Journal of Psychiatric Research 59 (2014) 1–7

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Fast BDNF serum level increase and diurnal BDNF oscillations are associated with therapeutic response after partial sleep deprivation

Maria Giese [a, e], Johannes Beck [b], Serge Brand [b], Flavio Muheim [b], Ulrich Hemmeter [c], Martin Hatzinger [d], Edith Holsboer-Trachsler [b], Anne Eckert [a, e, *]

[a] Neurobiology Laboratory for Brain Aging and Mental Health, Psychiatric Clinics of the University of Basel, Basel, Switzerland
[b] Center for Affective, Stress and Sleep Disorders, Psychiatric Hospital of the University of Basel, Basel, Switzerland
[c] Psychiatric Service Center St. Gallen, Wil, Switzerland
[d] Psychiatric Services Solothurn, Department of Adult Psychiatry, Solothurn, Switzerland
[e] Transfacultary Research Platform, Molecular & Cognitive Neuroscience, University of Basel, Basel, Switzerland

ARTICLE INFO

Article history:
Received 9 April 2014
Received in revised form
2 September 2014
Accepted 4 September 2014

Keywords:
BDNF
Sleep deprivation
Depression
Therapy response

ABSTRACT

Objective: Preclinical and clinical studies support a role for brain-derived neurotrophic factor (BDNF) in the pathophysiology of stress-related mood disorders. Furthermore, BDNF seems to be linked to antidepressant action. Available pharmacological treatments for depression are characterized by significant limitations with low efficacy and a major delay until treatment response. This demonstrates the urgent need for more efficient and fast-acting antidepressants. Besides ketamine, sleep deprivation (SD) as well as partial sleep deprivation (PSD) are effective and fast-acting antidepressant methods. However, the underlying molecular mechanisms of SD are not well understood; especially possible mechanisms explaining the rapid, but transient antidepressant effect of SD are unknown.
Methods: We evaluated serum BDNF from 28 patients suffering from major depressive disorder (MDD), who were naïve to SD therapy at seven different time points within a 32 h time window before (day 0) and after PSD (day 1). PSD-response was assessed by 6-Items of the *Hamilton Depression Rating Scale* (HDRS) before (day 0) and at follow-up after 2 weeks (FU2).
Results: PSD induced a very fast increase in BDNF serum levels at day 1 which parallels clinical findings, since levels increased with decreasing depression scores in all participants. Notably, responders showed a significant diurnal BDNF serum variation not only after PSD but already before PSD treatment, while diurnal profile of serum BDNF from non-responders did not vary.
Conclusions: The elasticity in diurnal serum BDNF variation is associated with favourable treatment response to PSD in patients suffering from MDD. Therefore, a normalized BDNF serum profile which oscillates in a circadian fashion seems to precede, rather than follow a favourable treatment outcome in depressed patients. Furthermore the fast increase of BDNF is comparable to effects seen with ketamine infusion.

1. Introduction

There is growing evidence that both the pathophysiology and the treatment of major depressive disorder (MDD) are linked to alterations of neurotrophic factor expression such as brain-derived neurotrophic factor (BDNF) in various brain regions, including the hippocampus (Duman and Monteggia, 2006). These can involve reversible changes, which explain the link between depressive episodes and subsequent recovery with neuronal plasticity. Exposure to stress, which is related with, but not required for the onset of MDD (Kendler et al., 1999) in humans, advances or worsens depressive episodes (Gold and Chrousos, 2002). Preclinical and clinical studies demonstrate that reductions of the total volume of neurons and neuronal loss occur in stress and depression in the adult hippocampus (Warner-Schmidt and Duman, 2006). These hippocampal alterations can be reversed by chronic antidepressant treatment (Warner-Schmidt and Duman, 2006).

Under chronic stress conditions the hypothalamic–pituitary–adrenal (HPA) axis regulation may become deregulated. Such HPA

* Corresponding author. Neurobiology Laboratory for Brain Aging and Mental Health, Transfaculty Research Platform Cognitive & Molecular Neuroscience, University of Basel, Psychiatric Clinics of the University of Basel, Wilhelm Klein-Strasse 27, 4012 Basel, Switzerland. Tel.: +41 61 325 5487; fax: +41 61 325 5577.
E-mail address: Anne.Eckert@upkbs.ch (A. Eckert).

http://dx.doi.org/10.1016/j.jpsychires.2014.09.005

axis alterations during an acute depressive episode and its normalization after successful treatment are major findings in patients with MDD (Holsboer-Trachsler and Seifritz, 2000; Holsboer-Trachsler et al., 1991; Holsboer and Barden, 1996).

