Increase of plasma brain-derived neurotrophic factor levels in two psychotic depressed patients responding to lithium addition to paroxetine treatment

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Abstract: We report two patients with psychotic depression who were successfully treated with a lithium addition to ongoing paroxetine treatment. In both cases, plasma brain-derived neurotrophic factor (BDNF) levels increased about 2-fold after lithium augmentation to paroxetine, compared with paroxetine treatment alone. Plasma paroxetine levels did not change after lithium addition. These results suggest that the increases in plasma BDNF levels reflect recovery from depressive symptoms in psychotic depression.

Keywords: psychotic depression, paroxetine, lithium, brain-derived neurotrophic factor

Introduction

It has been well established that about half of all treatment-refractory depressed patients respond to the addition of lithium to their ongoing antidepressant regimen, usually within 1–2 weeks (Lenox and Manji 1998). Zullino and Baumann (2001) reported in their review that lithium augmentation in depressive patients who do not respond to selective serotonin reuptake inhibitors (SSRIs) including citalopram, fluoxetine, paroxetine, and sertraline, may be an efficacious and generally well-tolerated treatment, with a response rate of at least 50% after a period lasting 1–2 weeks; there is as yet no clearer evidence for a pharmacokinetic interaction between lithium and SSRIs with pharmacodynamic consequences.

Recently, Karege et al (2002) reported that serum BDNF levels were significantly decreased in antidepressant-free depressed patients, and that serum BDNF levels were negatively correlated with the Montgomery-Asberg Depression Rating Scale. Shimizu et al (2003) also demonstrated that serum BDNF was significantly lower in an antidepressant-naïve depressed group than in either a treated or a control group, and that there was a significant negative correlation between serum BDNF and Hamilton Rating Scale for Depression (Ham-D) scores in all patients. Furthermore, they reported preliminary findings that decreased serum BDNF levels in antidepressant-naïve patients recovered to normal levels in association with lower Ham-D scores after treatment with antidepressant medication. Moreover, Lang et al (2004) demonstrated that decreased serum BDNF levels were observed in healthy volunteers with neuroticism, a depression-related personality trait. The authors also speculated that BDNF levels have some influence on central serotonergic activity. Recently, we reported that plasma BDNF levels increased 4 weeks after high-frequency repetitive transcranial magnetic stimulation treatment in treatment-refractory depressed patients, and the increase was related to the improvement of the depressive symptoms (Yukimasa et al 2006). Taken together, it is possible that serum or plasma BDNF level is one of the biological state markers for a depressive state.
In the present study, we report two cases of psychotic depression responding to lithium augmentation to an ongoing paroxetine regimen. In both cases, the plasma BDNF level increased after the lithium addition to the paroxetine treatment, and were related to the patient’s recovery from depressive symptoms.

Measurement of plasma BDNF and paroxetine
All blood samples were taken at 7 am before breakfast (at least 12 hours after the last medication). Seven milliliters of venous blood was drawn with the patient in the supine position, after the patient had been lying at rest. The plasma samples were quickly separated in a centrifuge (2000 g, 10 min, 4 °C) and stored at –80 °C until assay.

The plasma BDNF levels were measured using a BDNF Emax Immunoassay Kit (Promega, Madison, WI, USA) according to the manufacturer’s instructions. Plasma paroxetine was also analyzed by high-performance liquid chromatography (HPLC) according to the method of Gupta (1994). The protocol of this study was approved by the Ethics Committee of the University of Occupational and Environmental Health. All patients gave their consent to participate after having been informed of the study’s purpose.

Case reports
Case 1
The patient was a 60-year-old housewife with a major depressive disorder with psychotic features by DSM-IV criteria. She had first depressive episode at the age of 45-year-old. She was recovered from the depressive episode treated with imipramine (100 mg/day). She had second depressive episode (insomnia, depressed mood, restlessness, agitation, anxiety, fatigue) after interferon-alpha treatment for hepatitis C, however, she had no cognitive and neurologic impairment. Her score on the Ham-D was 32. She had not comorbid any other psychiatric and physical disorders. Within 6 weeks her depressive symptoms were successfully treated with paroxetine at 40 mg/day. She was maintained with paroxetine at 40 mg/day for 6 months and then paroxetine was tapered off. One year later, she became depressed again with depressive mood, anxiety, restlessness, agitation and mood incongruent persecutory delusion (her score in the Ham-D was 28). Paroxetine was re-started and increased up to 40 mg/day. Her plasma BDNF level just before paroxetine administration was 0.8 ng/mL. Four weeks later, there was no evidence of improvement of her depressive symptoms, her Ham-D score was still 25, and her plasma levels of BDNF and paroxetine were 0.9 ng/mL and 110 ng/mL, respectively. Lithium at 400 mg/day was added to the ongoing paroxetine. A week after the lithium addition, her depressive symptoms were dramatically improved (her Ham-D score was 12), and the improvement continued. Mild finger tremor transiently occurred after lithium augmentation without any treatment. She was remitted 2 weeks after the lithium augmentation (her Ham-D score was 7). Her plasma levels of BDNF, paroxetine, and lithium at 4 weeks after lithium addition were 1.8 ng/mL, 124 ng/mL, and 0.5 mEq/L, respectively.

