). 6/41 FM patients met the diagnostic criteria for recurrent major depression, but were not in a depressive mood state at the time point of blood collection for determination of BDNF in serum. In addition, 24/41 FM patients received antidepressive medication in low analgetic doses (amitriptyline \( \leq 10 \text{ mg}, \) fluoxetine \( \leq 20 \text{ mg}, \) doxepin \( \leq 10 \text{ mg} \) ). Patients with acute depressive episode according to the DSM-4 and ICD-10 classification criteria with BDI and HAM-D scores \( > 10 \) were excluded from the study. In addition, 45 healthy volunteers as control group (42 females and 3 males, mean age of 50.8 years) were matched. The control group had a careful exploration of the medical history. None of the control subjects had a known major depression or depressive episodes or an use of antidepressants. In addition, none of the FM patients and healthy controls received an estrogen replacement therapy. The regional ethical committee approved the study and written informed consent was obtained from each individual.

2.2. Measurement of BDNF serum concentration

Peripheral venous blood was sampled into serum tubes between 8:00 and 9:00 a.m. Tubes were immediately immersed in melting ice. To minimize the source of platelets, we centrifuged the serum within 30 min after gaining and stored it at \(-18^\circ C\) until further analysis. Serum levels of BDNF were measured using an enzyme-linked immunosorbsent assay (ELISA) kit (R&D Systems GmbH Wiesbaden-Nordenstadt, Germany) according to the manufacturer’s instructions.

All samples and standards were measured in duplicates, and the means of the duplicates were used for statistical analyses. The detection limit was 62.5 pg/ml. The intra- and interassay coefficients of variation were \(< 10\%\).

2.3. Statistical analysis

The data were presented as the mean \( \pm SD\). The statistical analysis of differences between the two groups was performed using the two-tailed \( t\)-test. The correlation between two variables was determined by using Kendall–Tau-\( b\)-test. Significance for the results was set at \( p < 0.05\). All statistical analyses were carried out using the statistical software package SPSS 12.0® (Munich, Germany).

3. Results

3.1. In vivo concentrations of BDNF in serum

As shown in Table 1, patients with fibromyalgia and healthy controls were comparable regarding number, age and gender.

As shown in Fig. 1, mean serum levels of BDNF in FM patients (19.6 ng/ml; SD 3.1) were significantly increased as compared to healthy controls (16.8 ng/ml; SD 2.7; \( p < 0.0001\)).

3.2. Effect of illness duration on BDNF serum concentration in FM

In FM patients, we found no significant correlation between BDNF serum concentration and mean illness duration (\( r = 0.1; p = 0.3\)).

3.3. Effect of preexisting recurrent major depression or low dose antidepressive medication on BDNF serum concentration in FM

In FM patients, we found no significant differences of mean BDNF serum concentrations between patients with \( (n = 6; 19.7 \text{ ng/ml; SD 3.1}) \) and without recurrent depression.

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>FM patients ( (n = 41) )</th>
<th>Control group ( (n = 45) )</th>
<th>( p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>5/36</td>
<td>3/42</td>
<td>0.5</td>
</tr>
<tr>
<td>Age ( \text{(mean} \pm SD) ) (years)</td>
<td>51.6 ± 9.5</td>
<td>50.8 ± 9.8</td>
<td>0.7</td>
</tr>
<tr>
<td>BDNF serum concentration ( \text{in ng/ml (mean} \pm SD) )</td>
<td>19.6 ± 3.1</td>
<td>16.8 ± 2.7</td>
<td>(&lt; 0.0001)</td>
</tr>
</tbody>
</table>
major depression (n = 35; 19.7 ng/ml; SD 3.1; p = 1.0) as well as with (n = 24; 20.0 ng/ml; SD 3.2) or without antidepressive medication in low analgetic doses (n = 17; 19.2 ng/ml; SD 2.9; p = 0.4).

3.4. Effect of age on BDNF serum concentration

There was no significant difference in age between FM patients and control group. We found no significant correlation between BDNF serum concentration and age in FM patients (r = 0.1; p = 0.2) and healthy controls (r = 0.1; p = 0.3).