BDNF has received much attention among candidate downstream effectors involved in antidepressant-mediated hippocampal neurogenesis. Indeed, chronic treatment with different classes of classic antidepressants (e.g. SSRIs and NSRIs) seems to be associated with increased BDNF expression in the hippocampus and neurogenesis (Duman and Monteggia, 2006); likewise, a direct infusion of BDNF into the hippocampus was sufficient to produce an antidepressant-like action in mouse models of depression (Berman et al., 2000; Shirayama et al., 2002). Taken together, multiple neurobiological mechanisms seem to be involved in mediating the therapeutic effects of antidepressant therapy. Some of these mechanisms seem to play a role for neuroprotection and neurogenesis. The complexity could explain the slow onset of action in antidepressant treatments (Duman, 2004). Furthermore, most currently available antidepressants primarily target the noradrenergic and serotonergic systems.

Recent evidence implicates a glutamatergic dysregulation (Berman et al., 2000; Zarate et al., 2006) introducing the N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine, which reveals rapid antidepressant efficacy at low doses (Berman et al., 2000). In particular, patients with treatment-resistant depression benefit from sub-anaesthetic doses of ketamine with quick and persistent antidepressant effects (Murrough et al., 2013; Zarate et al., 2006). It is suggested, that the NMDA receptor blockade leads to an up-regulation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor expression and subsequent activation of the intracellular mammalian target of rapamycin (mTOR) cascade involved in ketamine's antidepressant action (Li et al., 2010). This, in turn, is followed by an increase of synaptogenesis, which might be mirrored by the neuroplasticity marker BDNF (Autry et al., 2011; Duman and Li, 2012).

BDNF and its neurotrophic functions are connected particularly to neuronal survival, memory, learning, appetite and sleep (Duman et al., 2000; Faraguna et al., 2008), leading to the neurotrophin hypothesis which claims that stress-related mood disorders result from stress-induced decreases in BDNF expression (Duman et al., 1997). Successful antidepressant treatment is able to reverse this deficit and is mediated by an increase in BDNF levels (Duman et al., 1997). Cellular and molecular mechanisms underlying a rapid antidepressant effect, like those shown for ketamine, seem to be complex and indicate that neuronal plasticity is involved (Duman and Li, 2012). Furthermore, Haile et al. demonstrated a rapid increase of plasma BDNF levels 240 min after intravenous infusion (Haile et al., 2014).

Circulating BDNF is found in both human serum and plasma and a large amount is stored in human platelets (Fujimura et al., 2002). However, the source of peripheral BDNF is not yet clear. Since the protein can cross the blood brain-barrier in both directions, circulating BDNF is correspondingly associated with cortical BDNF concentrations (Karege et al., 2002) proposing peripheral BDNF as a promising candidate biomarker in the association with depression and antidepressant treatment response. Several studies showed that serum BDNF levels in drug-free MDD patients were significantly lower compared to healthy subjects (Shimizu et al., 2003). Other studies reported that plasma BDNF levels were lower in drug-free MDD patients (Karege et al., 2005; Lee et al., 2007). Some clinical studies have evaluated the changes of plasma or serum BDNF levels before and after antidepressant treatments among MDD patients and most studies report increases of BDNF levels after antidepressant treatment (Brunoni et al., 2011; Piccinni et al., 2008), although very recent data indicate that the increase in serum levels of BDNF during antidepressant treatment appears to be confined to some but not all antidepressants (Molendijk et al., 2011). Nevertheless, different antidepressant strategies including antidepressant drugs and electroconvulsive therapy (ECT) were associated with an increase of BDNF levels (Conti et al., 2007). Moreover, some studies provide important evidence that an antidepressant-induced increase in BDNF levels is more prominent in responders than non-responders (Lee and Kim, 2008) or even exclusively restricted to responders (Lee and Kim, 2008). Despite current findings of increased blood BDNF levels in long-term treatment interventions, the underlying mechanism of this systemic neurotrophic increase is not clarified. It could be a matter of downstream signalling initiated by distinct classes of antidepressants like SSRIs and NSRIs, independent of neurogenesis, or related to an adaptation device, which involves neuronal plasticity and neurogenesis, altering synaptic transmission.

Sleep deprivation (SD) is a clinically well-documented, robust, and fast-acting method for the treatment of severely depressed patients (Giedke and Schwarzler, 2002). Other than SD the whole night, partial sleep deprivation (PSD) in the second half of the night has also shown comparable antidepressant effects in patients with major depression (Giedke and Schwarzler, 2002). However, the underlying molecular and cellular mechanisms of SD are not well understood, especially those explaining the rapid, although transient, antidepressant effect of SD, since a relapse into depression occurs in most patients following the recovery night (Beck et al., 2010). Recent evidence indicates that an up-regulation of BDNF gene expression after SD in rats might be relevant for its mode of action (Conti et al., 2007; Hairston et al., 2004). Moreover, evidence also supports a role for BDNF in the modulation and mediation of circadian rhythms which seem to be disturbed in mood disorders. Interestingly, the presence of a diurnal BDNF rhythm was also recently demonstrated in healthy humans where plasma BDNF displayed highest concentrations in the morning, followed by a substantial decrease throughout the day, and the lowest values at midnight (Begliuomini et al., 2008). However, diurnal variation of blood BDNF was neglected until now in studies investigating MDD patients.

