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Association of BDNF Serum Concentrations with Central Serotonergic Activity: Evidence from Auditory Signal Processing

Undine E Lang[1], Rainer Hellweg[2] and Jürgen Gallinat*[,3]

[1]Department of Neurology, University of Tuebingen, Tuebingen, Germany; [2]Clinic for Psychiatry and Psychotherapy, Charité Medicine Berlin, Campus Benjamin Franklin, Germany; [3]Clinic for Psychiatry and Psychotherapy, Charité Medicine Berlin, Campus Charité Mitte, Germany

Disturbances of serotonergic neurotransmission in the brain have been implicated in the pathogenesis and maintenance of several psychiatric disorders. According to recent preclinical and clinical studies, the loudness dependence of auditory evoked potentials (LD) is related to the central serotonergic neurotransmission in humans. As the serotonergic phenotype has been reported to be associated with brain-derived neurotrophic factor (BDNF), we studied whether BDNF serum concentrations are related to LD in 109 healthy human volunteers (62 male, 47 female, age: 42.5 ± 13.1 years). Pearson correlation showed a significant negative correlation between the BDNF serum concentrations and the LD measured at Fz ($r = -0.259$, $p = 0.007$) and a trend for the Cz electrode ($r = -0.185$, $p = 0.055$). Although this association needs to be replicated, the results are in line with the assumption that low serum BDNF levels reflect low central serotonergic neurotransmission as indicated by a strong LD.
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INTRODUCTION

Disturbances of serotonin neurotransmission in the brain have been implicated in the pathogenesis and maintenance of several psychiatric disorders and symptoms, that is, depression, alcoholism, impulse control disorders, aggression, suicidal behavior, anxiety, and obsessive compulsive behavior (Senkowski *et al*, 2003; Heinz *et al*, 2001; Petty *et al*, 1996). The monoamine hypothesis of depression was first formulated 40 years ago (Schildkraut, 1965). For instance, levels of the major serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been reported to be lower than normal in the cerebrospinal fluid of patients with depression (Cheetham *et al*, 1991), although this is not a consistent finding (Gjerris, 1988). A relatively reliable observation is that activity of the serotonin transporter in platelets is reduced in patients with depression, a model for neuronal serotonin activity (Owens and Nemeroff, 1994). In line with this, an investigation with β-CIT single photon emission computed tomography reported evidence for a reduction in the activity of the transpoter in patients with depression compared with healthy controls (Malison *et al*, 1998). Moreover, an increase in the density of postsynaptic cortical 5-HT2 receptor-binding sites of depressed suicide victims and unmedicated depressed patients have been observed by post-mortem studies (Stanley and Mann, 1983; Yates *et al*, 1990) and PET investigations (Biver *et al*, 1997). It has been suggested that upregulation of cortical 5-HT2 receptors in depression is an adaptive response to reduced synaptic serotonin (Owens and Nemeroff, 1994).

In recent years, growth and function of monoamine-containing neurons have been extensively investigated with respect to neurotrophins. It has been suggested that depression or pathophysiological subgroups of depressive disorders may constitute a subtle form of neurotrophin-related neurodegeneration affecting serotonergic neurons (Altar, 1999; Duman *et al*, 1997). The neurotrophin brain-derived neurotrophic factor (BDNF) influences the phenotype, structural plasticity, and survival of serotonergic neurons (Eaton *et al*, 1995; Mamounas *et al*, 1995; Siuciak *et al*, 1996). In particular, BDNF promotes the sprouting of mature, uninjured serotonergic axons and chronic treatment with BDNF leads to enhancement of the regenerative sprouting of serotonergic axons, damaged by the neurotoxin p-chloroamphetamine (Mamounas *et al*, 1995, 2000). This BDNF-related stimulation of serotonergic phenotype, in terms of increased neuronal number and neuritic extension,

*Correspondence: Dr J Gallinat, Psychiatrische Universitätsklinik der Charité, im St. Hedwig-Krankenhaus, Örtlicher Bereich Moabit, Turmstr. 21, 10559 Berlin, Germany, Tel: +49 30 2311 2895, Fax: +49 30 2311 2903, E-mail: juergen.gallinat@charite.de
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would suggest that an increased serotonergic transmission is possibly underlying the antidepressant-like effects reported for BDNF (Siuciak *et al*, 1997).