Case 2
The patient was a 65-year-old housewife with a major depressive disorder with psychotic features by DSM-IV criteria. She had no previous depressive episodes. Three months after her husband died of bladder cancer, she became depressed with depressive mood, anxiety, agitation, restlessness, hypochondriasis, psychomotor retardation, insomnia, fatigue, and mood-incongruent persecutory delusion (her Ham-D score was 32). She had not comorbid any other psychiatric and physical disorders. Paroxetine was started and increased up to 40 mg/day. Her plasma BDNF level just before paroxetine administration was 1000 pg/mL. Four weeks later, her depressive symptoms had not improved, her Ham-D score had worsened to 35, and her plasma levels of BDNF and paroxetine were 1.1 pg/mL and 98 ng/mL, respectively. Lithium at 400 mg/day was added to the ongoing paroxetine treatment. Two weeks after the lithium addition, her depressive symptoms were gradually improved (her Ham-D score was 21), and the improvement continued. Her Ham-D scores 3 and 4 weeks after lithium addition were 15 and 7, respectively. Any adverse effects did not occurred after lithium addition. Her plasma levels of BDNF, paroxetine, and lithium at 4 weeks after lithium addition were 2.4 ng/mL, 108 ng/mL, and 0.4 mEq/L, respectively.

Discussion
Psychotic depression is known to be particularly resistant to treatment with tricyclic antidepressant drugs or SSRIs alone (Chan et al 1987; Matthews et al 2002); it has been reported that patients with psychotic depression respond better to a combination of antipsychotic drugs and antidepressant drugs than to antidepressant drugs alone (Nelson and Bowers 1978; Charney and Nelson 1981). Recently, we reported that combination treatments of risperidone with antidepressant drugs or mood stabilizers were effective for psychotic depression, and the influence of risperidone on dopaminergic activity is associated with its efficacy (Goto et al 2006). However, the combination treatments of typical or atypical antipsychotic
drugs with antidepressants drugs are sometimes accompanied with adverse side effects such as extrapyramidal symptoms, hyperprolactinemia, weight gain or hyperglycemia. Another strategy for psychotic depression is lithium augmentation to antidepressant drugs (Ebert 1997). The major finding in the present study is that plasma BDNF levels did not change after 4 weeks after paroxetine treatment; however, they increased about 2-fold at 4 weeks after lithium augmentation to paroxetine compared with paroxetine treatment alone, related with the recovery from depressive symptoms in both cases. The average plasma BDNF level in health volunteers is 2.2 ± 1.4 ng/mL (mean ± SD) (data not shown). Thus, the plasma BDNF levels of the two patients were recovered within normal levels. In the present cases, the lithium addition to paroxetine was effective for the treatment of psychotic depression. There is growing evidence indicating that BDNF may have a crucial role in mental disorders such as depression (Durman et al 1997) and schizophrenia (Shoval and Weizman 2005). Karege et al (2002) shown that serum BDNF levels of drug-free patients are lower than those of controls, and Shimizu et al (2003) found that serum BDNF levels of treated depressed patients do not different from control levels. Aydemir et al (2005) have reported that serum BDNF levels are lower in depressed patients than those in controls, and that treatment with antidepressant drugs for 12 weeks increases serum BDNF levels to control levels. Gonul et al (2005) have also reported that treatment with several antidepressant drugs for 8 weeks significantly increases serum BDNF levels to the same levels as those of control subjects. In addition, we have reported that serum BDNF levels in responders are significantly increased 2.6- and 1.8-fold 8 weeks after treatment with paroxetine or milnacipran, respectively (Yoshimura et al 2007). On the other hand, nonresponders are not. These results indicate that blood BDNF levels is a state marker for depressive states, and antidepressant drugs with or without lithium increase serum BDNF levels in both non-psychotic and psychotic depressed patients. In other words, blood BDNF levels might be a biological marker for the response to the pharmacological intervention in depressive state. Previously, we reported that treatment with paroxetine for 8 weeks, but not 4 weeks increased blood BDNF levels in the responders to paroxetine (Yoshimura et al 2007). In the present cases, lithium addition to the ongoing paroxetine increased the BDNF levels 4 weeks after the combination treatment. These results suggest that lithium augmentation to paroxetine might have more potent effects on the BDNF levels. The amount of plasma BDNF levels appear to be much lower than serum, because a lot of BDNF exist in platelet, and Karege et al (2005) reported that both serum and plasma levels were decreased in depressed patients compared with control subjects, suggesting that the alteration of serum or plasma BDNF is not due to the change in blood BDNF but rather is probably related to mechanisms of BDNF release, which is independent of platelet activity. Furthermore, plasma paroxetine concentrations did not change after the lithium augmentation, suggesting that pharmacokinetic interaction between paroxetine and lithium might not be associated with the mechanism for plasma BDNF increases and recovery from the psychotic depression by lithium augmentation to paroxetine. However, the possibility that paroxetine treatment might have increased plasma BDNF levels very slowly is not completely ruled out. In addition, there is a possibility that other mechanisms such as enhancing serotonergic and noradrenergic neurons (Terao et al 1992; Terao et al 2000) by lithium might be associated with their improvement.

In conclusion, lithium augmentation to ongoing paroxetine treatment was effective for the treatment of two psychotic depressive patients. Although plasma BDNF levels did not alter with only paroxetine treatment, they increased after lithium addition to paroxetine. Further study is needed to elucidate the mechanisms for the efficacy of the combination treatment of lithium and paroxetine and the increase of plasma BDNF levels induced by lithium augmentation to paroxetine.

References