In the present study, we wanted to explore the effect of partial sleep deprivation (PSD) as an alternative antidepressant intervention on serum BDNF levels. Therefore, we investigated the acute effect of PSD on serum BDNF levels within a time window of 12 h during the day after PSD night in MDD patients. Furthermore, due to the fact that BNDF levels oscillate in the periphery in a circadian fashion, we monitored daily variations in serum BDNF levels. In addition, we investigated whether baseline BDNF levels before PSD and treatment-associated changes are related to clinical and depressive symptoms and/or treatment response. Thus, this study was specifically designed to obtain, for the first time, results on potential fast-acting effects of PSD on BDNF and, concurrently, on daily peripheral BDNF profiles in MDD patients to explore the hypothesis if a diurnal BDNF pattern might be associated with prediction of antidepressant therapy response at a very early stage of intervention. This is in contrast to all other published studies where treatment related BDNF changes were collected and analyzed no earlier than one to six weeks of antidepressive therapy.

2. Material and methods

2.1. Subjects and study design

Twenty-eight in- and out-patients (13 men, 15 women, age 45.1 ± 12.1 years; range 19–65 years) with the diagnosis of major depression (DSM-IV and ICD-10) and according to the SCID

(Wittchen et al., 1987) participated in this study as previously published (Beck et al., 2010). Study design details, inclusion and exclusion criteria were previously described in details by Beck et al. (2010). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki and the study protocol was approved by the local ethics committee. All patients gave written informed consent after complete description of the study. Inclusion criteria comprised an HDRS-score of ≥15 and the presence of significant daytime sleepiness and severity of depression was evaluated by the 21-Item version of *Hamilton Depression Rating Scale* (HDRS) (Hamilton, 1967). In brief, all participants were naïve to sleep deprivation therapy and randomly assigned to either additional modafinil or placebo treatment, to test the effect of modafinil (200 mg/d) on microsleep during PSD (Beck et al., 2010). According to ethical considerations, all patients were treated with a monotherapy of 30 mg mirtazapine daily at 9 pm throughout the study, which started already 1 week before PSD intervention to ensure an adequate stabilization period in all patients. PSD-response was assessed by 6-items of the HDRS covering the items depressive mood, feelings of guilt, working and leisure activities, depressive inhibition, psychological symptoms of anxiety, and somatic symptoms (Bech et al., 1975). This subscale has been applied to assess changes of depression in particular during PSD since sleep-related items – present in the 21-items version – which could lead to a biased response, are excluded. An improvement of at least 30% from baseline was required to determine a PSD response. The modafinil group consisted of eight men and six women, age 46.2 ± 12.2 years ($n = 14$, HDRS 21-items before PSD 21.71 ± 6.56 and at day after PSD 15.71 ± 9.12; 6-items before PSD 9.43 ± 2.79 and at day after PSD 6.50 ± 3.69) and the placebo group of five men and nine women, age 43.9 ± 12.2 years ($n = 14$, HDRS 21-items before PSD 21.79 ± 4.72 and at day after PSD 12.64 ± 8.38; 6-items before PSD 8.71 ± 2.40 and at day after PSD 5.07 ± 3.85; values of all ratings were not different compared to modafinil) (Beck et al., 2010). Compared to placebo, modafinil was efficient in reducing daytime microsleep following partial sleep deprivation but did not enhance the antidepressive effects of PSD and did not stabilize antidepressive effects over two weeks (Beck et al., 2010).

2.2. Serum sampling

For serum sampling blood was obtained in a serum separator tube from the antecubital vein at seven different time points. Day 0 (before PSD) at 8 am ($t1$), 2 pm ($t2$) and 8 pm ($t3$) for baseline and day 1 at 1.30 am ($t4$) during PSD, 8 am ($t5$), 2 pm ($t6$) and 8 pm ($t7$) after PSD (Fig. 1). After 30 min of clotting time, whole blood was centrifuged at 1000 × g for 30 min to separate the serum. Serum was collected in aliquots to avoid several freezing cycles and kept at −80 °C before assaying.

2.3. Measurement of serum BDNF levels

Serum BDNF levels were assessed with an enzyme-linked immunoabsorbant assay (ELISA) kit (Promega BDNF Emax®, Madison, Wis., United States). Samples were appropriately diluted (between 1:100 and 1:150) and detection of total soluble BDNF was carried out in an antibody sandwich format as described in the manufacturer's protocol. The absorbance was measured within 30 min in a microplate reader set at 450 nm, and a correction wavelength set to 690 nm, to determine BDNF concentrations according to the standard curve. All assays were carried out in duplicate and means were calculated.