The BDNF-mediated stimulation of the neuronal serotonergic phenotype is likely mediated by tyrosine kinase receptor (TrkB)-dependent mechanisms (Rumajogee *et al*, 2002). Moreover, an upregulation of tryptophan hydroxylase mRNA—the rate-limiting enzyme in serotonin synthesis—has been demonstrated after BDNF injection in rat raphe nuclei (Siuciak *et al*, 1998).

With respect to human electrophysiology, efforts have been directed to identify indicators of central neurotransmitter activity. Since evidence for a modulation of the loudness dependence (LD) of the auditory evoked N1/P2-component by changes of the central serotonergic activity was reported in humans (von Knorring and Perris, 1981) and animals (Juckel *et al*, 1997, 1999) the LD was hypothesized to be such an indicator (Hegerl and Juckel, 1993). The LD denotes the amplitude change of auditory evoked potentials (AEPs) in response to different stimulus intensities. A strong LD has been proposed to indicate a low serotonergic activity and vice versa. For example, the LD in behaving cats was found being decreased by application of the 5-HT1a-receptor agonist 8-OH-DPAT and increased by the 5-HT2-receptor antagonist ketanserin (Juckel *et al*, 1997). Empirical clinical support for this hypothesis comes from studies showing that a strong LD in depressed patients is related to a favorable therapeutical outcome to serotonin agonistic agents (Gallinat *et al*, 2000; Hegerl and Juckel, 1993). Moreover, intraindividual changes of blood serotonin concentrations were negatively correlated with corresponding changes of the LD in patients with major depression (Hegerl *et al*, 1991). Furthermore, a strong LD was described in abstinent ecstasy users which are hypothesized to possess a diminished serotonergic activity (Tuchtenhagen *et al*, 2000), while patients with a serotonin syndrome, a possible side effect during SSRI treatment characterized by confusion, restlessness, myoclonus, and hyperthermia, were shown to have a weak LD (Hegerl *et al*, 1998). Also a significant effect of a functional polymorphism in the promoter region of the serotonin transporter gene 5-HTTLPR on the AEP intensity dependence has been observed (Gallinat *et al*, 2003).

In the present study, the LD was employed as indicator of the central serotonergic activity in humans to test the following hypothesis: A low concentration of serum BDNF is associated with a high LD indicating a low central serotonergic activity. This hypothesis was investigated in 109 carefully selected healthy subjects, who were also have been part of previously investigated samples (Lang *et al*, 2004; Gallinat *et al*, 2003).

SUBJECTS AND METHODS

Subjects

The study was approved by the ethics committee of the University Hospital Benjamin-Franklin, Free University of Berlin (Germany). All subjects were recruited by newspaper advertisement and gave written informed consent. The participants, who were of German descent, were interviewed by a research psychiatrist with structured clinical interviews (Mini-International Neuropsychiatric Interview, Sheehan *et al*, 1998). Exclusion criteria were axis-I or axis-II disorders, alcohol or illegal drug abuse, hearing disorder, significant cardiovascular, hepatic, renal, gastrointestinal, metabolic, or other systemic disease, concurrent psychiatric or neurological illness, organic mental disorder, seizure disorder, mental retardation, Parkinson's disease, toxic central nervous system depression, or any clinically relevant abnormalities. For further description, see Gallinat *et al* (2002).

Our study subjects were selected from a larger sample ($n = 376$) on the basis of the availability of electrophysiological data, BDNF serum concentrations, and NEO-FFI personality inventory (Costa and McCrae, 1992). A total of 109 healthy unrelated volunteers (62 male, 47 female, age: 42.52 ± 13.1) were investigated. All participants were also part of a sample ($n = 118$) reporting a correlation between BDNF serum concentration and personality traits (Lang *et al*, 2004) as well as part of a sample ($n = 185$) analysing the association between allelic variants of the serotonin transporter gene and the LD (Gallinat *et al*, 2003).