3.5. Effect of gender on BDNF serum concentration

Comparing BDNF serum values in male and female subjects, we found no significant gender differences in FM patients (n = 5; 19.3 ng/ml; SD 2.7; n = 36; 19.7 ng/ml; SD 3.2; p = 0.8) and healthy controls (n = 3; 15.0 ng/ml; SD 4.6; n = 42; 16.9 ng/ml; SD 2.6; p = 0.2).

4. Discussion

In this pilot study, we investigated for the first time BDNF serum levels of patients with fibromyalgia syndrome compared to healthy controls. Mean serum levels of BDNF in FM patients were significantly increased as compared to healthy controls (p < 0.0001), but independent from age, gender, illness duration, preexisting recurrent major depression or antidepressive medication in low analgetic doses. Our result is in line with a previous study, showing increased concentrations of nerve growth factor (NGF) in cerebrospinal fluid of patients with fibromyalgia (Giovengo et al., 1999). BDNF and NGF belong to the family of neurotrophic factors.

4.1. Pain and neuronal plasticity

The pathophysiology of pain involves the concepts of neuronal plasticity at all levels of the neuroaxis (brain, spinal cord and nociceptor neurons). Pain can be understood as an alarm signal to be aware of nocious stimuli in order to reduce movements, decrease metabolism and to increase healing processes. Numerous modulatory mechanisms for pain at all levels of the nervous system have been postulated including alterations of BDNF as a central modulator of neural plasticity. These mechanisms are involved in the perception of pain and associated emotional and behavioral phenomena.
4.1. The effect of pain on BDNF expression in the brain

In animal models, BDNF mRNA expression in hippocampus has been demonstrated to be decreased under condition of pain similar to stress and depression (Duric and McCarson, 2005). In contrast, rats suffering from chronic pain showed increased BDNF levels in the frontal cortex (Xu et al., 2000).

4.1.2. Involvement of BDNF in neuropathic pain

BDNF heterozygous (±) knockout mice exhibited a significant suppression of nerve ligation-induced thermal hyperalgesia compared with wild-type mice (Yajima et al., 2005). Conflicting results exist as regards production (Yajima et al., 2005) or reduction (Lever et al., 2003) of thermal hyperalgesia after intrathecal injection of BDNF. The effects of BDNF are mediated through binding to high-affinity trkB receptors. In chronic pancreatitis, BDNF has been demonstrated to be increased and associated with pain in pancreatic cells including nerve fibers and ganglia cells (Zhu et al., 2001).

4.2. Potential sources of BDNF in serum and plasma and influencing factors

The first evidence for the presence of BDNF in human serum and plasma emerged a decade ago (Rosenfeld et al., 1995). The average serum BDNF levels were more than 100-fold higher than the plasma BDNF levels (Radka et al., 1996). This difference is due to the degranulation of platelets during clotting process (Fujimura et al., 2002). Human platelets contain large amounts of BDNF protein (Pliego et al., 1997; Yamamoto and Gurney, 1990). It has been demonstrated, that the amount of BDNF in serum is similar to that in washed platelet lysates (Fujimura et al., 2002). Thus, the difference between serum and plasma BDNF levels appear to reflect the quantity of BDNF stored in circulating platelets.

The cellular sources of BDNF in human plasma have not yet been clearly defined. Potential sources are vascular endothelial and smooth muscle cells (Nakahashi et al., 2000; Donovan et al., 1995). In addition, activated macrophages or lymphocytes may be the source of BDNF (Braun et al., 1992; Kerschensteiner et al., 1999). Moreover, there is experimental evidence that BDNF can cross the blood-brain barrier (Poduslo and Curran, 1996; Pan et al., 1998). An animal-study found a positive correlation between serum and cortical BDNF levels (Karege et al., 2002a). According to these results, BDNF changes within the CNS might be paralleled by changes of BDNF plasma and serum levels. Nevertheless, data suggest, that the majority of BDNF in plasma and serum may be of peripheral origin as described above.

4.2.1. Influence of activated platelets on pain perception

Activation of platelets may contribute to nociceptor excitation and pain, since platelets store and, upon stimulation, release potential algogenic substances such as serotonin, histamine, precursor molecules of bradykinin and BDNF (Ringkamp et al., 1994). In this context, platelets are known to be activated in patients with migraine (Zeller et al., 2005). Since platelets are a major source of BDNF in serum, it may be reasonable to assume, that platelets are also activated in fibromyalgia, which could explain our result with a significant increase of BDNF serum concentration in those patients.