2.4. Questionnaires to assess potential confounders

Besides a sociodemographic questionnaire to assess sex, age and BMI, participants had to indicate substance consumption, which could interfere with biological analyses.

2.5. Statistical analysis

Analysis of variance (Two-way ANOVA) was used for multiple group parametric comparisons with *posthoc* Bonferroni-corrected *t*-tests. Associations between variables were computed with Pearson's correlations. To compare the effect size Cohen's *d* was calculated to compare serum BDNF values among subjects, responders and non-responders. The level of significance was set at $p \leq 0.05$.

Preliminary calculations revealed that BDNF serum levels were not associated with sex and age ($r_s < 0.20$, $p > 0.35$) and smoking (all $ts < 1.56$, $p > 0.13$). As a result, sex, age and smoking were not entered as co-variates.

3. Results

3.1. Daily serum BDNF profile from MDD patients before and after PSD

Pre-PSD at baseline (day 0), a daily variation pattern could be detected in serum BDNF levels from all participants ($n = 28$) which decreased during the day starting with the highest concentration in the morning until BDNF concentrations reached their lowest level after midnight (Fig. 2A). Post-PSD, serum BDNF levels of day 1 were increased to 10.4% (at 8 am), 16.2% (at 2 pm) and 20.7% (at 8 pm)

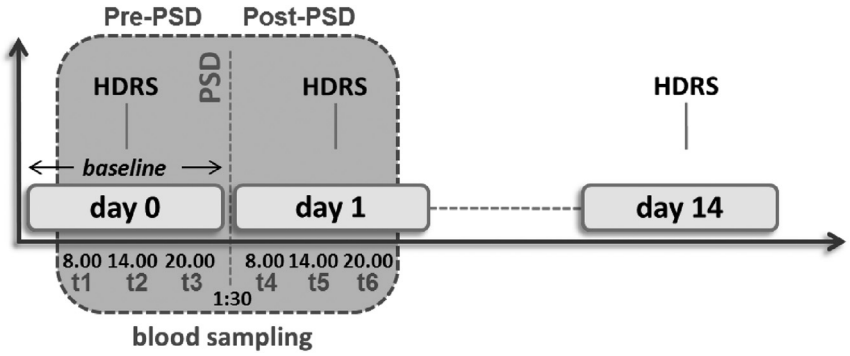

Fig. 1. Study design and serum sampling. Blood was drawn at day 0 (baseline) before PSD at 8 am ($t1$), 2 pm ($t2$), 8 pm ($t3$) and at 1:30 am ($t4$), 8 am ($t5$), 2 pm ($t6$) and 8 pm ($t7$) day 1 after PSD. Placebo controlled morning treatment with the stimulant modafinil started during PSD and was maintained over 14 days. PSD-response was assessed by 6-items of the *Hamilton Depression Rating Scale* (HDRS) at days 0, 1 as well as after 2 weeks (day 14, FU2) of on-going treatment.

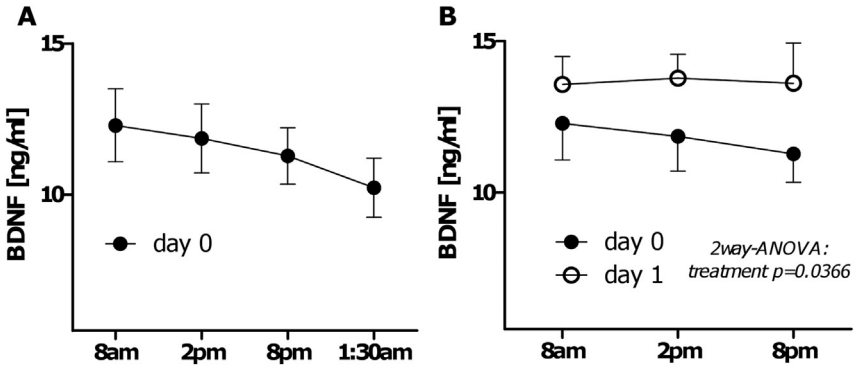

Fig. 2. Daily variation of serum BDNF levels. (A) Baseline serum BDNF levels (means ± SEM) decreased during the day starting with the highest concentration in the morning (8 am, $t1$) until they reached the lowest level after midnight (1:30 am, $t4$) in all patients. (B) After PSD serum BDNF levels (means ± SEM) were elevated throughout day 1, relative to levels at baseline (day 0) of 10.4% at 8 am, 16.2% at 2 pm and 20.7% at 8 pm. This difference in BDNF levels between baseline and day 1 was statistically significant ($F(1) = 4.46$; $p = 0.037$).

respectively, relative to the corresponding pre-PSD BDNF levels (Two-way ANOVA: treatment effect $F(1) = 4.46$; $p = 0.037$) (Fig. 2B).