Measurement of LD

Recording took place in an electrically shielded and sound-attenuated room adjacent to the recording apparatus (Synamps, Neuroscan®). Subjects were seated with open eyes in a slightly reclined chair with a head rest and were asked to look at the wall 3 m in front of them. Evoked responses were recorded with 32 electrodes referred to Cz. Pure sinus tones (1000 Hz, 40 ms duration with 10 ms rise- and 10 ms fall time, ISI randomized between 1800 and 2200 ms) of five intensities (79, 87.5, 96, 104.5, 113 dB sound pressure level) were presented binaurally in a pseudo-randomized form by audiometry-headphones. Data were collected with a sampling rate of 250 Hz and an analogous bandpass filter (0.16–50 Hz). In all, 350 ms prestimulus and 800 ms poststimulus periods were evaluated for 100 sweeps of every intensity (all together 500 sweeps). Before averaging, the first five sweeps were excluded in order to reduce short-term habituation effects. For artefact suppression, all trials were automatically excluded from averaging, if the voltage exceeded $\pm 100\,\mu V$ in any one of the 32 channels at any time point of the averaging period. For each subject, the remaining sweeps were averaged separately for the five stimulus intensities. At least 30 artefact-free sweeps/intensity had to be averaged. N1-peaks (50–150 ms) and P2-peaks (100–250 ms) were determined semiautomatically at the Fz- and Cz electrode (referred to linked-mastoids). The LD was calculated as linear regression slope with stimulus intensity as independent and N1/P2-amplitude as dependent variable (Gallinat *et al*, 2000).

Measurement of BDNF Levels

Endogenous levels of BDNF were measured in the rethawed serum samples using commercial ELISA kits in principle according to the manufacturer's instructions (Promega Inc., Mannheim, Germany), but adapted to the fluorometric technique used also for nerve growth factor determination (Hellweg *et al*, 2003) and described in detail previously

(Hellweg *et al*, 1989). The BDNF content was expressed as equivalents of recombinant human BDNF. The detection limit of the assay was 1 pg/ml. Determinations of recovery, specific and unspecific neurotrophin binding (the latter against mouse IgG_1 obtained from MOPC 21) involved quadruplicate fluorescence determinations for each serum sample (Hellweg *et al*, 2003).

Data Analysis

Kolmogorov–Smirnov test were employed to evaluate whether BDNF level is a normally distributed trait. Gender effects were tested using *T*-test for independent samples, age effects were determined with Pearson's correlation test. BDNF was correlated with the LD using partial correlation test (controlled for age). Results are presented as means $\pm$ one standard deviation. Analyses were computed using statistical software (SPSS 11.5®). A *p*-value of $p<0.05$ was considered significant, while $p<0.10$ was accepted in order to detect trends.

RESULTS

BDNF serum levels in the healthy human population amounted to 16.69 ± 7.7 ng/ml, the median amounted to 14.77 pg/ml. Kolmogorov–Smirnov test ($D=1.155$, $p=0.139$) showed that the BDNF serum concentrations in our sample were normally distributed. BDNF concentrations correlated significantly with age ($r=0.200$, $p=0.037$), but showed no gender differences (male 16.40 ± 7.6, female 17.07 ± 7.8 ng/ml; $T=0.451$, df $=107$, $p=0.653$; *T*-Test).

Age was negatively correlated with the LD measured at the Fz electrode ($r=-0.226$; $p=0.018$) as well as Cz electrode ($r=-0.294$; $p=0.002$). No gender effects were observed for the LD on both electrodes Fz ($T=0.857$; df $=107$; $p=0.393$) and Cz ($T=1.047$; df $=107$; $p=0.298$).