4.2.2. Hypocortisolism in fibromyalgia

Hypocortisolism has been observed in patients with different stress-related disorders such as FM, chronic fatigue syndrome, and post-traumatic stress disorder (Fries et al., 2005). As glucocorticoids suppress BDNF levels in the brain (Garcia, 2002) and blood (Lommatzsch et al., 2005a), hypocortisolism could favour increased BDNF serum concentration in FM. Interestingly, the constellation with increased BDNF and low cortisol serum levels in FM patients without depressive symptoms is in contrast to the findings in major depression. Unfortunately, cortisol levels are not given in our patients.

4.2.3. Inflammatory cytokines in fibromyalgia

Blood levels of the cytokines interleukin (IL)-6 and IL-8 are increased in FM patients (Wallace et al., 2001). IL-6 enhances BDNF secretion in monocytes (Schulte-Herbruggen et al., 2005). As IL-6 induces hyperalgesia, fatigue and depression and IL-8 promotes sympathetic pain, it may be hypothesized that they play an aetiopathogenetic role in fibromyalgia and in modulating FM symptoms.

4.2.4. No effect of illness duration on BDNF serum values in FM

The lack of correlation of BDNF serum values with illness duration in FM indicates, that increased BDNF serum concentration in FM is rather due to peripheral pain mediation than to an adaptation to chronic pain.

4.2.5. No effect of preexisting recurrent major depression or low dose antidepressive medication on BDNF serum concentration in FM

In major depression, BDNF serum concentration is known to be decreased (Karege et al., 2002b; Shimizu et al., 2003; Karege et al., 2005), and increased towards (partial) normalisation under antidepressive medication (Shimizu et al., 2003; Aydemir et al., 2005; Gervasoni et al., 2005).

In the present study, comparisons of FM patients with and without recurrent major depression as well as with or without antidepressive medication in low analgetie doses revealed no statistical significant differences, indicating, that the found increase of BDNF serum...
concentrations in FM patients is independent of preexisting major depression or antidepressive low dose medication. In addition, none of the FM patients and control subjects included in the study had a clinically relevant depressive episode.

4.2.6. No effect of age or gender on BDNF serum concentration

Lommatzsch et al. (2005b) reported that in 140 healthy, non-allergic adults (20–60 years old), BDNF levels in plasma decreased significantly with increasing age, whereas BDNF levels in platelets did not. When matched for weight, there were no significant gender differences regarding BDNF plasma levels.

The results from our study may not be biased by an age or gender effect, as there were no significant differences between FM and control group as regards age and gender ratio, nor did we find a significant correlation between BDNF serum concentration and age or a significant difference of mean BDNF serum values between male and female subjects in both groups. Thus, even though we found significantly increased BDNF serum values in FM patients, estrogen has been demonstrated in animals to increase nociception-evoked BDNF mRNA levels in various brain regions (Allen and McCarson, 2005) and FM shows a significant female predominance (Gran, 2003), we could not find in the present study a significant influence of gender on BDNF serum levels.

4.3. Conclusions

Data from literature suggest a role of BDNF for peripheral and central pain modulation. The results from our study indicate that an increase of BDNF in serum may be involved in the pathophysiology of pain in FM. Even though depression is a common psychiatric disorder associated with FM, our finding of increased BDNF serum concentrations in FM is in contrast to the known decrease of BDNF serum concentrations in major depression. In addition, age, gender, illness duration, preexisting recurrent major depression or antidepressive medication in low analgetic doses showed no significant influence on BDNF serum concentrations in FM patients. The lack of correlation of BDNF serum values with illness duration in FM indicates, that increased BDNF serum concentration in FM is rather due to peripheral pain mediation than to an adaptation to chronic pain. Nevertheless, how BDNF increases susceptibility to pain is still not known. Further studies have to follow, especially including other syndromes with acute or chronic pain and examining the correlation between BDNF, platelet activation markers, Cortisol, IL-6 and severity of clinical pain to elucidate the sources and the role of BDNF in these diseases.

References


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