3.2. No effect of additional treatment with modafinil on BDNF levels

To evaluate the effect of additional modafinil treatment starting at 1.30 am during PSD we compared serum BDNF levels of day 1 between patients with modafinil and placebo treatment. A series of Chi-square tests revealed no statistically significant associations between treatment condition and response (response day 1: $\chi^2(1, n = 25) = 0.24$, $p = 0.62$; response day 2: $\chi^2(1, n = 25) = 0.05$, $p = 0.82$; response FU1 $\chi^2(1, n = 25) = 0.27$, $p = 0.87$; response FU2: $\chi^2(1, n = 24) = 1.34$, $p = 0.27$).

3.3. Post-PSD BDNF and therapy response after 14 days

In a further step, we explored to what extent post-PSD serum BDNF levels of day 1 exhibited similar diurnal pattern characteristics for patients identified as long-term responders (35,7%, $n = 10$) and non-responders (64.3%, $n = 18$) (long-term HDRS-6 ratings after two weeks [FU2]; (Beck et al., 2010)) (Fig. 3A, B). PSD-response was assessed by a subscale of 6-items of the HDRS to assess changes of depression in particular during PSD, since sleep-related items, which are designedly excluded in this subscale, could lead to a biased response. Again, we recognized a prominent daily change of post-PSD serum BDNF levels, but only for long-term responders. Thus, FU2 responders showed significantly higher serum BDNF levels post-PSD on day 1 at 8 am ($t5$) ($t = 2.994$, $p = 0.007$) and 2 pm ($t6$) ($t = 2.851$, $p = 0.010$) compared to non-responders (Fig. 3B) leading to a significant group effect ($F(1) = 10.56$; $p = 0.002$). Furthermore, effect size calculations emphasized higher BDNF levels in FU2-responders at 8 am ($t5$) ($d = 1.54$) and 2 pm ($t6$) ($d = 1.37$) on day 1, relative to non-responders. Importantly, there was no observable diurnal baseline BDNF pattern for patients specified as non-responders after 2 weeks (Fig. 3B). However, a trend toward a slight diurnal change was recognizable (Fig. 3B), which was clearly less pronounced compared to responders. In agreement with other findings using different antidepressive treatment approaches (Dell'Osso et al., 2010; Okamoto et al., 2008) we could show a significant correlation of HDRS-6 improvement with increased post-PSD serum BDNF levels at 8 am ($t5$) in all patients after 2 weeks ($r_p = -0.612$; $p = 0.0025$) (Fig. 3C).

3.4. Pre-PSD BDNF and therapy response after 14 days

To explore if a diurnal variation could precede PSD we investigated in an additional step whether serum BDNF levels at baseline (day 0) exhibited diurnal pattern characteristics for patients identified as long-term responders (35,7%, $n = 10$) and non-responders (64,3%, $n = 18$) (Beck et al., 2010) (Fig. 4A, B). PSD-response was assessed by a subscale of 6-items of the HDRS to evaluate changes of depression particularly during PSD, since sleep-related items, which are excluded in this subscale, could lead to a biased response. Again, BDNF levels at baseline were higher in long-term responders,

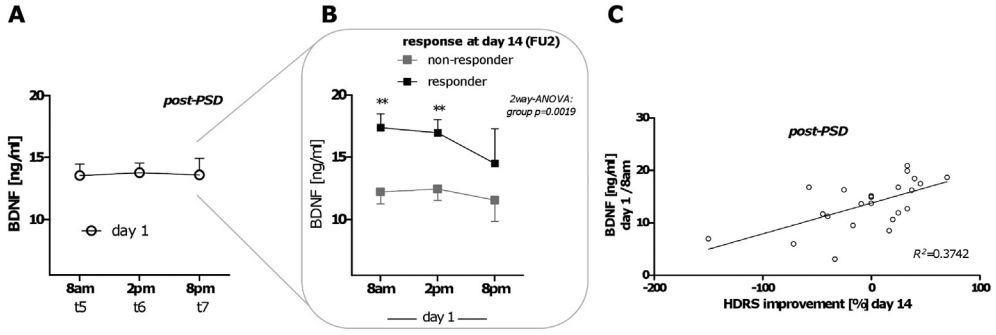

Fig. 3. Post-PSD serum BDNF levels. (A) After PSD (day 1) elevated serum BDNF levels (means ± SEM) vary modestly throughout the day. (B) When post-PSD serum BDNF levels (means ± SEM) were associated with long-term response after 14 days, a diurnal pattern was most prominent in subjects who were identified as responders. This peculiar diurnal variation did not exist for non-responders, since serum BDNF levels remained almost flat throughout the day. $^{**}p \leq 0.01$ vs. corresponding BDNF levels in non-responders. (C) Correlation between post-PSD serum BDNF levels and depression severity improvement. Improvement as percent change for Hamilton depression subscale (HDRS-6) ratings at day 14. Analyses showed a positive correlation of BDNF levels with improvement of depression severity across the sample ($r_p = 0.612$; $p = 0.002$).