Pearson correlation showed a significant negative correlation between the BDNF concentrations and the LD measured at Fz ($r=-0.259$, $p=0.007$; see Figure 1) and a trend for the Cz electrode ($r=-0.185$, $p=0.055$). The association between BDNF concentrations and the LD at Fz was also significant when a partial correlation (controlled for age) was performed ($r=-0.223$, $p=0.020$), while the correlation at the Cz electrode controlled for age was not significant ($r=-0.135$, $p=0.165$).

As previously reported (Lang *et al*, 2004; $n=118$), a significant negative correlation between BDNF serum concentration and the depression-related personality trait neuroticism was observed. This was also observed in the present subsample ($n=109$; $r=-0.193$; $p=0.048$; partial correlation controlled for age), indicating a lower BDNF concentration in subjects with a more depressed personality trait. To further investigate the link between behavior and serotonin, it was analyzed if more depressed individuals have lower serotonergic activity, which would be indicated by a higher LD. However, the correlation between neuroticism score and LD did not show a significant result (Fz: $r=0.121$, $p=0.218$; Cz: $r=0.100$, $p=0.306$; partial correlation controlled for age).

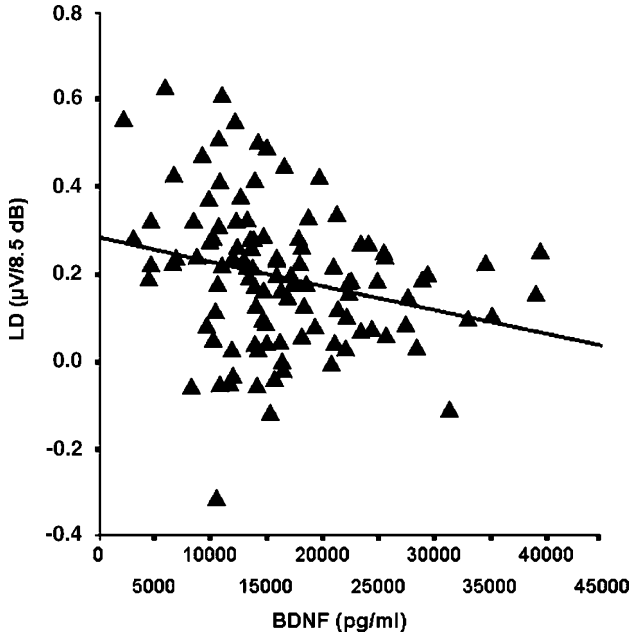

Figure 1 Correlation between BDNF serum concentration and the LD (Fz electrode referred to linked mastoids) in 109 healthy subjects ($r=-0.259$, $p=0.007$; Pearson).

DISCUSSION

In the present study, a negative correlation between BDNF serum concentrations and LD measured at Fz ($p=0.007$) and a trend in the same direction measured at Cz ($p=0.055$) was observed in healthy subjects. This result is compatible with the hypothesis that low concentrations of BDNF are associated with low levels of central serotonergic activity.

In line with this result, an augmentation of serotonergic activity within various brain areas following infusion of BDNF into the midbrain has been reported (Altar *et al*, 1994; Siuciak *et al*, 1996). Others observed a dose-dependent reduction of the serotonin uptake in B lymphoblasts after exposure to BDNF (Mössner *et al*, 2000). Apart from immediate serotonergic effects, BDNF has been reported to play a role in the development of serotonergic neurons (Eaton *et al*, 1995) as well as sprouting of serotonergic axons (Mamounas *et al*, 1995), which also may affect serotonergic function as indicated by the LD.