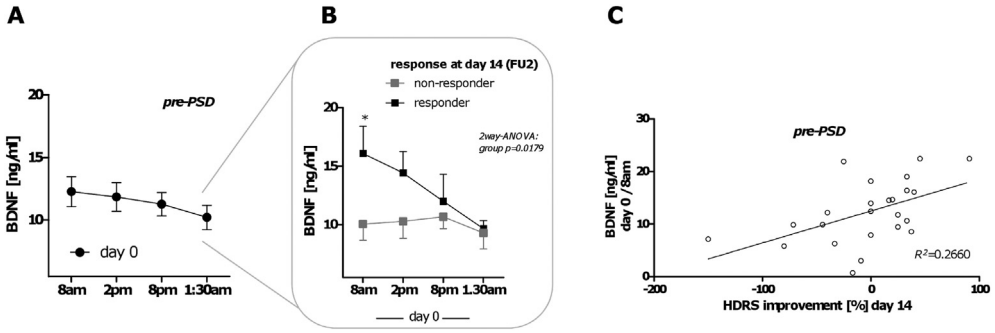

Fig. 4. Pre-PSD serum BDNF levels. (A) At baseline (day 0), before PSD intervention, serum BDNF levels (means ± SEM) vary throughout the day in a decreasing fashion. (B) When pre-PSD serum BDNF levels were associated with long-term response after 14 days, a diurnal pattern was most prominent in subjects who were identified as responders compared to non-responders. For non-responders serum BDNF levels (means ± SEM) remained flat throughout the day. $^{*}p \leq 0.05$ vs. corresponding BDNF levels in non-responders. (C) Correlation between pre-PSD serum BDNF levels and depression severity improvement. Improvement as percent change in Hamilton depression subscale (HDRS-6) ratings at day 14. Analyses showed a positive correlation of BDNF levels with improvement of depression severity across the sample ($r_p = 0.516$; $p = 0.001$).

especially at 8 am ($t1$) ($t = 2.264$, $p = 0.035$) (Two-way ANOVA: group effect $F(1) = 5.85$; $p = 0.0179$), compared to non-responders. Effect size calculations emphasized higher BDNF levels in FU2-responders at 8 am ($t1$) ($d = 0.91$) and 2 pm ($t2$) ($d = 0.71$) at pre-PSD baseline, relative to non-responders (Fig. 4B). Furthermore, we could identify a prominent daily change of pre-PSD serum BDNF levels in long-term responders. Once again, there was no diurnal BDNF pattern observable for patients identified as non-responders after 2 weeks (Fig. 4B). This finding was emphasized by a significant correlation of elevated pre-PSD serum levels at 8 am ($t1$) with HDRS-6 improvement in all patients after 2 weeks (Fig. 4C) ($r_p = 0.516$; $p = 0.001$).

4. Discussion

Key findings of the present study indicate that BDNF serum levels exhibited a significant diurnal variation. This diurnal pattern was especially prominent among responders when compared to non-responders in a sample of patients suffering from MDD. Subjects identified as responders after 2 weeks of follow-up (FU2) subsequent to PSD were associated with a daily change of serum BDNF post-PSD at day 1 and even pre-PSD at baseline (day 0). This variation of peripheral BDNF concentration revealed characteristics of a diurnal pattern since levels decreased during the day starting with the highest concentration in the morning, whereas non-responders did not exhibit diurnal serum BDNF variation. In consequence, we conclude that the presence of a diurnal serum BDNF profile in MDD patients is powerfully linked with therapy response.

Of note, there is limited data available on diurnal variation of blood BDNF levels in healthy subjects, but nothing is known from MDD patients in this regard.

Most biological functions are expressed in an oscillating manner within a 24-h circadian period, regulated by endogenous biological clocks. A growing body of evidence also supports a role for BDNF and its tropomyosine-related kinase receptor B (TrkB) in the modulation and mediation of circadian rhythms. High levels of BDNF and TrkB expression were demonstrated in the rat suprachiasmatic nucleus (SCN) and hippocampus (Katoh-Semba et al., 2008). It was reported that BDNF protein and mRNA levels in the rat SCN showed clear signs of variation over the course of a circadian cycle. The SCN content of BDNF protein remained low throughout the subjective day, began to rise early in the subjective night, and reached peak levels near the middle of the subjective night (Liang et al., 1998). Diurnal variation in BDNF protein expression levels was demonstrated in the cerebellum, hippocampus, and cerebral cortex (Katoh-Semba et al., 2008). Moreover, recognition that circadian rhythm disruption also plays a key role in mood disorders has led to the development of the new antidepressant agomelatine. Recent data from various groups showed that agomelatine led to an increase in BDNF expression in treated animals, and that this effect follows a specific temporal profile (Soumier et al., 2009). Interestingly, the presence of a diurnal BDNF rhythm was also recently demonstrated in healthy humans (only males were included in the study), where plasma BDNF displayed highest concentrations in the morning (8 am), followed by a substantial decrease throughout the day, with lowest values at midnight (Begliuomini et al., 2008). A similar circadian fluctuation in plasma BDNF levels was also found in women (Pluchino et al., 2009), even if the amplitude of the variation in BDNF levels appeared to be influenced by ovarian function with a blunted diurnal rhythm in the luteal phase.

In the present study, we could confirm parallel changes in diurnal variation of serum BDNF in patients identified as responders of both gender. Therefore, together all findings emphasize the importance of the presence of a circadian BDNF rhythm in human health and well-being, while its absence seems to have a negative impact on successful treatment outcome in MDD.

The decline in peripheral BDNF levels during the day may be ascribed to a circadian secretory model on the one hand. Therefore, it can be speculated that BDNF is secreted with a pulsatory circadian rhythm that is characterized by a progressive reduction in the amplitude of pulses throughout the day. On the other hand, it has been shown that brain BDNF is able to cross the blood–brain barrier via a rapidly saturable transport system (Pan et al., 1998). While brain BDNF peaks around midnight and thus may exert its modulating effect on neuroplasticity and long-term potentiation (Liang et al., 1998), peripheral BDNF in the blood, namely both, of plasma and serum, peaks in the morning at 8 am and exhibits its lowest expression level at midnight, indicating that BDNF cycles in opposite phases in brain and blood. Why there is a discrepancy in temporal expression profiles between blood and brain is not clear, but might be due to a rapid transition from brain to blood with a time delay of about 12 h or might reflect the endogenous circadian rhythm of BDNF in the periphery which oscillates in anti-phase to that of the brain. Importantly, this repeatedly reproduced result is in line with findings of Sartorius and colleagues, who investigated correlations and differences between serum and brain tissue BDNF levels after ECT in rats (Sartorius et al., 2009). They demonstrated a positive correlation between brain and serum BDNF concentrations providing evidence that it can be justified to measure serum BDNF levels but only by consideration of a time delay to monitor brain tissue alterations in the periphery.

Ultimately, it is not clear to what extent diurnal changes of blood BDNF are related to a circadian secretory model, sex hormones, malfunctions in hypothalamic–pituitary–adrenal (HPA) axis regulation, different activity during the day or other environmental factors.

Moreover, the present study demonstrated that diurnal BDNF serum variations were not changed by the adjuvant medication with modafinil as a stimulant during PSD, which is consistent with our previous finding showing that modafinil was not able to enhance the antidepressive effects of PSD and did not stabilize antidepressive effects over two weeks in these patients (Beck et al., 2010). In addition, PSD itself had also no significant impact on the diurnal serum BDNF profile. This further emphasizes the importance of the presence of a daily, circadian BDNF profile at baseline with regard to therapy response prediction. This is in line with data from Wolkowitz et al. (2011) who also found that serum BDNF levels (only measured at a single time point 10 am) before treatment with SSRI (escitalopram or sertraline) predicted SSRI response in depressed patients and that responders to treatment exhibited higher pre-treatment BDNF levels than did non-responders. Thus, one can speculate that diurnal BDNF variation represents a prerequisite for successful therapy response independent from the specific treatment strategy, e.g. antidepressants drugs or SD.

Furthermore, our findings confirmed that post-PSD BDNF serum levels were higher in long-term (HDRS-6 ratings after two weeks) responders (≥30% improvement in depression ratings) when compared to non-responders. Increased BDNF serum levels (peak levels at 8 am at day 1) were consistently associated with an improvement of depressive symptoms in all patients. This was also the case for pre-PSD serum BDNF levels (peak levels at 8 am at day 0). Our data are in line with other studies providing evidence that an antidepressant-induced increase in BDNF levels is more prominent in responders than non-responders (Okamoto et al., 2008) or even exclusively restricted to responders (Lee and Kim, 2008), while the early non-increase in serum BDNF levels predicted failure of antidepressant treatment (different classes of antidepressants) in patients with major depression (Tadic et al., 2011).