Recent basic and clinical research studies have shown evidence for a 'neurotrophin hypothesis' of depression (Garza *et al*, 2004; Manji *et al*, 2003; Russo-Neustadt, 2003; D'Sa and Duman, 2002; Duman *et al*, 1997). This hypothesis may be integrated with the long hypothesized role of monoamines in depression, since evidence for an association of BDNF and serotonin has been presented. For instance, animal studies reported that hippocampal BDNF mRNA levels are significantly increased after physical exercise, administered antidepressant medications and electroconvulsive therapy (Russo-Neustadt, 2003; Russo-Neustadt *et al*, 2000; Nibuya *et al*, 1995), while in turn, physical exercise, antidepressants (Meeusen *et al*, 1996; Chaouloff, 1994; Dey *et al*, 1992; Chaouloff *et al*, 1986), and electroconvulsive therapy (Gur *et al*, 2002; Shen *et al*, 2001)

have been shown to increase serotonergic neurotransmission. Interestingly, behavioral antidepressant-like properties of BDNF in animal models have been reported (Shirayama *et al*, 2002; Siuciak *et al*, 1997). This scenario is compatible with recent investigations supporting the serotonin deficit hypothesis in depression: A study employing α-methyl-tryptophan positron emission tomography found evidence for a reduced serotonin synthesis in limbic and paralimbic structures in patients with depression compared to controls (Rosa-Neto *et al*, 2004).

In analogy with the neurotrophin hypothesis of depression, low BDNF serum levels were found to be associated with high scores in depressive personality traits in healthy subjects (Lang *et al*, 2004). In line with this, genetic studies show that a BDNF-coding variant is associated with neuroticism in the NEO personality inventory (Sen *et al*, 2003). Depressive personality is a trait which has also been connected with low serotonergic neurotransmission (Sen *et al*, 2004; Heinz *et al*, 2001). Interpreting the associations between depressive personality trait and low BDNF concentration as well as between low BDNF level and a high LD, one would expect a positive correlation between the LD and depressive personality trait. However, no statistically significant correlation was found in the present study. This may indicate the limitation of the depressive personality trait as a model for affective disorders, since others reported a higher LD in bipolar or unipolar depressive patients (Friedman and Meares, 1979; Brocke *et al*, 2000), while a lower LD was reported in withdrawn alcohol-dependent patients with high harm avoidance scores, a behavioral characteristic related to depressive personality traits (Herrmann *et al*, 2002). Therefore, the present results have to be interpreted with caution and should not be generalized to the pathophysiology of depression.

Moreover, one has to bear in mind that BDNF serum changes in subjects with a strong LD or depressed subjects could be an epiphenomenona as the exact mechanisms of regulation of humoral BDNF levels are widely unknown. Platelets, brain neurons, and vascular endothelial cells are considered as candidate sources. A major source of the serum BDNF are platelets, which bind, store, and release BDNF upon activation and in response to coagulation stimuli (Fujimura *et al*, 2002; Yamamoto and Gurney, 1990). As platelets and neurons develop from a common embryonic precursor in the neural crest (Pearse, 1980), the peripheral BDNF concentration could possibly reflect the central neurotransmission state as it was stated also for serotonergic neurotransmission in platelets (Lesch *et al*, 1993). A parallel BDNF brain and serum situation is underlined by the finding of Karege *et al* (2002), who reported a positive correlation between brain and serum BDNF levels in rats, which underwent similar changes during maturation and aging processes and data showing neurotrophic factors from the blood stream can cross the blood–brain barrier under experimental conditions (Pan *et al*, 1998). However there are also conflicting results, showing that neurotrophins do not cross the blood–brain barrier (Pardridge, 2002).

Although several lines of evidence indicate an association between LD and serotonin (see Introduction), animal investigations reported also some effects of the dopamine and choline system (but not noradrenalin) on the LD (Juckel *et al*, 1997). Therefore, the moderate correlation between LD and BDNF serum concentration should be viewed with caution. However, the link between LD and serotonin is more consistent and also compatible with a recent animal study showing a high correlation ($r = -0.80$) between the N1/P2-amplitude and the 5-HT concentration in the auditory cortex (Manjarrez *et al*, 2001).

In conclusion, the present results are compatible with the hypothesis of enhanced serotonergic neurotransmission in humans with high BDNF serum concentrations. A decrease in serum BDNF levels might reflect low serotonergic neurotransmission and thereby influence the cascade, which may be also relevant in the pathophysiology of depression. However, the results have to be interpreted with caution since the significance is moderate. Moreover, a replication in an independent sample has to be performed.

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