In the present study, post-PSD BDNF levels were investigated at a very early stage of intervention, in this case within hours after PSD (up to 18 h by using a 6 h interval post-PSD, specifically at 8 am, 2 pm, and 8 pm). This is in contrast to all other published studies where treatment related BDNF changes were collected and analyzed no earlier than one up to six weeks after antidepressive therapy implicating classic antidepressants. Likewise with our results, recent studies applying the glutamate modulating compound ketamine to treat depression, have demonstrated a rapid onset of antidepressant effects (Berman et al., 2000; Liu et al., 2013; Zarate et al., 2006). Haile and colleagues showed that plasma BDNF levels increased 240 min post-infusion (0.5 mg/kg) in responders compared to non-responders. Furthermore, significantly increased BDNF levels were negatively correlated with depression ratings and highly predictive for clinical outcome up to 72 h post-infusion (Haile et al., 2014). These findings support our data that early changes of peripheral BDNF levels are already associated with clinical outcome. Importantly, early changes of BDNF levels after PSD and post-infusion of ketamine (Haile et al., 2014) underpin the hypothesis of a rapid adaptation mechanism. Remodelling of synapses and induction of neurogenesis (Duman and Aghajanian, 2014) attended by increased BDNF expression facilitates the hypothesis of a peripheral secretory model, which would fit with the observation of a circadian pattern. It seems that rapid changes to remodel neuronal networks involve the release of BDNF as a critical backbone which might also occur in the periphery, since serum BDNF levels increase within hours. However, we cannot conclude whether these peripheral changes of BDNF might stem from the brain or peripheral sources, as in this study only serum was assessed.

With good cause, the rapid effect of PSD reflected via BDNF levels, might be related to the rapid antidepressant effect of PSD at day 1, however relapse into depression occurs in most patients following the recovery night (already at day 2) (Beck et al., 2010). In agreement with our findings, others have consistently shown that prolonged wakefulness as a result of sleep deprivation, which can be considered as a stressor for the brain, leads to an increase in BDNF (Conti et al., 2007), while sleep disturbance was linked to reduction of BDNF levels (Giese et al., 2014), confirming a bidirectional stress model with which both can be explained. Chronic stress induces a deregulation of the HPA system leading in the long-term to sleep disturbances and decreased BDNF levels, whereas acute sleep deprivation, e.g. PSD, can be used as therapeutic intervention in some insomniac or depressed patients as a compensatory process to normalize BDNF levels (Giese et al., 2013).

Thus, the present study adds very important new evidence to the currently existing BDNF literature dealing with MDD: i) An a-priori diurnal BDNF serum level variation precedes a more favourable treatment outcome in depressive patients, and ii) PSD may exert a very rapid effect on serum BDNF levels within a time frame of several hours the day after PSD which parallels clinical findings. This supports the release hypothesis regarding rapid BDNF changes next to induced gene expression (Duman and Aghajanian, 2014). However, further results must be obtained in a larger patient population where serum and plasma levels could reveal, if rapid BDNF changes are related to induced gene expression and/or a matter of rapid adaption reflected by a peripheral release in line with a circadian profile. While rapid increase in serum BDNF levels after PSD suggests a direct effect of sleep deprivation; however, the observed associations with treatment response at day 14 during follow-up could be influenced also by long-term effects of the mirtazapine treatment starting at baseline, which is a limitation of our study.

For future studies, we suggest that next to analyses of pre- and post-treatment serum BDNF levels collected at a single time point per day, diurnal proof of peripheral BDNF should be monitored at baseline especially before intervention starts for the purpose of therapy response prediction. Moreover, the results of our study might provide a valuable model for the investigation of biomarkers in the treatment of MDD and other psychiatric disorders and might encourage research in the area of early predictors of therapy response in order to shorten the duration of psychopharmacological treatment until the determination of insufficient effectiveness. Further studies with a larger number of patients and different treatment strategies should be conducted to verify the results of our exploratory investigation and to elucidate the underlying mechanisms more closely, especially the role of the stress hormone system.

Contributor's declaration

Conceived and designed the experiments: Johannes Beck, Serge Brand, Ulrich Hemmeter, Martin Hatzinger, Edith Holsboer-Trachsler and Anne Eckert.

Performed the experiments: Maria Giese, Johannes Beck, Serge Brand and Flavio Muheim.

Analyzed the data: Maria Giese, Serge Brand, Johannes Beck.

Contributed reagents/materials/analysis tools: Martin Hatzinger, Edith Holsboer-Trachsler and Anne Eckert.

Wrote the paper: Maria Giese, Anne Eckert and Edith Holsboer-Trachsler.

Role of funding source

This project was supported by the Swiss National Science Foundation (SNF-Nr 320080-104022, E.H.).

Acknowledgements

This project was supported by the Swiss National Science Foundation (SNF-Nr 320080-104022, E.H.).

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